Sublingual Immunotherapy in Children: A Paradigm Shift in Managing Atopic Diseases Compared to Regular Therapy

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Abstract

Background:. Atopic diseases such as allergic rhinitis, asthma, and atopic dermatitis represent the most prevalent chronic disorders in children, significantly impairing quality of life and imposing a growing public health burden. Conventional therapy—including antihistamines, corticosteroids, and leukotriene receptor antagonists—offers symptomatic relief but fails to address the underlying immunologic dysfunction or modify the disease course. Allergen-specific immunotherapy (AIT) represents the only disease-modifying approach for allergic diseases. Sublingual immunotherapy (SLIT), a modern, non-invasive form of AIT, has gained increasing attention for its safety, convenience, and efficacy in pediatric populations.

Aim: This review aims to evaluate the comparative efficacy, safety, and long-term outcomes of sublingual immunotherapy versus conventional pharmacotherapy across different pediatric atopic conditions. It explores immunological mechanisms, clinical evidence, and practical considerations that make SLIT an emerging cornerstone in the management of allergic diseases in children.

Conclusion: Sublingual immunotherapy demonstrates significant advantages over standard pharmacologic treatments, including long-term remission, prevention of new sensitizations, and potential disease modification. Unlike conventional medications that temporarily suppress symptoms, SLIT acts by inducing immune tolerance through mucosal immunoregulation involving T regulatory cells, IL-10, and IgG4 production. Numerous pediatric trials and meta-analyses confirm its efficacy and safety in allergic rhinitis and asthma, with emerging evidence for benefits in atopic dermatitis and food allergy. Moreover, SLIT's favorable safety profile and ease of administration improve adherence compared with subcutaneous immunotherapy. While current data support SLIT as a transformative option in pediatric allergy management, limitations persist, including variability in dosing protocols, lack of biomarkers, and heterogeneous study designs. Future research should focus on identifying immunologic predictors of response, optimizing treatment regimens, and expanding evidence to younger age groups. Collectively, SLIT represents a paradigm shift from symptomatic control toward disease modification in pediatric allergy care, marking a pivotal advancement in preventive and personalized pediatric medicine.

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Keywords: *Sublingual Immunotherapy, Atopic Diseases, Regular Therapy*

Introduction

Atopic diseases, including allergic rhinitis, asthma, and atopic dermatitis, are among the most common chronic conditions in childhood, affecting up to 30–40% of the pediatric population worldwide. Their prevalence continues to rise, paralleling increasing urbanization and environmental exposure to allergens and pollutants [1]. These disorders impose a significant burden on children and their families, not only through chronic symptoms such as nasal congestion, wheezing, and pruritus, but also through school absenteeism, sleep disturbance, and impaired psychosocial development [2]. Despite decades of therapeutic progress, current standard pharmacologic interventions—comprising antihistamines, intranasal or inhaled corticosteroids, and leukotriene receptor antagonists—primarily target symptom relief without addressing the underlying immunologic mechanisms driving allergic inflammation [3].

The concept of allergen-specific immunotherapy (AIT) revolutionized allergy treatment by introducing a disease-modifying approach that acts on the cause of allergic sensitization rather than its symptoms. Subcutaneous immunotherapy (SCIT) was historically considered the gold standard for AIT but posed challenges in the pediatric population, including pain, the need for repeated injections, and risk of systemic reactions [4]. Consequently, sublingual immunotherapy (SLIT) has emerged as a promising alternative, offering improved safety, convenience, and patient adherence. Administered as allergen extracts placed under the tongue, SLIT induces mucosal immune tolerance through complex immunoregulatory mechanisms that modulate the Th2-dominant allergic response [5].

Although numerous clinical trials have demonstrated the efficacy of SLIT in reducing symptoms and medication use in children with allergic rhinitis and asthma, significant knowledge gaps remain regarding its long-term disease-modifying effects, optimal dosing regimens, and its comparative performance against standard pharmacologic therapies [6]. Moreover, evidence for SLIT's role in atopic dermatitis and food allergy is still emerging, warranting critical evaluation.

Aim:

This review aims to critically compare sublingual immunotherapy with conventional pharmacotherapy in the management of pediatric atopic diseases. It seeks to elucidate the immunological mechanisms, clinical outcomes, safety profile, and practical advantages of SLIT, highlighting its potential to shift pediatric allergy management from symptomatic control to immune tolerance induction and long-term remission [7].

Immunopathogenesis of Atopic Diseases in Children

Atopic diseases in children arise from a complex interaction between genetic predisposition and environmental exposures that skew the developing immune system toward a T-helper 2 (Th2)–dominant phenotype [8]. During early life, exposure to allergens such as house dust mites, pollen, or food proteins triggers antigen presentation by dendritic cells in predisposed individuals, leading to differentiation of naïve T cells into Th2 cells. These Th2 cells produce cytokines—interleukin (IL)-4, IL-5, and IL-13—that promote immunoglobulin E (IgE) synthesis by B cells and recruitment of eosinophils and mast cells [9]. The result is the characteristic allergic inflammation that underlies rhinitis, asthma, and dermatitis in children.

Mucosal barrier dysfunction also plays a critical role in pediatric atopy. Impaired epithelial tight junctions increase allergen penetration and sensitize immune cells through epithelial cytokines such as thymic stromal lymphopoietin (TSLP), IL-25, and IL-33 [10]. This process enhances allergic inflammation and perpetuates the cycle of sensitization and response. Early childhood is a particularly vulnerable window during which immune tolerance mechanisms are still developing, making immunomodulatory therapies such as sublingual immunotherapy (SLIT) especially relevant for long-term intervention [11].

In contrast, regular pharmacologic therapies, including antihistamines, corticosteroids, and leukotriene receptor antagonists, provide transient suppression of these inflammatory pathways but do not restore immune balance or prevent disease progression [12]. This limitation underpins the growing interest in immunotherapy-based approaches capable of modulating underlying immunologic mechanisms rather than merely controlling symptoms. SLIT acts on mucosal immunity—an essential component of early-life immune development—offering a more physiologic and preventive treatment paradigm [13].

Mechanisms of Sublingual Immunotherapy (SLIT)

Sublingual immunotherapy (SLIT) functions through complex immunologic mechanisms that aim to restore immune tolerance toward specific allergens rather than simply alleviating symptoms. Upon administration, allergen extracts placed under the tongue are absorbed by the oral mucosa, where they interact with antigen-presenting cells such as Langerhans cells and dendritic cells [14]. These cells process allergens and migrate to regional lymph nodes, promoting the induction of regulatory T cells (Tregs) that secrete interleukin (IL)-10 and transforming growth factor-β (TGF-β). These cytokines play a critical role in suppressing Th2-mediated allergic inflammation and enhancing immune tolerance [15].

SLIT leads to a gradual immunologic shift from an allergen-specific Th2 response to a more balanced Th1/Treg profile. This shift results in decreased production of IL-4, IL-5, and IL-13, alongside increased interferon-γ (IFN-γ) and IL-10 expression [16]. Clinically, this translates into reduced IgE synthesis and increased allergen-specific immunoglobulin G4 (IgG4) levels, which act as "blocking antibodies" that inhibit allergen–IgE binding and subsequent mast cell activation [17]. Furthermore, SLIT enhances the function of mucosal dendritic cells and promotes oral tolerance, a mechanism naturally involved in preventing food hypersensitivity and maintaining homeostasis in the oropharyngeal mucosa [18].

In contrast to regular pharmacotherapy—such as antihistamines and corticosteroids, which temporarily suppress histamine release or inflammation—SLIT modifies the underlying immune response. This disease-modifying property allows it to produce sustained benefits even after treatment cessation, a characteristic not achievable with conventional drugs [19]. Additionally, SLIT exhibits local mucosal immune activation without significant systemic exposure, contributing to its superior safety profile, especially in pediatric patients [20]. Over time, these immunologic changes reduce clinical reactivity to allergens, prevent the development of new sensitizations, and potentially alter the natural course of allergic disease, making SLIT a pivotal strategy for long-term management in children [21].

SLIT versus Regular Therapy in Allergic Rhinitis

Allergic rhinitis (AR) is one of the earliest and most prevalent manifestations of atopy in children, often serving as a precursor to asthma and other allergic conditions [22]. Conventional pharmacologic management of pediatric AR typically includes oral or intranasal antihistamines, corticosteroids, and leukotriene receptor antagonists, which provide prompt symptom relief by suppressing histamine release and reducing mucosal inflammation [23]. However, these agents do not modify the underlying allergic process, and symptoms frequently recur after treatment discontinuation. This limitation has fueled growing interest in sublingual immunotherapy (SLIT) as a disease-modifying approach capable of inducing long-term immune tolerance.

Clinical evidence strongly supports the efficacy of SLIT in reducing symptoms and medication use in children with allergic rhinitis. Randomized controlled trials (RCTs) and meta-analyses have consistently shown significant reductions in nasal and ocular symptoms compared with placebo or regular therapy [24]. A multicenter pediatric study using standardized grass pollen SLIT tablets demonstrated up to a 30–40% reduction in combined symptom-medication scores after three years of treatment, with benefits persisting for at least two years post-therapy [25]. This sustained efficacy contrasts with the transient control provided by antihistamines or corticosteroids, highlighting SLIT's potential to modify disease progression.

Beyond symptomatic control, SLIT has been shown to prevent the onset of new sensitizations and reduce the risk of developing asthma in children with allergic rhinitis [26]. This preventive potential is attributed to its ability to reprogram immune tolerance at the mucosal level, a mechanism absent in conventional drug therapy. Moreover, SLIT's noninvasive and home-based administration increases adherence compared with subcutaneous immunotherapy (SCIT), while maintaining a favorable safety profile [27]. Consequently, SLIT is increasingly being recognized not merely as an alternative but as a superior long-term strategy for managing pediatric allergic rhinitis, representing a shift from symptomatic suppression to immune modulation [28].

SLIT in Pediatric Asthma

Asthma frequently coexists with allergic rhinitis in children, with shared type 2 inflammatory pathways suggesting that allergen immunotherapy could improve lower-airway outcomes in sensitized patients. In pediatric trials, SLIT has demonstrated reductions in asthma symptom scores and rescue medication use compared with placebo or regular therapy, with the greatest benefits observed in children who also received SLIT for comorbid seasonal rhinitis. These effects are biologically plausible given SLIT's induction of Tregs and allergen-blocking IgG4, which attenuate downstream eosinophilic inflammation and airway hyperresponsiveness, outcomes not achieved by antihistamines and only transiently

suppressed by inhaled corticosteroids (ICS). Collectively, this positions SLIT as a disease-modifying adjunct to regular therapy in eligible, sensitized children. [29–31]

Evidence for **ICS-sparing** effects is growing. Randomized and pragmatic pediatric studies report that children receiving SLIT can maintain equivalent asthma control with lower daily ICS doses than those on regular therapy alone, alongside fewer exacerbations requiring oral steroids. Meta-analyses pooling pediatric-dominant cohorts show modest but clinically meaningful improvements in peak expiratory flow and symptom-free days, particularly in monosensitized children and when treatment duration reaches ≥3 years. Importantly, these benefits often persist for 1–2 seasons after stopping SLIT, contrasting with the rapid loss of control typically seen when regular pharmacotherapy is withdrawn. [32–34]

Safety and practicality are central in pediatrics. SLIT is generally well tolerated in asthmatic children with controlled disease, with adverse events most commonly limited to transient oral itching or mild throat irritation; systemic reactions are rare compared with subcutaneous immunotherapy. Current pediatric practice integrates SLIT as an add-on to guideline-based regular therapy in sensitized children whose asthma is at least partially controlled, avoiding initiation during acute exacerbations and titrating doses under specialist supervision. This approach leverages SLIT's long-term immune benefits while preserving the immediate symptom control of regular therapy, providing a balanced, step-up strategy tailored to childhood asthma. [35–36]

SLIT in Atopic Dermatitis and Food Allergy

Atopic dermatitis (AD) represents a chronic inflammatory skin disorder frequently associated with respiratory allergies, suggesting a shared immunopathogenic mechanism across the "atopic march." Although regular therapy for AD—including emollients, topical corticosteroids, and calcineurin inhibitors—targets skin inflammation and barrier repair, it does not address allergen sensitization that may perpetuate chronic disease. Recent studies have examined SLIT as an adjunctive approach to modify allergic responses contributing to AD exacerbations, particularly in children sensitized to house dust mites (HDM). Clinical trials have reported moderate but significant improvements in SCORAD (Scoring Atopic Dermatitis) and EASI (Eczema Area and Severity Index) scores following 12 to 18 months of HDM-SLIT compared to regular therapy alone, indicating a potential disease-modifying effect [37–39].

The immunologic rationale for SLIT in AD mirrors that observed in respiratory atopy—restoration of Treg function, downregulation of Th2 cytokines, and decreased allergen-specific IgE. However, therapeutic responses are heterogeneous and appear most pronounced in children with clear allergen sensitization rather than intrinsic (non-IgE-mediated) eczema. Regular topical and systemic therapies remain indispensable for acute symptom control, but combining them with SLIT may provide enhanced long-term remission and reduced corticosteroid dependence [40–41]. Nevertheless, large-scale, placebo-controlled pediatric trials are still limited, and standardization of allergen extracts and dosing regimens remains a challenge.

Food allergy (FA) represents another area of growing research interest for SLIT. Unlike regular management—which relies on strict allergen avoidance and emergency epinephrine use—SLIT offers a proactive immunomodulatory approach aimed at desensitization. Pediatric studies on peanut, milk, and hazelnut SLIT have demonstrated gradual increases in tolerated doses, reduction in allergic reactivity, and improved quality of life in sensitized children [42]. Compared with oral immunotherapy (OIT), SLIT tends to induce fewer systemic reactions, though at lower efficacy levels, making it a potentially safer first-line immunotherapy for younger patients. Continued investigation into optimal dosing, maintenance duration, and long-term tolerance is warranted to integrate SLIT effectively into routine pediatric allergy care [43–44].

Safety Profile and Adverse Events

Overall, SLIT has a favorable safety profile in children, characterized predominantly by local, self-limited reactions (oral pruritus, mild throat irritation, sublingual swelling) during the first weeks of treatment. Large position papers and meta-analyses report very low rates of systemic reactions and anaphylaxis with

SLIT—substantially lower than with subcutaneous immunotherapy (SCIT)—and comparable or better overall tolerability than many agents used as regular therapy (e.g., intranasal steroids, antihistamines) when considering long-term use. The benign nature of typical SLIT reactions supports home maintenance dosing after initial supervised administration. [45–48]

Initiation and monitoring practices in pediatrics prioritize safety without sacrificing convenience. Most guidelines recommend observing the first dose in a clinical setting, providing families with a clear action plan for local symptoms, and advising temporary dose delays for oral mucosal inflammation (stomatitis, mouth ulcers), febrile illness, or post-dental procedures. SLIT should not be initiated during uncontrolled asthma or active wheezing; exacerbations warrant stepping up regular therapy and stabilizing control before resuming SLIT. Caution is advised with beta-blockers (blunted response to epinephrine) and, in some protocols, ACE inhibitors; shared decision-making is essential if these drugs are necessary. Many centers supply an epinephrine autoinjector for families, even though severe systemic reactions to SLIT are rare, to ensure preparedness and confidence. [46–47]

Special situations include eosinophilic esophagitis (EoE) risk—well documented with oral immunotherapy (OIT) and exceedingly uncommon with SLIT, yet vigilance is prudent if persistent dysphagia or chest pain emerges. For children with atopic dermatitis or food allergy, SLIT's safety advantage over alternatives (e.g., SCIT for aeroallergens, OIT for foods) often favors its selection when efficacy is acceptable. Real-world pediatric registries corroborate high adherence and low discontinuation due to adverse events, particularly when families receive early counseling on expected local reactions and stepwise dose-adjustment strategies. Collectively, these data position SLIT as a safe, family-friendly, long-term modality that complements regular therapy while minimizing systemic risk. [35, 45, 49–51]

Age-Related Considerations and Practical Implementation

Initiation of sublingual immunotherapy (SLIT) in children typically aligns with developmental readiness for daily, supervised dosing and the ability to report local symptoms reliably. Many centers begin around early school age, although younger candidates may be considered when sensitization is clear and caregivers can ensure adherence and safety monitoring. Decisions should weigh disease burden, pattern of sensitization, comorbid asthma control, and family capacity for home administration, integrating SLIT as an adjunct to regular therapy rather than a replacement during initiation. Shared decision-making with caregivers is essential to set expectations for the gradual onset of benefit and the need for multi-year treatment. [46,50,52]

Formulation and dosing choices are driven by the target allergen, regulatory availability, and family preference. Standardized tablets (e.g., for grasses or house dust mite) offer fixed dosing and trial-based schedules, while liquid extracts allow individualized titration but require meticulous instruction. Most protocols use a brief dose-escalation phase followed by once-daily maintenance, delivered either continuously (perennial allergens) or pre/co-seasonally (pollens). Clinic-supervised first dosing, clear instructions for handling missed doses or intercurrent illness, and written plans for local reactions improve safety and confidence at home. [45–47,53–55]

Practical adherence strategies include structured caregiver education, demonstration of sublingual placement and hold time, and simple routines (same time each morning before toothbrushing or breakfast). Digital reminders, treatment diaries, and periodic pharmacist or nurse check-ins can reduce nonadherence, which commonly clusters in the first 8–12 weeks. Aligning SLIT follow-ups with routine asthma or rhinitis reviews streamlines care, while reinforcing that regular therapy (e.g., intranasal steroids, as-needed antihistamines, controller inhalers for asthma) should be continued initially and tapered only after sustained clinical response. Schools and caregivers should receive written action plans and medication authorization for rescue therapies. [27,48,56–58]

Clinic-to-home workflows should include screening for contraindications (uncontrolled asthma, active oral inflammation), medication review (beta-blockers; consider ACE inhibitor context), and readiness for emergencies, including provision and training in epinephrine autoinjector use despite the rarity of

systemic reactions with SLIT. Temporary dose interruption is prudent during febrile illnesses, active wheeze, significant dental procedures, or persistent oral ulcers, with reassessment before resumption. Objective monitoring (symptom-medication scores, ACT/cACT where applicable) every 3–6 months supports data-driven adjustments and informs stepwise reductions in regular therapy when control is stable. [46–47,50,57]

Long-Term Benefits and Disease Modification

One of the most compelling advantages of sublingual immunotherapy (SLIT) over regular therapy in pediatric atopy lies in its potential to alter the natural course of allergic disease. Unlike antihistamines or corticosteroids that control symptoms only during active use, SLIT induces long-lasting immunologic tolerance that persists beyond treatment cessation. Long-term follow-up studies have demonstrated sustained reductions in symptom-medication scores several years after discontinuing SLIT, confirming its disease-modifying capability. In contrast, regular pharmacotherapy must be maintained continuously to prevent relapse, with no evidence of durable immune remodeling. [19,25,59–60]

The preventive potential of SLIT has also been explored in the context of the "atopic march," where early allergic rhinitis often precedes asthma or additional sensitizations. Pediatric cohort studies indicate that SLIT can significantly lower the risk of developing new allergen sensitivities and reduce the incidence of asthma onset among children initially treated for rhinitis. This outcome reflects SLIT's modulation of the mucosal immune environment—specifically, sustained activation of regulatory T cells, increased IL-10 production, and generation of allergen-specific IgG4 antibodies. These immune changes persist for years after therapy completion, marking a fundamental shift from symptomatic suppression toward long-term immune regulation. [26,32,61–62]

From a mechanistic standpoint, disease modification through SLIT involves progressive dampening of allergen-driven Th2 inflammation and restoration of homeostatic mucosal barrier function. The persistence of these immunologic shifts supports the concept of early intervention: initiating SLIT in younger children may confer greater and more durable tolerance, particularly in monosensitized individuals. Early immune training during critical windows of immune plasticity could mitigate progression to multi-allergen sensitization and chronic asthma, outcomes unattainable with regular therapy alone. Current pediatric guidelines increasingly recognize these findings and advocate SLIT not merely as a symptom-relief option but as a preventive and disease-modifying intervention in childhood allergy care. [63–64]

Future Directions in Pediatric SLIT Research

Research in sublingual immunotherapy (SLIT) for children continues to evolve toward precision, safety, and personalization. One major direction involves identifying reliable **biomarkers of response**, such as changes in allergen-specific IgE/IgG4 ratios, cytokine signatures (IL-10, TGF-β), or T-cell transcriptomic patterns, which could help clinicians predict responders early in therapy. Presently, treatment outcomes vary substantially across individuals, reflecting differences in allergen exposure, genetic background, and mucosal immune maturity. The development of standardized predictive markers could enable tailored regimens—optimizing dose, duration, and allergen selection—thus improving efficacy and cost-effectiveness relative to uniform protocols currently applied. [65–67]

Novel formulations and delivery strategies represent another promising frontier. Advances in recombinant allergen technology, peptide-based vaccines, and adjuvanted SLIT extracts aim to enhance immunogenicity while minimizing adverse effects. Nanoparticle carriers and mucoadhesive gels are under investigation to improve antigen absorption and mucosal stability, which may reduce treatment duration and daily dosing burden. Such innovations, if validated in children, could increase adherence and broaden SLIT's applicability to early-life prevention, potentially intercepting the atopic march before clinical disease emerges. [68–70]

Digital health tools are also being integrated into pediatric SLIT management. Mobile applications, electronic diaries, and telemonitoring platforms support adherence tracking, adverse event reporting, and

real-time communication with clinicians. These systems allow for remote supervision of home-based therapy and data collection that can strengthen evidence in large-scale, real-world pediatric cohorts. In parallel, regulatory and research collaborations are exploring SLIT for **nontraditional indications**—such as mixed-allergen sensitization, early intervention in high-risk infants, and combination therapy with biologics—to extend its scope beyond current practice. Ultimately, the future of SLIT in pediatric allergy lies in precision immunotherapy: a paradigm that aligns mechanistic insight with individualized treatment to achieve sustained tolerance, disease prevention, and improved quality of life compared with regular therapy. [71–72]

Conclusion

Sublingual immunotherapy (SLIT) represents a major advancement in the management of pediatric atopic diseases, offering a shift from symptomatic relief toward genuine disease modification. Unlike regular therapy, which provides only transient control through anti-inflammatory or antihistaminic effects, SLIT acts on the underlying immunologic mechanisms responsible for allergic sensitization. By promoting regulatory T-cell activity, enhancing mucosal tolerance, and modulating allergen-specific antibody profiles, SLIT induces durable immune balance that can persist long after therapy cessation.

Clinical studies in children with allergic rhinitis, asthma, and, more recently, atopic dermatitis and food allergies, consistently demonstrate SLIT's capacity to reduce symptom severity, medication reliance, and new sensitizations. Its long-term benefits, combined with excellent safety and convenience, make it especially suited for pediatric populations where adherence and comfort are critical. The possibility of initiating therapy early in life adds a preventive dimension, potentially halting the atopic march and improving future respiratory outcomes.

Compared with regular pharmacologic approaches, SLIT achieves superior long-term control and improves quality of life without increasing systemic risk. Its home-based administration encourages family participation and empowers caregivers, reinforcing continuity of care beyond the clinical setting. Integration with guideline-based pharmacotherapy allows a smooth transition from symptom control to immune rehabilitation, supporting a comprehensive, individualized treatment framework for childhood allergy.

Future perspectives emphasize the refinement of SLIT through biomarkers, personalized dosing, and innovative formulations designed to enhance efficacy and adherence. With continued research and standardization, SLIT is poised to become a cornerstone of preventive pediatric allergy care. In essence, sublingual immunotherapy redefines therapeutic goals in childhood atopy—not merely to relieve symptoms but to reshape the immune trajectory of the developing child, offering lasting protection and a fundamentally improved quality of life.

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