

Sublingual Immunotherapy (SLIT) using the La Crosse Method™ Protocol

Introduction

Use of SLIT to treat allergies in the U.S. was first documented in the early 1900s with use growing in recent decades. Today, thousands of allergists, ENT allergists and physicians provide SLIT therapies to U.S. patients, with nearly 2000 trained in using the La Crosse Method Protocol. In Europe, SLIT has become a dominant treatment method.

How SLIT Works – Key Tenets of the La Crosse Method (LCM) Protocol

A primary concern regarding SLIT's use is dosing variability in the literature. The LCM addresses these and other concerns in the following tenets that are supported by scientific evidence.

1. Why Sublingual Administration

The area under the tongue is considered a privileged domain due to its dual properties: It is rich in T-cells and other antigen presenting cells that help induce tolerance, while poor in mast and other effector cells which can trigger reactions. The area also exhibits the highest permeability of any easily accessible mucosal surface – making it prime for delivering fast-acting medication and effective vaccines. Given the large number of dendritic cells in the mucosal area where foreign proteins are first introduced, the area plays a pivotal role in developing tolerance versus sensitization. Dendritic cells can also produce an unusually wide array of cytokines affecting cytotoxic and cellular immunity.²

2. Patient Specific Test-based Dosing

The LCM's incremental dosing is determined by blood, skin prick or intradermal dilution testing to define a tolerance level. Treatment tailored to each patient begins at the highest dilution that produced a near-negative skin test. Upward dose titration against declining skin reactivity is used for safe build-up and to avoid systemic and local reactions. Titrated dosing also accounts for varying patient reactivity levels and allergen batch variability. Patient-matched dosing reduces risk of reactions from needlessly high doses and unnecessary higher expense.

3. Dose Frequency

"Allergen persistence in the oral mucosa may be a far more relevant factor for gaining efficacy than allergen concentration."³ Various studies show that allergen delivered sublingually is retained up to 48 hours.^{4,5} Dosing multiple times daily provides continuous, uninterrupted allergen exposure to mast and other effector cells, minimizing peak and trough effects. Dose frequency may prove conducive to effector cell conditioning and may be the reason SLIT, titrated against skin test reactivity, lacks the side effects and associated failures of SCIT.² The LCM offers simple, consistent dosing schedules throughout treatment to support patient adherence – patients are prescribed one 90-day vial at a time.

4. Glycerin as a Diluent

Glycerin is a remarkable preservative used extensively in commercial products such as soaps, beverages and foods, among others. Using it as a 50% diluent in SLIT enables long-term extract storage, and allows treatment with multiple antigens simultaneously without allergens degrading or interacting with one another as they can with multi-allergen shot therapy.

Critical SLIT Attributes: Superior Patient Safety Profile and Convenience

Research supports SLIT's superior safety profile. The LCM has been used in over one billion doses, with few systemic and no life-threatening reactions reported. This allows treatment for the widest range of allergy sufferers including children of all ages, brittle asthmatics, severe skin conditions, contact allergies and severe food sensitivities. Because treatment is taken at home, LCM patients report improved adherence (some studies indicate 80-90%), a contrast from the poorer compliance statistics reported for SCIT.

The Complete Body of La Crosse Method Protocol (LCM) Research

Globally, the complete body of research regarding sublingual immunotherapy (SLIT) is extensive; comprehensive meta-analyses have been conducted by respected international organizations confirming the treatment's validity, which is outlined in Appendix 1.

More specifically, the LCM was initially developed and used in late 1960's; in the last 50 years, it has evolved, been studied and reported on thirty-eight (38) times involving nearly 2400 research subjects. The table below provides a synopsis (full study/report references available by request). Five patient outcome surveys follow in a separate table.

Year	Topic or Subject	Publication/Presentation	# subjects	General Findings
1969	Use of sublingual antigen in diagnosis and treatment of food allergy.	Annals of Allergy, Asthma, & Immunology 1969; 27(6): 289-94	4	Case studies, favorable patient response documented
1970	Treatment of respiratory disease with ultra-small doses of antigens. (molds)	Annals of Allergy, Asthma, & Immunology 1970; 28(10): 494-500.	8	Case studies, favorable patient response documented
1977	Value of Delayed Hypersensitivity Index in Patients with Malignancy	Annals of Allergy, 1977	N/A	Discusses role of identifying delayed reactions, valuable diagnosis tool
1982	Recognition and treatment of formaldehyde sensitivity	Clinical Ecology, Spring 1982, 27-30.	N/A	Explains successful testing and treatment approach
1993	Treatment of Mold Allergy using Intradermal Titration, RAST & Sublingual Antigens	AAOA Annual Meeting, Minneapolis, MN September 30, 1993	N/A	Explains the roles of testing and the correlation of mold allergy to asthma
1998	Intradermal Testing and Sublingual Desensitization for Nickel (contact allergy)	Cutis, Vol. 61, No. 3, pgs. 129-132. March 1998	39	85% of patients reporting noticeably better tolerance, average treatment 16 mos.
2001	Current use of sublingual-swallow immunotherapy	Current Opinion in Otolaryng Head & Neck Surgery, Vol.9, No.3, pgs.179-180, June 200	N/A	Extensive overview of LCM experience for ENT allergist lead publication
2003	Local Immunotherapy in Allergy	Karger, 2003, vol 82, pp 1-10: Markert UR, Elsner P.	N/A	First international book on SLIT, authors of 1 st chapter
2003*	Allergy Associates of La Crosse Patient Survey	University of Wisconsin La Crosse, College of Business	250	Validated instrument by UWL, administered 5x
2004	Sublingual Immunotherapy in the Treatment of COPD	Internal Study - ACAAI rejected	120	Retrospective study showing FEV1 improve-ment in 30% of pts.
2004*	Allergy Associates of La Crosse Patient Survey	University of Wisconsin - La Crosse	75	Random selection, favorable patient response
2005	Impact of sublingual immunotherapy on allergic conditions associated with asthma in pediatric patients	ACAAI Poster Presentation Nov 2005 (MPH Dissertation)	241	Patients treated for 2 yrs on Atopic March, 10 (4%) went on to develop asthma (stopping AM for most under treatment)
2005*	Allergy Associates of La Crosse Patient Survey	University of Wisconsin - La Crosse	112	Random selection, favorable patient response
2006	Sublingual Immunotherapy in the Treatment of Poison Ivy Dermatitis (contact allergy)	ACAAI Poster Presentation Nov 2006	115	Retrospective chart review, significant improvement followed treatment
2006	An Economic Analysis of Sub-lingual Allergen Immunotherapy	ACAAI Poster Presentation Nov 2006 - Dr. Marcus Shaker Dartmouth Children's Hospital	N/A	Determined SLIT is cost-effective and affordable at lower dose
2006*	Medicare - Allergy Associates of La Crosse Patient Survey	University of Wisconsin - La Crosse	214	Random selection, favorable patient response
2009	Emerging concepts of sublingual immunotherapy for allergy	Drugs of Today, 2009, 45(10); 737-750.	N/A	Peer reviewed compre-hensive overview of SLIT including mechanism.
2009	Allergy Symptom Response Following Conversion from Injection Immunotherapy to	Naval Medical Center Portsmouth, Dept of Otolaryngology/Head & Neck	30	U.S. Navy Medical Center using LCM validated successful conversion to SLIT for deployed

	Sublingual Immunotherapy	Surgery, peer presentation		troops unable to continue SCIT
2010	Safety of Sublingual Immunotherapy House Dust Mite Immunotherapy	AAAAI, Presentation March 2010	21	Lead in study to establish safety profile for 2011 study
2011	House Dust Mite Sublingual IT: Results of a US Trial	Journal Allergy & Clinical Immunology, [2011, 127(4):974-81.e1-7].	21	Comparison of high & low dose, lower medication needed by both
2011	Allergen-specific sublingual immunotherapy in the treatment of migraines: a prospective study	European Rev for Med and Pharm Sciences, 2011; 15: 1117-1121	7	Dr. Theodoropoulos study shows SLIT treatment reduces symptoms and related clinical marker.
2011	Allergen-specific IgE and IgG4 Measured by Microarray Technique in Patients with Clinical Improvement on Sublingual Immunotherapy	AAAAI Annual Meeting Poster Presentation March 2011	3	Drs. Morris, Theodoropoulos, Thompson. Improvements shown with clinical measures responding.
2012	Quality of life improvements with sublingual immunotherapy: a prospective study of efficacy.	Journal of Allergy (2012)	51	Peer review 2 yr patient study with Juniper RQLQ tool, significant improvement in 15 of 16 domains
2012	Multicenter open trial demonstrates efficacy of SLIT in canine atopic dermatitis.	Veterinary Dermatology, 2012, 23, S65.	271	55% of canines improved significantly, as an AIT product it is used worldwide for over 100,000 companion animals.
2013*	The effect and value of sublingual immunotherapy: a patient survey	World Allergy Org. Poster Presentation, December 2013.	299	Random study of patients, using validated patient satisfaction survey.
2015	Sublingual Immunotherapy for Allergic Fungal Sinusitis	Annals of Otolaryngology, Rhinology and Laryngology, 2015, Vol. 124(10) 782-787	8	U.S. Navy Medical Center using LCM shows reduced polyp recurrence.
2015	Sustained improvement of psoriatic lesions in the course of sublingual immunotherapy for airborne allergens: clinical evidence of cross-tolerance	European Review for Medical and Pharmacological Sciences (2015). 19: 392-395	1	Case study by Dr. Theodoropoulos shows patient improvement following SLIT therapy.
2015	Inhalant allergy compounding the chronic vaginitis syndrome; characterization of sensitization patterns, comorbidities and responses to SLIT	Arch Gynecol Obstet, DOI 10.1007/s00404-016-4081-2. (in conj. with OBGYN Dept. Univ. of Iowa, Univ. of WI La Crosse MPH	52	Retrospective treatment review showed significant resolution of symptoms following SLIT therapy.
2015	Allergychoices patient satisfaction survey	Internal Questionnaire (random distribution with prescriptions)	132	4 questions asked about treatment - affordability, effectiveness, convenience and adherence, all positive
2016	Clinical and immunological responses of dust mite sensitive, atopic dogs to treatment with SLIT	Vet Dermatol 2016; 27: 82-87.	10	Determine clinical and diagnostic impact of SLIT on atopic dogs - University of Wisconsin - Madison Veterinary Care - Dermatology.
2016	Sublingual Immunotherapy for Peanut Allergy	ACAAI Poster presentation 2015, FARE report June 2016	121	Determine clinical and diagnostic impact of SLIT on peanut and other foods among highly reactive pediatric patients.
2016	Allergychoices patient satisfaction survey	Internal study conducted using random sample of clients	113 (22.6 % resp. rate)	Four questions asked about treatment: affordability, effectiveness, convenience, adherence.
2017	Allergychoices patient satisfaction survey	Internal study conducted using random sample of clients	116 (23.2% resp rate)	Four questions asked about treatment: affordability, effectiveness, convenience, adherence
Total			2,389	

*The following table data represents detailed data referenced in studies denoted above. The data is compiled from five research studies conducted at Allergy Associates of La Crosse since 2003. Questionnaires were developed and administered in coordination with the University of Wisconsin – La Crosse. Demographic and prior allergy testing/treatment information for each is listed below the findings.



Patient data was evaluated and validated in 2018 by the Validation Institute, an independent team of population health scientists and biostatisticians who provide objective review to validate performance in healthcare. validationinstitute.com

KEY QUESTIONS	2003	2004	2005	Medicare '06	2013
Chronic Condition* prior to coming to AAOL Hypothesis: sublingual immunotherapy allows the treatment of patients that are significantly compromised by their allergies	51%	63%	73%	85%	N/A
Number of Dr visits now vs. prior to AAOL Hypothesis: actively treated sublingual immunotherapy patients will require less healthcare utilizations	48% less 1.19 v 3.69	68% less 1.61 v 5.01	60% less 2.2 v 5.5	58% less 1.9 v 4.5	82% less .65 v 3.56
ER visits now vs. prior to AAOL Hypothesis: actively treated sublingual immunotherapy patients will require less healthcare utilizations	80% less .15 v .76	81% less 11 v 57	86% less .1 v .7	58% less .6 v 1.4	95% less .02 v .41
Hospitalizations now vs. prior to AAOL Hypothesis: actively treated sublingual immunotherapy patients will require less healthcare utilizations	46% less .07 v .13	73% less 3 v 11	100% less 0 v .2	75% less .2 v .8	85% less .02 v .13
Medicine now vs. prior to AAOL Hypothesis: actively treated sublingual immunotherapy patients will require less healthcare utilizations	up to 50% less 2.19 v 2.59	50% less 1.62 v 3.23	40% less 1.5 v 2.5	13% less 2.7 v 3.1	47% less 5.46 v 10.21
School/work missed now vs. prior to AAOL Hypothesis: actively treated sublingual immunotherapy patients will require less healthcare utilizations	60% less 2.80 v 7.23	73% less .89 v 3.29	76% less .5 v 2.1	61% less 1.2 v 3.1	67% less 1 v 3
Quality of Life improved vs. prior to AAOL** Hypothesis: Does treatment via the La Crosse Method result in an improvement in the patients ability to participate in life	4.11	4.47	4.5	4.2	4.11
(5 = very positively 4=quite positively 3 = some 2 = very little 1 = not at all)					

Demographic Questions

Number of respondents	250	75	112	212	299
Average age	46	47.5	38	71	36-55
Tested for allergies before coming to AAOL	48%	54%	60%	47%	N/A
Treated with other Immunotherapy before AAOL	38%	16%	25%	25%	N/A

* The 2013 study was conducted in association with the University of Wisconsin-La Crosse. Some questions were not asked and are denoted by N/A.

** Chronic Conditions that are caused by allergies: asthma, sinusitis, eczema, urticaria, etc.

*** Respondents were asked to rate the impact of AAOL on their Quality of Life (QoL) on a scale of 1-5, 5 being the best. No respondents reported AAOL as negatively impacting their QoL.

Discussion Question

Why is SLIT still an off label treatment in the United States?

In the *Journal of Allergy and Clinical Immunology Practicum* 2017 January/February, the leading publication of U.S. allergists, the “Historical Perspective of SLIT...” discussion begins with this paraphrased statement “SLIT is widely prescribed for allergic respiratory conditions. It has been used in the treatment of AR (allergic rhinitis) with or without asthma for over three decades...in some regions it is used as much as Subcutaneous Immunotherapy (SCIT).”

Despite international use and growing use among other U.S. specialties, U.S. allergy leadership’s current view on SLIT suggests limited perspective and interest in researching certain multi-antigen SLIT treatment approaches, though research finds the SLIT mechanism to be both safe and effective. Only single-antigen, standardized dose SLIT tablets have received FDA approval to date; these products do not follow more than 50 years of allergy specialists’ use following SCIT practice parameters that advocate treating patients with multiple extracts simultaneously.

Allergists have focused primarily on two key points to dispute multi-antigen SLIT’s acceptance:

- Scientific support. They argue that the science behind liquid drops is inferior to formal “blinded” studies done for recently accepted single-antigen SLIT allergy tablets (tablets were approved only in the past five years; liquid SLIT, as noted, was used for the previous 30+ years).
- Multi-antigen treatment. Allergy leaders note that liquid SLIT uses multiple extracts mixed to treat patients’ allergies simultaneously (as most patients have multiple allergies), which is precisely the same way SCIT is used.

Though “blinded” clinical evidence to validate multi-antigen SCIT’s efficacy is lacking, treatment continues because efficacy was shown clinically. The SCIT method was “grandfathered” in by the FDA in the 1970s, when their *Summary Basis for Approval* for each extract used in SCIT stated that treatment dated back to the 1920s when biologics were not required to show efficacy (efficacy and safety data were required with the Drug Amendment of 1962). The FDA stated, “Because there are no adequate and well-controlled trials with this product to prove efficacy, the optimal treatment dose must be based on clinical response of each patient.” Because finding a homogeneous patient study group and controlling a study where multiple allergies are treated simultaneously is difficult, few “multiple extract” studies have been done for SCIT or for SLIT. We are caught in the prevailing single pharmaceutical product “gold standard” testing paradigm of the double-blind placebo controlled (DBPC) approach, which does not work when studying more than a single allergy (or condition).

However, significant meta-analyses of SCIT and SLIT show both are safe and effective (see Appendix 1). The meta-analyses include studies using a wide range of dosing approaches showing efficacy over a range of dosing levels. With both SCIT and SLIT, treatment begins with small amounts of extract(s) and builds to a therapeutic, maintenance dose.

It’s important to note that the FDA approves products used in a therapy by a practitioner, not therapies or protocols. Just as multi-extract SCIT therapy has not, and likely will never be, formally approved by the FDA based on DBPC studies (yet is widely accepted), neither will SLIT for the same reasons. It would seem logical that both therapies would be judged on the same merits, yet a separate standard has arisen for SLIT, even though the extracts used for SCIT and SLIT are the same FDA approved products.

This position paper follows the FDA’s logic, presenting existing evidence for the LCM Protocol, and demonstrating outcomes from 50 years of use based “optimal treatment doses based on the clinical response of each patient” and extensive worldwide studies. We hope readers can form their own conclusions in spite of allergy leadership’s mixed messages, recognizing that based on the data, SLIT is far too valuable of a treatment for the many allergic patients who do not have safe, viable options to fit their lifestyle needs, not to be considered a first line treatment.

Appendix 1

The Contemporary Body of Worldwide Allergy Industry SLIT Research

International Consensus Statement on Allergy and Rhinology: Allergic Rhinitis (ICAR-Allergic Rhinitis 2023)

Background: In the 5 years that have passed since the publication of the 2018 International Consensus Statement on Allergy and Rhinology: Allergic Rhinitis (ICAR-Allergic Rhinitis 2018), the literature has expanded substantially. The ICAR-Allergic Rhinitis 2023 update presents 144 individual topics on allergic rhinitis (AR), expanded by over 40 topics from the 2018 document. Originally presented topics from 2018 have also been reviewed and updated. The executive summary highlights key evidence-based findings and recommendation from the full document.

Methods: ICAR-Allergic Rhinitis 2023 employed established evidence-based review with recommendation (EBRR) methodology to individually evaluate each topic. Stepwise iterative peer review and consensus was performed for each topic. The final document was then collated and includes the results of this work.

Results: ICAR-Allergic Rhinitis 2023 includes 10 major content areas and 144 individual topics related to AR. For a substantial proportion of topics included, an aggregate grade of evidence is presented, which is determined by collating the levels of evidence for each available study identified in the literature. For topics in which a diagnostic or therapeutic intervention is considered, a recommendation summary is presented, which considers the aggregate grade of evidence, benefit, harm, and cost.

Conclusion: The ICAR-Allergic Rhinitis 2023 update provides a comprehensive that contributes to our current knowledge base and recommendations for patient evaluation and treatment.

ENT Allergists in the US, many who follow the AAOA Sublingual protocol or work with the La Crosse Method protocol, and outnumber general, ABAI, allergists, have already followed Europe's leads in the U.S. and have been using SLIT allergy care using sublingual.

World Allergy Organization, November 2009, Position Statement on SLIT

Delivery of SLIT in the community setting:

a. Primary Care Physicians/GPs should be armed with the knowledge of selecting the appropriate treatment relevant to the patient's illness and should be trained to make a comprehensive assessment, recognize treatment failure (inadequate therapy, mal-administered therapy, inadequate control) and exacerbations of illness.

b. They should be trained in all aspects of SLIT, including assessment of patients and administration of SLIT. Emphasis should be placed on detection and management of untoward side effects, possible local and SRs, adverse effects, and other untoward incidents in detail, and taught how to manage such incidents.

Scientific Evidence for Sublingual Immunotherapy

The complete body of sublingual immunotherapy research world-wide is extensive; more than 850 studies and papers have been presented on the subject over the past 50 years; detailed bibliography can be found at allergy-solutions.com/bibliography. It is impractical to offer this information in totality, however recent U.S. and International comprehensive meta-analyses were performed and have confirmed that SLIT is safe and effective based on a substantial number of modern, high quality studies performed around the world over the past 30 years. Beginning in 1986 with Dr. Glennis Scadding's multi-antigen SLIT study; through the mid-90s with the most comprehensive study ever performed comparing SLIT & SCIT in the largest double-blind-double-dummy SCIT vs. SLIT study to date; to recent studies of the single allergen SLIT tablets; findings have been consistent. Both SCIT and SLIT are efficacious; in terms of safety, SLIT is favored over SCIT. These assertions are made only after careful examination by world renowned research organizations assessing hundreds of studies worldwide. We have included concluding statements from the three largest, most respected, and most recent meta-analyses on the subject. Additionally, we provide full report links so that readers can determine of the research data's strength and conclusions.

The **Cochrane Collaborative** is the world's most-trusted research; their vision and mission statement note "Our work is internationally recognized as the benchmark for high-quality information about the effectiveness of health care." They issued **two reports** on allergy immunotherapy using SLIT, which were **published in 2003 and updated in 2010**.

The most extensive comparison of SCIT vs. SLIT was completed as a meta-analysis by a U.S. based research group as part of the **Agency for Healthcare Research and Quality**.

Sublingual immunotherapy for allergic rhinitis

Wilson DR, Torres Lima M, Durham SR, published in The Cochrane Library 2003, Issue 2

http://www.cochrane.org/CD002893/ENT_sublingual-immunotherapy-for-allergic-rhinitis-including-hay-fever

Main results

Twenty two trials involving 979 patients were included. There were six SLIT trials for House Dust Mite allergy, five for Grass, Pollen, five for Parietaria, two for Olive and one each for, Ragweed, Cat, Tree and Cupressus.

Four studies enrolled exclusively children. Seventeen studies administered the allergen by sublingual drops subsequently swallowed, three by drops subsequently spat out and two by sublingual tablets. Eight studies involved treatment for less than six months, ten studies for six to twelve months and four studies for greater than twelve months. All included studies were double-blind placebo-controlled trials of parallel group design. Treatment allocation concealment was considered adequate in all studies and the use of identical placebo preparations was almost universal.

There was significant heterogeneity for most comparisons, most likely due to widely differing scoring systems between studies. Overall, there was significant reduction in both symptoms (SMD -0.34, 95% confidence interval - 0.69 to -0.15; p=0.002) and medication requirements (SMD -0.43 [-0.63, -0.23]; p=0.00003) following immunotherapy. Subgroup analyses failed to identify a disproportionate benefit of treatment according to the allergen administered. There was no significant reduction in symptoms and medication scores in those studies involving only children but total numbers of participants were small, casting doubt on the validity of the conclusion. Increasing treatment duration does not clearly increase efficacy. The total dose of allergen administered may be important but insufficient data were available to analyse this factor.

Sublingual immunotherapy for allergic rhinitis (Update Review)

Radulovic S, Calderon MA, Wilson D, Durham S, published in The Cochrane Library 2010, Issue 12

PLAIN LANGUAGE SUMMARY (excerpt from)

In reviewing 60 trials, we found a significant reduction in symptom and medication scores in patients treated with sublingual immunotherapy compared to placebo. There were no serious adverse reactions reported in the included trials and no patient needed the use of adrenaline. This updated Cochrane Review therefore reinforces the earlier review's conclusions confirming the efficacy and safety of sublingual immunotherapy.

Sublingual Immunotherapy for the Treatment of Allergic Rhinoconjunctivitis and Asthma. A Systematic Review.

Prepared by the Johns Hopkins University Evidence-based Practice Center

<https://jamanetwork.com/journals/jama/fullarticle/1672214>

Research Focus for Clinicians

A systematic review was undertaken to summarize the evidence regarding the efficacy, comparative effectiveness, and safety of subcutaneous and sublingual immunotherapy for adult and pediatric patients. All included studies are randomized controlled trials (RCTs) and were published from January 1967 to May 2012. There are seventy four RCTs on the efficacy and safety of subcutaneous immunotherapy (SCIT), sixty RCTs on the efficacy and safety of sublingual immunotherapy (SLIT), and eight RCTs on head-to-head comparisons between both forms of immunotherapy. This summary is provided to assist clinicians in decision-making along with a patient's values and preferences.

Conclusions

- There is sufficient evidence to support the overall effectiveness and safety of both SCIT and SLIT for treating allergic rhinoconjunctivitis and asthma (Tables 1 and 2).
- However, there is not enough evidence to determine if either SCIT or SLIT is superior.
- SCIT and SLIT are usually safe, although local reactions are commonly reported regardless of the mode of delivery (Table 3).
- Serious, life-threatening reactions are rare, although they can occur (see SCIT, Table 3). SLIT studies mainly include patients with allergic rhinitis and/or mild asthma. Safety outcomes for SLIT should not be extrapolated to more severely affected patients.
- Most studies use a single allergen for immunotherapy (Table 4). It may be difficult to extrapolate these results to the use of multiple-allergen regimens, which are commonly used in clinical practice in the United States.
- Due to the wide variety of reported regimens, the target SLIT maintenance dose and the duration of therapy are unclear.

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1. Passalacqua, G., Compalati, E., Canonica, G.W. Sublingual Immunotherapy: Clinical Indications in the WAO-SLIT Position Paper. *World Allergy Organization Journal* 2010 Jul;3(7):216-219.
2. Theodoropoulos, D., Morris, M., Morris, D. Emerging Concepts of Sublingual Immunotherapy for Allergy. *Drugs of Today* 2009, 45(10):737-750.
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ADDITIONAL Recent Pivotal Studies

Largest Outcomes Based Sublingual Immunotherapy for allergic rhinitis

The EcAPSI Study, largest real-world study to date, 434,000 French patients in the NHS database, treated with allergy drops, significant impact on reducing asthma events/occurrence. <https://www.emjreviews.com/wp-content/uploads/2022/08/Infographic-The-EfficAPSI-study.pdf>

US-based multi-center food allergy study, dosing based on past studies using La Crosse Method equivalent dosing

Open-label study of the efficacy, safety, and durability of peanut sublingual immunotherapy in peanut-allergic children, University of North Carolina, lead Dr. Edwin Kim. Based on LCM dosing.

<https://pubmed.ncbi.nlm.nih.gov/36828080/> Journal of Clinical Immunology, October 2023

Agency for Healthcare Research and Quality (AHRQ)

Sublingual Immunotherapy for the Treatment of Allergic Rhinoconjunctivitis and Asthma. A Systematic Review.

Prepared by the Johns Hopkins University Evidence-based Practice Center

<https://jamanetwork.com/journals/jama/fullarticle/1672214>

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References – Key Tenets of the La Crosse Method Protocol (Page 1)

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