

Efficacy and Safety of Sublingual and Subcutaneous Immunotherapy in Children with Allergic Rhinitis: A Systematic Review of Randomized Trials Including Direct and Indirect Comparisons

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Background: Allergic rhinitis (AR) is a prevalent condition significantly impacting children's health globally. Allergen immunotherapy (AIT), via sublingual (SLIT) or subcutaneous (SCIT) routes, offers disease modification, but direct pediatric comparisons are limited. This systematic review evaluates the relative efficacy and safety of SLIT versus SCIT in children with AR based on randomized clinical trial (RCT) evidence.

Methods: A systematic literature search (PubMed, Embase, Cochrane Library, Scopus; July 2024) identified RCTs comparing SLIT vs SCIT, or either vs control, in children (≤ 18 years) with AR. Data on study design, participants, interventions, outcomes (symptom/medication scores, safety, adherence, immunological markers), were extracted. Methodological quality was assessed using the Cochrane Risk of Bias tool version 2 (RoB-2). Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed.

Results: Seven RCTs met inclusion criteria. Both SLIT and SCIT effectively reduced AR symptoms and medication use versus controls. Comparative efficacy was nuanced: several studies found comparable reductions in symptom/medication scores, while others suggested potential SCIT advantages for specific outcomes (asthma symptoms, Total Rhinitis Symptom Score from baseline). SLIT consistently showed a more favorable safety profile (mainly local reactions), whereas SCIT carried a higher risk of systemic reactions. Limited data suggested potential SLIT benefits in asthma prevention. Adherence data from included RCTs were sparse.

Conclusion: Both SLIT and SCIT are effective for pediatric AR. SLIT offers comparable efficacy for many outcomes with better safety/convenience, while SCIT may have advantages for certain outcomes but requires clinic administration. Treatment choice requires individualization based on efficacy, safety, adherence potential, and patient/family factors. Further high-quality, long-term comparative trials are needed.

Keywords: sublingual immunotherapy, subcutaneous immunotherapy, allergic rhinitis, children, systematic review

Introduction

Allergic rhinitis (AR) represents a significant global health challenge, particularly affecting pediatric populations where its prevalence has been increasing.¹ The condition can lead to substantial morbidity, impacting quality of life, sleep, and school performance.² While symptomatic treatments like antihistamines and intranasal corticosteroids manage

symptoms, allergen-specific immunotherapy (AIT) is the only treatment modality that targets the underlying immunological mechanisms, offering the potential for long-term disease modification and prevention of asthma development.^{3,4}

AIT can be administered via two primary routes: subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT). SCIT, the traditional method, involves regular injections of increasing allergen doses, while SLIT involves daily administration of allergen extracts under the tongue.⁵ Both aim to induce immune tolerance towards specific allergens.⁶

Numerous studies have established the efficacy of both SLIT and SCIT compared to placebo in pediatric AR.^{7–9} However, the relative merits of SLIT versus SCIT in this specific population remain less clear, presenting a common clinical dilemma. Factors such as efficacy, safety profile, onset of action, adherence, impact on comorbidities, and patient/family preferences influence treatment choices. SLIT is often favored for its superior safety profile and convenience, allowing for home administration,¹⁰ although some evidence suggests SCIT might induce faster symptom relief.¹¹ Immunological studies indicate potentially distinct pathways, with SCIT associated with stronger Th1 responses and Immunoglobulin G4 (IgG4) induction, and SLIT potentially promoting regulatory T cell (Treg) responses.¹²

Despite the widespread use of both modalities, direct head-to-head comparisons in children are relatively scarce. Existing meta-analyses have sometimes yielded conflicting results or combined adult and pediatric data,^{9,10,13} limiting their direct applicability to pediatric practice. Therefore, a focused systematic review synthesizing evidence solely from randomized clinical trials (RCTs) directly comparing SLIT and SCIT, or evaluating them against controls in pediatric AR, is crucial to inform clinical decision-making. This review aims to systematically evaluate and compare the efficacy and safety of SLIT versus SCIT for treating allergic rhinitis in children based on current RCT evidence, addressing the primary question of relative efficacy and secondary questions regarding safety, adherence, and potential long-term benefits.

Materials and Methods

Search Strategy

A systematic literature search was conducted in July 2024 across four electronic databases: PubMed, Embase, Cochrane Library, and Scopus. The search strategy combined Medical Subject Headings (MeSH) terms and keywords related to the interventions (“sublingual immunotherapy”, “subcutaneous immunotherapy”), condition (“allergic rhinitis”), population (“children”, “pediatric”), and study design (“randomized controlled trial”, “RCT”). No language or publication date restrictions were initially applied. This review followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines where applicable.

Eligibility Criteria

Studies were included if they met the following criteria:

- Population: Children and adolescents aged 18 years or younger diagnosed with allergic rhinitis (with or without comorbid asthma).
- Intervention: Sublingual immunotherapy (SLIT).
- Comparator: Subcutaneous immunotherapy (SCIT), placebo, or standard pharmacotherapy/no AIT. Studies comparing SLIT directly with SCIT were prioritized.
- Outcomes: Reported at least one relevant clinical or immunological outcome. Primary outcomes for this review were symptom scores and medication scores; secondary outcomes included adverse events, adherence/dropout, skin prick test (SPT) reactivity, provocation tests, asthma development, and immunological markers. Data extraction focused on quantitative results where available.
- Study Design: Randomized controlled trials (RCTs).

Exclusion criteria included: studies involving adults (>18 years) or mixed populations where pediatric data could not be isolated; non-randomized studies; case reports, reviews, or editorials; studies with incomplete data preventing extraction; and studies not reporting relevant outcomes.

Study Selection and Data Extraction

Following the database search, identified records were imported into reference management software (EndNote (Clarivate, Philadelphia, PA, USA)), and duplicates were removed. Four investigators independently screened titles and abstracts against the eligibility criteria. Full texts of potentially relevant articles were retrieved and assessed independently by two researchers for final inclusion. Disagreements regarding eligibility were resolved through discussion and consensus, with a fourth author consulted if necessary. A standardized data extraction form (developed using Microsoft Excel (Microsoft Corporation, Redmond, WA, USA)) was used to collect information from included studies. Extracted data included: first author, publication year, country, study design, AR diagnostic criteria, participant characteristics (sample size, age range/mean, gender distribution, disease duration, sensitization profile), intervention details (AIT modality, specific allergen, product/manufacture, dosing protocol, treatment duration), comparator details, outcome measures and results, dropout rates and reasons (if reported), and funding sources. Handling of different outcome scales involved extracting percentage change or standardized effect sizes where possible.

Risk of Bias Assessment

The methodological quality and risk of bias of included RCTs were independently assessed by two reviewers using the Cochrane Risk of Bias tool version 2 (RoB-2).¹⁴ This tool evaluates bias across five domains: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Each domain was judged as “low risk”, “some concerns”, or “high risk” of bias. An overall risk of bias judgment was assigned to each study. Discrepancies in assessment were resolved through discussion and consensus.

Meta-Analysis

A quantitative network meta-analysis was considered but ultimately not performed because the available evidence did not meet the assumptions required for a valid analysis. Only four randomized trials provided direct SLIT–SCIT comparisons, while the remaining studies compared a single modality with placebo or standard care, leaving no fully connected network of interventions. In addition, the included trials showed substantial clinical and methodological heterogeneity in allergen source (house dust mite, grass, cat), dosing regimens, treatment duration, and outcome definitions, and they reported effect estimates in non-uniform formats. These factors violate the transitivity and consistency assumptions essential for network meta-analysis, so the review was limited to a qualitative synthesis.

Results

Study Selection

The initial database search yielded 300 records. After removing 50 duplicates, 250 records were screened based on title and abstract. This led to the exclusion of 197 records. The full texts of the remaining 53 reports were assessed for eligibility. Of these, 46 were excluded for reasons such as incorrect population, study design, lack of relevant comparator or outcomes, or insufficient data. Ultimately, seven RCTs met the inclusion criteria and were included in this systematic review^{15–21} (Figure 1).

Risk of Bias Assessment

The overall risk of bias assessment using the RoB-2 tool indicated that most included studies (five out of seven) were judged to have a low risk of bias.^{17–21} Two studies were assessed as having “some concerns” or “high risk” primarily due to issues related to blinding (performance bias) or potential concerns in the randomization process.^{15,16} Specifically, Rolinck-Werninghaus et al¹⁵ raised some concerns regarding randomization and allocation, while Yukselen et al¹⁶ (double-dummy but unclear blinding effectiveness) and Marogna et al²⁰ (open-label design) had limitations related to blinding (Figure 2).

These factors warrant caution when interpreting subjective outcomes from these trials. Selective reporting of outcomes was generally not suspected across the studies. An overview of the risk of bias judgments across all studies for each domain is presented in Figure 3.

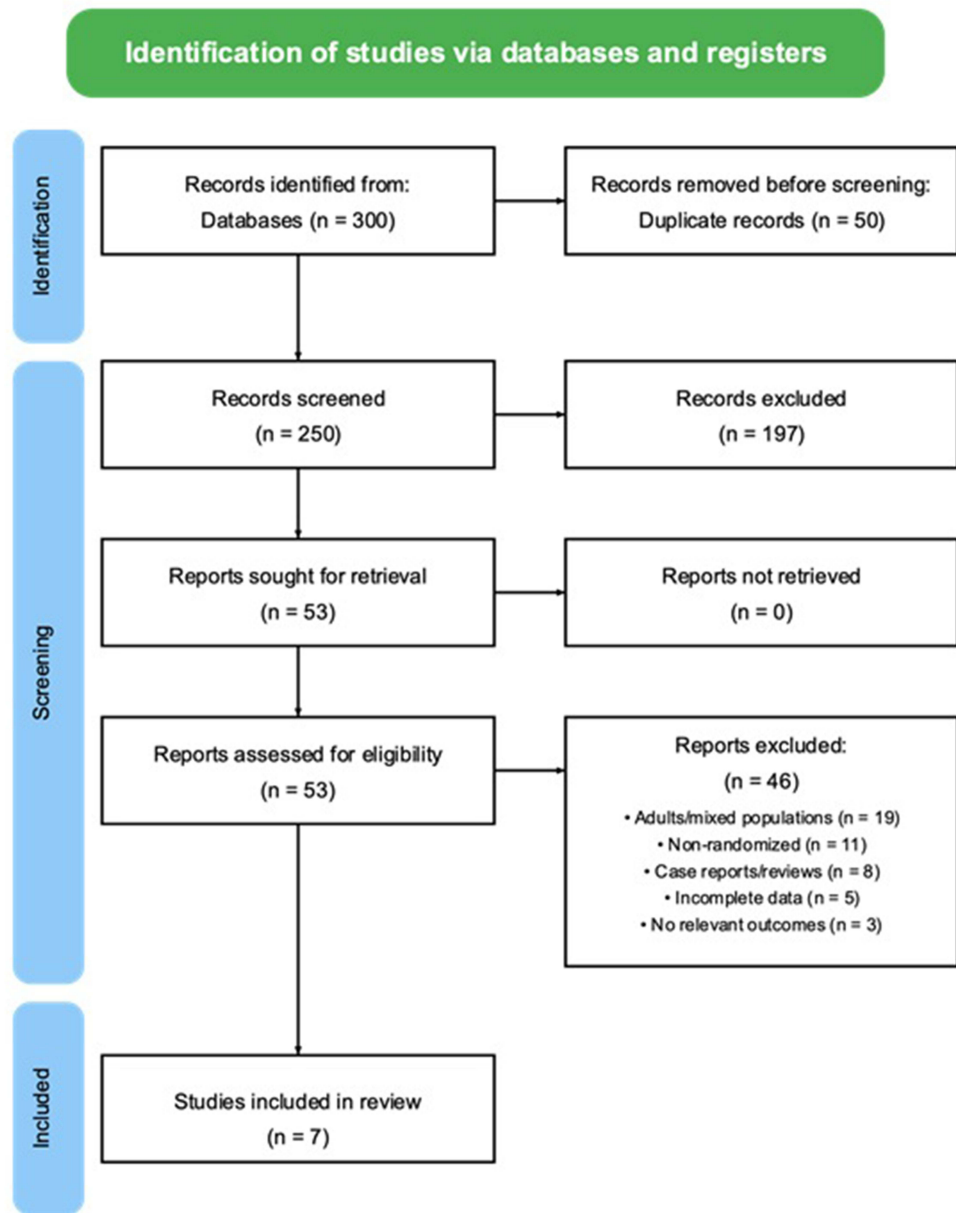


Figure 1 PRISMA flow diagram illustrating study selection process.

Study Characteristics

The seven included RCTs investigated the efficacy and safety of SLIT and/or SCIT in pediatric populations (age range generally 3–17 years) with AR, often associated with asthma. Study durations ranged from one year^{16–18,21} to three years.^{15,19,20} Allergens studied included grass pollen,^{15,21} house dust mites (HDM),^{16–19} and cat allergens,²¹ with some studies including polysensitized patients.¹⁸ Outcome measures varied but commonly included symptom scores (nasal, ocular, asthma), medication scores, visual analog scale (VAS), SPT reactivity, provocation tests, and immunological markers. Most studies included male participants more frequently than females. Baseline characteristics (disease duration, severity, Immunoglobulin E (IgE) levels, SPT results) were generally comparable between treatment groups within individual studies. Detailed characteristics are summarized in [Tables 1](#) and [2](#).



Figure 2 Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

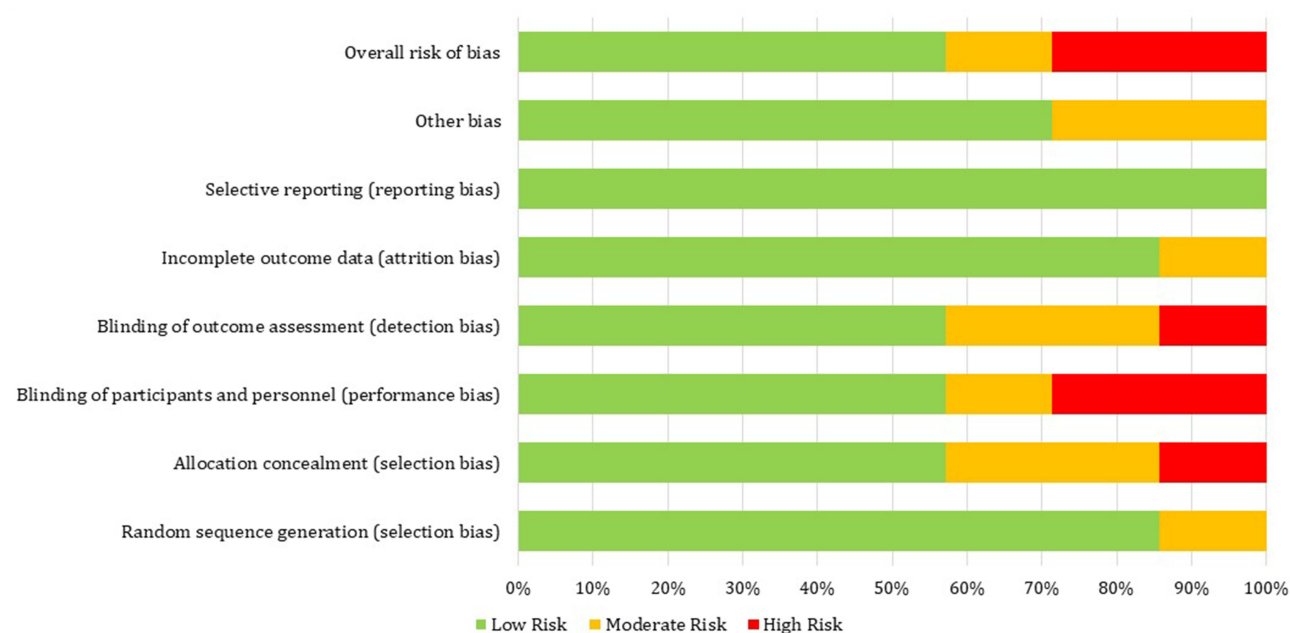


Figure 3 Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Efficacy Outcomes

Symptom Scores

Several studies reported on various symptom scores. Compared to placebo or control, SLIT significantly reduced combined symptom-medication scores (SMS), eye symptoms, and nasal symptoms after 3 years in one study,¹⁵ and improved SMS over 3 years in another.²⁰ SCIT significantly reduced rhinitis and asthma symptom scores compared to placebo after 1 year in one trial,¹⁶ although SLIT did not reach significance vs placebo in that study (interpret with caution due to RoB concerns). SCIT also reduced nasal allergen challenge responses (Total Nasal Symptom Score, TNSS).²¹ When comparing SLIT versus SCIT, comparable significant reductions in Total Rhinitis Symptom Score (TRSS) and Total Asthma Symptom Score (TASS) were found in one study,¹⁷ and comparable TNSS improvements were

Table 1 Characteristics of Included Studies

Study (Year, Country)	Study Design & Phase	Protocol NCT#	Total Patients	Participants per Arm (SLIT/SCIT/Placebo)	AR Diagnosis	Inclusion Criteria	AIT Modality	AIT Protocol	Main Outcomes
Rolinck-Werninghaus et al, 2004, Germany ¹⁵	RCT, double-blind, placebo-controlled	Not specified	97	SLIT group: 38 children Placebo group: 37 children	Seasonal allergic rhinoconjunctivitis (SAR) to grass pollen	Children with SAR to grass pollen	SLIT	Initial increasing doses (4 wks), then maintenance 3x/week (32 months). Placebo: Pangramin solution without allergen.	Changes in pollen count adjusted symptom and medication scores; Safety (adverse events).
Eifan et al, 2010, Turkey ¹⁷	RCT, open label	Not specified	50	SLIT: 16/SCIT: 16/ Placebo: 16	HDM-related asthma and rhinitis	Children 5–10 yrs, mild persistent asthma/rhinitis (GINA), mono-sensitized to HDM, positive SPT & sIgE ≥ 0.35 IU/mL, on steroids ≥ 2 yrs with no symptom reduction	SLIT & SCIT	SLIT: 1-mo induction, then maintenance 5 drops 3x/week. SCIT: 16-wk induction (weekly), then monthly maintenance.	Symptom/medication scores (upper/lower airways), SPT reactivity, new sensitizations, methacholine BHR, nasal provocation, immunological parameters (IgE, cytokines).
Yukselen et al, 2012, Turkey ¹⁶	RCT, double-dummy, placebo-controlled	Not specified	30	SCIT group: 10 children SLIT group: 10 children Placebo group: 10 children	Rhinitis and asthma caused by house dust mites	Not specified (children with rhinitis/asthma)	SLIT & SCIT	1 year treatment duration (details not specified).	Symptom/medication scores (rhinitis/asthma), HDM exposure level, lab parameters (IgE, IgG, cytokines).
Corren et al, 2022, USA ²¹	RCT, double-blind, placebo-controlled	UM1AI109565	121	1:1:1:1 Cat-specific SCIT plus tezepelumab SCIT alone Tezepelumab alone Placebo	Allergic rhinitis (seasonal to grass pollen)	History of SAR to grass pollen $\pm$ mild/moderate asthma; positive SPT & detectable sIgE to 5-grass pollen extract.	SCIT ($\pm$ Tezepelumab)	SCIT or placebo combined with tezepelumab or placebo for 1 year.	Change in total nasal symptom score (TNSS) AUC post-NAC; changes in cytokine/antibody levels.
Karakoc-Aydiner et al, 2015, Turkey ¹⁹	RCT, 3-year	Not specified	48 (31 completed)	SCIT: 12 patients SLIT: 9 patients Control group: 10 patients	HDM-induced asthma and rhinitis	Children with ≥ 1 yr history of HDM-induced asthma/rhinitis, documented HDM sensitization.	SLIT & SCIT	3 years treatment duration (details not specified).	Symptom/medication scores, VAS, lung function, BHR (methacholine), nasal provocation, SPT reactivity, IgE, IgG4, cytokine production.
Marogna et al, 2008, Italy ²⁰	RCT, open label	Not specified	216 (144 SLIT + drugs, 72 drugs only)	SLIT + drugs: 144/ Drugs only: 72	Rhinitis $\pm$ intermittent asthma	Children 5–17 yrs, rhinitis $\pm$ intermittent asthma ≥ 2 yrs, confirmed allergy (mites, grasses, trees, weeds).	SLIT (+ Drugs vs Drugs only)	Not specified in detail.	Changes in symptom plus medication score (SMS) over 3 years.
Wang et al, 2017, China ¹⁸	RCT	Not specified	68	SLIT: 39/SCIT: 39	Allergic rhinitis (HDM focus)	Not specified (children with AR, HDM allergy).	SLIT & SCIT	SLIT: Standardized step-up Der f drops. SCIT: Multi-allergen injections based on SPT/sIgE/symptoms, concentration increase, frequency decrease based on efficacy.	Improvement in AR symptoms, TNSS, TMS, serum IL-4 level.

Abbreviations: AIT, Allergen Immunotherapy; AR, Allergic Rhinitis; AUC, Area Under the Curve; BHR, Bronchial Hyperresponsiveness; Dx, Diagnosis; GINA, Global Initiative for Asthma; HDM, House Dust Mite; Ig, Immunoglobulin; IL, Interleukin; mo, month; NAC, Nasal Allergen Challenge; NCT, National Clinical Trial; PBMC, Peripheral Blood Mononuclear Cell; RCT, Randomized Controlled Trial; RoB, Risk of Bias; SAR, Seasonal Allergic Rhinoconjunctivitis; SCIT, Subcutaneous Immunotherapy; SLIT, Sublingual Immunotherapy; SMS, Symptom-Medication Score; SPT, Skin Prick Test; TASS, Total Asthma Symptom Score; TMS, Total Medication Score; TNSS, Total Nasal Symptom Score; TRSS, Total Rhinitis Symptom Score; VAS, Visual Analog Scale; wk, week; yr, year.

Table 2 Baseline Characteristics of Participants

Study	Total Patients	Age (Years)	Gender (M/F)	Disease Duration	Severity/Other Characteristics	IgE Levels (kU/L or IU/mL)	Lung Function	SPT Results (mm)
Rolnick-Werninghaus et al 2004 ¹⁵	97	3-14 (detailed breakdown provided in source)	65/32	Pre-study season scores provided	Atopic dermatitis: 17.5%	Total: Geo mean 264; Specific (grass): Geo mean 36.1	Not reported	Median threshold dose (HEP): 2.41
Eifan et al 2010 ¹⁷	50	Mean: 7.1 (Range: 5–10)	22/28	Mean: 27.8 months (Range: 12–48)	Mild persistent asthma/rhinitis (GINA); Mono-sensitized HDM; On steroids $\geq$ 2 yrs	D. pteronyssinus specific: Mean 67.4 (Range: 2–100)	Methacholine PC20 provided	D. pteronyssinus: Mean 8.8
Yukselen et al 2012 ¹⁶	30	Mean: 10.2 (SD: 3.0)	17/13	Rhinitis: Median 66 mo (Range: 36–144); Asthma: Median 48 mo (Range: 12–120)	Not specified	Not specified	Not specified	Not specified
Corren et al 2022 ²¹	121	See source Table I	See source Table I	Not specified	History of SAR (grass) $\pm$ mild/mod asthma	Not reported	FEV1/FVC measured	Cat allergen: Mean wheal 9.1
Karakoc-Aydiner et al 2010/2015 ¹⁹	48	Mean: 10.3	16/15 (for 31 completed)	Median: 28.5 months (IQR: 24–36)	$\geq$ 1 yr history HDM-induced asthma/rhinitis	Not reported	FEV1: Mean 97.8% predicted	Not reported
Marogna et al 2008 ²⁰	216	SLIT+drugs: Mean 10.7; Drugs only: Mean 10	SLIT+drugs: 104/40; Drugs only: 43/29	Not specified	Rhinitis + intermittent asthma: ~60%; Rhinitis only: ~40%	Not specified	Positive methacholine challenge: ~57%	Not specified
Wang et al 2017 ¹⁸	68	Mean: 9.5 (SD: 2.5)	33/35	Not specified	Polysensitized (all HDM + others)	IL-4 (ng/L): 57.8	Not reported	Antigen types provided

Abbreviations: FEV1, Forced Expiratory Volume in 1 second; FVC, Forced Vital Capacity; Geo mean, Geometric mean; GINA, Global Initiative for Asthma; HDM, House Dust Mite; HEP, Histamine Equivalent Prick; Ig, Immunoglobulin; IQR, Interquartile Range; mo, month; mod, moderate; PC20, Provocative Concentration causing 20% fall in FEV1; RCT, Randomized Controlled Trial; SAR, Seasonal Allergic Rhinoconjunctivitis; SD, Standard Deviation; SLIT, Sublingual Immunotherapy; SPT, Skin Prick Test.

seen in another.¹⁸ However, one study reported a significantly greater reduction in asthma symptoms with SCIT versus SLIT,¹⁶ and another found significant improvement from baseline TRSS only with SCIT at year 3.¹⁹

Medication Scores (TMS)

Reductions in medication use were observed with both modalities. SLIT significantly reduced medication scores (TMS) compared to placebo.¹⁵ SCIT also significantly reduced medication scores for rhinitis and asthma compared to placebo in one study, whereas SLIT did not reach significance vs placebo in that trial.¹⁶ Studies directly comparing the two routes generally found significant and comparable reductions in TMS for both SLIT and SCIT compared to control/baseline.^{17–19}

Visual Analog Scale (VAS)

Three studies utilized VAS to assess symptom severity.^{16,17,19} Significant reductions in VAS were observed within both SLIT and SCIT groups compared to baseline.^{17,19} When compared to controls, SCIT significantly reduced VAS scores,^{16,19} while the reduction with SLIT versus placebo was not statistically significant in one study.¹⁶

Skin Prick Test (SPT) Reactivity

Studies assessing SPT reactivity consistently found significant reductions in wheal diameter or skin reactivity to relevant allergens (primarily HDM) following treatment with both SLIT and SCIT compared to baseline.^{16,17,19} No significant differences between the effects of SLIT and SCIT on SPT reactivity were highlighted in the studies reporting this comparison.^{16,17}

Nasal and Bronchial Provocation Tests

Nasal sensitivity, assessed via provocation tests, was reduced by both treatments. Two studies found that both SLIT and SCIT significantly increased the nasal provocation threshold dose for HDM, with no significant difference observed between the two AIT groups.^{16,17} One study reported that SLIT significantly reduced bronchial hyperresponsiveness, measured by methacholine challenge, compared to controls after 3 years.²⁰

Prevention of New Sensitizations and Asthma Development

Data on long-term preventative effects were limited but suggested potential benefits. Two studies reported no new allergen sensitizations in SLIT, SCIT, or control groups during their 1-year follow-up.^{16,17} One 3-year study found that children receiving SLIT had significantly lower odds of developing mild persistent asthma compared to the control group receiving only drug therapy.²⁰

Immunological Markers

Changes in immunological markers were reported in several studies. Significant decreases in serum-specific HDM-IgE levels were observed with both SCIT and SLIT, with no significant difference between groups.^{16,17} Similarly, comparable significant decreases in peripheral blood mononuclear cell (PBMC) Interleukin-4 (IL-4) levels were found after 1 year of either SLIT or SCIT.¹⁸ Increases in specific IgG4 levels were noted with both treatments, although potentially more pronounced with SCIT, based on one included study¹⁹ and external literature.¹²

Safety and Adherence

Adverse Events

The reviewed literature indicates distinct safety profiles. SLIT was primarily associated with local adverse events (eg, oral itching, gastrointestinal discomfort), generally reported as mild and transient.¹⁰ SCIT was associated with both local injection site reactions and a recognized higher risk of systemic adverse events, some potentially severe.¹⁰

Adherence/Dropout Rates

Reporting of adherence and dropout rates was limited in the source material for the included studies. One study reported that 31 out of 48 participants completed the 3-year trial (overall completion rate ~64.6%).¹⁹ Dropout rates for the other included RCTs^{15–18,20,21} were not specified in the reviewed source text.

Discussion

This systematic review consolidates evidence from seven RCTs on the use of SLIT and SCIT for pediatric allergic rhinitis, confirming the efficacy of both modalities compared to control interventions.^{15–17,19} The central clinical question, however, revolves around their relative merits. Synthesizing the available pediatric data reveals a nuanced picture: while SLIT and SCIT often demonstrate comparable effectiveness in reducing overall symptom and medication scores,^{17–19} potentially differing safety profiles, adherence patterns, and effects on specific outcomes necessitate careful consideration in clinical practice. Interpretation of comparative efficacy is further complicated by pronounced heterogeneity among the included trials. Allergen sources varied widely (house-dust mite, grass, mixed seasonal allergens), dosing regimens ranged from daily drops to weekly or monthly injections, and treatment durations spanned one to three years. Outcome measures were likewise inconsistent, encompassing different symptom–medication score definitions, visual analog scales, and provocation tests. These variations reduce comparability across studies, contribute to the observed variability in results, and limit the ability to draw firm pooled estimates.

The finding of comparable efficacy across several studies^{17–19} aligns with some previous reviews encompassing broader populations or different methodologies.^{9,10} For instance, reductions in TMS and improvements in SPT reactivity appeared similar between SLIT and SCIT groups where directly compared.^{16–19} However, this review also highlights inconsistencies potentially driven by heterogeneity or study limitations. Yukselen et al¹⁶ reported a statistically significant advantage for SCIT over SLIT concerning asthma symptom reduction, and Karakoc-Aydiner et al¹⁹ noted significant improvement from baseline TRSS only with SCIT at 3 years. While these findings warrant attention, the RoB assessment urges caution in interpreting results from Yukselen et al¹⁶ due to potential blinding issues. Furthermore, the heterogeneity in allergen types (HDM vs pollen), AIT protocols (single vs multi-allergen, specific products), and outcome measures across the included studies significantly complicates direct comparisons and precludes a definitive conclusion on efficacy equivalence or superiority based solely on this dataset.

Perhaps the clearest distinction emerging from this review and broader literature¹⁰ lies in the safety profiles. SLIT's association primarily with mild, local adverse effects contrasts sharply with the recognized risk of systemic reactions, albeit infrequent, associated with SCIT.¹⁰ This difference has profound clinical implications: SLIT's favorable safety profile permits home administration, significantly increasing convenience and accessibility for families, whereas SCIT mandates administration in a clinical setting equipped to manage potential systemic reactions. This practical difference often becomes a deciding factor in shared decision-making, particularly for younger children or those with needle aversion.

Adherence represents another critical factor influencing real-world effectiveness. While clinician-administered SCIT might intuitively seem to ensure better adherence, the available data from the included RCTs are sparse. Only one study provided completion data,¹⁹ showing significant dropout over 3 years, though not broken down by treatment arm. Findings from external cohort data, however, suggest a different pattern; one study reported potentially superior adherence with SCIT (no dropouts) compared to SLIT (20.5% dropout),¹¹ highlighting a discrepancy that requires confirmation within well-designed comparative trials. The convenience of home-based SLIT must be weighed against the need for consistent daily commitment from the patient and family over several years.

Beyond immediate symptom control, AIT aims for long-term disease modification. This review includes evidence suggesting SLIT may play a role in preventing asthma development and reducing bronchial hyperresponsiveness in predisposed children,²⁰ a crucial potential benefit given the link between AR and asthma (the “allergic march”). While SCIT also possesses disease-modifying capabilities,³ the specific evidence for asthma prevention within this set of pediatric SLIT trials²⁰ is noteworthy. Furthermore, neither therapy appeared to induce new sensitizations within the study durations.^{16,17}

The differing safety and response profiles of SLIT and SCIT may reflect variations in their underlying immune effects, but current pediatric data remain limited. Both approaches promote immune tolerance, as shown by reductions in Th2-associated markers such as IL-4 and allergen-specific IgE,^{16–18} together with increases in blocking IgG4 antibodies. Small studies suggest SCIT may induce a stronger Th1 skew, whereas SLIT may favor regulatory T-cell responses,^{12,19} but these findings are inconsistent and not clearly linked to clinical outcomes. Larger head-to-head trials incorporating standardized immunologic endpoints are needed to clarify whether these mechanistic differences translate into meaningful differences in efficacy or durability of benefit.

The primary limitation is the small number of included studies, particularly the few that directly compare SLIT and SCIT head-to-head. Substantial clinical and methodological heterogeneity—spanning patient populations (age, comorbidities, sensitization patterns), interventions (allergen types, products, dosing protocols), comparators, and outcome measures—prevented meta-analysis or valid network meta-analysis and limits the generalizability of the findings. Methodological concerns, especially issues with blinding in some studies,^{15,16,20} further temper confidence in subjective outcomes. Reporting of important aspects such as adherence, quality of life, and cost-effectiveness was limited. Moreover, follow-up durations were generally confined to the active treatment period (1–3 years), providing little insight into long-term remission or post-discontinuation outcomes.

For clinicians managing pediatric AR, this review underscores that both SLIT and SCIT are viable, effective options. The choice requires careful individualization through shared decision-making with the family. Key discussion points should include the comparable efficacy for core AR symptoms versus potential SCIT advantages for specific outcomes (eg, possibly asthma), weighed against SLIT's superior safety profile and convenience versus SCIT's requirement for clinic visits but potentially better adherence in some settings. Patient age, severity, comorbidities (especially asthma), specific allergen sensitization, family lifestyle, and access to care are crucial factors.

Future research priorities should include larger, high-quality head-to-head RCTs comparing standardized, currently available SLIT (eg, tablets) and SCIT protocols in well-defined pediatric populations (stratified by age and presence/severity of asthma). These trials must incorporate validated quality-of-life instruments, robust adherence monitoring, cost-effectiveness analyses, and long-term follow-up (eg, 2–5 years post-treatment) to assess remission. Mechanistic studies embedded within these trials should investigate comparative longitudinal changes in key immunological markers (Tregs, Bregs, IgG4 subclasses, cytokine profiles) to elucidate differential pathways and identify potential biomarkers of response. Addressing the current evidence gaps is essential for optimizing AIT selection and outcomes for children with allergic rhinitis.

Conclusion

Current evidence—though limited and heterogeneous—indicates that both SLIT and SCIT reduce symptoms and medication use versus controls, and most head-to-head trials report similar efficacy, though isolated studies suggest potential advantages for SCIT in specific outcomes. SLIT demonstrates comparable efficacy to SCIT for many clinical outcomes and offers a more favorable safety profile with predominantly local side effects, potentially reducing the risk of asthma development and new sensitizations. SCIT may provide more pronounced or rapid symptom relief in some instances but carries a higher risk of systemic reactions and requires clinic-based administration. The choice between SLIT and SCIT should be individualized through shared decision-making, considering the specific allergen, disease severity, patient age, comorbidities, patient/family preferences, adherence potential, and healthcare setting resources. High-quality comparative research with long-term follow-up is needed to further refine treatment strategies.

Data Sharing Statement

Data sharing is not applicable to this article as no new datasets were generated or analyzed during the current study; all data were extracted from previously published studies cited herein.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no conflicts of interest.

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