

INVITED ARTICLE

Undertreatment of allergy: Exploring the utility of sublingual immunotherapy

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ABSTRACT

Allergic syndromes are highly prevalent and are comprised of a wide variety of clinical problems, including rhinitis, conjunctivitis, atopic dermatitis and urticaria, asthma, and food allergies. Numerous studies have shown that allergic syndromes are both underdiagnosed and undertreated. This is related to many factors, including trivialization of allergic conditions by physicians and patients, failure to adhere to diagnostic and treatment guidelines, and dissatisfaction with conventional pharmacologic treatments. Immunotherapy involves the administration of allergen extracts in an attempt to induce immunologic tolerance and has been used for the treatment of allergic syndromes and the prevention of long-term complications. Conventional subcutaneous immunotherapy is effective but is also associated with a risk of serious adverse events, requires administration by a trained health care professional, and is contraindicated in certain populations. By contrast, sublingual immunotherapy has been used extensively in Europe and possesses most of the benefits of subcutaneous immunotherapy along with increased safety, tolerability, and convenience. This narrative review explores data from selected clinical studies and concludes that sublingual immunotherapy may be well suited to fill the gap posed by the undertreatment of allergic syndromes in the United States.

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Allergic syndromes, including rhinitis, conjunctivitis, atopic dermatitis, urticaria, asthma, and food allergies, are frequent health problems in the United States and abroad, affecting approximately one quarter of the population.^{1–3} In fact, allergic disease ranks as the fifth leading chronic disease in the United States among all ages and the third most common among children under 18 years old.³ Furthermore, the prevalence of allergic syndromes continues to increase,^{4–11} especially among children.^{4–6} For example, the combined prevalence of allergic rhinitis, peanut allergies, and asthma nearly doubled in the United States from 1980 to 2000. This is possibly because of decreased exposure to allergens during critical developmental periods

and increased prevalence of allergens in the environment because of industrialization.^{12,13}

Allergic syndromes are often perceived as a nuisance by patients and clinicians alike and perhaps less worthy of directed and aggressive diagnosis and treatment when compared with other chronic illnesses, such as diabetes and hypertension.¹⁴ This paradigm ignores the fact that early diagnosis and treatment of more “minor” allergic diseases, such as rhinitis, may prevent progression and long-term complications, such as the development of sinusitis and asthma,¹⁵ and that rhinitis and asthma are associated with significant impairments in quality of life in terms of work productivity, school performance, activities of daily living, and overall well-being and enjoyment of leisure time.^{16–20}

Another consideration is the small but real risk of allergy-related patient mortality. Approximately 150 people in the United States die annually from anaphylaxis to food,²¹ and approximately 40 people die annually from reactions to insect stings.²² Furthermore, nearly 180,000 deaths by asthma are annually reported worldwide, and, although asthma-related mortality decreased in the United States from 1965 to 1977, it subsequently doubled from 1978 to 1989.²³

As a result of this high prevalence and ability to affect daily functioning, allergic syndromes exact a high economic toll. One analysis estimated annual costs of \$7.9 billion in the United States, of which \$4.5 billion was spent on direct care and \$3.4 billion on indirect costs, primarily related to lost work productivity and school absenteeism.²⁴

UNDERTREATMENT OF ALLERGY

More than a third of those with allergic syndromes are undiagnosed or undertreated relative to medical society guidelines. This figure is likely higher in young children, the elderly, minority groups, inner city and rural populations, and low-income families.^{25–27} Early diagnosis and treatment of allergic syndromes is critical to preserve patient quality of life, to reduce direct and indirect economic costs, and

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potentially to modulate the course of the disease and prevent progression and irreversible complications. Although effective treatments exist, the disease often remains undiagnosed and improperly treated, despite clear diagnostic and therapeutic guidelines. Of the approximately 39 million people in the United States who experienced allergic rhinitis in 1987, only 4.8 million (12.3%) sought medical treatment.¹⁸ Similar trends in undertreatment have been noted throughout Europe.²⁸⁻³⁰

Physicians may fail to screen for allergies, overestimate compliance, overestimate patient satisfaction with therapy, underestimate disease severity, and fail to advance therapy according to treatment guidelines when suboptimal control is present or if initial measures are ineffective.^{7,28,31-36} In the study by Nolte et al,²⁸ only 12 of 231 patients eligible for immunotherapy were offered this treatment modality. In other cases, adequate medical education is lacking regarding prevention as the goal of therapy rather than symptomatic treatment.^{30,33}

Even in the face of expert medical care for allergic syndromes, patient- and medication-related factors may preclude adequate symptomatic control. In a study by Loh et al³¹ and in many other studies,^{33,34} compliance with conventional medical therapy for allergic syndromes was suboptimal. In a study by Demoly et al,³³ only 54.7 percent followed their prescriptions scrupulously, and 44 percent used frequent self-medication. Reasons for noncompliance with medical therapy include dissatisfaction with efficacy, deterioration of efficacy, lack of 24-hour relief, bothersome side effects, cost, and a desire to avoid seeing a doctor.^{30,34}

In other cases, treatments for allergy may adversely affect work productivity. For example, 50 percent of workers who treated their allergic rhinitis with sedating antihistamines functioned at 75 percent efficiency for 14 days per year and were more likely to sustain occupational injuries (odds ratio, 1:5).³⁵ Other studies show that nonsedating antihistamines only partially reduce these problems.³⁶⁻³⁸

Similar results were reported in the Allergies in America Survey,⁷ a 2006 investigation encompassing more than 2,500 nasal-allergy patients and 400 health care providers. The survey revealed that health care providers overestimated patients' satisfaction with prescribed management of nasal allergies. Indeed, patients reported experiencing significant side effects of treatment, including a drying sensation (34%), dripping down the throat (33%), drowsiness (33%), headaches (25%), and bad taste (22%). Furthermore, 37 percent of patients stopped taking prescription intranasal allergy medication secondary to lack of efficacy.

IMMUNOTHERAPY: FILLING THE GAP

Immunotherapy (or desensitization) involves the administration of allergen extracts in an attempt to induce immunologic tolerance and may be better suited toward "capturing" the population of undertreated patients and improving

outcomes. Allergen immunotherapy is indicated for the treatment of allergic rhinitis, allergic asthma, and stinging insect venom hypersensitivity, and the most widely used form of immunotherapy in the United States is via subcutaneous injection with relevant antigens (Table 1).³⁹ Mechanistic explanations proposed to explain its therapeutic effects include an increase in immunoglobulin G activity, generation of suppressor T-cell clones, immune deviation from the TH2 to TH1 phenotype, and the induction of T-cell tolerance⁴⁰ (Fig 1).⁴¹

Subcutaneous Immunotherapy

Numerous clinical studies have documented the efficacy of subcutaneous immunotherapy (SCIT) in both adults and children (Table 2).^{39,42} For example, a 1995 meta-analysis of 20 randomized, placebo-controlled trials reported that SCIT was associated with symptomatic improvement with an odds ratio of 3.2 (95% confidence interval, 2.2-4.9) and medication reduction with an odds ratio of 4.2 (95% confidence interval, 2.2-7.9).⁴² The inclusion of another 20 studies in a revised meta-analysis in 2003⁴³ confirmed that SCIT significantly reduced allergic symptoms. Other studies have shown that SCIT was associated with a significant improvement in quality of life⁴⁴⁻⁴⁷ and that SCIT had long-lasting effects even after discontinuation^{48,49} with a concomitant reduction in the future risk of developing asthma⁴⁸⁻⁵¹ and a reduction in the development of new allergen sensitivities.^{52,53}

Clinical data support the notion that immunotherapy is severely underutilized. Indeed, as reviewed previously, Nolte et al²⁸ reported that only about 5 percent of patients who met indications for immunotherapy were offered this modality as a treatment option.

Despite its efficacy and ability to modulate the course of the disease long-term, several factors may limit the use of SCIT to its full potential. First, local allergic reactions to SCIT are common, with a frequency ranging from 26 percent to 86 percent of injections.⁵⁴ More importantly, severe systemic and sometime life-threatening reactions can occur.^{55,56} In a survey of physicians, 273 of 646 respondents reported near-fatal reactions to SCIT during the period of 1990 to 2001.⁵⁷ Furthermore, 41 fatalities were identified during that time, translating into an average of 3.4 deaths per year, which is consistent with results reported by other surveys.^{58,59} Second, SCIT is contraindicated in populations that have a higher risk of allergic reactions or those that would have a higher risk of death in the context of severe allergic reactions, including those younger than 5 years, those receiving beta-blockers, and those with severe or uncontrolled asthma or significant cardiovascular disease.⁶⁰ Third, SCIT typically requires injections administered in a clinical setting and subsequent careful observation for any signs of anaphylaxis. This is problematic in that injection is a less desirable delivery system for children, and the direct and indirect costs (in terms of time away from work or school) associated with regular visits to a physician's office

Table 1
Clinical indications for allergen immunotherapy³⁹

Indication	Criteria
Allergic rhinitis	Symptoms of allergic rhinitis after natural exposure to aeroallergens, demonstrable evidence of clinically relevant specific immunoglobulin (Ig)E antibodies, and one of the following: <ul style="list-style-type: none"> ● Poor response to pharmacotherapy or allergen avoidance ● Unacceptable adverse effects of medications ● Desire to avoid long-term pharmacotherapy and reduce the cost of medication ● Coexisting allergic rhinitis and asthma ● Possible prevention of asthma in children
Allergic asthma	Symptoms of asthma after natural exposure to aeroallergens, demonstrable evidence of clinically relevant specific immunoglobulin E (IgE) antibodies, and one of the following: <ul style="list-style-type: none"> ● Poor response to pharmacotherapy or allergen avoidance ● Unacceptable adverse effects of medication ● Desire to avoid long-term pharmacotherapy and reduce the cost of medication ● Coexisting allergic rhinitis and allergic asthma
Hymenoptera stings allergy	<ul style="list-style-type: none"> ● History of a systemic reaction to a Hymenoptera sting (especially if the reaction was associated with respiratory or cardiovascular symptoms) and demonstrable evidence of clinically relevant specific IgE antibodies* ● Age >16 years, history of a systemic reaction limited to the skin, and demonstrable evidence of clinically relevant specific IgE antibodies ● History of a systemic reaction to imported fire ant and demonstrable evidence of clinically relevant specific IgE antibodies

Adapted from Joint Task Force on Practice Parameters.³⁹

*Patients younger than 16 years who present with a history of only cutaneous symptoms to Hymenoptera stings may not require immunotherapy.

pose significant barriers (eg, monetary, time, and convenience).⁶¹

Sublingual Immunotherapy

Although still not widely used and studied in the United States, there is a significant body of literature documenting the efficacy and safety of sublingual immunotherapy (SLIT) in Europe, where there is extensive clinical experience with this approach.⁶² Various meta-analyses and reviews of SLIT have been published over the past decade. For example, Malling⁶³ conducted an analysis of 23 SLIT studies (523 study patients and 492 controls) and verified an effective or

possibly effective response to SLIT in 61 percent of the studies. Passalacqua et al⁶⁴ published a review of 25 SLIT studies conducted between 1986 and 2003 and reported that SLIT was effective for the treatment of allergic rhinitis in 22 (88%) of these studies. Leatherman et al⁶² performed an analysis of 36 SLIT studies published in or before 2004 and concluded that SLIT is an effective method of immunother-

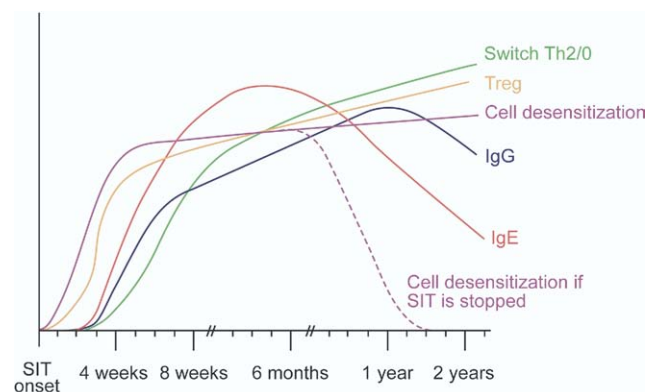


Figure 1 Early and late putative mechanisms of allergen specific immunotherapy (SIT).⁴¹ (Reprinted with permission.⁴¹)

Table 2
Improvement of symptoms and reduction in medication and bronchial hyperresponsiveness after immunotherapy^{39,42}

Outcome measure	Immunotherapy target	
	House-dust mite*	Other allergens*†
Symptom improvement	2.7 (1.7-4.4)	4.8 (2.3-10.1)
Reduction in medication	4.2 (2.2-7.9)	ND
Reduction in bronchial hyperresponsiveness	13.7 (3.8-50.0)	5.5 (2.8-10.7)

Abbreviation: *ND*, not done.

Adapted from Abramson MJ, Puy RM, Weiner JM: Is allergen immunotherapy effective in asthma? A meta-analysis of randomized controlled trials. *Am J Respir Crit Care Med* 1995; 151:969-74 and Joint Task Force on Practice Parameters.³⁹

*Odds ratios (95% confidence intervals).

†Pollen, mold, or animal dander.

Table 3
Medication scores and symptom scores for 855 patients with seasonal allergic rhinitis^{68,70}

Treatment group	Medication scores	Symptom scores
2500 SQ-T (~0.5 mg of Phl p 5)	$P = 0.38^{\dagger}$	$P = 0.96$
25,000 SQ-T (~5 mg of Phl p 5)	$P = 0.96$	$P = 0.46$
75,000 SQ-T (~15 mg of Phl p 5)	Reduced by 28%, $P = 0.047$	Reduced by 16%, $P = 0.071$
If only patients treated with 75,000 SQ-T for at least 8 weeks were considered	Reduced by 29%, $P = 0.012$	Reduced by 21%, $P = 0.002$

Patients were treated with 1 of 3 sublingual doses of *Phleum pratense* (Phl p 5) or placebo tablets for a mean duration of 18 weeks. Reprinted with permission.^{68,70}

NOTE: P values are versus placebo.

apy administration for the treatment of allergic rhinitis, conjunctivitis, and asthma, regardless of types of allergens or age range. Wilson et al⁶⁵ presented a more rigorous review of the efficacy of SLIT in a Cochrane review and a subsequent updated meta-analysis. This analysis included 979 patients from 22 studies and concluded that SLIT therapy resulted in a significant reduction in mean symptom scores ($P = .002$) and medication use ($P = .0003$) when compared with placebo therapy.

More recent studies have confirmed that SLIT is effective in adults and children⁶⁵⁻⁶⁹ (Table 3).^{68,70} For example, in a study of 855 patients with grass pollen allergy and allergic rhinitis randomized to placebo or one of three grass tablet doses, there was a significant reduction in symptom and medication scores in the highest-dose subgroup who were treated for at least 8 weeks before the grass pollen season compared with the placebo group.⁶⁸ Niu et al⁷¹ studied the efficacy of SLIT versus placebo in 97 children (age range, 6-12 years) with mild to moderate asthma with a single sensitization to mite allergen in Taiwan. SLIT resulted in superior daily ($P = .011$), nighttime ($P = .028$), and daytime ($P = .009$) asthmatic scores as well as improved pulmonary function indices after 24 weeks of treatment. Tolerance with high-dose SLIT was good, with few minor adverse events reported. Furthermore, Rak et al⁷² studied patients with grass pollen–induced rhinoconjunctivitis and reported that quality of life scores were approximately 25 percent higher in those treated with SLIT than in those treated with loratadine or placebo.

Several other studies have directly compared the efficacy of SCIT and SLIT. For example, three studies of patients with a grass allergy⁷³⁻⁷⁵ reported that SCIT and SLIT had equal efficacy, with one study reporting that SLIT was better tolerated.⁷⁵ A double-blind study in 71 patients with birch allergy also showed equal efficacy when comparing SCIT and SLIT.⁷⁶ More recently, Mauro et al⁷⁷ randomized 47 patients with pollen allergies to receive SCIT or SLIT. There was no significant difference in mean symptom-medication scores between SCIT and SLIT. Finally, in their meta-analysis, Leatherman et al⁶² remarked that SLIT and SCIT had comparable efficacy.

Similar to SCIT, SLIT can prevent the onset of new sensitizations. In a study involving more than 500 patients,

the rate of occurrence of new sensitizations was 5.8 percent in the active group and 38 percent in the control group ($P < .001$).⁷⁸ More importantly, a study of SLIT use in children⁷⁹ showed that SLIT was associated with a reduced risk of subsequently developing asthma (Fig 2).⁸⁰

One area in which SLIT appears to have an advantage when compared with SCIT is safety.⁸¹ The majority of adverse events related to SLIT are minor and self-limiting. These include itching, lip edema or oral discomfort, and abdominal pain. Rare cases of rhinitis or urticaria requiring antihistamine treatment have been reported. Regardless, the dropout rate related to these side effects in clinical studies has been very low.⁸¹ In Mauro et al's recent study of 47 patients with pollen allergies,⁷⁷ systemic reactions occurred in 16 percent of those treated with SCIT but in none of those treated with SLIT.

SLIT also appears to be safe in many populations in which SCIT is contraindicated. For example, its safety profile has been confirmed in clinical trials in children less than 5 years old in whom the most frequently reported side effects were related to local itching and oral discomfort. Agostinis et al⁸² used SLIT in 36 children (age range, 23 months-3 years 10 months) with either asthma or rhinoconjunctivitis and reported that therapy was effective, with only two children experiencing adverse events (mild abdominal

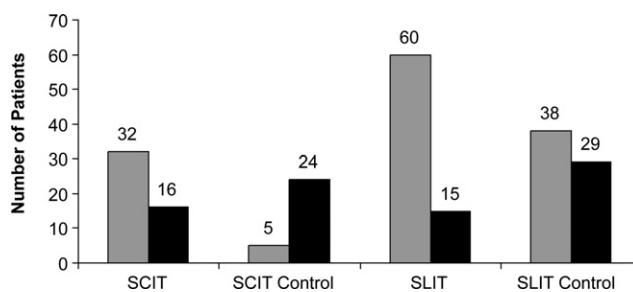


Figure 2 Preventive effect of SCIT and SLIT in children (SCIT 5-year odds ratio = 2.68 [1.3-5.7], SLIT 3-year odds ratio = 3.80 [1.5-10.0]). In a prospective study, 205 children with a clinical history of grass- or birch-induced rhinoconjunctivitis were randomized to receive SCIT for 3 years or to an open control group. There was a statistically significant reduction in the risk for developing asthma at 5-year follow-up (2 years after discontinuing immunotherapy).⁸⁰ (Reprinted with permission.⁸⁰)

pain). Pajno et al⁸³ evaluated the safety of SLIT in 354 children (age range, 5-12 years) with allergic asthma. Minor adverse events occurred in less than 10 percent of patients, and wheezing was observed in only two children (0.88%). Oral/pharyngeal itching, abdominal pain, urticaria, and rhinoconjunctivitis all occurred in less than 1 percent, and there were no anaphylactic or other serious reactions. Similar results were reported in a meta-analysis of 9 studies of 441 pediatric patients (ages, 3-18 years).⁸⁴

Before 2006, there were no reports of serious or near-fatal reactions associated with SLIT. Since that time, three case reports of nonfatal anaphylaxis caused by SLIT have been published. One patient with latex hypersensitivity had anaphylactic shock 20 minutes after reaching the maximal dose on the fourth day of latex rush sublingual immunotherapy,⁸⁵ whereas the other 2 reported cases of SLIT anaphylaxis involved patients treated with multiple inhalant allergens, one of whom had asthma as well as peanut and tree nut allergy.^{86,87} Regardless, the risk of serious allergic reactions appears greater with SCIT than with SLIT.

In contrast to SCIT, there is no absolute requirement for regimented physician contact for the delivery of SLIT. Thus, the theoretic concern is that outcomes would suffer secondary to suboptimal adherence and less frequent opportunities for physician-directed adjustments in ineffective regimens. However, Lombardi et al⁸⁸ reported that adherence was 95 percent for pollen SLIT and 97 percent for mite SLIT, whereas Passalacqua et al⁸⁹ reported an SLIT adherence rate at 3 months of greater than 90 percent.

The potential pharmacoeconomic benefits associated with SLIT relative to SCIT remain unclear. Because SLIT is not always reimbursed by US insurance providers, the minimization of both direct costs (ie, fewer office visits and no injection fees) and indirect costs (a decrease in lost work or school absenteeism to attend clinic visits) may be offset by higher out-of-pocket payments. Further study would be of benefit to determine whether the presumed lower costs associated with SLIT are realized, particularly as the US regulatory milieu for SLIT becomes clearer and insurers begin to absorb the costs of therapy.

CONCLUSIONS

Allergic syndromes are an expanding epidemic with increasing health issues, poorer quality of life, and high socioeconomic costs. Many patients are either undiagnosed or undertreated. Conventional pharmacologic therapy can be effective but is still associated with suboptimal control in a significant proportion of the population, either because of limited efficacy or poor adherence.

Immunotherapy is an effective treatment that can modulate the course of the disease and prevent long-term complications. However, subcutaneous delivery of immunotherapy is limited by the potential for serious adverse effects, contraindications to its use, and the need for physician supervision during administration.

By contrast, SLIT possesses most of the benefits of subcutaneous immunotherapy, appears to be safer and better tolerated among a wider population of patients, and is more convenient. These properties suggest that SLIT may have the benefits necessary to fill the gap associated with the undertreatment of allergic syndromes seen in the United States.

However, the determination of the full potential of SLIT requires additional research to characterize the relative efficacies of different dosing regimens, treatment schedules, escalation protocols, and the utility of single versus multiple antigen therapy.

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