Perception and practice of sublingual immunotherapy among practicing allergists

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Background: Currently, little information is available regarding who is using sublingual immunotherapy (SLIT) in the United States, what product they may be using, how they are dosing that product, and what perceived effect it may be having on patients.

Objective: To gather information regarding the perception and use of SLIT among practicing allergists in the United States.

Methods: On behalf of the American College of Allergy, Asthma and Immunology (ACAAI) Immunotherapy and Diagnostics Committee, an electronic survey was sent to all practicing allergists of the ACAAI in March 2007.

Results: The survey response rate was 25.7% (828/3,217) in which 92.5% of the respondents (766/828) practiced in the United States. For 61.7% (471/763) the most cited reason for not using SLIT was lack of approval by the Food and Drug Administration (FDA). If SLIT were an FDA-approved form of immunotherapy, 65.7% would use it to treat allergic rhinitis, 45.5% would use SLIT to treat patients younger than 5 years, and 40.9% would use it to treat moderate to severe asthma. A total of 5.9% (45/766) of US allergists reported using SLIT. Most perceived SLIT to be as effective (44.7%) or more effective (10.5%) than subcutaneous immunotherapy (SCIT). Most allergists who used SLIT (65.9%) had it reimbursed by patients paying out of pocket. The most commonly used extract (79.1%) was a commercially available extract used for SCIT. Some practitioners (53.5%) required their patients to administer doses of SLIT in their office, but 81.8% only required that this be done with the first dose. Practitioners gave epinephrine injectors to 41.5% of their patients receiving SLIT.

Conclusions: Although only 5.9% of US allergists reported using SLIT, most of the 828 surveyed (766 US allergists) viewed SLIT as safe and effective and would consider using SLIT if it were an FDA-approved therapy.

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INTRODUCTION

Oral immunotherapy was first suggested in 1900,[1] with its first use reported by Black in 1927.[2] The concept of sublingual immunotherapy (SLIT) was born out of oral immunotherapy. SLIT has been used as a form of immunotherapy in Europe for the past few decades. During this time, several papers have addressed the safety and efficacy in the treatment of allergic rhinitis and asthma, including a recent meta-analysis[3] and review.[4] In 1998, the World Health Organization (WHO) recognized SLIT and local nasal immunotherapy (LNIT) as viable alternatives to SCIT.[5] That same year the European Academy of Allergology and Clinical Immunology adopted similar language toward SLIT.[6] In 2001, a WHO position paper extended the indication of SLIT to children.[7] Despite wide acceptance in Europe, SLIT has been slow in gaining momentum in the United States. There is currently no Food and Drug Administration (FDA)–approved SLIT product, no practice parameter for the use of SLIT, and no *Current Procedural Terminology* code for this therapy. At this time, there is little information regarding who is using SLIT in the United States, what product they may be using, how they are dosing that product, and what perceived effect it may be having on patients. Understanding SLIT's current impact in the United States will better equip the allergy community to set regulations and practice parameters in the future should it become an approved alternative to SCIT. The goal of this paper is to further understand the current perception and utilization of SLIT among a population of mainly US allergists.

METHODS

On behalf of the American College of Allergy, Asthma and Immunology (ACAAI) Immunotherapy and Diagnostics Committee, an electronic survey (Fig 1) was sent to practicing allergists of the ACAAI in March 2007. The survey was again sent to the same allergists 2 weeks later to increase the response rate. The survey consisted of 8 questions if the survey participant had never used SLIT and consisted of 21 questions for those who had previously prescribed SLIT. The survey was approved by the Wilford Hall Medical Center institutional review board.

RESULTS

A total of 3,217 electronic letters were successfully sent, and 828 allergists (25.7%) responded. At least 95% of respondents answered each of the questions that applied to them in

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1. How would you describe your current practice?
   A) Clinical B) Academic C) Mixed clinical and academic
2. Have you completed a fellowship in Allergy and Immunology?
   A) Yes B) No
3. Where is your practice located?
   A) Northeast United States B) Northwest United States
   C) Southeast United States D) Southwest United States
   E) Midwest United States F) Outside the United States
4. Do you prescribe subcutaneous aeroallergen immunotherapy (SCIT) in your practice?
   A) Yes B) No
5. Do you believe that SLIT is safer than subcutaneous immunotherapy?
   A) Yes B) No
6. What is the biggest barrier from you using SLIT in your practice?
   A) Cost B) Side effects C) Not an FDA approved therapy D) Dose required
   E) Effective dose not known F) No barriers
7. If SLIT were an approved form of immunotherapy in the U.S., in which patients would you consider using SLIT? (select all that apply)
   A) Would not use SLIT in any patients B) Patients older than 18 years of age
   C) Patients 5 – 18 years of age D) Patients <5 years of age
   E) Mild asthmatics F) Moderate-severe asthmatics
   G) Allergic rhinitis
8. Have you ever used sublingual immunotherapy (SLIT) in your practice?
   A) Yes B) No

(If you answered no to number 8, then you are done with this survey – thank you.)
(If you answered yes to number 8, then please continue on with remainder of questions.)

9. Has your experience with SLIT been under a study protocol or part of your clinical practice?
   A) Study protocol B) Clinical practice C) Both
10. How would you rate your experience with SLIT thus far in your career?
   A) Extensive experience in treating patients with SLIT
   B) Some experience in treating patients with SLIT
   C) Little experience in treating patients with SLIT
   D) No experience in treating patients with SLIT
11. If you have used SLIT, then what type of extract did you use for your SLIT? (select all that apply)
   A) Commercially available extract used for injection immunotherapy
   B) Commercially available extract used for sublingual immunotherapy
   C) Dissolvable tablets
   D) Other extract (please describe): _____
12. For which type of allergens have you used SLIT? (select all that apply)
   A) Grasses B) Weeds C) Trees D) Dust Mite E) Dog
   F) Cat G) Mold H) Foods I) Other
13. Do you require the patient to administer any of the SLIT doses in your office?
   A) Yes
      If so, how many visits:_____
      If so, how long do they have to wait in your office:_____
   B) No
14. What is maintenance dose for your patients on SLIT?
   A) 0.05 mL per maintenance dose B) 0.1 mL C) 0.2 mL D) 0.3 mL
   E) 0.4 mL F) 0.5 mL G) 1.0 mL H) Other_____
15. What is the maintenance vial used for your patients on SLIT?
   A) Manufacturer stock vial
   B) 1:1 volume:volume (10 fold dilution of stock vial)
   C) 1:10 volume:volume (100 fold dilution of stock vial)
   D) 1:100 volume:volume (1000 fold dilution of stock vial)
   E) Other_____
16. What is the maintenance schedule used for your patients on SLIT?
   A) Daily dose B) Twice daily dosing C) Every other day
   D) Twice a week E) Three times a week F) Weekly
   G) Other_____
17. How is SLIT reimbursed? (select all that apply)
   A) Patient pays out of pocket B) Insurance is billed
   C) SLIT is submitted to insurance with subcutaneous immunotherapy codes (95115 and 95117)
   D) Other:_____
18. Approximately how many patients have you put on SLIT over the last 3 years?
   A) 1-10 B) 11-20 C) 21-50 D) >50
19. How would you rate the effectiveness of SLIT compared to subcutaneous immunotherapy (SCIT)?
   A) Not effective at all B) Less effective than SCIT
   C) Just as effective as SCIT D) More effective than SCIT
20. What percentage of your patients have experienced each of the following side effects while on SLIT?
   A) Oral itching B) Rhinitis / Conjunctivitis C) Urticaria / Angioedema
   D) Nausea / Vomiting / Diarrhea / Cramping E) Asthma exacerbation
   F) Other (please describe)_____
21. Do you routinely prescribe epinephrine injectors for all your patients on SLIT?
   A) Yes but they have never used it B) Yes and they have had to use it
   C) No

Figure 1. Questionnaire sent to allergists on sublingual immunotherapy (SLIT).

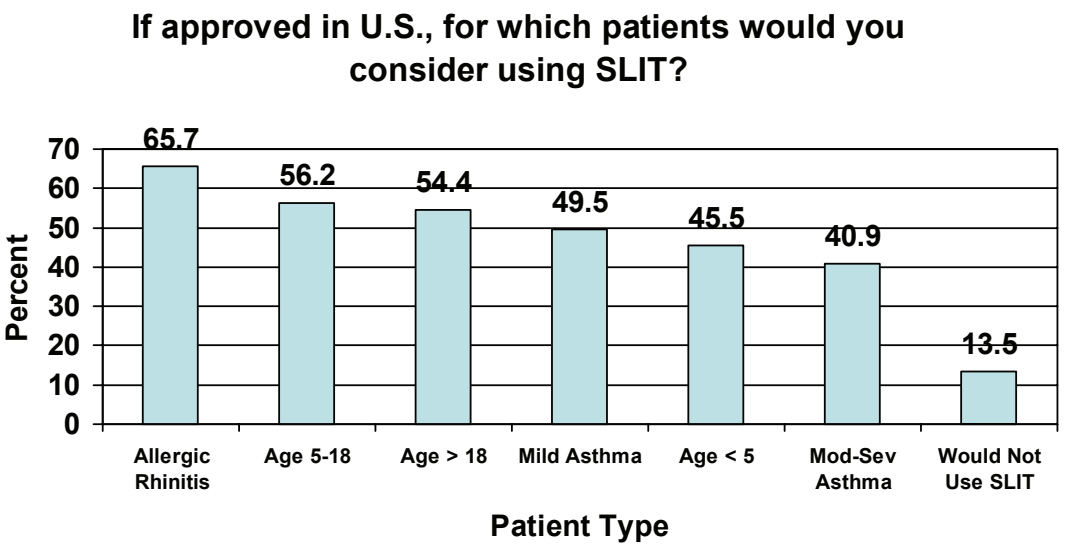


Figure 2. Responses to the question, "If approved in the United States, for which patients would you consider using SLIT [sublingual immunotherapy]?"

the survey. Of the respondents, 92.5% practiced within the United States, and of these, 93.5% reported having completed a fellowship in allergy and immunology. The geographic US distribution was as follows: 24.3% from the Northeast, 6.4% from the Northwest, 22.8% from the Southeast, 21.0% from the Southwest, and 25.5% from the Midwest. The background for 76.5% was clinical, 8.6% academic, and 14.9% a mixed practice. Of those practicing in the United States, 67.4% prescribed SCIT. Among responders, 73.4% (554/755) viewed SLIT as a safer therapy than SCIT. In 61.7% (471/763) the greatest barrier to using SLIT was that it is not an FDA-approved therapy. Other barriers to SLIT were the unknown effective dose in 27.5%, the dose required in 5.1%, cost in 2.4%, and adverse effects in 0.3% of survey responders. If an approved therapy, 65.7% would use SLIT for allergic rhinitis, 56.2% would use it in 5- to 18-year-olds, 54.4% would use in those older than 18 years, 49.5% would use it for patients with mild asthma, 45.5% would use it for patients younger than 5 years, and 40.9% would use it for patients with moderate to severe asthma. A total of 13.5% (102/758) answered that they would not use SLIT even if it were an approved therapy in the United States (Fig 2).

SLIT was prescribed by 5.9% (45/766) of US respondents. Of these allergists, 97.7% used it as part of their clinical practice rather than solely under a study protocol. In ranking their experience with SLIT, 27.3% reported extensive experience, 36.4% some experience, and 34.1% little experience. A commercially available extract for SCIT was used by 79.1% (34/43) of the allergists prescribing SLIT. A commercially available SLIT product was used in 14.0% and a dissolvable tablet form in 7.0% of patients prescribed SLIT. Common allergens used for SLIT (Fig 3) were grasses (81.4%), dust mite (76.7%), weeds (74.4%), trees (65.1%), cat (53.5%), molds (51.2%), dog (44.2%), and foods (16.3%). Patients were required to administer SLIT in the office by 53.5% (23/43) of US practitioners. However, 81.8% of these practitioners required only the first dose to be administered in the office (Fig 4), and 86.0% required a wait time of 30 minutes or less. Maintenance doses varied from 0.05 to 1 mL, with no one reporting doses greater than 1 mL. One-third used the manufacturer's stock vial as their maintenance vial, but others used 10-fold to 1,000-fold dilutions. The maintenance schedules used were a daily dose by 65%, twice daily by 10%, and 3 times a week by 10% of SLIT prescribers. According to the survey, 65.9% of responders received reimbursement by the patient paying out of pocket. The patients' insurance was billed 26.8% of the time. The remaining responders did not bill because SLIT was used in a research setting. Of the US allergists using SLIT, 40.5% reported having prescribed SLIT to more than 50 patients during the past 3 years. This was followed by 37.8% having 1 to 10 patients, 16.2% having 11 to 20 patients, and 5.4% having 21 to 50 patients receiving SLIT during the same period. The background for 48.3% was clinical, 1.7% academic, and 50.0% mixed practice. SLIT was considered just as effective as SCIT by 44.7% of responders and more effective than SCIT by 10.5% of responders. However, SLIT was believed to be less effective in 36.8% and not effective in 7.9% when compared with SCIT. For patients receiving SLIT, 41.5% of allergists (17/41) dispensed injectable epinephrine, with 11.8% (2/17) reporting having had patients who needed to use their epinephrine injector.

The most common adverse effects (Fig 5) reported by allergists who dispensed SLIT were gastrointestinal (84.6%), oral pruritus (78.9%), rhinitis or conjunctivitis (50.0%), asthma (36.7%), and urticaria or angioedema (34.5%). For most allergists, these adverse effects occurred in only 1% to 10% of their SLIT patients. Other adverse effects reported, but far less common, were inflamed uvula, bad taste, fatigue, headaches, and eczema.

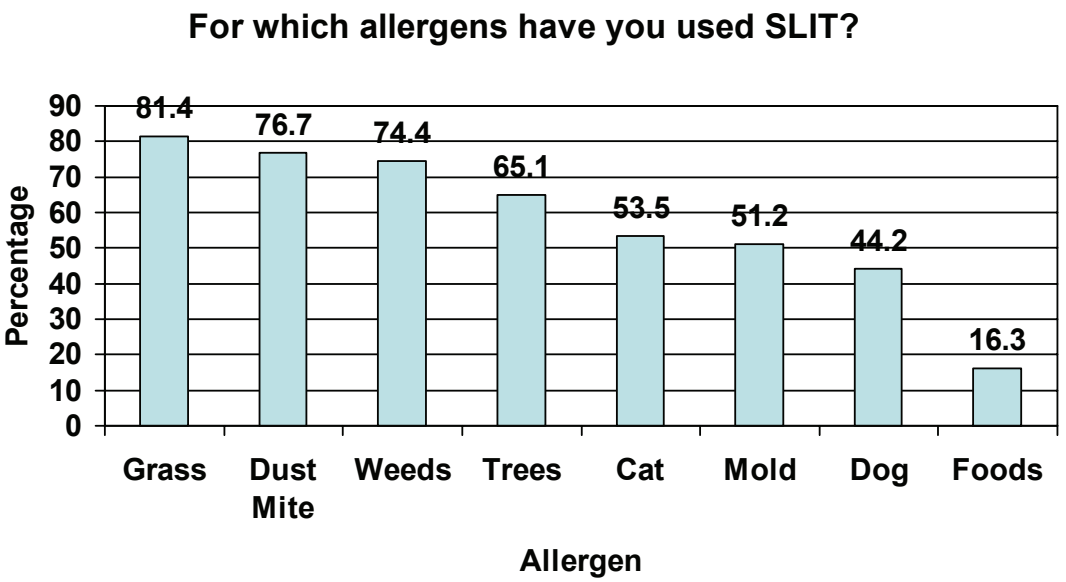


Figure 3. Responses to the question, "For which allergens have you used SLIT [sublingual immunotherapy]?"

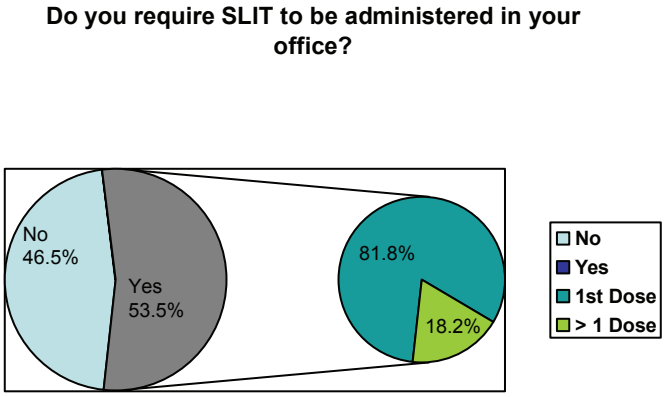


Figure 4. Responses to the question, "Do you require SLIT [sublingual immunotherapy] to be administered in your office?"

Although most respondents of the survey practiced from within the United States, 58 survey participants practiced outside the United States. Table 1 compares the US vs non-US responders. Overall, those practicing outside the United States had a higher rate of using immunotherapy, with 82.8% having used SCIT and 62.1% (36/58) having used SLIT. This same group from outside the United States had 91.2% (52/57) who believed SLIT to be safer than SCIT. The biggest barrier to using SLIT in those practicing outside the United States was cost in 22.4%, although 27.6% reported no barriers to using SLIT. Patients paid out of pocket in 71.9% of those practicing outside the United States. Only 25.0% of practitioners required their patients to take any doses of SLIT in their offices, and only 12.5% prescribed epinephrine injectors to their SLIT patients. Finally, 63.3% believed SLIT to be just as effective as SCIT, and 6.7% believed that SLIT was more effective than SCIT.

DISCUSSION

The purpose of this survey was to better understand the opinion and experience of US allergists in regard to SLIT. SLIT has been used outside the United States for more than 2 decades. During this time there has been expanding research on the efficacy and safety of SLIT. Despite this, SLIT has not been adopted in the United States, where SCIT still remains the gold standard. Although SCIT has demonstrated efficacy, there are also potential drawbacks where SLIT could have a purpose.

Several studies have looked at noncompliance with SCIT. Rates of noncompliance have been shown to be anywhere from 10.7% to 50%.[8–12] Most of these studies show inconvenience as the primary factor leading to noncompliance.[8,9,11] When comparing delivery within an allergy clinic as opposed to a nonallergy office, Tinkelman et al[10] demonstrated a significant improvement in compliance when SCIT was administered in an allergy clinic. Fewer studies have looked at compliance with SLIT. Pajno et al[13] reported on 2,774 children undergoing SCIT, SLIT, or LNIT. LNIT had a high rate of noncompliance of 73.2%, whereas the SLIT noncompliance rate was 21.5% and the SCIT noncompliance rate was 10.9%. In this study, SCIT had a better rate of compliance than SLIT. Lombardi et al[14] wrote a letter to the editor describing a telephone survey of patients receiving SLIT with a dissolvable tablet. Patients were asked to count how many tablets they had remaining, and this was compared with a computerized program estimate. They observed a cumulative compliance of 97.3%. Although there will always be some degree of noncompliance in medicine, it seems that compliance may be better ensured when immunotherapy is administered and observed in the clinic. However, patients state that inconvenience is the main reason for noncompliance, and

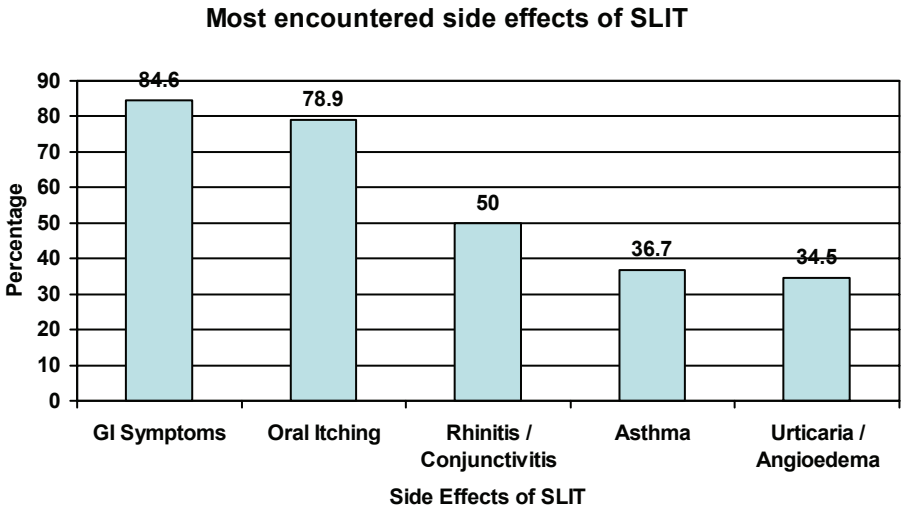


Figure 5. Most encountered adverse effects of sublingual immunotherapy (SLIT). GI indicates gastrointestinal.

Table 1. US vs Non-US Comparison of Survey Responses

Survey response	Within the United States (n = 766), No. (%)	Outside the United States (n = 58), No. (%)
SCIT use	512/760 (67.4)	48/58 (83)
SLIT use	45/766 (5.9)	36/58 (62)
SLIT safer than SCIT	554/755 (73.4)	52/57 (91)
Cost a barrier to SLIT use	18/763 (2.4)	13/58 (22)
Pay out of pocket	27/41 (65.9)	23/32 (72)
SLIT given in office[a]	23/43 (53.5)	9/36 (25)
Prescribe epinephrine	17/41 (41.5)	4/28 (12)
SLIT efficacy greater than or equal to SCIT efficacy	21/38 (55.3)	21/30 (70)

Abbreviations: SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy.
[a] At least 1 dose.

SLIT may offer an advantage over SCIT since most allow SLIT to be administered in the patient's home. This may especially be true with pediatric patients, for whom suboptimal compliance has been reported (only 16% of Medicaid-enrolled children completed 3 years of SCIT).[15] Studies are needed that compare compliance in home SLIT vs SLIT delivered in an allergist's office.

In this survey, a variety of adverse effects were attributed to SLIT. Gastrointestinal symptoms and oral itching were the most frequently reported adverse effects with SLIT. Some of the more unique adverse effects reported by only 1 survey respondent each were inflammation of the uvula, bad taste, fatigue, headache, and eczema. One reason SLIT has gained popularity in other countries is the perceived lower potential for serious adverse effects, including death, compared with SCIT. Severe systemic adverse effects associated with SCIT have been reported to occur at a rate between 0.5% and 6%.[16] However, other resources show that systemic reactions to SCIT occur in less than 0.5% of doses,[32] and near fatal reactions occur at a rate of 1 per 1,000,000 doses.[33] Until recently, no anaphylactic reactions had been reported for SLIT, and still no fatalities have been reported at this time. However, reports of SLIT anaphylaxis have been made in both Europe[17,30] and the United States.[18] Anaphylaxis to latex allergy SLIT has also been reported.[19] Some authors speculate that the rate of systemic reactions associated with SLIT is underreported because many systemic reactions may not be reported when SLIT is administered in the home.[18] Although SLIT is now known to cause anaphylaxis, several studies have documented its safety.[20–24,26]

SLIT use within distinct patient populations, its administration location, and the epinephrine prescribing practices of providers were queried in this survey. Almost half (45.5%) of allergists reported that if SLIT were FDA approved they would use it in children younger than 5 years and 40.9% would use it in those with moderate to severe asthma. In those who had used SLIT, 53.5% of these allergists required their patients to receive SLIT in their office, but 82% only required this with the first dose. Also, only 41.5% of these same allergists believed they needed to provide epinephrine autoinjectors to their patients receiving SLIT. Interestingly, 11.8% of the patients who received epinephrine autoinjectors

used them at some point. These are patients who would have perhaps been recognized and treated in a clinic had they been receiving SCIT.

Local reactions can occur in both SLIT and SCIT. In this survey, local gastrointestinal reactions and oral pruritus were the most common reactions. All the adverse effects reported occurred in less than 10% of the doses given. The survey was not constructed to determine whether these local adverse effects diminished over time. A recent survey by Coop and Tankersley[25] showed that most practitioners dose adjust for local reactions to SCIT. There have been some who have reported success with dose adjustment of SLIT for local gastrointestinal reaction in children.[31]

It is evident from this survey that many different antigens have been used in SLIT, including pollens, pet dander, and foods (Fig 3). One of the main drawbacks to SLIT is that there is limited sublingual space to accommodate extract, and this would limit how many antigens could be used at any given time. In Europe, most studies have used extracts with a single allergen or a grass mixture, although a recent study demonstrated efficacy with a 5-grass pollen tablet.[26] This is different from what is typically seen in the United States, where most patients have multiple allergens in their extracts. If SLIT were to be used in these US patients, then potentially the dose required to cover all these allergens would be too big a volume for the capacity of the sublingual space. The survey addressed the maintenance volume for individual allergens, and no survey participant reported using more than 1 mL. However, the survey did not inquire whether the patient was receiving SLIT monotherapy or multiple allergen therapy. If multiple antigens were to be delivered, a lower total dose would have to be used per antigen, the separate antigens would have to be used at different times, or the SLIT would have to be taken more frequently to get acceptable amounts to achieve clinical effect.

Because of the greater volume of extract needed for SLIT, it can be argued that SLIT would be more costly when compared with a course of SCIT. However, it could also be surmised that a course of SLIT would save on facility costs and ancillary help needed in giving immunotherapy in a clinic setting as seen with SCIT. Unfortunately, no current studies have reported an economic comparison of SLIT vs SCIT. However, a few studies have investigated the economic feasibility of SLIT. Berto et al[27] looked at direct costs of a SLIT group compared with a pharmacotherapy only group. SLIT was found to be less expensive and more effective than pharmacotherapy alone. Currently, 65.9% of US practitioners prescribing SLIT receive compensation by the patient paying out of pocket. If FDA approved, it would be anticipated that more insurance plans would reimburse for SLIT.

At this time, there appears to be a wide variance in the extract used and the dose given for SLIT. From this survey, 79.1% of practitioners using SLIT in the United States are using extract that is FDA approved only for SCIT. However, in Europe, specific extracts are produced and used for SLIT, and these come in both liquid and tablet forms. It is evident that ongoing studies are needed to further clarify the optimal dose needed, the best vehicle to deliver, and the effect of multiple allergens in SLIT. At 5.9%, this survey shows that only a few US respondents are using SLIT in their practice. This number could possibly change in the near future and is likely to increase should SLIT become an FDA-approved therapy. If this were the case, it would then be worthwhile to develop guidelines for the use of SLIT to help standardize the process, much like the practice parameters available for SCIT.[28]

One interesting result of this survey was the percentage of practitioners using immunotherapy outside the United States compared with those practicing within the United States. It was to be expected that those outside the United States would use SLIT more often (62.1% vs 5.9%). However, outside the United States a higher percentage of their practitioners were using SCIT compared with those in the United States (82.8% vs 67.4%) (Table 1). Although in this group a smaller percentage of practitioners had a purely academic role (1.7% vs 8.6%), this probably does not fully account for the difference. Also, the overall rate of 68.4% in all those surveyed differs from another recent survey sent to the same ACAAI members, which showed that 99.3% reported using SCIT.[25] Perhaps the percentage is different secondary to different subpopulations of the ACAAI membership responding to the 2 different surveys. This is an example of the inexactness of a survey that must be taken into account.

Using a survey to gather data comes with some expected shortcomings. It cannot be anticipated how many people from a given group or subpopulation of that group will respond to the survey. We anticipated that we would only get respondents who had an inherent interest in the topic. This has the potential to skew certain response rates for some of the questions. We decided to send the survey twice, 2 weeks apart, to maximize participation. Despite this, we only had a 25.7% response rate. Another drawback to this survey was that not everyone responded to each question and thus created some variance in denominators. Lastly, we found that our questions with open-ended answers allowed for more freedom and variety of answers, which was often too cumbersome to digest. The information on maintenance vials and schedules was so diverse and often confusing that quality data reporting for these 2 questions was not practical. In future surveys, we would limit the use of open-ended questions and/or require respondent to choose among provided answer options.

To our knowledge, this is the first report on the perception and practice of SLIT among US allergists. The information reported herein can help guide more experience and research in this therapy. We believe that there is still more research that needs to be undertaken to help further delineate the optimum dosing and formulation of SLIT. If FDA licensing for SLIT extracts comes to fruition, this survey can serve as a baseline for comparison in the future as the acceptability and practice of SLIT use in the United States increases. Once FDA approval occurs, we agree with recent recommendations

to administer SLIT with preparations that are as or more safe and effective than those currently used for SCIT.[29]

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