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Survey on immunotherapy practice patterns: dose, dose adjustments, and duration

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ABSTRACT

Background: Practical issues dealing with the administration of allergen immunotherapy (AIT) by European and US allergists are not well known. Several concerns are only partially covered by guidelines.
Objective: To survey AIT practice patterns among worldwide members of the American Academy of Allergy, Asthma and Immunology (AAAAI).
Methods: A web-based survey was conducted among AAAAI members on dosing, dose adjustment after missed doses, and duration of AIT.
Results: A total of 1,201 replies (24.7% response rate of which 10% of responses were from non-US and non-Canada members). A total of 57% to 65% of the US-Canadian dosing falls within the recommended Practice Parameter ranges (9.4%-19% too low). Dose adjustment after missed doses is based on time elapsed since the last administered dose by 77% of US-Canadian and 58% of non–US-Canadian allergists. Doses are reduced when a patient comes in more than 14 days for 5 weeks after the last administration and initial dosing restarted after more than 30 days for 12 weeks since last administration during the build-up or maintenance stage. After missing 1 to 3 doses, the dosing schedules were mostly followed (build-up phase: repeat last dose, reduce by 1 dose, reduce by 2doses; maintenance phase: reduce by 1 dose, reduce by 2 doses, reduce by 3 doses). AIT is prescribed for a median of 3 years by non–US-Canadian allergists but for a median of 5 years by 75% of US-Canadian allergists. Main reasons for continuing beyond 5 years were "after stopping, symptoms reappeared" or "patient afraid to relapse."
Conclusion: Many patients receive less than recommended doses. Two areas in which to plan further research are establishment of an optimal dose-adjustment plan for missed applications and exploration of the maximum appropriate duration of immunotherapy.

Introduction

The first trial of allergen immunotherapy[1] (AIT) was published 100 years ago. Immunotherapy remains the only treatment capable of modifying the natural history of allergic diseases, including allergic rhinoconjunctivitis and asthma. Lately, several guidelines on AIT have been developed with the aim of standardizing this form of treatment.[2–6] However, recent data are lacking regarding the extent to which recommended dosing is being followed.[7,8] Several areas in AIT lack appropriate validated recommendations; therefore, in these instances, clinical judgment must be used regarding dose adjustment after missed doses and duration of AIT.

Table 1 addresses how these issues have been covered in currently available guidelines. In the present study, these 3 areas were selected for evaluation for the following reasons. First, anecdotal reports refer to frequent low dosing within the United States.[7] Second, the literature concerning dose adjustments after gaps in administration is scarce. A pilot observational study of 16 missed-dose adjustment schedules demonstrated the extensive variation that exists among the protocols.[9] Most immunotherapy guidelines either do not delineate specific dose-adjustment protocols or suggest schedules that have not been validated with research.[2–4,6] Third, the planned duration of subcutaneous immunotherapy (SCIT) is not well established.[10] Several trials have shown that 3 years of immunotherapy might be enough; 3 years of grass and/or birch pollen immunotherapy in Europe conferred long-term effect in patients with hay-fever[11–13] and house dust mite asthma, although allergic rhinitis improved still further after a 5-year course.[14] Des Roches et al[15] documented a relationship between

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Table 1
Guidelines on immunotherapy published in the last 5 years: dose, dose adjustment after administration gaps, and duration of immunotherapy[a]

Guidelines or Practice Parameter origin	Dose	Dose adjustment after a gap in administration	Duration
Europe[2] (sponsored by EAACI)	5–20 μg of purified major allergen; an individualized dose with high clinical efficacy without major adverse effects	No proposed protocol[1]	No duration stated
United States[4] (sponsored by AAAAI and ACAAI)	Table with probable effective dosing limits expressed in BAU	A proposed protocol not based on prospective or retrospective studies	A decision about continuation should generally be made after 3–5 years of effective treatment.
Mexico[5] (sponsored by CMICA)	Table with probable effective dosing limits for the different products on the national market; individualized per patient	A proposed protocol based on a retrospective study	Pollen SCIT: at least 3 years; other allergens: at least 3–5 years; SCIT with more complex allergens might need >3 years
Great Britain[6] (sponsored by BSACI)	5–20 μg of purified major allergen, but it is patient dependent	No proposed protocol	Grass pollen SCIT: 3 years; longer duration probably needed for other aeroallergens
Canada[3] (sponsored by CSACI)	Table with recommended maintenance doses adapted from US Practice Parameter[21,27]	No proposed protocol[2]	Successful treatment is normally performed for 3 to 5 years

Abbreviations: AAAAI, American Academy of Allergy, Asthma and Immunology; ACAAI, American College of Allergy, Asthma and Immunology; BAU, bioequivalent allergy units; BSACI, British Society of Allergy and Clinical Immunology; CMICA, Mexican College of Clinical Immunology and Allergy; CSACI, Canadian Society of Allergy and Clinical Immunology; EAACI, European Academy of Allergy and Clinical Immunology; SCIT, subcutaneous immunotherapy.
[a]"Reduce the scheduled dose if the interval between injection sessions has been exceeded." "Recommend adjusting doses after missed injections."

the duration of the actual administration of SCIT and the duration of efficacy of SCIT after its cessation, and Hedlin et al[16] found that 5 years after cat or dog SCIT symptoms on exposure to pets were still reduced, although the nonspecific bronchial hyperreactivity had almost returned to preimmunotherapy values. Another trial found a 30% relapse rate after a 3- to 4-year immunotherapy course with rye grass.[17] Most guidelines indicate that more complex allergens and perennial exposure probably need SCIT beyond the 3-year time limit.[4,6]

In view of the uncertainty and lack of evidence base, we have explored how these issues are handled by practicing allergists in United States and elsewhere in their everyday clinics. We hypothesized that despite the availability of Practice Parameters at both national and international levels, the lack of a firm evidence base would inevitably be associated with a wide variation in dosing schedules. Our intention was to explore this potential diversity and hence the need for further research to inform best practice in the future.

Methods

A questionnaire (Appendix) was developed targeting practicing allergists and focused on their usual dosing, dose adjustments after a gap in administration, and duration of SCIT in their daily clinics. Members of the Immunotherapy, Allergen Standardization, and Allergy Diagnostics Committee of the American Academy of Allergy, Asthma and Immunology (AAAAI) were invited to take the pilot survey. Suggested changes were adopted. Thereafter, the Needs Assessment Committee of the AAAAI extensively reviewed and corrected the survey, resulting in its final version. We used an online survey dissemination tool (Survey Monkey; SurveyMonkey.com, Palo Alto, California[18]). In September 2010, an invitation to participate was sent out by AAAAI to all its members followed by 2 reminders to nonrespondents. The website was held open for 3 weeks. All replies were captured anonymously in Microsoft Excel files (Microsoft Corp, Redmond, Washington).

We used descriptive statistics. Several subgroup analyses were performed according to the following divisions (Table 2): US-Canadian allergists vs non–US-Canadian allergists, location of practice, type of practice, practice size, and years in practice. For intergroup comparisons the Pearson χ^2 test was applied. However, when one of the groups had fewer than 5 elements, we used the Yates χ^2 correction. With a confidence interval of 95%, $P < .05$ was considered statistically significant.

Before analysis, some minor corrections had to be made to the data. For question 26 respondents answered in days (30, 60, 90, 120) when our question asked for an answer in weeks; therefore, these values were converted into weeks (4, 9, 13, 17). For question 29 on the percentage of patients who stopped immunotherapy after 1 years, 2 years, and so on, all values were calculated back to the percentage of patients discontinuing per year, and the results are presented in Figure 1B. Finally, several respondents added a comment on continuing immunotherapy beyond 5 years only in certain high-risk venom-allergic patients, so an extra category was created to report these replies.

Results

There were 1201 respondents (24.7%) to 4870 surveys sent, of which slightly more than 10% were sent to non–US-Canadian allergists. Eighty-two surveys were excluded because respondents did not prescribe SCIT and 5 refused to participate, leaving 1114 surveys for analysis. Of those, 59 respondents did not fill in their country of residence. Nine hundred forty-eight respondents (90%) practice in the United States or Canada. The other 107 replies came mainly from practices in Europe, Latin America, and the Far East (40, 27, and 22 practices, respectively) and some from the Middle East, Australia, and South Africa. Most respondents came from

Table 2
General findings of the survey on immunotherapy practice patterns

Variable	Response rate, No. (%)
National and international replies (n = 1,055)	
United States and Canada	948 (90)
Other countries	107 (10)
Location of practice (n = 1,061)	
Urban	451 (42)
Suburban	558 (53)
Rural	52 (5)
Type of practice (n = 1,052)	
Academic practices	322 (31)
Nonacademic practices	720 (69)
Size of practice (No. of patients receiving immunotherapy)[a] (n = 996)	
Small (<100 patients)	295 (30)
Medium (100–400 patients)	452 (45)
Large (>400 patients)	249 (25)
Years in practice (n = 1,057)	
<5 years	241 (23)
6–10 years	135 (13%)
11–15 years	112 (11)
>15 years	569 (54)

[a]Five did not agree to participate; 82 did not undergo immunotherapy at the time of the survey.

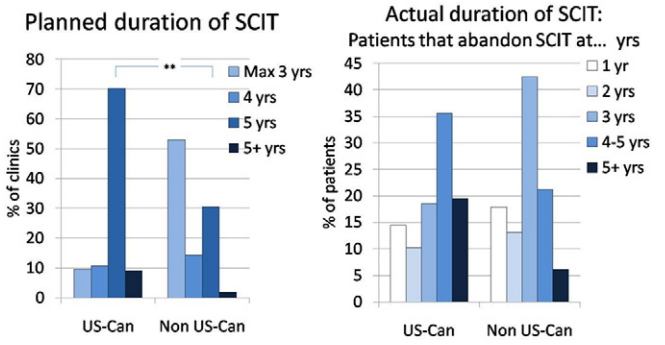

Fig. 1. Duration of subcutaneous immunotherapy (SCIT) as planned *(A)* and as actually given (perceived) *(B)*. The prescribed duration of SCIT is represented on the left (US-Canadian allergist group: n = 457; non–US-Canadian allergist group: n = 49). To get an idea of how long immunotherapy is actually given, allergists were asked which percentage of their patients abandons SCIT at 1 year, 2 years, 3 years, and so on (right: US-Canadian group: n = 409; non–US-Canadian group: n = 43).

suburban, nonacademic, middle-sized practices in the United States and Canada, with more than 15 years of experience. Details of the respondent population can be found in Table 2.

Maintenance dosing of SCIT

For the evaluation of the maintenance dose, results were divided into replies from the United States and Canada and replies from outside these countries. Because of the differences in extracts available for immunotherapy and the techniques of dosing in different parts of the world, median doses and dose ranges were only calculated for the US-Canadian group, in which the replies were more or less homogeneous.

Figure 2 shows the percentage of US-Canadian respondents whose reported dosing of SCIT was below recommended, low recommended, high recommended, or above recommended, according to the dosing recommendations of the Practice Parameters on Immunotherapy Third Update[4] for some of the most important allergens. Median maintenance doses, as reportedly used by the US-Canadian respondents, are also reported (in bioequivalent allergy units [BAU]). For US-Canadian respondents, only 57% to 65% of the standardized extract maintenance dosing falls within the dose ranges recommended in the Practice Parameters.[4] Of special interest are the 9.7% to 19.3% below-recommended doses because these are probably associated with loss of efficacy.

Subgroup analysis (eTables 1 and 2) showed that below-recommended dosing is less frequent in academic vs nonacademic practices for *Dermatophagoides farinae* (5.6% vs 12.6%; $P = .04$) and *Dermatophagoides pteronyssinus* (6.3% vs 12.9%; $P = .01$). In addition, below-recommended dosing was less frequent in practices with experience of less than 15 years vs practices with more than 15 years of experience (7.2% vs 13.4%; $P = .03$). For *D pteronyssinus,* dosing according to the Practice Parameters is more frequent in academic centers (76% vs 62%; $P = .01$), in practices with less than 15 years of experience (74% vs 59%; $P = .002$), and in smaller practices with fewer than 100 patients (74% vs 62%; $P = .04$) compared with nonacademic centers, practices with more than 15 years of experience, or medium-large practices. For SCIT with cat extract, too low dosing is statistically significantly less frequent in academic vs nonacademic centers (9.7% vs 21.8%; $P = .006$), practices with less than 15 years of experience vs those with more than 15 years of experience (10% vs 26%; $P < .001$), and small vs large practices (12.5% vs 22.8%; $P < .001$) and vs middle-large practices (21.7%; $P = .003$). Also, there were higher rates of correct dosing in clinics with less than 15 years of experience vs clinics with more than 15 years of experience (74% vs 57%; $P = .008$) and in small clinics compared with medium-large practices (74% vs 61%; $P = .008$). For grass SCIT, too low dosing is less frequent in practices with less than 15 years of experience compared with clinics with more than 15 years of experience (5.9% vs 11.9%; $P = .02$). Correct dosing is more frequent in small clinics (65% vs 53%; $P = .04$) and in clinics with less than 6 years of experience (70% vs 49%; $P = .002$) vs large clinics or those with more than 15 years of experience.

For tree pollen maintenance dosing, 36 respondents expressed the dose in BAU (median, 2,000 BAU; range, 1–30,000 BAU), 125 respondents expressed the dose in protein nitrogen units (PNU) with a median of almost 5,400 PNU given (range, 50–10,000 PNU), and 219 replies (46%) referred to weight/volume extracts, with a median of 0.5 mL being administered from a 1:175 (wt/vol) vial. A number of colleagues found some difficulty in replying to this particular question, so these latter results must be interpreted with caution.

Thirty-eight percent of the US-Canadian respondents reduced the dose of *D pteronyssinus* when combined with *D farinae* and also changed the dose of *D farinae* when combined with *D pteronyssinus*, as recommended.[4] Fewer allergists in rural areas lower the dose when combining both mites compared with allergists practicing in urban areas ($P = .04$). Non–US-Canadian allergists expressed maintenance doses in many different units, which made subgroup analysis impossible (50% in allergy units [AU], 16% in microgram [μg], 10% in index of reactivity, and others in therapeutic units, standard quality units, and milliliters [mL]).

Dose adjustment schedules for missed doses

Most allergists who replied to the survey (84.2%) adjusted the dosing after a missed dose based on the time elapsed since the last dose administered. A total of 76 of 481 adjusted the dose based on the time elapsed since the last scheduled, but never administered, dose. The most frequently mentioned dose-adjustment schedule is depicted in Figure 2, both for missed doses during the build-up phase and for missed doses during the maintenance phase. The schedule is simple: one goes a certain number of doses back, based on the number of doses missed since the last administered dose.

Fifteen percent of practices used another method: 10% reduced the next dose by a certain percentage, varying from 10% to 90%, depending on how delayed the timing of the patient's next visit. The other 5% of respondents lower the next dose after a gap in

Fig. 2. Categories of programmed maintenance dosing for *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, cat, and grass pollen reported by US-Canadian respondents. The categories of maintenance dosing were determined based on the probable effective maintenance dose as stated in the Practice Parameters on Immunotherapy, Third Update.[4] The recommended doses were divided into low recommended and high recommended. *D pteronyssinus* and *D farinae*: low recommended, 500 to 1,000 AU; high recommended, 1,001 to 2,000 AU; cat: low recommended, 1,000 to 2,000 BAU; high recommended, 2,001 to 4,000 BAU; grass: low recommended, 1,000 ot 2,000 BAU; high recommended, 2,001 to 4,000 BAU. Maintenance doses outside these intervals were considered below and above the recommended dosing, respectively.

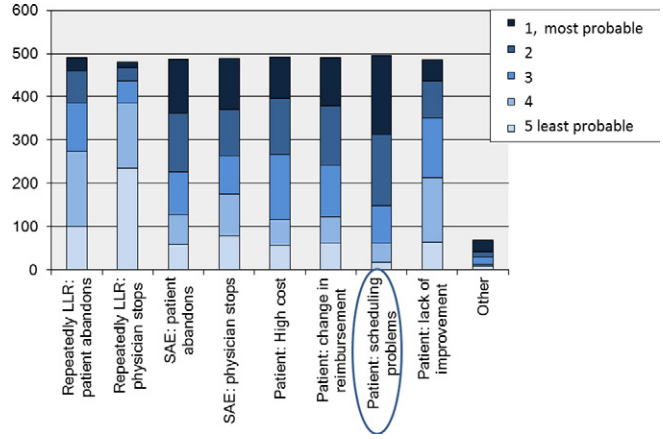

Fig. 3. Reason(s) for premature discontinuation of subcutaneous immunotherapy (SCIT) from most probable (1) to least probable (5). Reasons are listed on the x-axis and number of replies on the y-axis. LLR indicates large local reaction; SAE, systemic adverse event.

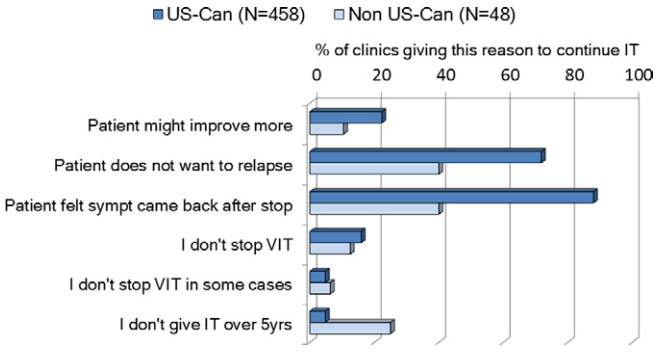

Fig. 5. Prescribing allergists' reason(s) to continue subcutaneous immunotherapy beyond 5 years.* All that apply were selected, so total is more than 100%. IT indicates immunotherapy; sympt, symptoms; VIT, Venom immunotherapy.

administration by a certain volume, varying from 0.1 to 0.5 mL. No major differences were found in the dose-adjustment schedules used by non–US-Canadian respondents after a gap in immunotherapy administration.

Immunotherapy was completely restarted after a gap during the build-up phase of a median of more than 90 days for the US-Canadian allergists (mean, 84 days) and after a median gap of more than 30 days after the last given dose for the non–US-Canadian respondents (mean, 44 days). During the maintenance phase, allergists restart from the beginning when the gap between doses is a median of more than 12 weeks (US-Canadian allergists: mean, 16 weeks; non–US-Canadian allergists: mean, 12 weeks).

Planned and actually perceived duration of immunotherapy

Seventy percent of US-Canadian allergists plans to give SCIT for 5 years as opposed to 30% of the non–US-Canadian allergists ($P < .01$) (Fig 1A). The actual perceived duration of SCIT, as expressed by the respondents, reflects the same difference between US-Canadian and non–US-Canadian practice of SCIT. According to US-Canadian allergists, most of their patients receive 4 to 5 years of SCIT, whereas non–US-Canadian practitioners state most of their patients receive 3 years of SCIT (Fig 1B). For both groups, the most frequent reasons for premature discontinuation of SCIT are patient related: scheduling problems and the experience of systemic adverse events (Fig 3). Figure 4 shows the estimated quantity of patients who receive SCIT for more than 5 years, again demonstrating the generally longer duration of SCIT in US-Canadian clinics. According to the surveyed allergists, the 2 prime reasons for continuing SCIT beyond 4 years are as follows: "after stopping the patient felt symptoms came back and was reinitiated" and "the patient has improved very well and does not want to relapse" (88% and 72%, respectively). Non–US-Canadian allergists also chose these 2 responses as the top 2 reasons to continue SCIT beyond 5 years (Fig 5).

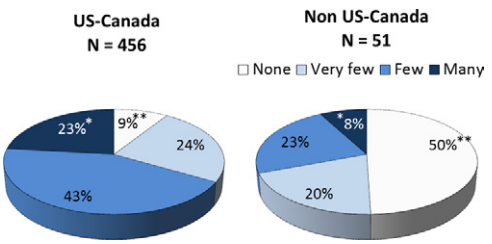

Fig. 4. Quantity of patients in their clinic that respondents estimate are receiving subcutaneous immunotherapy beyond 5 years (percentage of respondents). US-Canadian allergists: left side circle; non–US-Canadian allergist: right side circle. *$P <$ .05 (Fisher exact test). **$P < .001$ (Pearson χ^2 test).

Discussion

Previous Zoomerang surveys have been sent out to AAAAI members in 2004 and 2006 on other matters concerning AIT,[19] but this is one of the first studies looking at the viewpoint of the practicing allergist on SCIT dosing, dose adjustments, and duration of SCIT. Moreover, the fact that 10% of the respondents were non–US-Canadian allergists allows for a broader view, beyond the American borders and comparison between SCIT as performed in the United States and Canada as opposed to SCIT practiced outside the United States and Canada.

Typically, Internet surveys performed in the past by the AAAAI generated response rates of 15% to 20%. The recent Zoomerang survey had 554 replies to 3,435 questionnaires sent to practicing allergists (16%). The fact that we had a higher response rate is probably because of the enhanced electronic communication nowadays but also might reflex the increased interest of the membership in immunotherapy. Resending the invitation to participate to those who had not replied after the first round was a tool we used to improve the response rate.

Our data reveal that SCIT dosing in the United States and Canada is still not standardized among practicing allergists. Most US-Canadian allergists are dosing in the low-recommended dose range, whereas 9.7% to 19.3% of the US-Canadian respondents dose below recommended levels. This is especially true for SCIT with cat extracts. However, for some allergens, such as house dust mite and grass pollen, 23% to 33% of respondents report SCIT dosing above the recommend range. Further analysis of our data shows that the apparent high dosing schedules might be erroneous in some cases: we believe that those replies of 10,000 AU and 30,000 AU refer to the concentration per milliliter of the stock vial from which the patient's vial is prepared rather than to the actual dose given to the patient; to determine the exact quantity of allergen administered to the patient, a phased interrogation might lead to more accurate replies from all respondents. Subgroup analysis demonstrates that dosing is more in accordance with the recommendations of the US Practice Parameters in academic clinics, clinics with less than 15 years of experience, and smaller clinics. This is a consistent pattern, seen in 3 of the 4 surveyed allergens, giving robustness to this finding. One possible explanation for this finding might be that younger colleagues had their allergy training when the Practice Parameters on immunotherapy with dosing recommendations on SCIT were already published, as opposed to colleagues trained before 1996. Our data are in accordance with a recent, large, systemic evaluation of cat AIT prescribing patterns in which 82.6% of all doses between 2007 and 2009 were correct,[20] as opposed to

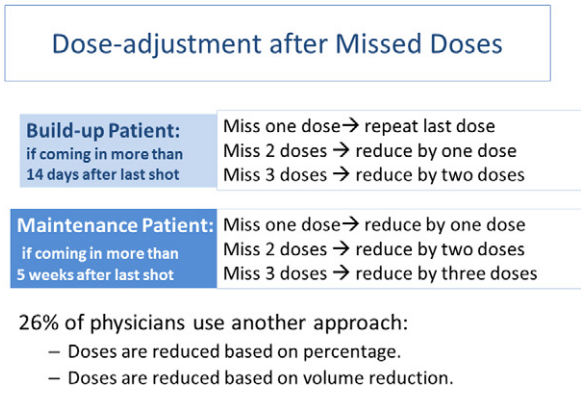

Fig. 6. Most frequently used schedule for dose adjustment after missed doses during the build-up phase (n = 510) and during the maintenance phase (n = 492). A dose adjustment is generally made with a median gap of more than 14 days after the last administration during the build-up phase or with a median gap of more than 5 weeks since the last administration during the maintenance phase in both the US-Canadian allergist group and the non–US-Canadian allergist group.

dosing before 2003; dosing recommendations for cat allergen did not come out until the first update of the Practice Parameters on immunotherapy in 2003.[21,22]

Dose adjustment after a gap in administration is done similarly in and outside the United States and Canada, with the most frequently mentioned schedule depicted in Figure 6. We believe that this is an important observation because it is a protocol that results from the experience of a significant group of specialists. The protocol is simple, and adjusted doses do not need to be calculated, as is required in other protocols (eg, volume- and percentage-based protocols). Moreover, the same protocol is used for build-up and maintenance phases, which is important in reducing error rate, because the more complex or inconsistent a process, the more likely errors can occur.[21,23] Recently, the first retrospective study evaluating a dose-adjustment schedule was published by Webber and Calabria[22,24] and is already used in national guidelines.[5] The Webber protocol and the schedule adopted by most respondents to this survey apply the same adjustment steps, the only difference being at what time point to proceed with the dose adjustment. The Webber protocol uses weeks elapsed since the last administration, whereas our survey's respondents adjust after 1, 2, 3, and so on missed doses. These protocols could be a good starting point for a prospectively designed trial aimed at establishing an evidence-based dose adjustment schedule to be recommended by all guidelines.

The planned duration of immunotherapy is clearly longer inside vs outside the United States and Canada as is the actual duration as perceived by the prescribing allergist (Figs 1B and 4). However, recall bias and distorted observation can easily alter a physician's perception of the patient's treatment.[23–26] The high perceived percentage of patients undergoing long-term immunotherapy, as stated by our respondents, strikingly contrasts with the findings of the review of the Florida Medicaid database: 3 years of immunotherapy is accomplished by 16% of all immunotherapy patients.[25,27]

A possible explanation for the longer planned duration of immunotherapy in United States and Canada might be the variation in allergen sensitization in US patients[28] as opposed to European patients,[29–31] with the former more frequently showing multiple allergen sensitivities to perennial allergens. It might be true that in these cases SCIT, using a mixture of multiple allergens, needs to be longer than 3 years to produce a maintained effect after discontinuation. In this context, the prime reason for continuing SCIT beyond 5 years is interesting: "on stopping (SCIT) symptoms came back and the patient was restarted on SCIT." Because many allergists with long-term experience report this observation in and outside the United States and Canada, it should be a topic of further research. On the other hand, one can question how legitimate the second most mentioned reason, patient's fear of relapsing, is and whether continuing SCIT based on this reason is a medically sound decision.

In conclusion, this survey points out that for the standardized extracts 9.7% to 19.3% of US-Canadian respondents use doses below those recommended by Practice Parameters; it also shows in which subgroups this reality is more frequent. Some of the probable effective doses for SCIT as recommended in US guidelines may be questionable because they are not based on studies conducted with US products.[4,26,32] The fact that a considerable percentage of allergists dose outside these limits might be an indication of the need of more precise dose-finding trials with US allergen products. Also, this survey indicates what the mostly used dose-adjustment schedule is after missed doses and demonstrates why SCIT is often continued beyond 3 or even 5 years. Well-designed trials are needed to address these latter 2 issues to guide future recommendations.

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References

[1] Noon L. Prophylactic inoculation against hay fever. *Lancet*. 1911;1:1572–1573.
[2] Alvarez-Cuesta E, Bousquet J, Canonica GW, Durham SR, Malling HJ, Valovirta E. Standards for practical allergen-specific immunotherapy. *Allergy*. 2006; 61(suppl 82):1–20.
[3] Leith E, Bowen T, Butchey J, et al. Consensus Guidelines on Practical Issues of Immunotherapy-Canadian Society of Allergy and Clinical Immunology (CSACI). *Allergy Asthma Clin Immunol*. 2006;2:47–61.
[4] Cox L, Nelson H, Lockey R, et al. Allergen immunotherapy: A Practice Parameter Third Update. *J Allergy Clin Immunol*. 2011;127(1 suppl):S1–S55.
[5] Larenas-Linnemann D, Ortega-Martell JA, Del Rio-Navarro B, et al. Mexican clinical practice guidelines of immunotherapy 2011 [in Spanish]. *Rev Alerg Mex*. 2011;58:3–75.
[6] Walker SM, Durham SR, Till SJ, et al. Immunotherapy for allergic rhinitis. *Clin Exp Allergy*. 2011;41:1177–1200.
[7] Chacko T. Are we following practice parameter guidelines on allergen immunotherapy? *Ann Allergy Asthma Immunol*. 2008;100:178.
[8] Nelson HS. The use of standardized extracts in allergen immunotherapy. *J Allergy Clin Immunol*. 2000;106(1 pt 1):41–45.
[9] Montgomery JR. The need for standardizing the aeroallergen immunotherapy missed-dose adjustment protocol. *Allergy Asthma Proc*. 2008;29:425–426.
[10] Cox L, Cohn JR. Duration of allergen immunotherapy in respiratory allergy: when is enough, enough? *Ann Allergy Asthma Immunol*. 2007;98:416–426.
[11] Durham SR, Walker SM, Varga EM, et al. Long-term clinical efficacy of grass-pollen immunotherapy. *N Engl J Med*. 1999;341:468–475.
[12] Jacobsen L, Niggemann B, Dreborg S, et al. Specific immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10-year follow-up on the PAT study. *Allergy*. 2007;62:943–948.
[13] Eng PA, Borer-Reinhold M, Heijnen IA, Gnehm HP. Twelve-year follow-up after discontinuation of preseasonal grass pollen immunotherapy in childhood. *Allergy*. 2006;61:198–201.
[14] Tabar AI, Arroabarren E, Echechipia S, Garcia BE, Martin S, Alvarez-Puebla MJ. Three years of specific immunotherapy may be sufficient in house dust mite respiratory allergy. *J Allergy Clin Immunol*. 2011;127:57–63, e1–3.
[15] Des Roches A, Paradis L, Knani J, et al. Immunotherapy with a standardized *Dermatophagoides pteronyssinus* extract, V: duration of the efficacy of immunotherapy after its cessation. *Allergy*. 1996;51:430–433.
[16] Hedlin G, Heilborn H, Lilja G, et al. Long-term follow-up of patients treated with a three-year course of cat or dog immunotherapy. *J Allergy Clin Immunol*. 1995;96(6 pt 1):879–885.
[17] Ebner C, Kraft D, Ebner H. Booster immunotherapy (BIT). *Allergy*. 1994;49: 38–42.
[18] Allergen Immunotherapy: A Practice Parameter Second Update. *J Allergy Clin Immunol*. 2007;120(3 suppl):S25–S85.
[19] Coifman RE, Cox LS. 2006 American Academy of Allergy, Asthma & Immunology member immunotherapy practice patterns and concerns. *J Allergy Clin Immunol*. 2007;119:1012–1013.

[20] Robertson BD, McCoy RL, Nelson MR, Haymore BR. Effect of allergen immunotherapy practice parameters on cat extract prescribing patterns, 1993-2009. *Ann Allergy Asthma Immunol*. 2011;107:437–440.
[21] American Academy of Allergy, Asthma and Immunology and American College of Allergy, Asthma and Immunology. Allergen Immunotherapy: A Practice Parameter. *Ann Allergy Asthma Immunol*. 2003;90(1 suppl 1):1–40.
[22] Joint Task Force on Practice Parameters, representing the American Academy of Allergy, Asthma and Immunology, the American College of Allergy, Asthma and Immunology, and the Joint Council of Allergy, Asthma and Immunology. Practice Parameters for Allergen Immunotherapy. *J Allergy Clin Immunol*. 1996; 98(6 pt 1):1001–1011.
[23] Dain S. Normal accidents: human error and medical equipment design. *Heart Surg Forum*. 2002;5:254–257.
[24] Webber CM, Calabria CW. Assessing the safety of subcutaneous immunotherapy dose adjustments. *Ann Allergy Asthma Immunol*. 2010;105:369–375.
[25] Hunter PR, Bickerstaff K, Davies MA. Potential sources of bias in the use of individual's recall of the frequency of exposure to air pollution for use in exposure assessment in epidemiological studies: a cross-sectional survey. *Environ Health*. 2004;3:3.
[26] Kulig M, Bergmann R, Edenharter G, Wahn U; Multicenter Allergy Study Group. Does allergy in parents depend on allergy in their children? recall bias in parental questioning of atopic diseases. *J Allergy Clin Immunol*. 2000;105(2 pt 1):274–278.
[27] Hankin CS, Cox L, Lang D, et al. Allergy immunotherapy among Medicaid-enrolled children with allergic rhinitis: patterns of care, resource use, and costs. *J Allergy Clin Immunol*. 2008;121:227–232.
[28] Gergen PJ, Turkeltaub PC. The association of individual allergen reactivity with respiratory disease in a national sample: data from the second National Health and Nutrition Examination Survey, 1976-80 (NHANES II). *J Allergy Clin Immunol*. 1992;90(4 pt 1):579–588.
[29] Bousquet PJ, Chinn S, Janson C, Kogevinas M, Burney P, Jarvis D. Geographical variation in the prevalence of positive skin tests to environmental aeroallergens in the European Community Respiratory Health Survey I. *Allergy*. 2007; 62:301–309.
[30] Dahl R, Kapp A, Colombo G, et al. Efficacy and safety of sublingual immunotherapy with grass allergen tablets for seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol*. 2006;118:434–440.
[31] Dahl R, Stender A, Rak S. Specific immunotherapy with SQ standardized grass allergen tablets in asthmatics with rhinoconjunctivitis. *Allergy*. 2006;61:185–190.
[32] Larenas-Linnemann D, Esch R, Plunkett G, et al. Maintenance dosing for sublingual immunotherapy by prominent European allergen manufacturers expressed in bioequivalent allergy units. *Ann Allergy Asthma Immunol*. 2011;107: 448–458, e3.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.anai.2012.03.009.

eTable 1
Dosing mean and median totals for the United States and Canada

Totals	Too low, No. (%)	Low recommended, No. (%)[a]	High recommended, No. (%)[a]	Too high, No. (%)	Mean	Median	Comment
Dermatophagoides farinae with *Dermatophagoides pteronyssinus* (n = 565)	80 (14.7)	237 (41.9)	114 (20.2)	134 (23.7)	2,155	1,000	1–60,000 μg: mean, 10.9; median, 10 (1–54)
D farinae without *D pteronyssinus* (n = 495)	55 (11.1)	192 (38.9)	119 (24)	130 (26.3)	2,484	1,000	1–90,000 μg; mean, 10.86; median, 10 (1–20)
D pteronyssinus with *D farinae* (n = 506)	78 (15.4)	238 (47)	79 (15.6)	111 (21.9)	1,937	1,000	1–30,000 μg: mean, 9.6; median, 10 (3–20)
D pteronyssinus without *D farinae* (n = 437)	50 (11.4)	197 (45)	88 (20.1)	102 (23.3)	2,183	1,000	1–30,000 μg: mean, 10.9; median, 10 (4–20)
Cat (n = 480)	91 (19)	223 (46.5)	87 (18.1)	78 (16.2)	3,224	2,000	1–60,000 μg: mean, 13.1; median, 14 (8–17)
Grass (n = 395)	37 (9.7)	94 (23.8)	131 (33.2)	133 (33.7)	11,410	4,000	1–1,000,000 μg: mean, 16.3; median, 15 (8–30)

[a]House dust mite: low recommended, 500 to 1,000 AU/mL; high recommended, 1,001 to 2,000 AU/mL; cat and grass: low, 1,000 to 2,000; high, 2,001 to 4,000 BAU/mL.

eTable 2
Dosing means and medians for subgroups in the United States and Canada

Subgroup	Too low, No. (%)	Low recommended, No. (%)[a]	High recommended, No. (%)[a]	Too high, No. (%)	Mean	Median (range)	Comment
Dermatophagoides farinae alone[b]							
Urban (n = 164)	18 (11.0)	58 (35.4)	47 (28.7)	41 (25.0)	2243	1,500 (1–20,000)	No statistically significant differences between groups
Suburban (n = 298)	36 (12.1)	117 (39.3)	64 (21.5)	81 (27.2)	2519	1,000 (1–90,000)	
Rural (n = 33)	1 (3.0)	16 (48.5)	8 (24.2)	8 (24.2)	2,873	1,000 (1–10,000)	
Academic (n = 107)	6 (5.6)	40 (37.4)	34 (31.8)	27 (25.2)	2,487	1,600 (1–20,000)	*P* between too low dosing = .04; dose adjust in mixed house dust mite, 41.9 vs 36.8
Nonacademic (n = 389)	49 (12.6)	152 (39.1)	85 (21.9)	103 (26.5)	2,458	1,000 (1–90,000)	
<6 Years of practice (n = 96)	4 (4.2)	45 (46.9)	23 (24.0)	24 (25.0)	3053	1,000 (1–24,000)	Too low dosing more frequent in practices of >15 y vs <6 y/<15 y, *P* = .01/.03
6–10 Years of practice (n = 60)	8 (13.3)	16 (26.7)	19 (31.7)	17 (28.3)	3,682	1,650 (1–90,000)	
11–15 Years of practice (n = 52)	3 (5.8)	23 (44.2)	14 (26.9)	13 (25.0)	1,960	1,200 (14–10,000)	
>15 Years of practice (n = 284)	38 (13.4)	107 (37.7)	63 (22.2)	76 (26.8)	2,123	1,000 (1–15,000)	
<100 Patients (n = 106)	8 (7.5)	41 (38.7)	32 (30.2)	25 (23.6)	2,154	1,600 (1–20,000)	No statistically significant differences between groups
100–400 Patients (n = 240)	31 (12.9)	87 (36.3)	56 (23.3)	66 (27.5)	2,741	1,200 (1–90,000)	
>400 Patients (n = 133)	15 (11.3)	55 (41.4)	28 (21.1)	35 (26.3)	2,228	1,000 (1–14,000)	
Dermatophagoides pteronyssinus alone[c]							
Urban (n = 140)	15 (10.7)	61 (43.6)	34 (24.3)	30 (21.4)	2,088	1,000 (1–20,000)	Adjust 56/140 = 40; significant difference with rural *P* = .04
Suburban (n = 266)	33 (12.4)	122 (45.9)	47 (17.7)	64 (24.1)	2,198	1,000 (1–30,000)	
Rural (n = 31)	2 (6.5)	14 (45.2)	7 (22.6)	8 (25.8)	2,300	1,000 (1–10,000)	Adjust 8/32 = 25
Academic (n = 96)	6 (6.3)	45 (46.9)	28 (29.2)	17 (17.7)	2,148	1,000 (1–20,000)	Academic vs nonacademic too low dose *P* = .06; correct dose *P* = .01; dose adjust in mixed house dust mite (55 vs 40)
Nonacademic (n = 341)	44 (12.9)	152 (44.6)	60 (17.6)	85 (24.9)	2,183	1,000 (1–30,000)	
<6 Years of practice (n = 88)	4 (4.5)	47 (53.4)	23 (26.1)	14 (15.9)	2,164	1,000 (1–20,000)	Correct dosing in <15 y of practice statistically significant more frequently than in >15 y of practice *P* = .002
6–10 Years of practice (n = 50)	6 (12.0)	21 (42.0)	11 (22.0)	12 (24.0)	2,442	1,000 (1–30,000)	
11–15 Years of practice (n = 51)	4 (7.8)	26 (51.0)	11 (21.6)	10 (19.6)	1,824	1,000 (1–10,000)	
>15 Years of practice (n = 244)	34 (13.9)	101 (41.4)	43 (17.6)	66 (27.0)	2,227	1,000 (1–30,000)	
<100 Patients (n = 96)	8 (8.3)	48 (50.0)	23 (24.0)	17 (17.7)	1,852	1,000 (1–20,000)	Correct dosing in small practice statistically significant more frequently than in medium-large practices *P* = .04
100–400 Patients (n = 210)	27 (12.9)	90 (42.9)	37 (17.6)	56 (26.7)	2,329	1,000 (1–30,000)	
>400 Patients (n = 116)	13 (11.2)	50 (43.1)	26 (22.4)	27 (23.3)	2,163	1,000 (1–10,000)	
Cat[d]							
Urban (n = 158)	26 (16.5)	76 (48.1)	33 (20.9)	23 (14.6)	2,944	2,000 (1–60,000)	No statistically significant differences between groups
Suburban (n = 290)	59 (20.3)	132 (45.5)	49 (16.9)	50 (17.2)	3,359	2,000 (4–60,000)	
Rural (n = 33)	7 (21.2)	15 (45.5)	5 (15.2)	4 (12.1)	2,619	1,500 (20–28,000)	
Academic (n = 103)	10 (9.7)	46 (44.7)	29 (28.2)	19 (18.4)	3,807	2,000 (3–60,000)	*P* = .006; correct dose *P* = .06
Nonacademic (n = 371)	81 (21.8)	175 (47.2)	58 (15.6)	57 (15.4)	3,018	2,000 (1–60,000)	
<6 Years of practice (n = 93)	7 (7.5)	50 (53.8)	18 (19.4)	19 (20.4)	4,202	2,000 (1–60,000)	Too low dose *P* <.001/<.001/<.001 vs <6 y, <10 y, and <15 y, correct dose vs 15 years *P* = .008
6–10 Years of practice (n = 62)	5 (8.1)	35 (56.5)	16 (25.8)	6 (9.7)	3,556	2,000 (2–60,000)	
11–15 Years of practice (n = 51)	9 (17.6)	24 (47.1)	10 (19.6)	8 (15.7)	2,722	2,000 (21–20,000)	
>15 Years of practice (n = 269)	70 (26)	112 (41.6)	43 (16)	44 (16.4)	2,866	1,500 (1–50,000)	

eTable 2
(*Continued*) Dosing means and medians for subgroups in the United States and Canada

Subgroup	Too low, No. (%)	Low recommended, No. (%)[a]	High recommended, No. (%)[a]	Too high, No. (%)	Mean	Median (range)	Comment
<100 Patients (n = 112)	14 (12.5)	56 (50)	27 (24.1)	15 (13.4)	3,106	2,000 (1–60,000)	Too low dose: small vs large and small vs middle-large $P < .001/.003$
100–400 Patients (n = 228)	48 (21.1)	99 (43.4)	40 (17.5)	41 (18)	3,405	2,000 (2–60,000)	
>400 Patients (n = 123)	28 (22.8)	57 (46.3)	19 (15.4)	19 (15.4)	2,962	1,750 (5–40,000)	Correct dose small vs med-large $P = .008$
Grass pollen[e]							
Urban (n = 130)	13 (10.0)	34 (26.2)	44 (33.8)	39 (30.0)	10,310	3,500 (1–400,000)	Too low; supplemental pdf
Suburban (n = 240)	23 (9.6)	54 (22.5)	80 (33.3)	83 (34.6)	12,062	4,000 (10–1,000,000)	
Rural (n = 25)	1 (4.0)	5 (20.0)	8 (32.0)	11 (44.0)	9,760	4,000 (500–100,000)	
Academic (n = 88)	5 (5.7)	23 (26.1)	30 (34.1)	31 (35.2)	23,556	4,000 (1–1,000,000)	Too low
Nonacademic (n = 306)	32 (10.5)	70 (23.0)	102 (33.4)	102 (33.4)	7,761	4,000 (1–100,000)	
<6 Years of practice (n = 77)	4 (5.2)	26 (33.8)	28 (36.4)	19 (24.7)	6,771	3,000 (1–100,000)	Too low dose <10 y vs >10 y/15 y $P = .03/.02$; correct dosing more frequent in practices with <6 y experience vs >15 y $P = .002$
6–10 Years of practice (n = 67)	3 (4.5)	13 (19.4)	25 (37.3)	16 (23.9)	22,528	4,000 (1–1,000,000)	
11–15 Years of practice (n = 42)	4 (9.5)	11 (26.2)	14 (33.3)	13 (31.0)	7,236	3,000 (36–100,000)	
>15 Years of practice (n = 219)	26 (11.9)	43 (19.6)	65 (29.7)	85 (38.8)	10,821	4,000 (1–400,000)	
<100 Patients (n = 98)	6 (6.1)	30 (30.6)	34 (34.7)	28 (28.6)	10,046	3,500 (1–400,000)	Too low dose; correct dosing small vs large = .04
100–400 Patients (n = 193)	18 (9.3)	40 (20.7)	65 (33.7)	70 (36.3)	13,043	4,000 (1–1,000,000)	
>400 Patients (n = 91)	11 (12.1)	19 (20.9)	27 (29.7)	34 (37.4)	9,204	4,000 (5–100,000)	

[a]House dust mite: low recommended, 500 to 1,000 AU/mL; high recommended, 1,001 to 2,000 AU/mL; cat and grass: low, 1,000 to 2,000; high, 2,001 to 4,000 BAU/mL.
[b]Too low dosing is less frequent in academic vs nonacademic practices and in practices with less than 6 years and less than 15 years of experience vs practices with more than 15 years of experience.
[c]Practice Parameters recommended dosing more frequently in academic centers, in practices with less than 15 years of experience, and in smaller practices compared with nonacademic centers, practices with more than 15 years of experience, or medium-large practices. Dose adjustment when *D pteronyssinus* is combined with *D farinae* is done more frequently in urban practices vs rural practices.
[d]Too low dose statistically more frequent in nonacademic vs academic centers, practices with more than 15 years of experience vs less than 15 years, 10 years, and less than 6 years of experience, large practices vs small practices, and large-middle size practices vs small practices. Higher rate of correct dosing in clinics with less than 15 years of experience vs clinics with more than 15 years of experience and in small clinics vs medium-large practices.
[e]Too low dosing is less frequent in practices with less than 10 years of experience compared with clinics with more than 10 years and more than 15 years of experience. Correct dosing is more frequent in small clinics and in clinics with less than 6 years of experience vs large clinics or clinics with more than 15 years of experience.