



Perception and practice of sublingual immunotherapy among practicing allergists in the United States

A follow-up survey

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ABSTRACT

Background: Limited information is available regarding the current perception and practice of sublingual immunotherapy (SLIT) use among US and international allergists. In light of 4 recent US Food and Drug Administration (FDA)–approved SLIT options, perceptions and practices may be changing.

Objective: To provide updated information about current allergists' practice and perception of SLIT relative to 2007 and 2011.

Methods: On behalf of the American College of Allergy, Asthma, and Immunology (ACAAI) Immunotherapy and Diagnostics Committee, an electronic survey was sent to all US and international allergists who were members of the ACAAI. Data were compared with previous surveys conducted and published in 2007 and 2011.

Results: Of the 305 respondents, 268 (87.9%) practiced in the United States. A total of 197 of 268 respondents (73.5%) reported experience using SLIT compared with 45 of 766 US allergists (5.9%) in 2007 and 59 of 519 US allergists (11.4%) in 2011 ($P < .001$). Of the 188 respondents in the United States who used SLIT in their practice, 129 (68.6%) used FDA-approved SLIT tablets only, 44 (23.4%) used both FDA-approved SLIT tablets and SLIT drops using an extract that is FDA approved for subcutaneous immunotherapy, and 15 (8.0%) reported using only SLIT drops. Limitation of only treating one allergen was the primary barrier in using SLIT among 197 of 268 respondents (73.5%).

Conclusion: There has been a significant increase in SLIT use in the last 5 years, with 73.5% of respondents reporting experience with it. With 4 FDA-approved SLIT therapies, this likely contributes to its more widespread use. The greatest barrier to SLIT use is the limitation of only treating one allergen.

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Introduction

The use of subcutaneous immunotherapy (SCIT) is a well-established treatment modality for allergic rhinoconjunctivitis since it was initially described by Noon in 1911.¹ Sublingual immunotherapy (SLIT) has been used in Europe for decades but is gaining popularity in the United States, especially with the recent US Food and Drug Administration (FDA) approval of several SLIT products. Current products include Oralair (Stallergenes, Antony, France), which contains 5 northern grass pollens (Kentucky blue grass, orchard, perennial rye, sweet vernal, and Timothy); Grastek (Merck, Whitehouse Station, New Jersey), which contains Timothy grass pollen; Ragwitek (Merck), which contains short ragweed; and

Odactra (ALK, Swindon, Wiltshire, United Kingdom), which contains house dust mite.

Information is limited about the current trends of SLIT use. An initial study by Tucker and Tankersley² in 2008 on behalf of the American College of Allergy, Asthma, and Immunology (ACAAI) Immunotherapy and Diagnostics Committee was the first to evaluate perceptions and practices among allergists. A follow-up study by this same group in 2013 gathered additional information about the changes in perception and practice of SLIT among practicing allergists since the original survey.³ The purpose of this article is to provide updated information relative to the 2008 and 2013 reports. Furthermore, additional survey questions specific to recent FDA-approved products were included in an effort to better characterize prescribing patterns.

Methods

On behalf of the ACAAI Immunotherapy and Diagnostics Committee, an electronic/internet-based survey (eFigure 1) was sent to all

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US and international ACAAI member allergists on June 27, 2018. The survey was sent 2 additional times to the same group at 2- and 4-week intervals to enhance response rates (July 18, 2018, and August 16, 2018). The survey was similar to previous surveys sent to allergists in the previous 2 studies but with additional survey questions specific to new FDA-approved products. The survey consisted of only 8 questions for those who had never used SLIT, 32 questions if the respondent used FDA-approved SLIT tablets, and 41 total questions if SLIT tablets and/or drops had been used. The survey was approved by the University of Tennessee Health Science Institutional Review Board. A χ^2 and Fisher exact test analysis was conducted using GraphPad software, 2018 (GraphPad Software, San Diego, California).

Results

Demographics

Of 2817 surveys sent, 305 allergists (10.8%) responded. Of the 305 respondents, 268 (87.9%) practiced within the United States and 37 (12.1%) outside the United States. Of the 268 within the United States, 54 (20.1%) identified their geographic location to be in the Midwest, 59 (22.0%) in the Northeast, 14 (5.2%) in the Northwest, 84 (31.3%) in the Southeast, and 57 (21.3%) in the Southwest. Regarding practice description, most reported practicing in a clinical setting: 238 (78.0%) of the 305 total respondents, 218 (81.3%) of the 268 US respondents, and 20 (54.1%) of the 37 respondents outside the United States. Those reporting a mixed academic/clinical practice included 46 of the 305 total respondents (15.1%), 29 of the 268 US respondents (10.8%), and 17 of the 37 respondents outside the United States (45.9%). Academic-only practice respondents included 21 of the 305 total respondents (6.9%), all respondents who practiced in the United States, and 21 of the 268 respondents who practiced outside the United States (7.8%). Those completing a fellowship in allergy and immunology included 28 of the 305 total respondents (9.3%), 253 of the 268 US allergists (94.1%), and 31 of the 37 outside the United States (83.8%).

Experience with SCIT and SLIT

Among the 268 US respondents, 243 (90.7%) reported using SCIT in their practice, whereas 197 (73.5%) reported using SLIT. Of the 197 who had used SLIT, 188 responded with the extent of their use:

21 (11.2%) reported extensive experience, 72 (38.3%) reported little experience, and 95 (50.5%) reported some experience. Of the 188 responding with use in the previous 3 years, 20 (10.6%) had used SLIT in more than 50 patients, 117 (62.2%) had used SLIT in 1 to 10 patients, 34 (18.1%) had used SLIT in 11 to 20 patients, and 17 (9.0%) had used SLIT in 21 to 50 patients. Of those 37 allergists outside the United States, 30 (81.1%) used SLIT, and 9 of 24 (37.5%) who quantified their use stated they had used SLIT in more than 50 patients in the previous 3 years.

Types of SLIT Used

Of the 188 respondents in the United States who used SLIT in their practice, 129 (68.6%) used FDA-approved SLIT tablets only, 44 (23.4%) used both FDA-approved SLIT tablets and SLIT drops using extract that is FDA approved for SCIT, and 15 (8.0%) reported using only SLIT drops. (Fig. 1). Together, 59 US respondents (31.4%) reported using SLIT drops. Among those using SLIT in their practice, the top 3 allergens were grass, weed, and house dust mite, correlating with the FDA-approved allergens (Fig. 2). Of the FDA-approved products, 150 of 188 US respondents (79.8%) had used Grastek, 108 of 188 had used Ragwitek (57.4%), 90 of 188 had used Oralair (47.9%), and 78 of 188 had used Odactra (41.5%) (Fig. 3). Thirty-six of 188 respondents (19.1%) reported having patients taking 2 or more FDA-approved tablets at the same time.

Opinions of SLIT Safety and Efficacy

In the United States, regardless of their experience with it, 202 of 268 allergists (75.4%) believed that SLIT was safer than SCIT, and 209 (78.0%) opined that SLIT was considered to be less effective than SCIT. Forty-eight (17.9%) found SLIT to be just as effective as SCIT, and 3 (1.1%) found it more effective than SCIT. Eight of 268 (3.0%) found SLIT was not effective at all. Among the 197 US allergists reporting actual use with SLIT, 150 (76.1%) also thought it was less effective than SCIT.

Perception of Contraindications and Barriers to Prescribing SLIT

The following conditions were reported to be absolute contraindications to SLIT among 188 US prescribers, eosinophilic esophagitis in 148 (78.7%), severe asthma uncontrolled by pharmacotherapy in

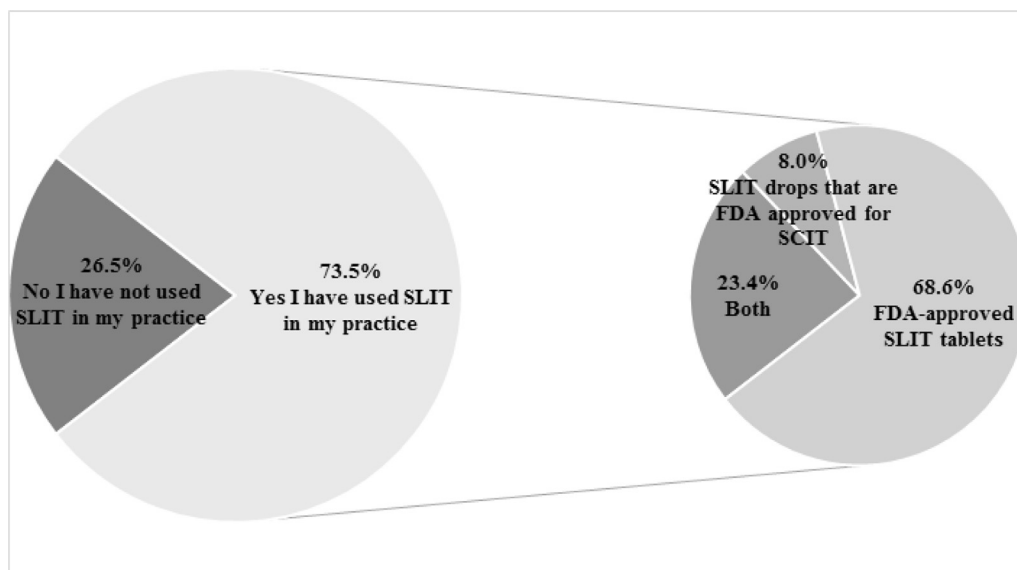


Figure 1. Percentage of US respondents who have used sublingual immunotherapy (SLIT) in their practice. Of those respondents, the percentage of respondents who used SLIT tablets, SLIT drops that are approved by the US Food and Drug Administration (FDA) for subcutaneous immunotherapy (SCIT), or both is shown.

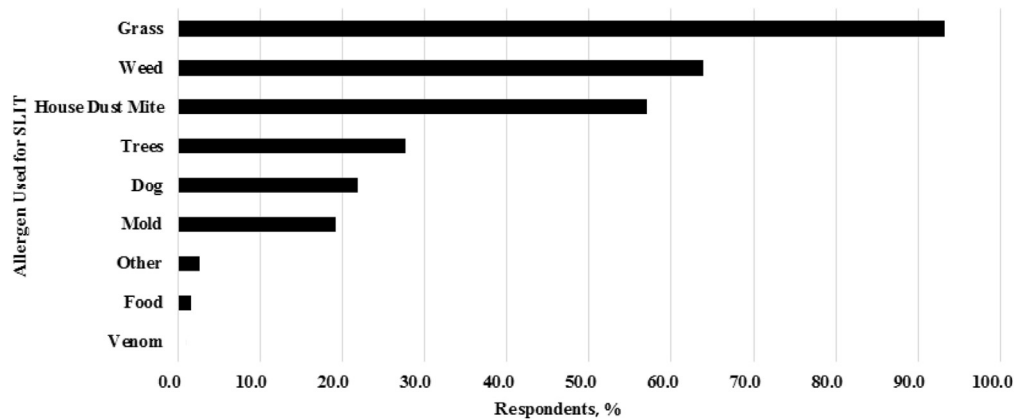


Figure 2. US responses to the question, “For which type of allergens have you used sublingual immunotherapy (SLIT)?”

133 (70.7%), patient’s inability to communicate effectively with physician in 132 (70.2%), β -blocker use in 73 (41.6%), pregnancy in 72 (38.3%), significant cardiovascular disease in 69 (36.7%), concomitant SCIT use in 64 (34.0%), previous anaphylaxis with SCIT use in 30 (16.0%), and angiotensin-converting enzyme inhibitor use in 6 (3.2%). [Table 1](#) gives the barriers that US allergists reported kept them from using SLIT in their practice.

Administration Logistics

Addressing administration logistics among the 188 allergists who responded, 181 US SLIT prescribers (96.3%) required that at least 1 SLIT dose was administered in their office. For in-office administration, 165 (87.8%) required at least 1 dose, 5 (2.7%) required 2 doses, 8 (4.3%) required 3 doses, and 3 (1.6%) required more than 3 doses. Most allergists (148 [78.7%]) required a 30-minute wait after SLIT administration, whereas 15 (8.0%) required a patient wait time of less than 30 minutes, 18 (9.6%) required a wait time of 31 to 60 minutes, and 1 (0.5%) required a wait time of greater than 60 minutes.

Among 188 US respondents, 108 (57.4%) reported no specific timing recommendations for dosing. Sixty-nine (36.7%) recommended morning dosing, 9 (4.8%) recommended evening dosing,

and 2 (1.1%) recommended afternoon dosing. Regarding timing of SLIT relative to meals, 171 (91.0%) reported advising patients not to take food or beverage for 5 minutes after taking SLIT, and 17 (9.0%) believed that timing relative to meals did not matter in terms of what they recommend.

Prescribing Patterns for US Prescribers Using SLIT Drops With Extract Approved for SCIT

Of the 59 of the 188 US respondents (31.4%) using SLIT drops with extract that is FDA approved for SCIT, 52 responded with whether they used a build-up schedule, and 46 (88.5%) said they did. Of the 46 using a buildup schedule, 10 (21.7%) required 5 or fewer doses, 14 (30.4%) required 6 to 10 doses, 4 (8.7%) required 11 to 15 doses, 8 (17.4%) required 16 to 20 doses, 4 (8.7%) required 21 to 25, and 6 (13.0%) required greater than 25 doses to reach maintenance.

Regarding dose adjustment for missed doses, 21 of 46 SLIT prescribers (45.7%) using a build-up schedule administered a lower dose based on number of days past due, whereas 18 (39.1%) simply repeated the previous dose, and 7 (15.2%) did not adjust for missed doses. Dosing information pertaining to reported potency of cumulative maintenance doses, volume and frequency of individual

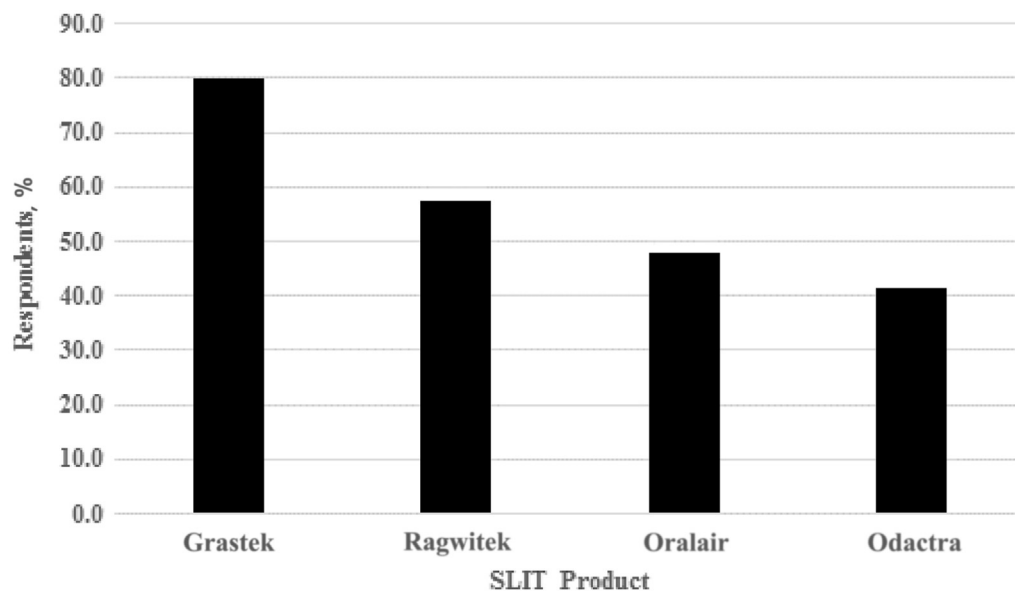


Figure 3. In response to the question, “Which FDA-approved SLIT [sublingual immunotherapy] products have you used in your practice?” by US respondents.

Table 1
US Survey Responses to Barriers to Using SLIT

Barrier	No. (%) of US responders (N = 268)
Limitation of treating to only one allergen	197 (73.5)
Only 4 FDA-approved products	174 (64.9)
Reimbursement issues	111 (41.4)
Insurance limitations on what months SLIT tablets can be started	93 (34.7)
Patient nonadherence	91 (34.0)
Effective dose not known	79 (29.5)
Adverse effects	50 (18.7)
Inadequate training or experience	44 (16.4)
Potential adverse effect on my SCIT practice	42 (15.7)
Dose required	41 (15.3)
No barriers	6 (2.2)
Other	55 (20.5)

Abbreviation: SLIT, sublingual immunotherapy.

maintenance dose administration, and maintenance vials is included in Table 2.

Consent, Education, and Follow-up

Before SLIT initiation among the 188 US allergists responding, 119 (63.3%) obtained written informed consent. Educational

Table 2
Reported SLIT Dosing Information by US Respondents

Reported SLIT dosing information	No. (%) of US responders
Potency of cumulative monthly maintenance dose	
SLIT dose LESS potent than SCIT dose	5/52 (9.6)
SLIT dose equivalent to SCIT dose	12/52 (23.1)
SLIT dose > 1–10 times greater than SCIT dose	15/52 (28.8)
SLIT dose > 10–20 times greater than SCIT dose	8/52 (15.4)
SLIT dose > 20–30 times greater than SCIT dose	5/52 (9.6)
SLIT dose > 30–40 times greater than SCIT dose	4/52 (7.7)
SLIT dose > 40–50 times greater than SCIT dose	1/52 (1.9)
SLIT dose > 50–100 times greater than SCIT dose	2/52 (3.8)
SLIT dose > 100 times greater than SCIT dose	0/52 (0.0)
Frequency of individual maintenance dose administration	
Once daily	46/52 (88.5)
2–4 times per day	2/52 (3.8)
5–7 days per week	3/52 (5.8)
Every other day (3–4 days per week)	0/52 (0.0)
Once weekly	0/52 (0.0)
Twice weekly	1/52 (1.9)
2–3 times per month	0/52 (0.0)
Once monthly or less frequent	0/52 (0.0)
Volume of individual maintenance dose administered	
≤ 0.05 mL	0/52 (0.0)
> 0.05–0.2 mL	10/52 (19.2)
> 0.2–0.4 mL	16/52 (30.8)
> 0.4–0.6 mL	12/52 (23.1)
> 0.6–0.8 mL	4/52 (7.7)
> 0.8–1 mL	6/52 (11.5)
> 1 mL	4/52 (7.7)
Maintenance vial used	
Manufacturer stock vial	29/52 (55.8)
1:1 (vol/vol) (10-fold dilution of stock vial)	3/52 (5.8)
1:10 (vol/vol) (100-fold dilution of stock vial)	1/52 (1.9)
1:100 (vol/vol) (1000-fold dilution of stock vial)	1 (1.9)
1:1000 v/v (10,000-fold dilution of stock vial)	17/52 (32.7)
More dilute than 1:1000 (vol/vol)	1 (1.9)

Abbreviations: SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy.

materials provided by allergists included a combination of written and verbal education in 141 respondents (75.0%), all verbal education in 33 respondents (17.6%), and a combination of written, verbal, and electronic media–based education in 14 (7.4%). Ninety-one (48.4%) reported providing patients with a written adverse reaction plan. Of the 188, 165 (87.8%) reported prescribing an epinephrine autoinjector for all patients given SLIT. Nine respondents (4.8%) reported having at least 1 patient who had to use epinephrine.

Of the 188 US allergists responding, clinic follow-up after initiating SLIT therapy was advised within 1 week in 3 (1.6%), within 1 month in 37 (19.7%), within 1 to 3 months in 80 (42.6%), within 3 to 6 months in 54 (28.7%), and within 6 to 12 months in 14 (7.4%). SLIT prescribers reported that 24 patients (12.8%) are adherent with therapy less than 25% of the time, 46 (24.5%) reported that patients are adherent with therapy 26% to 50% of the time, 43 (22.9%) reported patients are adherent with therapy 51% to 75% of the time, and 62 (33.0%) reported patients are adherent with therapy more than 75% of the time.

Adverse Reactions to SLIT

In the event of an adverse reaction, 23 of 188 (12.2%) SLIT prescribers reported having office personnel contact the patient to assess for adverse reaction, 177 (94.1%) instructed patients to contact the office with adverse reaction, 139 (73.9%) asked about adverse reactions at each follow-up visit, and 58 (30.9%) queried about adverse reactions at the time of each SLIT refill. Regarding dose adjustments for local reactions such as oral itching or gastrointestinal reactions to SLIT, 12 practitioners (6.4%) reported always dose adjusting, 111 (59.0%) never dose adjust, 44 (23.4%) occasionally dose adjust, and 21 (11.2%) usually dose adjust.

When asked if respondents noticed that local SLIT reactions (eg, oral itching, gastrointestinal reactions) diminish over time, 183 allergists responded. Thirty-four (18.6%) said always, 12 (6.6%) said never, 33 (18.0%) said occasionally, and 104 (56.8%) said usually.

Financial

Fifty-two allergists who used SLIT drops responded regarding reimbursement details with the ability to choose more than one choice. A total of 51 (98.1%) reported patients paid out of pocket, 3 (5.8%) billed with SCIT codes (95115 and 95117), and 2 (3.8%) used SLIT in a research setting.

Additional Survey Results from Non-US Allergists

Although most respondents of the survey practiced from within the United States, 37 survey participants practiced outside the United States. Table 3 compares US and non-US respondents. Overall, those practicing outside the United States had a higher rate of using SLIT, with 30 (81.1%) having used SLIT and 27 (73.0%) using SCIT. In this same group from outside the United States, 33 (89.2%) believed SLIT to be safer than SCIT. Regarding efficacy compared with SCIT, 18 (48.6%) believed SLIT was just as effective, 15 (40.5%) believed SLIT was less effective, and 4 (10.8%) believed SLIT was more effective.

Patients paid out of pocket 93.3% (14 of 15 responding) of the time in practices outside the United States. Nineteen of 24 practitioners (79.2%) required their patient to take at least 1 dose or more of SLIT in their offices. Only 2 of 24 practitioners (8.3%) prescribed an epinephrine autoinjector to their patients receiving SLIT, but none had ever used it.

Discussion

The goal of this study was to obtain updated information regarding the perception and practice of allergists compared with

Table 3

US vs Non-US Comparison of Survey Responses for Selected Questions

Survey response	No. (%) of US respondents (n = 268)	No. (%) of non-US respondents (n = 37)	P value
SLIT use	197/268 (73.5)	30/37 (81.1)	.42
SCIT use	243/268 (90.7)	27/37 (73.0)	.004
SLIT safer than SCIT	202/268 (75.4)	33/37 (89.2)	.06
SLIT given in office ^a	181/188 (96.3)	19/24 (79.2)	.006
Prescribe epinephrine	155/188 (82.5)	1/23 (4.4)	<.001
Pay out of pocket	51/52 (98.1)	14/15 (93.3)	.40
SLIT efficacy greater than or equal to SCIT efficacy	51/268 (19.0)	22/37 (59.5)	<.001

Abbreviations: SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy.

^aAt least 1 dose.

previously collected data. Since the 2013 publication, there has been expanding research on the efficacy and safety of SLIT.^{4–7} Allergy immunotherapy modulates immunologic mechanisms of the underlying disease and is considered the only therapeutic option with the potential to provide long-term posttreatment efficacy and alter the natural course of allergic disease.⁴ Most importantly, there are now 4 FDA-approved SLIT products that have been available in the United States since 2014 after the last SLIT survey was conducted. For the comparison of survey results with the 2008 and 2013 surveys, significant changes in both SCIT and SLIT use were evident (Table 4). SCIT use increased from 67.4% in 2008 to 90.7% in 2018. SLIT use was reported as 5.9% in 2008, 11.4% in 2013, and 73.5% in this study ($P < .001$). Because the percentage of US respondents using SLIT in their practice was higher in this data set relative to the previous 2 surveys, this allowed us to gain a better insight into SLIT prescriber practices.

We found notable and significant differences compared with the survey data obtained previously. In the previous 2 surveys, the top reported barrier was lack of an FDA-approved SLIT therapy. Now that there are FDA-approved products, the top barrier to using SLIT is the limitation of treating with only one allergen. This barrier is problematic because polysensitized (responsive to ≥ 2 allergens on skin prick testing or in vitro specific IgE testing) patients make up 50% to 80% of patients seeking care for allergic rhinitis.^{8–9} Of note in this survey, of the allergists treating with FDA-approved SLIT tablets, 19.1% reported treating with more than 1 allergen. Although not a contraindication, the prescribing information for all 4 FDA-approved products state that concomitant dosing with other allergen immunotherapy may increase the likelihood of local or systemic adverse reactions to subcutaneous or sublingual allergen immunotherapy. Further studies are needed to determine safety, efficacy, and optimal formulations for multiallergen SLIT because no studies have found efficacy with multiple allergens as a mixture.¹⁰ Because the FDA requires combination therapies to perform better than the individual therapies alone (eg, inhaled corticosteroid and long-acting β -agonist combination therapy) to grant approval, it may be many years before the United States has FDA-approved combination SLIT tablets.

Although it may seem intuitive that all allergists use SCIT in their practice, only 67.4% of respondents in 2008 reported SCIT use and 78.2% in 2013. In this survey, US allergists reported an increase in SCIT use to 90.7% ($P < .001$ for 2008; $P < .001$ for 2013). Among US respondents, 75.4% believe that SLIT is safer than SCIT, which is a statistically significant increase from 2013 data of only 66.7% ($P = .01$). The safety of SLIT has been well established, with no reported fatalities. In contrast, although rare in light of the number of patients receiving SCIT, there have been more than 80 confirmed fatalities attributable to SCIT in the United States since 1973.^{11–13}

Reflective of the prescribing information for the new FDA-approved SLIT therapies, this survey reflects adherence with FDA recommendations for SLIT administration. Rates of in-office initial dosing were 96.3% compared with 53.5% in 2008 ($P < .001$) and 80.4% in 2013 ($P < .001$). In addition, there was an increase in autoinjectable epinephrine prescriptions, with 82.4% of practitioners prescribing in 2018 compared with only 41.5% in 2008 ($P < .001$) and 62.8% in 2013 ($P = .004$). Overall, data demonstrated increased SLIT use relative to 2008 and 2013, which also corresponds to the availability of FDA-approved SLIT products in the United States.

The perception of efficacy of SLIT relative to SCIT has changed significantly since the previous 2 surveys. Only 19.0% of US respondents view SLIT efficacy as equal to or even greater than SCIT efficacy, compared with 55.3% in 2008 ($P < .001$) and 43.1% in 2013 ($P < .001$). This finding is interesting because there have been more than 80 randomized and controlled clinical trials of SLIT, which confirm its efficacy as least as a class effect.^{13,14} Furthermore, now that the FDA has approved 4 SLIT tablets, there should be no debate on the efficacy of SLIT, especially for these scientifically supported products.^{4,5,7,14} However, additional evidence is needed to definitively compare the equivalent efficacy of SLIT and SCIT.^{11,14–18} There are 2 probable reasons for the low opinions and significant difference from previous surveys of perceived SLIT efficacy compared with SCIT. The wording and positioning of the question in the current survey is the first reason. All 3 surveys had 8 screening questions that all respondents answered. In the first 2 surveys, the seventh question was related to whether the allergist would use

Table 4

Comparison of 2008, 2013, and 2018 Overall US Survey Responses for Selected Questions

Survey response	No. (%) of US respondents in 2008 (n = 766)	No. (%) of US respondents in 2013 (n = 522)	No. (%) of US respondents in 2018 (n = 268)	P value
SLIT use	45/766 (5.9)	59/519 (11.4)	197/268 (73.5)	<.001
SCIT use	512/760 (67.4)	402/514 (78.2)	243/268 (90.7)	<.001
SLIT safer than SCIT	554/755 (73.4)	344/516 (66.7)	202/268 (75.4)	.01
SLIT given in office ^a	23/43 (53.5)	45/56 (80.4)	181/188 (96.3)	<.001
Prescribe epinephrine	17/41 (41.5)	32/51 (62.8)	155/188 (82.4)	<.001
Pay out of pocket	27/41 (65.9)	48/52 (92.3)	51/52 (98.1)	<.001
SLIT efficacy greater than or equal to SCIT efficacy	21/38 (55.3)	22/51 (43.1)	51/268 (19.0)	<.001

Abbreviations: SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy.

^aAt least 1 dose.

SLIT if there was an FDA-approved product. In the current survey, this question was made obsolete by the FDA-approved products, and the SLIT efficacy question became the seventh screening question (question 7 in eFig. 1). All 8 screening questions were identical in all 3 surveys with the exception of the seventh question. In the previous 2 surveys, US respondents had to have experience with SLIT drops to answer the efficacy question. The fact that they were using SLIT drops would lead to high-efficacy opinions compared with SCIT. In the current study, the efficacy question was a screening question, and respondents may not have had experience with any of the SLIT products or may have only had experience with drops, tablets, or both. In addition, in the current survey, the efficacy question did not differentiate between the FDA-approved SLIT products and SLIT drops. Given the drastic difference in opinions on efficacy from the previous surveys and an established bar of efficacy leading to FDA approval of the tablets, it is most probable that US allergists were answering the question with SLIT drops in mind given the lack of an FDA-approved product for drops in the United States based on established efficacy doses.

Even with 4 FDA-approved SLIT tablet products, 31.4% of US respondents are still using SLIT drops of FDA-approved extract for SCIT. In this survey, reported dosing concentrations, volumes, and schedules varied significantly among respondents. As indicated in Table 2, there was a notable degree of disparity concerning cumulative monthly SLIT drop maintenance dosing relative to SCIT. This dosing ranged from a dose less potent than the SCIT dose (9.6%) to a dose greater than 50 to 100 times than the SCIT dose (3.8%). Despite data demonstrating effective and safe doses for SLIT tablets,^{4-5,7} challenges remain in identifying appropriate doses for SLIT drops. SLIT drops are not FDA approved, and their use is off-label without any clinical indication. On the basis of the dose ranges in this survey, SLIT drops are probably being prescribed at doses no more efficacious than placebo, misleading patients and unnecessarily using financial resources that could be invested in known effective doses with either optimum dose SCIT or FDA-approved SLIT tablets. Off-label use of aqueous SLIT extracts is not endorsed by the Joint Task Force of the American Academy of Allergy, Asthma, and Immunology and the ACAAI.¹⁰ The advantage of the currently available FDA-approved SLIT tablets is that every patient receives a safe and effective dose with a standardized allergen in a standardized dose with no variation across the country or among patient population. It would be anticipated that SLIT tablet use will continue to increase with clinical experience and in the setting of FDA approval of additional tablets in the future.

Survey data indicate that most US respondents (98.1%) rely on patient out-of-pocket payment for SLIT drops compared with 65.9% in 2008 ($P = .003$) and 92.3% in 2013 ($P = .36$). The logistics and time commitment of SCIT with in-office administration followed by a 30-minute wait are not feasible for some patients, and SLIT then becomes a viable option. A subset of patients willing to pay out of pocket for SLIT drops continues to drive a market need not yet being met by the 4 FDA-approved tablets. Although not queried in this survey, it is suspected that the perceived ability to meet a patient need, a reasonable profit margin, and the ability to avoid engaging with insurance carriers for reimbursement serve as the motivating factors for the 31.4% of US allergists providing SLIT drops. There have been no notable advances in insurance reimbursement and billing for SLIT preparation or administration in the United States during the last several years. Applicable *Current Procedural Terminology (CPT)* codes are not available. Importantly, the current *CPT* codes used in the context of immunotherapy administration (95115, 95117, and 95165) apply to only SCIT and not other routes of immunotherapy. Expense is the most frequent reason for immunotherapy discontinuation, as previously reported by 36.4% in an investigation that assessed adherence to various immunotherapy routes in pediatric patients.¹⁹ We hope that the availability now of 4 FDA-approved SLIT tablet

products covered under many insurance plans will improve adherence for those patients choosing SLIT over SCIT. It will be interesting to see in the next several years whether market forces and increasing deductibles drive more patients to seek SLIT tablets rather than paying out of pocket for off-label SLIT drops.

Table 3 compares US and non-US responders for selected questions. Although in previous surveys those practicing outside the United States had a higher rate of SLIT use, with the availability of 4 FDA-approved SLIT tablets, this current study shows that the difference between SLIT use between US and non-US responders was not statistically significant ($P = .42$). Non-US responders used a lower rate of SCIT (73.0% [27/37]) than US responders ($P = .004$).

The primary limitation of this survey is the low response rate. In an effort to optimize the number of responders, the survey was sent via e-mail in similar fashion as 2008 and 2013, with 2 mailings at subsequent 2-week and 4-week intervals. With the initial survey in 2008, there was a 25.7% response rate (828 of 3217), which decreased to 17.3% in 2013 (543 of 3130) and further decreased to 10.8% (305 of 2817) during this survey period ($P < .001$). Survey fatigue may be the most likely explanation for the low response rate because other surveys from the ACAAI and other allergy organizations were sent during the 2018 period. In addition, this survey was sent in the summer months, when practitioners may have taken vacation or were preparing for a new academic year. The length of the survey may have been an additional factor for the low response rate. Four additional questions were added to this survey version relative to the 2013 survey, and several questions were modified to address the FDA-approved SLIT products. This longer survey may have adversely affected response rates because of the additional time required for survey completion. An additional limitation was that not all respondents answered all applicable questions, resulting in denominator variation. A final limitation of the potential for a positive selection bias exists in the setting of the relatively low response rate because respondents could be individuals with a particular interest in immunotherapy, most notably SLIT.

This third SLIT survey provides comparison data reflecting trends during the last decade in perceptions and practices among allergists in and outside the United States. The availability of 4 new FDA-approved SLIT products has provided a standardized tablet that is safe and effective with no variation in dosing around the country or among patient populations. This availability has resulted in a significant increase in SLIT use in the United States, with 197 of 268 allergists (73.5%) reporting experience with SLIT. Among reporting US SLIT prescribers, 173 of 188 92.0% reported use of at least 1 of the tablets. Because the primary barrier for more widespread use of SLIT tablets is the limitation of treating to only 1 allergen, strategies for administering multiallergen SLIT tablets requires more exploration and research.

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eSupplement

1. How would you describe your current practice?
2. Have you completed a fellowship in Allergy and Immunology?
3. Where is your practice located?
4. Have you prescribed subcutaneous immunotherapy (SCIT) in your practice?
5. Do you believe that sublingual immunotherapy (SLIT) is safer than SCIT?
6. What are the biggest barriers in using SLIT in your practice? (Select all that apply)
7. How would you rate the effectiveness of SLIT compared to SCIT?
8. Have you ever used SLIT in your practice?

(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 remaining questions.)

9. In which age groups have you used SLIT? (Select all that apply)
 10. In which clinical conditions have you used SLIT? (Select all that apply)
 11. How would you rate your experience with SLIT?
 12. Approximately how many patients have you put on SLIT over the last 3 years?
 13. What do you consider as an absolute contraindication(s) to starting SLIT? (Select all that apply)
 14. What SLIT formulations have you used?
 15. Which FDA-approved SLIT products have you used in your practice (select all that apply)
 16. For which type of allergens have you used SLIT? (Select all that apply)
 17. How many SLIT doses do you require the patient to receive in your office?
 18. How long do you recommend the patient wait in your office after receiving a SLIT dose?
 19. What time of day do you recommend dosing SLIT?
 20. Do you obtain written informed consent before initiating SLIT?
 21. What educational materials are provided to your patients prior to SLIT initiation?
 22. Do you recommend SLIT dosing with food or beverage?
 23. Do you provide your SLIT patients with a written adverse reaction plan?
 24. What system do you have in place for patients to report adverse reactions? (Select all that apply)
 25. How long after starting SLIT therapy do you advise formal clinic follow-up appointment?
 26. Approximately what percentage of your patients on SLIT are compliant with therapy?
 27. What percentage of your patients have experienced each of the following side effects while on SLIT?
 28. Do you routinely dose-adjust for local reactions (e.g., oral itching or local GI reactions) to SLIT?
 29. Do you notice that local SLIT reactions (e.g., oral itching, local GI reactions) diminish over time?
 30. Do you routinely prescribe autoinjectable epinephrine for all your patients on SLIT?
 31. Do you have patients on two or more FDA-approved SLIT tablets concurrently?
 32. Do you use SLIT drops that are not FDA-approved?
-

(If you answered No to number 32, then you are done with this survey – thank you!)

(If you answered Yes to number 32, then please continue on with the remaining 9 questions.)

33. Do you utilize a build-up schedule for your patients on SLIT drops?
34. If you utilize a buildup schedule, how many doses are required in your build-up schedule?
35. If you utilize a build-up schedule, how do you dose-adjust for missed doses?
36. What is maintenance dose for your patients on SLIT drops?
37. What is the maintenance vial used for your patients on SLIT drops?
38. What is the maintenance schedule used for your patients on SLIT drops?
39. What is the relative potency of your cumulative maintenance monthly SLIT drops dose compared to your cumulative maintenance monthly SCIT dose?
40. How are SLIT drops reimbursed? (Select all that apply)
41. What percentage of your patients are receiving SLIT drops monotherapy (as opposed to multiple allergen SLIT)?

**Please note: We were unable to include answers choices for the questions due to journal page limits. If you would like a copy of the full survey, please contact corresponding author. Thank you.*

eFigure 1. Sublingual Immunotherapy 2018 Follow Up Survey Questions.