

Sublingual Immunotherapy

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KEYWORDS

- Sublingual immunotherapy • Allergen-specific immunotherapy
- Allergic rhinitis • Subcutaneous immunotherapy • Asthma

Key Points: SUBLINGUAL IMMUNOTHERAPY FOR ALLERGY

- SLIT has been shown in multiple studies to be efficacious in allergic rhinitis for adults and children.
- SLIT has also been shown to be helpful in asthma and in preventing the development of new sensitivities to allergens.
- Studies have shown immunologic changes in SLIT that are similar to SCIT, suggesting a similar mechanism of action.
- SLIT enjoys a good safety profile, allowing for the convenience of dosing in the home and in individuals unable to tolerate injections, such as young children, although a few cases of anaphylaxis have been reported.
- The majority of literature has been published in Europe, with multiple factors making the translation of dosing to the United States difficult. Future studies will help continue to clarify optimal dosing and schedule in the United States.

The incidence of allergic disease has increased significantly over the past 40 years.¹ Allergic rhinitis is a very common health problem associated with considerable decreases in quality of life, and affects 5% to 22% of Americans.² Although it is typically not a life-threatening disease, medical management costs are substantial. More than \$1 billion are spent on management of allergic rhinitis every year in the United States.³ If the apparent trend of increasing atopy continues, a growing number of patients will be affected by the decreased quality of life associated with allergic rhinitis, and the increasing societal economic burdens associated with treatment of the disease and losses in worker productivity.

The mainstays of treatment for allergic rhinitis include avoidance of allergen, pharmacotherapy, and immunotherapy. Immunotherapy involves administering increasing

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concentrations of allergen to sensitized individuals to reduce allergic symptoms caused by natural exposures to these allergens. When immunotherapy is administered over an adequate duration, the body gradually adapts the immune response to the sensitized allergen and allows for increased tolerance.

Immunotherapy is an alternative for individuals who are refractory to avoidance of allergens or medical therapy. Unlike pharmacotherapy or avoidance, allergen-specific immunotherapy has the advantage of providing potential continued symptom suppression after discontinuation of therapy, preventing or halting progression of asthma, and preventing the development of new allergies.⁴⁻⁶ Currently, the most common form of allergen-specific injection immunotherapy in the United States is subcutaneous injection immunotherapy (SCIT), which not only has been proven to be efficacious in reducing symptoms but also effects measurable immunologic changes in individuals who have undergone this treatment.⁷

Allergen-specific injection immunotherapy was introduced approximately 100 years ago, and currently 7 to 10 million allergy immunotherapy injections are administered annually in the United States.⁸ However, injection immunotherapy is associated with rare but real risks of anaphylaxis and death. Injection immunotherapy must be administered in an appropriately supervised physician's office on a repeated basis, from once a week to once a month over several years. For many young children, needle-phobic patients, and areas with limited access to specialists, injection immunotherapy is not a realistic treatment option.

Over the years, different routes of allergen-specific immunotherapy administration have been investigated as alternatives to injection immunotherapy.⁹ Previous studies of oral immunotherapy found that this route was not efficacious, and the same is true of bronchial immunotherapy, which also confers a high risk of bronchospasm. Local nasal immunotherapy has been shown to significantly improve allergy symptoms and decrease the need for allergy medications. However, local nasal immunotherapy must be carefully administered to prevent bronchospasm, and it frequently provokes rhinitis on administration. None of these alternative dosing routes has gained popularity in the clinical arena. Sublingual immunotherapy (SLIT), in which the allergen is held under the tongue for an interval and then either swallowed or spit out, was first introduced in the United States in the 1940s, but it did not gain widespread acceptance at that time.

Concerns over safety, patient convenience, and patient tolerability of injection allergen immunotherapy led to renewed interest in alternative forms of immunotherapy. In 1986, the British Committee for the Safety of Medicine questioned the risk-benefit ratio of SCIT after several deaths occurred.¹⁰ Although subsequent investigation found the deaths to be from avoidable human error, this report greatly increased interest in developing alternative routes of immunotherapy. Interest in SLIT steadily increased after sublingual administration of dust mite allergen was reported in 1986.¹¹ Since the early reports more than 2 decades ago, investigators have published increasing data on the safety and efficacy of SLIT, primarily in Europe. Data supporting the clinical use of SLIT began to increase, and in 1998 the World Health Organization (WHO) concluded that SLIT was an acceptable means of immunotherapy.¹² Further publications by the European Academy of Allergy and Immunology and the Allergic Rhinitis and Its Impact on Asthma (ARIA) treatment guideline support the use of SLIT in allergen desensitization in children and adults.^{7,13}

The use of SLIT in clinical practice has increased in Europe over the past 2 decades. The European clinical experience includes SLIT in the form of oral aqueous and tablet formulations. Its excellent safety profile has allowed it to be administered in the convenience of the home, and the lack of needles makes it an attractive option in the

pediatric population. Interest in SLIT has also been increasing in the United States, with some clinicians offering this treatment modality to patients. However, because no sublingual allergens are currently approved by the U.S. Food and Drug Administration (FDA), these practitioners are using allergens approved for injection immunotherapy in an off-label route of administration.

IMMUNOLOGIC RESPONSE

Several articles have addressed the immunologic effects of SLIT, both local and systemic. Experts believe the interaction of the allergen in the sublingual mucosa may be important in the mechanism of action. A study involving radiolabeled SLIT found evidence of radioactivity in the oral cavity for 2 to 20 hours after initial administration of SLIT; this is thought to possibly be caused by the local uptake of antigen by dendritic cells.¹⁴ Other studies have focused on potential local immune changes in the oral submucosa. A study comparing sublingual mucosal biopsies of subjects receiving SLIT with those of controls found no difference in CD3+, CD1a+, or CD68+ cell counts.¹⁵ However, another study found that sublingual salivary eosinophil cationic protein was significantly reduced after 7 months of SLIT.¹⁶

A larger number of studies have focused on the systemic immunologic responses induced by SLIT, particularly examining changes in serum inflammatory mediators. Several studies have shown that one of the most consistent changes in inflammatory mediators is the reduction of serum eosinophil cationic protein (ECP). This decrease has been seen in both children and adults after 6 to 24 months of treatment with SLIT.^{17–20} The decrease in ECP was found to correspond with a decrease in serum eosinophil counts.²¹ The most widely studied antibody responses to SLIT include changes in IgE and IgG4. Studies show decreases in antigen-specific IgE after treatment with SLIT; antigen-specific serum IgG4 has shown a dose-response increase to SLIT after the first year of use, and then a plateau in levels.^{22–24} SLIT has also been shown to suppress skin prick test after treatment,^{23,25,26} although this seems to be affected by duration of treatment, with suppression in skin responses seen after 18 to 24 months of use.

The immunologic changes seen after SLIT administration are similar to those seen after administration of SCIT. Both induce changes in skin testing, increases in allergen-specific IgG4, and decreases in antigen-specific IgE. These findings suggest a similar mechanism underlies both routes of immunotherapy. SCIT induces changes in regulatory T cells that lead to increased tolerance of antigen, and SLIT probably acts in a similar manner.²⁷

EFFICACY

Several recent large reviews and meta-analyses discuss the efficacy of SLIT. In 2005, Wilson and colleagues²⁸ published the first large-scale meta-analysis entitled “Sublingual Immunotherapy for Allergic Rhinitis,” which examined 979 pediatric and adult subjects pooled from 22 randomized, double-blind, placebo-controlled studies of SLIT. This meta-analysis found significant reductions in symptom and medication scores with SLIT, and concluded that it was effective in treating allergic rhinitis. The authors acknowledged, however, the large heterogeneity in dosages and treatment schedules among the studies.

In 2006, the American Academy of Allergy, Asthma and Immunology (AAAAI) and the American College of Allergy, Asthma, and Immunology (ACAAI) formed a task force that was charged with providing a comprehensive, updated report on SLIT for the North American Allergy community.²⁹ The ACAAI/AAAAI task force reviewed

104 articles addressing SLIT dosing, efficacy, immunologic response, and safety. The doses used in the studies varied by 30,000-fold, with frequency ranging from daily to weekly; few comparative studies were found regarding optimal dosing and schedules. Of the 47 studies that met criteria for clinical efficacy, most showed some evidence of this. Studies suggested a dose–response effect, but a consistent relationship among treatment dose, duration, and efficacy was not found. Although the task force found evidence for the efficacy of SLIT in treating allergic rhinitis, many questions remain regarding SLIT, including what is the effective dose and schedule.

Other SLIT studies have examined efficacy in specific subpopulations, such as asthmatics. In 2006, Calamita and colleagues³⁰ performed a systematic review of the efficacy of SLIT in asthma. This review included randomized controlled clinical trials involving adult and pediatric patients and conducted from 1974 to 2005; 1706 patients from 25 studies met study inclusion criteria. The authors found that SLIT was beneficial for asthma treatment in terms of symptoms, medication use, lung function, and bronchial provocation. However, the authors concluded that the effects, although statistically significant, were small in scale.

The pediatric population is another subgroup in which the efficacy of SLIT is studied frequently. In 2006, Penangos and colleagues³¹ published a meta-analysis focusing on the use of SLIT in patients aged 3 to 18 years. Ten studies met selection criteria, and 484 patients from these studies were evaluated. The authors found a significant reduction in symptoms and medication use after SLIT. Subset analysis showed a greater improvement related to seasonal allergens as opposed to perennial, and for patients receiving therapy for greater than 18 months. The authors concluded that SLIT was an effective form of therapy for allergic rhinitis in the pediatric population. An updated review in 2008 found evidence of efficacy with SLIT for grass allergies in children, but the evidence of efficacy in dust mite allergy was inconsistent.³²

Other pediatric studies have examined the potential protective effects of SLIT on the pediatric population. For example, Novembre and colleagues³³ studied whether short-term coseasonal SLIT for grass allergen would benefit children compared with a control group taking standard allergy and asthma medications. The SLIT group underwent 3 years of therapy. At the conclusion of the study, the control group was found to be 3.8 times more likely to have developed asthma than the SLIT-treated group. The authors concluded that SLIT not only improved seasonal allergic rhinitis symptoms but also reduced the development of seasonal asthma in children with grass pollen allergy.

Another study by Marogna and colleagues³⁴ in 2008 also focused on the preventative effects of SLIT in children. In this study, 216 children were randomized to receive either medications alone or SLIT plus medications for 3 years. New sensitizations to allergens were found in 34.8% of controls compared with 3.1% receiving SLIT. Mild persistent asthma also occurred less frequently in the SLIT group. The number of children with positive methacholine challenge tests decreased significantly after 3 years in the SLIT group only, suggesting that SLIT reduces both new sensitizations and bronchial hyperreactivity. Di Rienzo and colleagues³⁵ also evaluated the duration of these positive SLIT effects in children. The children in this study received either 4 to 5 years of SLIT ($n = 35$) or allergy medications ($n = 25$). The patients were evaluated at baseline, end of SLIT, and 4 to 5 years after SLIT discontinuation. The SLIT group was found either to be less likely to have asthma or to have improved asthma. The positive clinical effects were maintained for 4 to 5 years after discontinuation of SLIT.

Several recent publications have focused on the efficacy of a specific form of SLIT, the grass tablet.^{36,37} The sublingual grass antigen tablet is currently available in Europe, and efforts seem to be underway to bring it to the United States. These multicenter,

double-blind, and placebo-controlled studies have shown a significant reduction in allergy symptoms in grass-sensitized patients. The grass tablet has also decreased the need for medication, improved asthma, and improved disease-specific quality of life. Efficacy seems to be greater if the grass tablet is given preseason. Administration of the grass tablet has also led to corresponding immunologic changes seen with allergen-specific immunotherapy, such as an increase in antigen-specific IgG.

Similar to the grass tablet studies, most SLIT studies have been single allergen studies; however, most allergic patients in the United States are polysensitized. In the United States, most practitioners use multiantigen treatment when using allergy-specific immunotherapy to treat polysensitized patients. Of the few studies performed on the use of SLIT in polysensitized patients, one published in the United States in 2009 evaluated the quality of life using multiantigen SLIT.³⁸ Patients undergoing multiantigen SLIT were found to have statistical improvement in 12 of 14 domains of the Mini Rhinoconjunctivitis Quality of Life Questionnaire. This study, although small, offered encouraging pilot results of multiantigen SLIT. A subsequent larger European study of SLIT in polysensitized subjects found similar gains in disease-specific quality of life.³⁹

The literature has attempted to answer the important question of how SLIT compares with SCIT in terms of efficacy. Although studies have found both modalities to be efficacious,^{40–43} no agreement has been reached on which treatment is more effective. In a double-blind, placebo-controlled study performed in 2004⁴³ comparing SLIT and SCIT in birch pollen-sensitive subjects, both therapies decreased symptoms and medication scores compared with placebo. Although SLIT had a higher safety profile, a nonsignificant greater improvement occurred in the SCIT group. Among the varied findings in multiple studies, no clear cut answer seems to exist regarding the efficacy of SLIT versus SCIT; this is an area that would benefit from future, large-scale, randomized, placebo-controlled studies.

SAFETY

The safety profile of SLIT compared with traditional SCIT is one of the reasons for increased interest in the sublingual dosing route. In Europe, SLIT has been dosed at the patient's home rather than the physician's office because of its perceived improved safety profile. However, there have been reported side effects and adverse reactions to SLIT. SLIT studies have typically broken down the adverse events into local and systemic reactions. Local reactions include oral irritation and itching, with an estimated prevalence of 0.68 per 1000 doses.²⁹ Reported systemic reactions to SLIT include asthma, urticaria, gastrointestinal symptoms, and other systemic reactions that have been severe enough to require hospitalization, according to a recent large review.²⁹ This review of SLIT also examined safety of SLIT comparison with SCIT; in 1,019,826 SLIT doses, 14 serious adverse events were reported. The rate of systemic reactions was 0.6% for SCIT versus 0.056% SLIT, and the prevalence of death was 1 per 2.5 million for SCIT versus no reported deaths for SLIT. These findings indicate an improved safety profile of SLIT over SCIT.

However, as the use of SLIT has increased in Europe over the past 20 years, severe systemic and anaphylactic reactions have been reported in clinical use. The first report of anaphylaxis in Europe was in an asthmatic child undergoing SLIT with a dust mite and pollen mix at maintenance dosing.⁴⁴ This reaction occurred during peak spring pollen season. Other reports of anaphylaxis in the Netherlands involved the use of the sublingual grass tablet; two individuals who had previous reactions to SCIT experienced severe systemic reactions to their first dose of grass tablet.⁴⁵ The authors suggested that the first dose of grass tablet be given to patients in a supervised setting in

a physician's office. Finally, a report of SLIT anaphylaxis in the United States⁴⁶ occurred in a patient with asthma who was being treated with multiantigen therapy while in the escalation phase. Large-scale reviews of SLIT have been unable to find consistent relationships between adverse events and dose, or whether these occur in escalation versus maintenance therapy.²⁹ However, a recent clinical study did not find skin test sensitivity, asthma, gender, or age to be risk factors predictive of adverse events.⁴⁷

Although SLIT has a good safety profile that appears to be better than SCIT, and has been dosed in Europe in the home for 20 years, serious reactions have been reported, suggesting that clinicians offering SLIT should perform some common sense safety precautions. For example, patient vials should be labeled with more than one patient identifier to avoid distribution to the wrong patient. Mixing should be performed in a quiet environment where no outside distractions can lead to errors in mixing. Patients must be thoroughly educated on how to perform proper dosing at home, and consideration given to administering the first dose in the office. Patients receiving allergen-specific immunotherapy should be instructed on the signs and symptoms of anaphylaxis. Patients should be trained on how to use an epinephrine auto injection device and should be given a prescription for the device. These steps and precautions may provide increased safety for patients receiving SLIT.

DOSING

Although different dosing techniques are available for SCIT, fairly standard techniques for escalation and maintenance doses have been adopted and taught by the major allergy associations in the United States. The optimal dosage, timing of administration, and optimal length of treatment with SLIT are not as clearly defined. One of the earliest references to SLIT dosing in the otolaryngology literature is found in a training manual written by French Hansel and Jack Anderson in the late 1950s.⁴⁸ Most modern dosing information available in the literature comes from European studies using antigens that are not available in the United States. Multiple factors make it difficult to compare the effective doses used in these published studies. A direct correlation has been difficult to establish between the antigen content of sublingual preparations used in most published European studies and the antigen content of products available in the United States. These factors have made the effective dose of SLIT using the liquid-based antigen preparations available in the United States more difficult to establish. Fortunately, more information is becoming available, and some general insight can be obtained from the large number of sublingual studies available in the literature, providing some basis for determining an effective dose. One fairly consistent finding from previous studies is that higher doses of antigen are necessary for SLIT than for SCIT. It is also clear that a level of safety has been shown over wide variations in dosing amounts for SLIT. Furthermore, several larger studies conducted in North America within the past few years give some measure of what is an effective dose.

Correlations should be attempted between the antigen units reported in studies conducted outside the United States and those currently available in the United States to establish a comparable dosing strategy. Larenas-Linnemann and Cox⁴⁹ published their efforts to determine the antigen content in the SLIT products used in many of the European sublingual studies and available on the European pharmaceutical market. Determining the true antigen content is often challenging, and they concluded that they were unable to accurately determine the microgram allergen contents sufficiently to correlate with allergen products available in the United States. This conclusion has some limitations, however. The major allergen content of many of the sublingual products from European antigen suppliers is identified in the study. The study mentions

that these should not be compared directly with micrograms of antigen available in United States because of differences in the technique used to determine major allergen content. This same limitation would therefore also need to be applied to SCIT. Recommendations have been made on target microgram doses for SCIT based on studies using antigens from one allergen manufacturer.⁵⁰ Given the cost limitations in replicating large dose-response studies to include multiple allergen extract providers, it is reasonable to make some correlations with an established effective microgram dose and apply that microgram dose for treatment using extract from a separate manufacturer, both for SCIT and SLIT. However, more dose-response studies are needed for both SLIT and SCIT to evaluate what dose of antigen produces good results without producing excessive risk.

Most algorithms use daily dosing. Variation exists in the duration of dosage escalation, but the overall trend is toward very short periods of escalation or no escalation at all.⁵¹ Sambugaro and colleagues⁵² published an induction phase comparison in 2003. The randomized open study included three different induction schedules (8-, 15-, and 20-day inductions, respectively) and a control group. All three groups had a once-daily maintenance phase for a total treatment duration of 2 years. The authors found no significant difference in the rate of adverse events with the three different induction groups. Reviews of substantial numbers of clinical trials have not shown a correlation between adverse events and different durations of escalation.^{29,53} The tablet-based SLIT products available in Europe do not use dose escalation, but rather start at the maintenance dose with the first dose. Once the maintenance dose is achieved, it is continued daily in most clinical trials. The target sublingual maintenance dose has not been established for any commercially available allergen product in the United States, but recent data allow some generalizations to be made.

Although no dosing schedule can be found on the product labels for antigens available in the United States, several practical observations can be made. The maintenance dose used in clinical trials has ranged from 3 to 500 times the typical SCIT injection dose for the given study center.⁵³ Most of the European antigen manufacturers' recommendations for monthly maintenance SLIT dose are between 5 and 45 times the dose they recommend for SCIT maintenance treatment with their products.⁴⁹ Several recent North American-based SLIT studies can provide some insight into potential effective dose ranges. Greer Laboratories conducted a study evaluating the efficacy of SLIT for short ragweed using their liquid short ragweed antigen product currently labeled for SCIT use.⁵⁴ The study showed a reduction in rhinoconjunctivitis symptoms and antiallergy medication use scores for both the 4.8 and 48 Amb a 1 unit doses versus placebo. The reduction only reached statistical significance for the higher dose. Compared with other recent studies, the Greer study included a relatively low number of participants. Nonetheless, the study did not produce as vigorous improvements as desired, and did not allow for inclusion of SLIT dosing on the short ragweed product label. The study does at least provide a target dosing range within which improvements were observed.

The results of two large North American studies using tablet-based timothy grass SLIT were recently reported. The first study was conducted in the pediatric population⁵⁵ and showed a significant reduction in total combined symptom and medication scores (26% reduction) and individual daily symptom (25% reduction) and medication use scores (66% reduction). This study replicated the previous findings with the product in similar studies conducted at European centers. The maintenance dose used in this study was approximately 15 µg of Phl p 5 timothy antigen. A study in the adult population⁵⁶ using the same timothy grass tablet resulted in a significant reduction in total combined symptom and medication scores, individual

daily symptom scores, and daily medication use scores (20%, 18%, and 26% reductions, respectively). However, approximately 85% of the patients in both of these studies were multisensitized to other nongrass antigens but were treated only for timothy grass. Although these studies show significant efficacy for a tablet-based SLIT product that is not currently available commercially in the United States, they provide a reasonable maintenance microgram target dose for timothy grass SLIT that can be prepared with currently available liquid antigen products, with reasonable expectations of safety and efficacy. More large studies are underway at European centers evaluating the efficacy of tablet-based SLIT for house dust mite and birch antigens. These studies will provide more insight into approximate microgram dosing ranges necessary for efficacy for other antigens.

The timing of SLIT has also been a topic of discussion and study. In different clinical trials, the antigen has been delivered perennially, preseasonal, and coseasonal, and coseasonal alone. Perennial administration of SCIT for 3 to 5 years is generally preferable for long-term maintenance of the improvement after immunotherapy completion. A recent study⁵⁷ evaluated the use of a five grass sublingual mixture delivered coseasonally only for three consecutive grass pollen seasons. The study showed a significant reduction in combined symptom and medication scores, and individual daily symptom scores. The reduction seen in daily medication scores did not reach significance. These patients were also followed up for 3 years after completion of the active treatment. A continued reduction in all three parameters was seen, but only daily symptom scores maintained statistically significant reductions. This study shows that SLIT given only during the season at least may generate improvements, which may improve the willingness of some patients to use the treatment. Another study evaluated the efficacy of dust mite SLIT given intermittently versus continually over a year.⁵⁸ One group was given SLIT treatment daily for a year, and a second group alternated between 2 months of active treatment and 2 months off treatment. Both treatment groups showed a significant reduction in allergy symptoms and overall quality of life measures. This study was only preliminary, but at least showed that improvement could be achieved with intermittent dosing schedules. The long-term effect is unknown with this type of dosing schedule. Another publication investigated the efficacy of coseasonal and perennial SLIT.⁵⁹ The authors performed an independent patient data meta-analysis of three open, prospective, observational studies of SLIT using standardized allergen extracts in patients with allergic rhinoconjunctivitis with and without asthma to compare the effectiveness of perennial and coseasonal treatments, and ultra-rush and standard titrations. A total of 1052 patients were assessed, and symptom improvement was seen in all treatment groups, with no significant difference between perennial, coseasonal, ultra-rush, and standard titration protocols. This study is obviously limited by a lack of controls, but does show that multiple options may be available for sublingual dosing that can be tailored to the needs of individual patients.

Durham and colleagues⁶⁰ recently published a report analyzing the sustained effect of 3 years of active SLIT with timothy grass tablets in 257 subjects who had previously shown significant improvement in daily symptom and medication scores during a 3-year trial of sublingual timothy grass tablets. One year after completing active SLIT treatment, these subjects were reevaluated during grass season and were found to maintain a significant reduction in allergy symptoms (26% reduction) and medication use (29% reduction) scores compared with the placebo group. The study is important because it involves a large number of patients in a well-designed and controlled study who showed significant sustained improvement in both symptom and medication use scores at least 1 year posttreatment after the active SLIT treatment was given perennially for 3 years.

A large collection of world literature now supports the efficacy and safety of SLIT, and this treatment modality has been advocated as effective by the WHO,¹² the World Allergy Association,⁶¹ the European Academy of Allergy and Clinical Immunology,⁶² and the ARIA study.⁷ Although an FDA-approved SLIT allergen extract product is not currently available in the United States, this does not indicate that SLIT cannot be effective in the United States, especially after it has shown efficacy in multiple other countries. Although the optimal dose of SLIT prepared with liquid-based antigen extract products available in the United States needs to be clarified, the amount of information available allows physicians to make reasonable estimations of possible effective doses for appropriate patients. The great safety profile shown with SLIT allows a cushion of safety while the most effective sublingual dose is determined for different antigens. It is certainly reasonable for physicians to extrapolate the existing data to offer SLIT to patients. Numerous physicians are offering SLIT to their patients across the United States, with anecdotal good success in improving allergic disease. Many medications are commonly used in an FDA off-label manner when a physician determines this to be appropriate for an individual patient. In fairness, much of the SCIT doses in use are extrapolated from limited amounts of dose-response data for a limited number of antigens. All of the antigen extracts available in the United States have FDA labeling for single-antigen use, but allergists more commonly deliver these antigens in multiallergen vials. The use of multiallergen SCIT is an off-label use of an FDA-approved product. In addition, no data support that the same amount of antigen is required to produce symptom improvement with SCIT when given in combination with other antigens versus giving the antigen by itself; therefore, either greater or lesser amounts may be required for each individual antigen when delivering multiantigen immunotherapy. Experts have generally assumed and placed into practice that the same amount of antigen should be delivered whether single or multiantigen immunotherapy is used. To exclude SLIT as a reasonable treatment option because of the lack of an FDA-approved dose would be selectively applying the standard to SLIT, while not requiring it for SCIT. All of these limitations should be discussed with patients undergoing immunotherapy. The hope is that more information will become available about the optimal dose of antigen for SLIT for different antigen preparations available in the United States, or that an FDA-approved product will become commercially available. In the meantime, individual physicians must evaluate the appropriateness of SLIT for individual patients in their practice, and use the best information currently available to determine what dose of antigen to deliver.

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