

# Sublingual Immunotherapy in Children: The Recent Experiences

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## Abstract and Introduction

### Abstract

**Purpose of review** Sublingual immunotherapy (SLIT) is indicated for the use in pediatric patients suffering from allergic rhinitis or allergic rhinoconjunctivitis caused by environmental allergens, such as ragweed pollen, grass pollen, and dust mite. This review focuses on recent and relevant studies associated with the use of SLIT for these allergens in children by examining efficacy, safety, and immunological data in comparison to subcutaneous immunotherapy, therapeutic treatments, and placebo.

**Recent findings** In several of the case studies examined in this article, involving mainly grass and dust mite allergic patients, SLIT has been shown to have similar efficacy to subcutaneous immunotherapy. SLIT has been proven as a safer therapy. In comparing the adverse events related to both therapies, SLIT has fewer cases of anaphylaxis and fewer incidents of local reactions of mild-to-moderate severity. In comparison to therapeutic treatments and placebo, SLIT significantly improved symptom and medication scores. In addition to allergic rhinitis and allergic rhinoconjunctivitis, additional uses for SLIT in pediatric patients, such as asthma, atopic dermatitis, and food allergies, are under development.

**Summary** SLIT treatment is a well tolerated and effective approach to treat allergic rhinitis and allergic rhinoconjunctivitis in pediatric patients. Three SLIT tablets are currently approved by the US Food and Drug Administration to treat grass and ragweed allergies. The research discussed in this review will further the knowledge of physicians searching for an alternative treatment for their pediatric patients.

### Introduction

Sublingual immunotherapy (SLIT) is a type of specific immunotherapy utilized to treat allergic rhinitis or allergic rhinoconjunctivitis (ARC).<sup>[1]</sup> SLIT is ideally suited for use in children because it is needleless and convenient (given at home). Over 75 clinical research studies have been performed to prove the clinical efficacy of SLIT with at least 20 of those trials including only children.<sup>[1,2]</sup> SLIT has become recognized as a low-risk, high-benefit option for adults and children suffering from allergic rhinitis or ARC, and more recently, clinical trials have begun to demonstrate efficacy in diseases such as asthma, atopic dermatitis, and food allergies.<sup>[3]</sup> The most-studied SLIT allergens for pediatrics are dust mite and grass. Currently, three nature-based tablets have gained approval by the US Food and Drug Administration (FDA), two grass (Oralair and Grastek) and one ragweed (Ragwitek).<sup>[4]</sup> No SLIT dust mite tablets have been approved in the US, Grastek (Merck Sharp & Dohme Corp. Whitehouse Station, New Jersey, USA) is approved by FDA for individuals 5–65 years old, Oralair (Stallergenes S.A., Antony, France) is approved for individuals 10–65 years old, and Ragwitek (Merck Sharp & Dohme Corp. Whitehouse Station, New Jersey, USA) is approved for individuals 18–65 years old. Twenty-eight research trials conducted from 2009 to 2012 included children.<sup>[4]</sup> SLIT has been proven as a well tolerated therapy for not only adults but also children.<sup>[5]</sup> Specifically, children did not have any more adverse events than adults in any SLIT studies.<sup>[3]</sup> The use, benefit, and safety of SLIT in children and recent, relevant clinical trials, which are presented in ,<sup>[6,7–20]</sup> will be discussed.

### Table 1. Sublingual immunotherapy in pediatric patients

Study (year)	Sample size[ age (years)]	Diagnosis	Allergen (s)	Study treatment arms	Double-blind	Study duration	Results
De Castro <i>et al.</i> (2013) [6]	140 (6–14)	Allergic rhinitis Allergic asthma	Grass pollen or house dust mite	SLIT vs. symptomatic therapy	No	36 months	SLIT significantly decreased asthma and allergic rhinitis symptom scores
Nolte <i>et al.</i> (2013) [7]	565 (18–50)	Allergic rhinitis/rhinoconjunctivitis	Ragweed pollen	SLIT vs. placebo	Yes	12 months	Daily medication and daily allergic rhinitis symptom scores significantly decreased compared with placebo
Pastorello <i>et al.</i> (2013) [8]	47 (12–45)	Allergic rhinitis	Grass pollen	SLIT	Yes	24 months	SLIT caused a significant decrease in use of oral antihistamines and nasal decongestants in patients who were unresponsive to drugs
Wahn <i>et al.</i> (2008) [9]	278 (5–17)	Allergic rhinoconjunctivitis	Grass pollen	SLIT vs. placebo	Yes	7 to 8 months	The SLIT treatment reduced symptom and medication scores in both children and adolescents
							SLIT was found effective in both children and adolescents

Blaiss <i>et al.</i> (2011) [10]	345 (5–17)	Allergic rhinoconjunctivitis with or without asthma	Grass pollen	SLIT vs. placebo	Yes	23 weeks	through reducing the total medication and symptom scores in comparison to the placebo group. The quality of life also improved for these patients by 18% in comparison to placebo
Maloney <i>et al.</i> (2014) [11]	1501 (5–65)	Allergic rhinitis/rhinoconjunctivitis with/without asthma	Grass pollen	SLIT vs. placebo	Yes	26 months	SLIT was effective in treating allergic rhinitis in North American adults and children
Marcucci <i>et al.</i> (2012) [12]	30 (mean age 11.3)	Allergic rhinitis	Grass pollen	SLIT vs. no treatment	UNK	5 months	SLIT treatment of grass pollen enhances specific immunoglobulin E synthesis, which is involved in the same allergen components that occur during natural exposure
Aydogan <i>et al.</i> (2013) [13]	22 (5–10)	Allergic rhinitis	<i>Dermatophagoides pteronyssinus</i> or <i>D. farinae</i>	SLIT vs. placebo	Yes	12 months	SLIT significantly improved skin, nasal, and bronchial reactivity
Bergmann							SLIT therapy at 300 IR and 500 IR was well tolerated and

<i>et al.</i> (2013) [14]	595 (18–50)	Allergic rhinitis	<i>D. pteronyssinus</i> or <i>D. farinae</i>	SLIT vs. placebo	Yes	12 months	significantly decreased symptom scores as compared with placebo
Yukselen <i>et al.</i> (2013) [15]	32 (mean average 11.5)	Allergic rhinitis Asthma	<i>D. pteronyssinus</i> or <i>D. farinae</i>	SLIT vs. SCIT	Yes	24 months	No significant difference found between SCIT and SLIT symptom scores
Trebuchon <i>et al.</i> (2014) [16]	736 (5–17)	Allergic rhinitis with or without asthma	<i>D. pteronyssinus</i> or <i>D. farinae</i>	SLIT	No	24 months	SLIT was found to be effective and satisfactory by the patients in this 'real-life' setting retroactive study
Shao <i>et al.</i> (2014) [17]	264 (3–13)	Allergic rhinitis with or without asthma	<i>D. farinae</i>	SLIT vs. no treatment	No	12 months	SLIT significantly decreased symptom and VAS scores from baseline and significantly reduced rhinitis medication scores over the control group
Chen <i>et al.</i> (2013) [18]	122 (3–14)	Allergic rhinitis Allergic asthma	<i>D. farinae</i>	SLIT at ages 3–6 vs. SLIT at ages 7–14	No	36 months	No significant difference between the two groups of children
Kim <i>et al.</i> (2011) [19]	18 (1–11)	Food allergy	Peanut	SLIT vs. placebo	Yes	12 months	After 6 months of treatment, SLIT patients were able to ingest significantly more peanuts than the

							placebo group
Fleischer <i>et al.</i> (2013) [20]	40 (12– 37)	Food allergy	Peanut	SLIT vs. placebo	Yes	44 weeks	After 44 weeks of SLIT, patients were able to ingest 10 times as much peanut as they could at baseline

IR, index of reactivity; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; UNK, unknown; VAS, visual analog scale.

## Allergic Rhinitis Prevalence and Therapy

Allergic rhinitis or ARC, the primary indication for use of SLIT, is a chronic upper airway inflammatory disease, which usually presents with symptoms of sneezing, rhinorrhea, nasal congestion, and itching, as well as eye symptoms. Allergic rhinitis can be either intermittent or persistent, and sources of allergic rhinitis can be pollen, dust mites, mold, and animal dander.<sup>[21]</sup> In addition, allergic rhinitis can be a precursor or risk factor for other diseases in these children, such as asthma, otitis media, and chronic sinusitis. Nasal congestion can cause interrupted sleep and thus fatigue. Concurrently, children may suffer from mental, cognitive, or emotional problems.<sup>[22,23]</sup>

The Allergies, Immunotherapy, and Rhinoconjunctivitis (AIRS) surveys were conducted, involving 2765 individuals who were 5 years and older and diagnosed with either hay fever, allergic rhinitis, ARC, or nasal or eye allergies and 500 healthcare providers in the United States. Of the nine symptoms rated, nasal congestion was rated as the most bothersome and red, itchy eyes as the second most bothersome symptom. From the physician's view, red, itchy eyes are the most common symptom with which patients present. Over half of the patients also reported that their allergies impacted them 'a lot' or a moderate amount.<sup>[24]</sup> Nearly 76% of the individuals took over-the-counter medication to treat their allergies, and antihistamines were the most common (88%) over-the-counter choice to treat these symptoms. Through the survey of physicians, it was discovered that the confirmation of allergies differed across the healthcare facilities in which some utilized allergy tests and others did not.<sup>[25]</sup>

Another point of the AIRS survey was to see how much patients used and understood allergen immunotherapy (AIT). Almost half of the individuals knew what AIT is, and about 21% of individuals used subcutaneous immunotherapy (SCIT), whereas only 1.8% used SLIT drops. The most common reason individuals who use a form of AIT, either SCIT or SLIT, is that their symptoms were not relieved with other allergy medications. Most reported some or full relief of symptoms, but there was no difference between the relief received by SCIT and SLIT users. AIT was overall seen as very well tolerated by the majority of people (58.3%). Less than half of the participants believed that AIT could control symptoms for multiple years (44.7%) or that it could cure an individual of allergy symptoms (42%). Some individuals answered 'don't know' for whether AIT could control symptoms for multiple years (33.6%), whether it was well tolerated (29.3%), or whether it can cure allergy symptoms (27.5%).<sup>[26]</sup> The AIRS survey gives a good representation of the nasal and ocular symptoms and the medications used to treat them from the point of American patients and the healthcare providers and how education on AIT for patients could improve.

Current treatment for allergic rhinitis depends on the severity of the symptoms. The initial treatment for children who are allergic to inhalants is allergen avoidance.<sup>[27]</sup> Pharmacotherapy is the next step in treatment, including second-generation antihistamines taken orally or intranasally,<sup>[22]</sup> intranasal corticosteroids, and leukotriene receptor antagonists.<sup>[21]</sup> A range of treatment plans are currently used for allergic rhinitis, but focused here is the use of specific immunotherapy and the

increasing amount of data supporting the efficacy and safety of SLIT in children.

SCIT, the main type of allergen-specific immunotherapy used for over 100 years, is currently approved by FDA as a treatment for allergic rhinitis in both children and adults. SLIT is another type of allergen-specific immunotherapy in which a drop or tablet is placed under the tongue. Currently, there are very limited data directly comparing SCIT and SLIT. A systematic meta-analysis by Dretzke *et al.*<sup>[28]</sup> compared both the safety and efficacy of SCIT and SLIT as a treatment for seasonal allergic rhinitis. SCIT and SLIT demonstrated statistically significant improvements in symptom, medication, and quality of life scores in comparison to placebo. However, the overall effects of SLIT vs. placebo were slightly less than the SCIT vs. placebo comparisons. On the one hand, pediatric patients on SCIT were found to have statistically significant improvements in symptom and medication scores after 3 years of treatment. On the other hand, in SLIT pediatric patients, medication scores were not significantly improved when compared with placebo. In a limited number of head-to-head studies comparing SCIT and SLIT, no significant differences were reported.<sup>[28]</sup> More head-to-head studies will clearly be needed.

The adverse events noted for both SCIT and SLIT consisted of mostly local reactions of mild-to-moderate severity. Only six episodes of anaphylaxis have occurred during SLIT trials, and SCIT has presented with more accounts of severe or fatal incidences.<sup>[3]</sup> Nineteen percent of the systemic reactions were considered severe during SCIT trials, compared with only 2% in SLIT trials.<sup>[28]</sup>

Moreover, in a publication by De Castro *et al.*,<sup>[6]</sup> SLIT was supported in pediatrics with allergic rhinitis and allergic asthma. Patients either received SLIT or symptomatic therapy for 3 years, at the baseline recording, 44.3% of the active treatment group had persistent rhinitis compared with 34.3% in the control group. At the end of the observation period, the active treatment group had only 20% of patients with persistent rhinitis, whereas the control group had 37.1% of patients with persistent rhinitis.<sup>[6]</sup> A meta-analysis by Canonica *et al.*<sup>[2]</sup> looked at 17 trials, which included grass, dust mite, *Alternaria*, and ragweed allergens. All but one of the trials showed SLIT to have a significant effect independently of the allergen. The analysis also looked at head-to-head comparisons, one of which involved 48 children who were monosensitized to dust mite. SCIT, SLIT, and pharmacotherapy were administered alone for 1 year. Both SCIT and SLIT were superior to pharmacotherapy and did not differ in clinical efficacy.<sup>[2]</sup> Kim *et al.*<sup>[29]</sup> further supports that SLIT is a better overall choice through a meta-analysis comparing SCIT and SLIT in children in relation to efficacy. The authors also call for more head-to-head studies of SCIT and SLIT in children to show a distinct difference between the two.<sup>[29]</sup>

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## Recent Sublingual Immunotherapy Research

Most of the research conducted with SLIT in children used grass or dust mite-specific immunotherapy. Other allergens, including ragweed, have been researched but significantly less than grass and dust mite. The studies focused on the ragweed SLIT safety and efficacy have been large studies focused on adults, but have yielded that SLIT significantly decreased symptom and medication scores compared with placebo<sup>[7,30]</sup> and was well tolerated by patients.<sup>[31]</sup> Some relevant and recent studies, which included or focused on pediatric patients, are discussed here.

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## Grass Sublingual Immunotherapy

Several studies have specifically looked at SLIT when treating grass allergies. In a study performed by Pastorello *et al.*,<sup>[8]</sup> patients who were unresponsive to drugs found significant improvements on a five-grass pollen SLIT tablet. A significant improvement in visual analog scores and rescue medication score was observed after 1 year on the SLIT therapy.<sup>[8]</sup> Moreover, in a meta-analysis performed by Devillier *et al.*<sup>[32]</sup> looking for randomized, double-blind controlled grass SLIT studies, SLIT was found to have a higher relative clinical impact than leukotriene receptor antagonist and second-generation antihistamines in pediatric patients.

Another study by Wahn *et al.*<sup>[9]</sup> involved 278 male and female individuals between the ages 5 and 17 with ARC for at least 2 years that was attributable to seasonal grass allergies. The tablet in the study contained five-grass allergen extracts and was compared to a placebo. The treatment started 4 months before grass pollen season was expected to begin and continued throughout the season. The dose was increased by 100 index of reactivity every day over 3 days. To measure safety and efficacy, medication and rhinoconjunctivitis total symptom scores were recorded. The compliance between the placebo group and the active treatment group were 95 and 94%, respectively. The rhinoconjunctivitis total symptom scores of the active group during pollen season were significantly lower than that of the placebo group, with the active group showing a mean improvement of 28% and a median improvement of 39.3% ( $P = 0.0010$ ). All six of the symptoms studied had lower mean scores in the treatment group compared with placebo group, and four of the six symptoms (runny nose, nasal congestion, itchy eyes, and watery eyes) had statistically significant lower means ( $P < 0.0380$ ). The mean rescue medication score of the treatment group was significantly improved from that of the placebo group ( $P = 0.0064$ ). The active group showed a mean improvement of 24.1% and median improvement of 48.7% in rescue medication score. The active treatment group had taken rescue medication 35.4% of the days, compared with the 46.5% of days in the placebo group ( $P = 0.0146$ ). Overall, it was shown that the treatment was well tolerated and effective in reducing symptoms because of allergic rhinitis caused by grass pollen in 5–17-year-old patients.<sup>[9]</sup>

In a study by Blaiss *et al.*,<sup>[10]</sup> 345 children who suffered with grass pollen ARC from ages 5 to 17 were randomized to placebo or timothy grass SLIT tablet for 23 weeks during grass pollen season. The patients took the first three doses under medical supervision and then daily thereafter at home. Those who received the SLIT therapy saw a significant improvement of 26% in medication and symptom scores over the placebo group, specifically, an improvement of 28% for ocular symptoms scores and 23% for nasal symptom scores. In addition, the quality of life, assessed by weekly Rhinoconjunctivitis Quality of Life Questionnaire scores, of the SLIT patients was improved compared with the placebo group by 18%. This study was the first one of its kind—seeking efficacy and safety of timothy grass SLIT in North American pediatric patients. Regarding the safety of SLIT, no life-threatening events occurred, and oral pruritus and throat irritation were the most common adverse events. SLIT was well tolerated.<sup>[10]</sup>

Additionally, a double-blind, randomized, placebo-controlled study by Maloney *et al.*<sup>[11]</sup> also looked at patients with grass allergies. This study involved patients from 5 to 65 years of age who were given either a tablet with grass pollen extract (MK-7243) or placebo tablet 12 weeks prior to pollen season and continued throughout the season. Of the 1501 randomized patients, 283 were under 18 years of age. This was the first study in North America in which only the first dose of study medication was supervised by a physician in comparison to Blaiss *et al.*<sup>[10]</sup> and all other previous North American studies, which required the first three doses to be taken under medical supervision. The pediatric patients in the study showed a 32% reduction in total combined score (combined daily medication score and daily symptom score) compared with placebo during the grass pollen season. Overall, SLIT patients saw a 23% reduction in total nasal symptom scores and a 24% reduction in total ocular symptom scores over the grass pollen season when compared with placebo. They concluded that not only was the grass pollen extract tablet effective for adults and pediatric patients with ARC, but it was also well tolerated, as adverse events were limited to local application site reactions, with no serious treatment emergent adverse events.<sup>[11]</sup>

Finally, a study looked specifically at 30 pediatric patients with grass pollen allergy manifesting in allergic rhinitis for at least 2 years. Of these patients, 19 underwent SLIT treatment, with 11 in a control group. The SLIT treatment build-up took place over 4 days, starting in February at 30-60-120-240 index of reactivity, with maintenance doses of 240 administered three times a week until the end of June. The treatment was well tolerated, as only nine patients had local reactions, and no systemic reactions were recorded. The study<sup>[12]</sup> also reported that SLIT treatment of grass pollen enhances specific immunoglobulin E synthesis, involving the same allergen components that occur during natural exposure.

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## Dust Mite Sublingual Immunotherapy



Aydogan *et al.*<sup>[13]</sup> conducted a randomized study involving pediatric patients who were skin-tested positively to house dust mite (HDM) and were not diagnosed with asthma. The purpose of the study focused on the effectiveness of SLIT on HDM-allergic nonasthmatic children. The total symptom scores of both the active and placebo groups improved from the baseline. SLIT was proven successful in decreasing the skin, nasal, and bronchial reactivity to methacholine.<sup>[13]</sup>

Children who suffer from allergic rhinitis or ARC are more susceptible to develop asthma than those who do not.<sup>[14]</sup> In addition to reducing the symptoms of children suffering from allergic rhinitis, SLIT could also prevent the allergic march. The therapy could improve lung function and bronchial reactivity, causing a decrease in asthma symptoms. In a study involving pediatric patients, it was found that after 3 years of SLIT treatment for allergic rhinitis, eight out of 45 children developed asthma, whereas, 18 out of 45 children in the placebo group developed asthma. Another study<sup>[3]</sup> found that after 3 years of SLIT treatment, a child's risk for asthma was significantly decreased for seven more years. In addition, the Grazax Asthma Prevention study is currently being conducted and focusing on the preventive nature of grass SLIT on asthma. Children are on a regimen of Grazax or placebo for 3 years and have a 2-year follow-up to determine whether the SLIT prevents the development of asthma. This will serve as a focal study in the relationship of SLIT and the 'allergic march'.<sup>[33]</sup>

Yukselen *et al.*<sup>[15]</sup> conducted a 3-year study involving a 1-year run-in, 1-year randomized placebo-controlled, double-blind, double-dummy, treatment, and 1-year follow-up with an open-phase arm with active treatment for all patients. During the study, patients were randomized to receive either active SCIT or SLIT for 2 years or a 1-year period. All pediatric patients were diagnosed with persistent allergic rhinitis to HDM and mild persistent asthma. These investigators also found that SLIT and SCIT are both significantly effective treatments for allergic rhinitis and asthma after 2 years. However, SCIT was found to significantly decrease symptom scores, medication-use scores, HDM-specific bronchial provocation, and sputum eosinophils after 1 year when SLIT was found to decrease these measures significantly after 2 years but not after 1 year. In regard to significantly reducing the allergic rhinitis symptoms of the children, SCIT and SLIT were comparable and not significantly different.<sup>[15]</sup>

Furthermore, Trebuchon *et al.*<sup>[16]</sup> performed an analysis of patients in a 'real-life' setting using HDM SLIT. They followed 736 patients through an allergy specialist office. The study yielded that the target dose for HDM SLIT is less than 150 index of reactivity per day. The study<sup>[16]</sup> found that SLIT was equally effective and satisfying for adults and pediatric patients.

With the use of SLIT, an appropriate lower age limit must be attained. Two clinical studies determined the lower age limit for HDM specifically. Shao *et al.*<sup>[17]</sup> discovered that SLIT for a dust mite allergy was effective in children 3–13 years old. Chen *et al.*<sup>[18]</sup> found that after comparing preschool-aged children, 3–6 years old, and school-aged children, 7–14 years old, no difference was found in the effectiveness of SLIT. In both of these studies, no significant difference was found between the two age groups designated regarding safety or efficacy. The World Allergy Organization SLIT position paper also supported the same age range as noted by those studies<sup>[34]</sup>.

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## Other Uses for Sublingual Immunotherapy

In addition to allergic rhinitis, ARC, and asthma, SLIT efficacy has also been assessed in atopic dermatitis and food allergies. SLIT was proven to reduce eczema symptoms in atopic dermatitis patients.<sup>[35]</sup> However, only a few clinical research studies have been done in this area. Pajno *et al.*<sup>[36]</sup> found, in a double-blind, randomized, placebo-controlled study in children from age 5 to 16 years who were diagnosed with atopic dermatitis, SLIT was effective in reducing atopic dermatitis (SCORing Atopic Dermatitis) after 9 months of treatment. Also, rescue medication scores for those on SLIT improved significantly from baseline to the end of the treatment of 18 months. Adverse events noted by participants were localized swelling of mouth, lips, face, or oral itching, all of which were considered mild and did not require additional medication. However, two participants experienced intense itching within 1 h of dosing and were discontinued following



use of intramuscular chlorpheniramine and betamethasone. The researchers found SLIT to be effective in treating atopic dermatitis but suggested that it be initiated under medical supervision.<sup>[36]</sup> SLIT was also found to be clinically effective in treating food allergies using peach extract, hazelnut extract, and peanut extract.<sup>[37,38]</sup> In the first peanut SLIT study, those who received SLIT had an altered immunological response following the 12-month trial. These patients were able to ingest twenty times more peanut extract than the placebo group.<sup>[19]</sup> In another study,<sup>[20]</sup> treatment patients were able to ingest significantly more peanut powder after 44 weeks of treatment than the baseline. Although SLIT is not the primary treatment used for food allergies, it will be more of a topic in the near future.

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## Improvements in Pediatric Sublingual Immunotherapy Research

Areas of improvement exist to further support the efficacy and standardization of SLIT. Many adolescent allergic rhinitis patients suffer from multiple allergies, but not much research exists for polysensitization and the use of multiple extracts in SLIT. The efficacy of SLIT for multiple allergens should be sought out more diligently, for this is one area that SCIT is more effective.<sup>[39]</sup> Furthermore, through a review of multiple HDM-SLIT trials, Calderon *et al.*<sup>[40]</sup> noted that the ideal patient for SLIT therapy has yet to be found. In addition, the length of treatment to not only decrease disease symptoms but also have a lasting effect has not been discovered yet. Finally, the dose regimen for SLIT is not fully determined. Finding a more standardized dosing regimen to deliver SLIT would possibly lead to the FDA approval of more SLIT tablets and drops.<sup>[40]</sup> These examples of improvement do not only lie within the realm of HDM-SLIT trials but rather have been points for all SLIT research. All of the studies to this point have provided information on these topics but more advances could be made to make SLIT a more viable option.

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## Conclusion

SLIT has proven efficacy in children through the trials mentioned while being on par with the efficacy of SCIT and superior to other allergic rhinitis treatment regimens in limited head-to-head comparisons. It has proven to help patients suffering from not only allergic rhinitis and ARC, but also asthma, atopic dermatitis, and food allergies in limited studies. SLIT has an excellent side-effect profile, with minimal systemic reactions, and few incidences of anaphylaxis or life-threatening responses.<sup>[41]</sup> Three SLIT tablets, for the treatment of ragweed or grass pollen allergies, are currently approved by FDA, but with more substantial research, and with more SCIT to SLIT head-to-head comparisons, more tablets or SLIT drops could be approved in the future. Children have been the focus of SLIT research in the recent years because of the needleless and convenient approach. The good safety profile and benefit to risk ratio show that SLIT is a good treatment option for children with allergic rhinitis and ARC.

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## Sidebar

### Key Points

- SLIT is a well tolerated and effective form of specific AIT utilized for pediatric patients.
- Three SLIT tablets are currently approved by FDA (Oralair, Grastek, and Ragwitek).
- SLIT has been found to be effective in treating allergic rhinitis and ARC in adults and children, and, in more limited studies, asthma, atopic dermatitis, and food allergies.
- More head-to-head comparisons between SLIT and SCIT are needed to determine relative levels of safety and efficacy.

### References

1. Lin SY, Erekosima N, Kim JM, *et al.* Sublingual immunotherapy for the treatment of allergic rhinoconjunctivitis and asthma. *JAMA* 2013; 309: 1278–1288.
2. Canonica G, Cox L, Pawankar R, *et al.* Sublingual immunotherapy: World Allergy Organization position paper 2013 update. *World Allergy Organ J* 2014; 7:6.

\*\* A 2013 update to the World Allergy Organization paper looked at a SLIT pediatric study involving several allergens, including grass, dust mite, *Alternaria*, and ragweed. This showed the efficacy of SLIT, independent of the allergen. Head-to-head comparisons of SLIT and SCIT were also reviewed, showing little difference in efficacy.

3. Passalacqua G, Garelli V, Sclifo F, Canonica GW. Sublingual immunotherapy for allergic rhinitis and conjunctivitis. *Immunotherapy* 2013; 5:257–264.

\*\* This review article touches on the history of SLIT. It also provides a review of the efficacy and safety of SLIT in large clinical trials and meta-analyses. In addition, the authors discuss the unmet needs of SLIT research and other uses for SLIT, which will be studied more in the future.

4. Bartholow A, Pleskovic N, Drori J, Skoner DP. Review of the use of sublingual allergen immunotherapy in children. *Ped Aller Immun and Pulmon* 2014; 27:3–7.

\* Twenty-eight studies were reviewed to look at the efficacy and safety profiles of SLIT use in pediatric populations.

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\* This case controlled study looked at monosensitized and polysensitized pediatric patients over 3 years to find efficacy of SLIT, in relation to medication and symptom scores, over therapeutic treatment.

7. Nolte H, Hébert J, Berman G, *et al.* Randomized controlled trial of ragweed allergy immunotherapy tablet efficacy and safety in North American adults. *Ann Allergy Asthma Immunol* 2013; 110:450–456.
8. Pastorello EA, Losappio L, Milani S, *et al.* 5-grass pollen tablets achieve disease control in patients with seasonal allergic rhinitis unresponsive to drugs: a real-life study. *J Asthma Allergy* 2013;6:127–133.
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\*\* This was the first study to medically monitor patients during the first dosing only. In addition, this is the largest published immunotherapy trial involving adults and children thus far. This study showed not only the efficacy of SLIT treatment of grass allergens in pediatric patients in North America, but also the safety of treatment, as adverse events were limited to local site reactions, with no major treatment-related adverse events.

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15. Yukselen A, Kendirli SG, Yilmaz M, *et al.* Two year follow-up of clinical and inflammation parameters in children monosensitized to mites undergoing subcutaneous and sublingual immunotherapy. *Asian Pac J Allergy Immunol* 2013; 31:233–241.

\*\* This research study here is a 3-year study comparing SLIT, SCIT, and placebo in dust mite allergic children. It provided data for individuals on SLIT and SCIT therapy for 1 year and then 2 years. The study design consisted on symptom and medication scores, nasal provocation tests, nasal and sputum eosinophil testing, and allergen laboratory levels. The researchers discovered that SLIT is significantly different from the baseline after 2 years of treatment, and SCIT yielded significantly different results from baseline after 1 year of treatment.

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### **Conflicts of interest**

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