SUBLINGUAL IMMUNOTHERAPY

by

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As members of the DNP Project Committee, we certify that we have read the DNP Project prepared by Melissa L. Ferrell, entitled Sublingual Immunotherapy and recommend that it be accepted as fulfilling the DNP Project requirement for the Degree of Doctor of Nursing Practice.

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STATEMENT BY AUTHOR

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SIGNED: Melissa L. Ferrell
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DEDICATION

I would like to dedicate this DNP project to my family. To my husband Roland and children, Reilly, McKenna, and Hayden for supporting me and for being so willing to take up the slack so that I could further my graduate education. I hope I have been an example to you that you can accomplish anything you set your mind to do. To my parents for instilling a love of learning through their dedication to education and for their continual support and encouragement.
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ABSTRACT

One of the most common reasons people seek primary care and emergency care is to reduce the symptoms of allergies, such as hay fever. To meet this high demand, several recent FDA-approved methods for treating seasonal and perennial allergies have been developed, including sublingual immunotherapy tablets. Furthermore, no longer must a patient endure allergy shots; this can now be delivered sublingually. Although this method has been shown to have high safety and efficacy, very few clinicians actually utilize this form of therapy. The purpose of this paper is to describe the use of sublingual immunotherapy among Nurse Practitioners and discuss barriers that may prevent its use. Nurse Practitioners working in primary care settings were surveyed regarding their use of sublingual immunotherapy. Although many nurse practitioners treat patients with allergic disease, not one participant reported using sublingual immunotherapy. This discussion outlines some of the reasons NPs are not currently utilizing this method of allergy treatment and the findings are compared with the extant literature. This paper culminates in an evidence-based algorithm to outline best practices for utilizing sublingual immunotherapy to reduce allergy symptoms.
INTRODUCTION

Runny nose, itchy, watery eyes, wheezing, and episodes of sneezing are common, yet aggravating allergy symptoms most people will experience at some point in their life. Allergic rhinitis, rhinosinusitis, allergic asthma, allergic rhinoconjunctivitis, and hives (urticaria) are common diagnoses often associated with allergic disease. Allergic rhinitis is on the rise and currently affects 30-40% of adults and children and is one of the most common reasons to utilize healthcare services (Dranitsaris & Ellis, 2014; Wallace & Dykewicz, 2008). In 2012, it was estimated that more than 17 million adults in the U.S. suffered from, or sought care for allergic rhinitis (Blackwell, Lucas, & Clarke, 2014; Wise & Schlosser, 2012). Allergies are responsible for 3.5 million lost work days and two million lost school days each year (Nathan, 2007). In 2002, it was estimated that the total direct and indirect costs associated with allergic rhinitis in the U.S. were $11.58 billion (Schoenwetter, Dupclay, Appajosyula, Botteman, & Pashos, 2004). Long-term untreated allergy symptoms have the potential to aggravate asthma symptoms, increase respiratory complications, and decrease the quality of life for those suffering with allergic disease (Deliu et al., 2014).

The most practical way to relieve allergy symptoms is merely to avoid the stimulant. Unfortunately, that solution is often unrealistic or difficult, and many people may reach for medications to reduce the unpleasant symptoms. Antihistamines, nasal steroids, and nasal rinses are typically the first-line treatment for allergies. However, these interventions are less than effective, as upwards of 40% of patients who report allergy symptoms, describe their symptoms as not well controlled by traditional pharmacological treatments (Durham, Yang, Pedersen, Johansen, & Rak, 2006). If these treatments fail to provide adequate relief of allergy symptoms, allergen immunotherapy (AIT) may provide an alternative treatment. Furthermore, while
subcutaneous injection has been the predominate route to deliver AIT, sublingual immunotherapy is a painless, highly effective means to deliver the same treatment. Although three sublingual tablets were approved by the Federal Drug Administration in 2014 (Food and Drug Administration [FDA], 2014), sublingual immunotherapy may not be widely used in primary care settings by providers, such as Nurse Practitioners (NPs). The purpose of this paper is to describe the use of sublingual immunotherapy among NPs in primary care.

**Background**

**Allergic Response**

An allergic response is a cascade of events precipitated by an allergen. An allergen is a protein or glycoprotein with a defined amino acid sequence that is capable of binding Immunoglobulin E (IgE) and provoking an immediate hypersensitivity reaction (Miguéres et al., 2014; Shah & Grammer, 2012). Allergic disease is thought to stem from an imbalance between regulatory T cells (T regs) and T helper (TH) 2 cells (Ling et al., 2004). This may occur due to the inability of the T regs to suppress the allergen activation (Ling et al., 2004). Histamine is released from mast cells and basophils and also plays a key role in the production allergen-specific IgE (Akdis & Akdis, 2014). Increases in eosinophils, mast cells, and basophils are also found in conjunction with allergic disease (Akdis & Akdis, 2014). Figure 1 outlines the physiologic process in the suppression of allergic inflammation.
Figure 1. The role of T reg and B reg cells in the suppression of allergic inflammation


**Allergen Immunotherapy**

Allergen immunotherapy (AIT) is the desensitization process used to induce tolerance to allergens. Desensitization is accomplished through repeated exposure to allergen extracts in increasing quantities (Akdis & Akdis, 2014; Marogna et al., 2009). AIT can be given by subcutaneous injection or sublingually, as a tablet or by drops placed under the tongue. Moderate-to-severe allergic rhinitis and mild-to-moderate allergic asthma are common indications for AIT (Miguere, et al., 2014). Thus far, AIT is the only treatment with the potential to promote long-term remission of allergy symptoms, possibly stop allergic disease progression, and may prevent the development of new allergies and asthma (Canonica et al., 2014; Hankin & Cox, 2014).
Significance of the Problem

Recent advances have been made in the treatment of allergies with allergen immunotherapy. Prior to the approval of the sublingual tablets, only subcutaneous injections were FDA-approved and aqueous drops continue to be an off-label route of administration. However, the drops may actually have more patient appeal as they can be self-administered at home. There is also less need for multiple medical visits and the lack of needles may be more favorable for children or those with needle phobias (Calderon, Penagos, Sheikh, Canonica, & Durham, 2011). Sublingual immunotherapy may be an attractive alternative over allergy shots as it is pain-free, easily administered, and has an excellent safety profile. However, despite the advantages, this therapy is rarely used,

The current practice of sublingual immunotherapy by Nurse Practitioners’ is difficult to ascertain as minimal data can be found in the literature. Previous surveys designed to describe practice patterns for sublingual immunotherapy have specifically targeted allergist, otolaryngologist, or random health care providers and not specifically NPs (Leatherman et al., 2014; Tucker, Tankersley, & ACAAI Immunotherapy and Diagnostics Committee, 2008). As additional information regarding its safety and efficacy becomes available, primary care providers, including NPs, may increasingly be asked to prescribe sublingual immunotherapy. In rural healthcare settings, sublingual immunotherapy may be a feasible treatment option when specialty care is limited. Sublingual immunotherapy has the potential to be a mainstream, immune-modifying treatment alternative for allergic disease and as an adjunct therapy for asthma. Increasing Nurse Practitioners knowledge of sublingual immunotherapy, including when to refer for specialty care, should foster an improvement in healthcare outcomes.
Purpose Statement

The purpose of this paper is to describe the use of sublingual immunotherapy by Nurse Practitioners in primary care. The specific aims are: 1) describe current evident-based research regarding sublingual immunotherapy, 2) describe how NPs are using sublingual immunotherapy in practice, and 3) develop best practice recommendations for the use of sublingual immunotherapy in primary care. This paper will contribute to the expanding role of allergen sublingual immunotherapy as a treatment modality for allergic disease by NPs.

LITERATURE REVIEW

The purpose of this literature review was to evaluate the current research regarding the safety and efficacy of sublingual immunotherapy, discuss the gaps in knowledge, and present a summary of current evidence regarding sublingual immunotherapy. The findings of this literature review were used to develop a survey to describe prescribing practices among NPs. Survey results were used in conjunction with current evidence to develop best practice recommendations for NPs in the use of sublingual immunotherapy.

Method

A systematic search of the Cochrane Library, PubMed, and EMBASE was performed using the keyword “sublingual immunotherapy” with dates ranging from 2009 to 2014. Articles were limited to randomized controlled trials, published in English, with human subjects, and included full text. Articles were excluded if they were specific to latex, venom, food, pets, migraines, epicutaneous or intralymphatic immunotherapy, or oral desensitization. A total of 21 studies were obtained from PubMed or extrapolated from systematic reviews. These studies
were analyzed for dosing regimens, symptom and medication scoring systems, and adverse events.

**Dosing**

The allergen extracts used in sublingual immunotherapy are typically the same aqueous solutions FDA-approved for subcutaneous immunotherapy. Currently, there is not an international standardized expression or measurement for allergen extracts. Concentrations have been found to vary between manufacturers. This has posed substantial challenges in comparing randomized controlled studies to evaluate effective dosing parameters. Each lab varies in how it labels the allergen extracts. Extracts are measured in bioequivalent allergy units (BAU/mL), allergen units (AU/mL), protein nitrogen units (PNU), and by weight/volume (w/v) of the extract. The quality of the allergen extract greatly influences the efficacy; allergen extracts from one manufacturer cannot be compared with another until standardization and controlled trials are performed (Ridolo et al., 2014).

One challenge that has proven to be a barrier in determining the efficacy of sublingual immunotherapy is the variety of dosing regimens used in studies. Studies reveal quite different build-up or up-dosing administration schedules. Maintenance dosing regimens and dosing units also varied between studies. Allergen dosing units were frequently reported as: IR (Index of Reactivity), RU/mL (Rast Units per milliliter), IR/mL, drops, puffs, and µg. These differences further compound the confusion in establishing recommended dosing guidelines. Treatment lengths also ranged significantly with some studies as short as eight months and others as long as five years. Dosing schedules for allergies can be year round (perennial), seasonal, or preseasonal (prior to and through the end of the peak allergy season) (Ahmadianifar,
Symptom Scoring

Variations in symptom and medication scoring tools contribute to the heterogeneity in reporting clinical outcomes. A commonly used method to evaluate symptoms is a four-point scale. The points are often applied as follows: 0 points: no symptoms; 1 point: mild symptoms; 2 points: moderate symptoms; and 3 points: severe symptoms (Aydogan et al., 2013; Bush et al., 2011). Commonly measured symptoms include; rhinorrhea (nose blowing/runny nose), sneezing, itchy nose, nasal congestion (blocked nose), postnasal drip, red itchy eyes, watery (tearing/tear flow), gritty eyes, cough, wheeze, dyspnea, chest tightness, breathlessness or shortness of breath. Other symptoms used to evaluate the efficacy of study outcomes include throat symptoms, ear symptoms, headache, dry cough, ocular swelling, and chest congestion (Bozek, Ignasiak, Filipowska, & Jarzab, 2013).

The inclusion of a visual analogue scale and/or a Quality of Life questionnaire, in addition to a point-value scoring system, further contributed to variations in study outcomes. The visual analogue scale is a measurement tool used to grade symptoms by choosing a point along a scale (Eifan et al., 2010; O’Hehir et al., 2009). Quality of Life questionnaires include the Allergy Control SCORE (ACS), Control of Allergic Rhinitis and Asthma Test (CARAT), Rhinitis Control Assessment Test (RCAT), Allergic Rhinitis Control Test (ARCT), and Pediatric and Adolescent Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ and AdolRQLQ, respectively) (De Bot et al., 2012). These questionnaires are used to gauge the severity and control of the allergic disease (Demoly et al., 2013). Rarely, were studies replicated that employed similar dosing, symptom scoring, and medication scoring systems.
Medication Scoring

In addition to symptom scoring, medication scoring is often used to quantify the amount and frequency of allergy-related medication used in conjunction with allergen immunotherapy. Medication selection and the point-valuation applied for similar medications often differed between studies. For example, some studies applied one point for each dose of oral antihistamine while others applied two, three or four points (Aydogan et al., 2013; Ott et al., 2009; Skoner et al., 2010). Most studies either allowed the patient to continue taking antihistamines and/or rescue asthma medications as needed, or only allowed certain medications to be taken while participating in the study.

Studies were found to either report symptom and medication scores individually or as a combined score. These results were then used to measure the efficacy of sublingual immunotherapy. A review of the literature revealed that the frequency in which study participants were asked to record symptoms and medication use varied. Scores were reported typically once or twice a day, at follow-up visits, daily during peak season, annually, or only after treatment cessation. The World Allergy Organization (WAO) proposes that the ideal study should provide a balanced evaluation of the symptom and medication scores (Canonica et al., 2009).

Adverse Events

The safety profile of subcutaneous immunotherapy is often a deterrent for many clinicians and patients. Non-fatal reactions from subcutaneous immunotherapy has a prevalence rate as low as 0.13% and up to 34% in rush immunotherapy studies (Cox, Larenas-Linnemann, et al., 2010). In 2004, Berstein and colleagues reported that 41 fatalities occurred over a 12 year period (Berstein, Wanner, & Borish, 2004). This equated to an estimated one fatality per 2.5
million injections or 3.4 deaths per year (Bernstein et al., 2004). The cause of death was often attributed to delayed treatment of anaphylaxis. In contrast, there have been no reported deaths from sublingual immunotherapy.

Side effects are also common for both subcutaneous and sublingual routes of administration, however, inconsistency exists in defining and differentiating between local and systemic reactions. Local reactions for subcutaneous immunotherapy include redness and/or swelling at the injection site and generalized pruritus (Cox, Larenas-Linnemann, et al., 2010). Sublingual immunotherapy side effects are typically oral in nature, but can include generalized itching, soreness, oropharynx swelling, and facial flushing (Ahadiafshar et al., 2012; Bozek et al., 2013). Oral side effects are usually self-limiting and resolve shortly after administration. Antihistamines can be prescribed for prevention and/or treatment of local side effects.

Key elements that should be included when reporting systemic adverse reactions are: 1) patient characteristics (severity of allergic disease, co-morbidities, risk factors), 2) the type of allergen extract used, 3) the route of administration, 4) the dose of the antigen given during the up-dosing and maintenance phases, 5) the dosing schedule (conventional, cluster or rush), and 6) the experience of the treating physician in the early identification and treatment of the systemic reaction (Calderon et al., 2014).

**Current Practice Guidelines**

The current practice of sublingual immunotherapy is varied as demonstrated by the number of dosing regimens, symptom and medication scoring tools, and methods for identifying and recording adverse events. In the U.S., only about 11.4% of allergists prescribe sublingual immunotherapy and multi-allergen, aqueous or glycerinated formulations, prepared in the physician’s office are typically used (Cox, 2014). In comparison, sublingual immunotherapy is
prescribed by about 45% of European clinicians and they tend to prescribe single-allergen, depot extracts prepared by allergen extract manufacturers (Cox, 2014). Sublingual immunotherapy is an approved treatment for allergies by the European Medicinal Agency (EMEA) (Cox, 2014). However, in the U.S., FDA-approval necessitates additional randomized controlled trials (RCTs) to determine effective administration regimens, appropriate patient selection, and standardization of allergen extracts (Compalati, Braid, & Canonica, 2013).

Although sublingual immunotherapy is supported by the World Allergy Organization (WAO) and the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines, it is only recently being recognized as a treatment option in the U.S. (Brozek et al., 2010; Canonica et al., 2009). The Otolaryngology – Head and Neck Surgery recently published new guidelines for the treatment of allergic rhinitis and recommended sublingual or subcutaneous immunotherapy for patients that are not responding to pharmacological measures (Seidman et al., 2015). In February 2015, experts at the American Academy of Allergy, Asthma, and Immunology (AAAAI) began drafting additions to the Joint Task Force Practice Parameter specifically for sublingual immunotherapy (Cox, 2015; Cox, Nelson & Lockey, 2010).

**Gaps in the Literature**

In reviewing the literature, several key findings were lacking. There is very little consensus as to the ideal dosing frequency, allergen concentration, and length of treatment for sublingual immunotherapy. Patient selection criteria and primary endpoints are also quite varied. Although, all the studies reviewed were randomized controlled trials, they often had small sample sizes and the potential for publication bias. Additional randomized, placebo-controlled, double-blind trials with similar dosing protocols are needed for individual and multi-allergen mixtures. This will help to determine the most efficacious and cost-effective dosing regimen.
with the fewest adverse events. Studies are also needed to confirm the indications for alternative allergic diagnoses, such as eosinophilic esophagitis, allergy-induced urticaria, angioedema, food allergies, atopic dermatitis, and moderate to severe asthma. Long-term studies will help to confirm immunologic changes and reaffirm the mechanism of action for sublingual immunotherapy.

Conclusion

Numerous observational and retrospective studies, without randomization, blinding or placebo groups, have been published that provide descriptive information for sublingual immunotherapy. These studies are important as they provide suggested dosing regimens and the length of treatment potentially required for sustained desensitization. Many of the randomized controlled trials are considered to be suggestive, rather than demonstrative because they lack sufficient high quality evidence (Canonica et al., 2009). As additional large scale randomized, double-blind, placebo-controlled trials are completed using similar primary endpoints and dosing regimens, the statistical significance and generalization of results should improve.

METHODS

Conceptual Framework

The Plan-Do-Study-Act (PDSA) model for quality improvement was the framework used to describe how NPs are using sublingual immunotherapy. Sublingual immunotherapy may be a safe and effective alternative when standard drug therapy is ineffective, yet it is unknown how many NPs are currently prescribing this in practice. The PLAN stage was to query NPs to see if and how sublingual immunotherapy is being prescribed in practice. In the DO stage, an 8-question survey was developed and administered to NPs throughout the U.S. In the STUDY stage, survey results were analyzed, variances and similarities were documented and unexpected
outcomes were identified. The knowledge gained in this study leads to the ACT stage in the PSDA cycle. Evidence-based findings from the literature and survey results were used to develop an algorithm for NPs to improve best practice when treating patients with sublingual immunotherapy. The PDSA cycle can then be repeated to future research, if additional changes are needed to further improve outcomes.

**Protection of Human Subjects**

Prior to data collection, grant exemption from the Institutional Review Board at the University of Arizona was obtained. Each recipient received the following: (1) a cover letter introducing the principle investigator (PI) and the purpose of the survey, (2) a disclosure form explaining the anticipated time commitment, voluntary nature of the survey, how responses will be used in this DNP project, and how participants will be protected in the study, (3) an 8-question survey, and (4) a stamped return envelope addressed to the PI. No identifiable information was requested in the survey. It was anticipated that only respondents who could read and write English would participate and no expected vulnerable populations were included.

**Study Design**

A stratified, randomized sampling of 500 actively practicing NPs from the American Association of Nurse Practitioners (AANP) membership database was obtained. Surveys were then mailed to each potential participant. Participants were asked to return the survey within 14 days.

**Setting and Sample**

NPs self-reporting family practice, pediatrics, and/or allergy/immunology as their specialty were included in the study. Participants were excluded if they are not actively practicing or were not active members of the AANP.
**Survey**

This survey specifically targeted NPs actively practicing in the U.S. The aims of this survey were: 1) discover the number of NPs prescribing sublingual immunotherapy and to which patient population, 2) discover what types of allergy testing are being performed, 3) discover treatment preferences (single versus multi-allergen), and 4) determine what barriers may exist that prevent NPs from employing this therapy.

**Analysis**

Quantitative results were counted and expressed as a percentage of respondents. Qualitative responses were analyzed and reported according to common themes and trends.

**RESULTS**

**Description of the Sample**

A total of 157 surveys were returned, two of which were excluded, as the respondents stated that they were retired and did not complete the survey (N=155). The majority of respondents in this sample were Family Nurse Practitioners. Additional areas of NP specialization included Adult Gerontology Acute Care, Adult Gerontology Primary Care, emergency department, neurology, lipidology, addiction, HIV/AIDS, internal medicine in the Veteran’s Administration, and orthopedics. Several participants reported more than one area of specialization.
Table 1

Demographics by specialty

<table>
<thead>
<tr>
<th>Nurse Practitioner Specialty</th>
<th>Response</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family Nurse Practitioner</td>
<td>152</td>
<td>98.06%</td>
</tr>
<tr>
<td>Adult-Gerontology Primary Care</td>
<td>1</td>
<td>0.65%</td>
</tr>
<tr>
<td>Pediatric Nurse Practitioner</td>
<td>0</td>
<td>0.00%</td>
</tr>
<tr>
<td>Neonatal Nurse Practitioner</td>
<td>0</td>
<td>0.00%</td>
</tr>
<tr>
<td>Woman's Health Nurse Practitioner</td>
<td>0</td>
<td>0.00%</td>
</tr>
<tr>
<td>Certified Nurse Midwife</td>
<td>0</td>
<td>0.00%</td>
</tr>
<tr>
<td>Certified Registered Nurse Anesthetist</td>
<td>0</td>
<td>0.00%</td>
</tr>
<tr>
<td>Other</td>
<td>9</td>
<td>5.81%</td>
</tr>
<tr>
<td>Adult-Gerontology Acute Care</td>
<td>1</td>
<td>0.65%</td>
</tr>
<tr>
<td>Emergency Department</td>
<td>1</td>
<td>0.65%</td>
</tr>
<tr>
<td>FNP - Neurology</td>
<td>2</td>
<td>1.29%</td>
</tr>
<tr>
<td>Lipidologist, Anti-Coagulation Mgmt</td>
<td>1</td>
<td>0.65%</td>
</tr>
<tr>
<td>Addiction</td>
<td>1</td>
<td>0.65%</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>1</td>
<td>0.65%</td>
</tr>
<tr>
<td>VA-Internal Medicine</td>
<td>1</td>
<td>0.65%</td>
</tr>
<tr>
<td>Orthopedics</td>
<td>1</td>
<td>0.65%</td>
</tr>
</tbody>
</table>

The sample represented NPs from 45 of the 50 states. All states of licensure reported by participants were counted, including those reporting licensure in multiple states. Texas and Florida were most widely represented by the sample, followed by California, Indiana, and Virginia. Three NPs did not disclose the state in which they were licensed.
Table 2

*State distribution of licensure by respondents.*

<table>
<thead>
<tr>
<th>No. of participants</th>
<th>States by Scope of Practice</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Restricted</td>
</tr>
<tr>
<td>&gt; 6 Participants</td>
<td>Florida</td>
</tr>
<tr>
<td></td>
<td>Texas</td>
</tr>
<tr>
<td></td>
<td>California</td>
</tr>
<tr>
<td></td>
<td>Virginia</td>
</tr>
<tr>
<td>5-6 Participants</td>
<td>N. Carolina</td>
</tr>
<tr>
<td></td>
<td>Oklahoma</td>
</tr>
<tr>
<td></td>
<td>Michigan</td>
</tr>
<tr>
<td>3-4 Participants</td>
<td>Tennessee</td>
</tr>
<tr>
<td></td>
<td>Georgia</td>
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<tr>
<td></td>
<td>S. Carolina</td>
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<td>Massachusetts</td>
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<td></td>
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<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>1-2 Participants</td>
<td>Missouri</td>
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</table>

**Results**

Interestingly, no NPs in this sample currently prescribe sublingual immunotherapy in their practice. Allergy testing performed or ordered by NPs was infrequently done. Over 80% (N=126) of the sample did not perform any type of allergy testing, but rather referred patients to an allergist. A small percentage of NPs ordered serum IgE blood testing, RAST testing, serum food allergy testing or performed intradermal or scratch/puncture skin tests.
In this sample, 39% (N=60) of NPs responded that they would consider prescribing sublingual immunotherapy, but limited or no knowledge about how to manage this therapy was a barrier. Sixty percent (N=94) responded that they would not consider prescribing sublingual immunotherapy. Of the 94 who would not consider prescribing this treatment, one-third (N=30) reported working in a subspecialty that does not treat allergies and one-third (N=31) would rather refer to an allergist. Overwhelmingly, the most common barrier to prescribing sublingual immunotherapy was limited or no knowledge of how to prescribe or initiate (N=92). The second most common reason cited as a barrier to prescribing was the NPs preference to refer patients to an allergist for allergy shots. The off-label designation was a barrier for a small percentage of NPs and lack of insurance reimbursement was problematic for about 10% (N=16) of those surveyed. Additional barriers included a concern for malpractice, the need for physician oversight, prescribing limited by individual practice protocols, lack of knowledge regarding the applicability in geriatric or pregnant populations, and lack of staffing for patient monitoring.
Table 3

Results

<table>
<thead>
<tr>
<th>Currently Prescribing SLIT?</th>
<th>Response</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>0</td>
<td>0.00%</td>
</tr>
<tr>
<td>No</td>
<td>155</td>
<td>100%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SLIT Patient Population</th>
<th>Response</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 5 years old</td>
<td>0</td>
<td>0.00%</td>
</tr>
<tr>
<td>5-18 years old</td>
<td>0</td>
<td>0.00%</td>
</tr>
<tr>
<td>19-65 years old</td>
<td>0</td>
<td>0.00%</td>
</tr>
<tr>
<td>&gt; 65 years old</td>
<td>0</td>
<td>0.00%</td>
</tr>
<tr>
<td>I do not prescribe</td>
<td>137</td>
<td>88.39%</td>
</tr>
<tr>
<td>N/A or Did not respond</td>
<td>18</td>
<td>11.61%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Allergy Testing</th>
<th>Response</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Puncture/scratch skin test</td>
<td>1</td>
<td>0.65%</td>
</tr>
<tr>
<td>Intradermal skin test</td>
<td>1</td>
<td>0.65%</td>
</tr>
<tr>
<td>Serum IgE blood test</td>
<td>20</td>
<td>12.90%</td>
</tr>
<tr>
<td>None-referral to specialist</td>
<td>126</td>
<td>81.29%</td>
</tr>
<tr>
<td>Other - none</td>
<td>1</td>
<td>0.65%</td>
</tr>
<tr>
<td>Other - Adult food allergy test</td>
<td>1</td>
<td>0.65%</td>
</tr>
<tr>
<td>Other - RAST</td>
<td>1</td>
<td>0.65%</td>
</tr>
<tr>
<td>Did not respond</td>
<td>5</td>
<td>3.23%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SLIT Formulation</th>
<th>Response</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single-allergen</td>
<td>0</td>
<td>0.00%</td>
</tr>
<tr>
<td>Allergen-specific</td>
<td>0</td>
<td>0.00%</td>
</tr>
<tr>
<td>Multi-allergen</td>
<td>0</td>
<td>0.00%</td>
</tr>
<tr>
<td>Sublingual tablets</td>
<td>0</td>
<td>0.00%</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>0.00%</td>
</tr>
<tr>
<td>Do not prescribe</td>
<td>142</td>
<td>91.61%</td>
</tr>
<tr>
<td>SLIT tablets if appropriate</td>
<td>1</td>
<td>0.65%</td>
</tr>
<tr>
<td>Did not respond</td>
<td>11</td>
<td>7.10%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Would you consider prescribing SLIT?</th>
<th>Response</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>60</td>
<td>38.71%</td>
</tr>
<tr>
<td>No</td>
<td>94</td>
<td>60.65%</td>
</tr>
<tr>
<td>I currently prescribe</td>
<td>0</td>
<td>0.00%</td>
</tr>
<tr>
<td>Maybe</td>
<td>1</td>
<td>0.65%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Barriers preventing SLIT prescribing</th>
<th>Response</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;Off-label&quot;</td>
<td>5</td>
<td>3.23%</td>
</tr>
<tr>
<td>Minimal or no insurance reimbursement</td>
<td>16</td>
<td>10.32%</td>
</tr>
<tr>
<td>Limited/no knowledge of SLIT</td>
<td>92</td>
<td>59.35%</td>
</tr>
<tr>
<td>Prefer to refer for allergy shots</td>
<td>42</td>
<td>27.10%</td>
</tr>
<tr>
<td>None, I currently prescribe</td>
<td>0</td>
<td>0.00%</td>
</tr>
<tr>
<td>Other</td>
<td>41</td>
<td>26.45%</td>
</tr>
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</table>
DISCUSSION

This study was aimed at describing NPs practice of using sublingual immunotherapy for allergies. It was anticipated that the number of NPs prescribing this therapy would be small, however, it was surprising that among the sample (N=155) no participants reported using sublingual immunotherapy. The following discussion relates the results from this project to the current literature and helps to outline the factors that may limit the use of sublingual immunotherapy.

Scope of Practice

Currently, the scope of practice and prescribing regulations for Nurse Practitioners differ among the 50 states. More than half of the states have either restricted or limited scope of practice. Respondents with NP licensure in Florida (N=11), Texas (N=10), California (N=8), and Virginia (N=7) had the highest rates of survey responses and those states have some of the most restrictive practice regulations ("AANP," n.d.). Forty-one percent (N=68) of the respondents reported licensure in a state with restricted scope of practice, 30% (N=50) reported licensure in a reduced scope of practice state, while only 28% (N=47) practice in a state allowing full scope of practice. NPs practicing in states with restricted practice require supervision, delegation, or team-management in order to provide care ("AANP," n.d.).

Practice Patterns and Beliefs

Although descriptions of practice patterns using allergen immunotherapy can be found in the literature, elucidating concrete numbers of prescribers is challenging. The Allergies, Immunotherapy, Rhinoconjunctivitis (AIRS) survey sought to describe practice patterns, attitudes, and beliefs from healthcare providers treating allergic rhinoconjunctivitis (ARC) with AIT (Leatherman et al., 2014). This study surveyed 500 healthcare providers, including 50 NPs,
who provided care at least once a week to at least one patient with (ARC) (Leatherman et al., 2014). Total responses from NPs and Physician Assistants (PAs) were combined and 10% reported using sublingual immunotherapy (Leatherman et al, 2014). However, raw data from this study is unpublished. Additionally, Cox (2014) reports that since 2000, it is estimated that over one billion doses of sublingual immunotherapy have been administered in the U.S. by physicians, physician assistants, and NPs, but does not further quantify how many doses have been prescribed by NPs alone. These studies provide supplementary information to this study and confirm that there is a small number of NPs prescribing sublingual immunotherapy. Further studies would be warranted to evaluate if targeted education influences prescribing practices.

**Barriers**

Barriers to diagnosing allergies and treating with sublingual immunotherapy differ between healthcare specialties. In a survey of U.S. allergists (N=520), the most common reasons for not prescribing sublingual immunotherapy included lack of FDA-approval, lack of established practice parameters, unknown effective dose, and inadequate training (Sikora et al., 2012). While the lack of FDA-approval is a significant prescribing barrier for allergist, it was not a significant barrier for a majority of NPs in this study. In comparison, this survey demonstrated that a lack of general prescribing knowledge is more of a significant barrier for NPs. Lack of training was also cited as the primary barrier preventing otolaryngologist and other physicians from prescribing AIT in the AIRS study (Leatherman et al., 2014). This difference in perceived barriers between allergists, NPs, and other healthcare providers, is an expected outcome as allergists are trained specifically to treat and manage allergic disease. It was anticipated that limited or no knowledge of treating allergic disease with allergen immunotherapy would be common among NPs. The findings in the AIRS study also illustrates
that the variability in training influences practices and beliefs between specialties (Leatherman et al., 2014). As additional sublingual immunotherapy tablets and potentially aqueous solutions, gain FDA-approval, it is likely that awareness of AIT and prescribing knowledge will increase. Targeted education and collaboration between specialties will serve to improve the diagnosis and treatment of allergic disease, including the evidence-based use of AIT (Leatherman et al., 2014).

**Skin Testing**

Evidence-based treatment guidelines for diagnosing allergic disease recommend the skin prick test (SPT) as the first-line diagnostic tool, in conjunction with the patient history and physical assessment. In this study, serum IgE testing was used more frequently than SPT to diagnose allergies (12.9% and 0.65%, respectively). However, the majority of NPs did not perform any allergy testing (81.29%) and referred patients to a specialist for further management. These results are similar to the AIRS study as 24.7% of NPs and PAs combined, used blood tests to diagnose ARC, while only 1.1% performed skin testing, and 71.9% did neither (Blaiss et al., 2014). The “Joint Force Practice Parameter” recommends initial allergy testing by SPT as it is safe, less expensive and more sensitive that serum IgE testing, and results are immediate (Cox, Nelson, & Lockey, 2010). Serum IgE testing should be reserved for those that are unable to have skin testing or if further diagnostic information is needed.

**Study Limitations**

Due to the homogeneity of survey responses, it is unknown if a larger sample size would yield significantly different results. The lack of NPs prescribing sublingual immunotherapy in this study could also be attributed to the fact that none of the respondents reported allergy and immunology as a subspecialty. Study results may be generalizable to Family Nurse Practitioners, but may not be applicable to other specialties. The following section discusses
how the findings in this study may be applied to DNP practice to improve best practice when prescribing sublingual immunotherapy.

**Implications in DNP Practice**

The results of this study indicate the need for NP education in treating allergic disease. This includes NPs practicing in rural areas, who may confronted with limited referral options due to geographic and financial limitations. The World Allergy Organization recommends collaboration between primary care providers and allergist in treating patients with allergen immunotherapy (Canonica et al., 2014). Improving education for providers on diagnosing and treating allergies as well as improving community awareness are also sanctioned by the World Allergy Organization (Canonica et al., 2014). Current evidence supports the use of allergen immunotherapy as a treatment modality when other therapies have failed, but this therapy is not frequently employed in practice. Clinical guidelines and consensus statements from experts in allergen immunotherapy were used to develop an algorithm to guide NPs when treating allergic disease with sublingual immunotherapy (Canonica et al., 2009; Canonica et al, 2014; Cox et al., 2010; Wise & Schlosser, 2012). Figure 2 outlines the algorithm.

The first step in treating allergic disease begins with a patient evaluation. The patient history and physical assessment must be consistent with allergic disease and other potential causes of symptoms should be ruled out. Once the diagnosis of allergic disease has been made, the next step is to structure a management plan.

Management options include symptom control therapies, allergy testing, or referral to a specialist, such as an otolaryngologist or allergist for further evaluation. If the patient is well-controlled using non-pharmacological treatments, antihistamines and/or nasal steroids, then allergen immunotherapy is usually not indicated. If the patient continues to be symptomatic,
then allergy testing and further management is necessary. Positive allergy testing may indicate
the need for allergen immunotherapy.

The final stage is to develop a treatment plan. If sublingual immunotherapy is an
appropriate treatment option, a NP must then decide to either refer to a specialist or follow safe
and efficacious recommendations. An evaluation of different sublingual treatment options is
important in determining the safest, most efficacious, and cost effective treatment for the patient.
Patients not improving with sublingual immunotherapy or have a history of increased risk for
anaphylaxis, or potential structural abnormalities should be referred to a specialist.
Figure 2

Algorithm for Evaluation and Management of Allergies with Allergen Immunotherapy

**EVALUATION**

**PATIENT HISTORY**
- PHYSICAL EXAM
- DX (+) ALLERGIES

(Cox et al., 2010)

**MANAGEMENT**

Avoidance
- Sinus Irrigation
- 2nd Generation Antihistamines
- Nasal Steroids

(Wise & Schlosser, 2012)

Allergy testing
- (+) SPT or
- (+) Serum IgE test

(+) Symptom Reduction

Referral to specialist for further evaluation

(+) Symptom Reduction

(+) Symptom Reduction

**TREATMENT**

Sublingual immunotherapy
- tablets
- drops

Mono-sensitized
- Consider treatment with offending allergen only
  - Tablets
  - Aqueous Drops

Poly-sensitized
- (few allergens, correlated symptoms)
- Consider treatment with antigen-specific immunotherapy

Poly-sensitized
- (many allergens, correlated symptoms)
- Consider treatment with multi-allergen formulation
  - min. studies/many anecdotal reports

Allergist/Immunologist
- Otolaryngology (ENT)

Structural problems
- Surgical intervention
- Subcutaneous Immunotherapy
- Sublingual Immunotherapy

(Cox & Jacobson, 2009)
Dissemination of Results

NPs would benefit from additional education regarding sublingual immunotherapy. The results of this study will be submitted to the Journal of Nurse Practitioners (JNP) for potential publication. Study results may be submitted to future NP conferences for further dissemination of recommendations for best practice when prescribing sublingual immunotherapy.

Conclusion

The media and market availability of medications often influence treatment and prescribing practices among NPs and other clinicians. With the recent over-the-counter availability of commonly prescribed nasal steroids and the FDA-approval of three sublingual tablets, allergy treatment is a predominant topic of interest. This study demonstrated the need for additional education for NPs in the area of allergen immunotherapy. Increased knowledge of the most recent indications and treatment options, as well as testing and referral knowledge, may potentially alleviate many of the barriers associated with sublingual immunotherapy. This will improve best-practice and expand treatment options for patients.
Appendix A

LITERATURE REVIEW TABLE

Randomized controlled trials (RCTs) – Databases: EMBASE, PubMed, Cochrane Library
Key words: sublingual immunotherapy

<table>
<thead>
<tr>
<th>Author/ Title</th>
<th>Study Design/ Methods</th>
<th>Purpose</th>
<th>Sample Size</th>
<th>Results</th>
<th>Conclusions</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ahmadianfshar, A., Maarefvaand, M., Taymourzadeh, B., Mazloomzadeh, S., &amp; Torabi, Z. (2012). Efficacy of sublingual swallow immunotherapy in children with rye grass pollen allergic rhinitis: a double-blind placebo-controlled study</td>
<td>Randomized, DBPC study of 5-18 year olds with rye grass pollen allergy rhinitis or rhinoconjunctivitis for &gt; 2 years &amp; positive SPT to rye grass Rye grass spray extracts 10, 100, 300 IR</td>
<td>The effects of SLIT on symptom score and medication and skin prick test (SPT) evaluation of patients with allergic rhinitis</td>
<td>N=24 (5-18 years) N=12 treatment group N=12 placebo</td>
<td>Significant reduction in symptom score at 21 weeks for treatment group Significant reduction in medication scores at 15 weeks for treatment group Adverse effects increased in placebo group from 19th-22nd week. Significant reduction in wheal diameter from baseline to 6 months for rye</td>
<td>Study showed that SLIT is safe and effective for treatment of allergic rhinitis in 5-18 years and high doses of allergen may be safely administered at home.</td>
<td>Small sample size Short duration of treatment Statistical significance only calculated for SPT</td>
</tr>
<tr>
<td>Amar, S. M., Harbeck, R. J., Sills, M., Silveira, L. J., O’Brien, H., &amp; Nelson, H. S. (2009). Response to sublingual immunotherapy with grass pollen extract: monotherapy versus combination in multiallergen extract</td>
<td>Single-center, randomized, double-blind, placebo-controlled trial with SLIT Treated for 10 months</td>
<td>To examine whether the efficacy of SLIT w/timothy extract was reduced when combined with other allergen extracts</td>
<td>N=54 N=17 MAT Timothy 1mL 100,000 BAU/mL 680 µg/mL Phl p 5 &amp; 9 mL 50% gly. Soln (19 µg Phl p 5) plus 1 mL 1:20 w/v in 50% glycerin, maple, ash, juniper, American Elm, cottonwood, Kochia, ragweed, sagebrush, Russian Thistle N=19 TM Timothy 1mL 100,000 BAU/mL 680 µg/mL Phl p 5 &amp; 9 mL 50% gly. Soln (19 µg Phl p 5) N=17 Placebo</td>
<td>No significant differences in pre-post symptom scores (P=0.96) or medication scores (p=0.7) in all 3 groups. Nasal challenge improved w/TM vs. placebo (p=0.03), no diff. MAT vs. placebo (P=0.11) tSPT TM (P=0.001) improvement vs. placebo, MAT (P=0.04) vs. placebo Timothy-specific IgG4 increased in TM only (P=0.005); Decrease IFN-γ in TM only (P=0.005)</td>
<td>Clinically relevant responses achieved with monotherapy; MAT showed limited response</td>
<td>Low grass pollen count during observational season, all 3 groups had improved medication &amp; symptom scores</td>
</tr>
<tr>
<td>Author(s)</td>
<td>Study Design</td>
<td>Outcome Measures</td>
<td>Sample Size</td>
<td>Results</td>
<td>Study Type</td>
<td></td>
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<tr>
<td>Aydogan, M., Eifan, A. O., Keles, S., Akkoc, T., Nursoy, M. A., Bahceciler, N. N., &amp; Barlan, I. B. (2013).</td>
<td>Randomized to active or placebo by double-blind method for 12 months. DSS, medication scores, baseline lung functions, bronchial hyper reactivity, nasal provocation &amp; skin prick tests</td>
<td>Asses the clinical efficacy and safety of house dust mite (HDM) SLIT for children with AR monosensitized to HDM without asthma</td>
<td>N=18 Active group; cum dose 11.7 mg Der p1 &amp; 28.2 mg Der f1 N=10 Placebo</td>
<td>No significant differences detected between groups based on total rhinitis symptoms/medication scores (P&gt;0.05). Decrease in total conjunctivitis symptoms for both groups, but no statistical difference (p&gt;0.05). No difference in cough, wheezing or asthma symptoms</td>
<td>Small sample size</td>
<td></td>
</tr>
<tr>
<td>Bozek, A., Ignasiak, B., Filipowska, B., &amp; Jarzab, J.</td>
<td>Randomized DBPC trial 60-75 year olds for 3 years Storalor 300 SR Der p &amp;</td>
<td>Assess nasal symptom scores during HDM season, reduce</td>
<td>N=111 60-75 years w/AR &amp; HDM allergy N=51 SLIT</td>
<td>Total nasal symptom score reduced 44% (P&lt;0.05) in HDM</td>
<td>Significant clinical improvement in active group w/SLIT &amp; well tolerated.</td>
<td>7-point visual analogue scale used to pick up small differences</td>
</tr>
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<tr>
<td>House dust mite sublingual immunotherapy: a double-blind, placebo-controlled study in elderly patients with allergic rhinitis</td>
<td>Der f 50/50% extract Average cumulative dose 421 200 IR of allergens for all 3 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>medicatio n use &amp; monitor adverse advents during immunotherapy</td>
<td>N=57 placebo</td>
<td></td>
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</tr>
<tr>
<td>SLIT; 6% in placebo after 3 yrs. Total medication score decreased in HDM group 35% (P&lt;0.05); no change in placebo group (P=0.56)</td>
<td>Aging immune system does not appear to influence the effectiveness of immunotherap y.</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>No systemic adverse reactions</td>
<td>differences in nasal reaction and diaries filled weekly to simplify the procedur e for older adults, but could reduce the reliabilit y of the results.</td>
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<tr>
<td>Compare the safety and physiolog ic effects of high vs. low-dose Dermato phagoide s farinae vaccine (HDM) in adults 18-50 with ≥ 2 yr. hx of allergic rhinitis, positive SPT to D. Farinae, and in vitro D</td>
<td>N=31 N=10 High-dose (4200 allergen units 70 µg of Der f 1/d) N=10 Low-dose (60 allergen units 1 µg Der f 1/d) N=11 Placebo</td>
<td></td>
<td></td>
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<tr>
<td>AE’: All subjects tolerated the highest targeted daily dose of treatment. 55.6% high-dose 57.1 low-dose 60% placebo Symptoms and medication use: No significant differences between treatment group &amp; SLIT with high-dose D farinae appears to be safe and tolerable in adults. No significant differences were found in symptom scoring or medication use between the 3 groups.</td>
<td>Dust samples were low and self-collected by study participa nts.</td>
<td></td>
<td></td>
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<tr>
<td>Small sample size</td>
<td>All participa nts were poly-sensitize d to other aeroaller gens</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
| Cortellini, G., Spadolini, I., Patella, V., Fabbri, E., Santucci, A., Severino, M., ... Passalacqua, G. | **farinae-specific serum IgE > 2x that of non-allergenic control** | Placebo after 12 months. IgE serum slight, but statistically non-significant increase in high-dose group at 6 mo. & end of study. IgG4 levels in high-dose significantly increased at 6 mo (P=.03) & end of study (P=.02).
Bronchoprovocation: significant increase in high dose group only (P=.04 vs placebo).

**Randomized, prospective, double-blind, placebo-controlled, 2 parallel groups trial**
Patients with rhinitis with or without intermittent asthma and ascertained

**To assess the efficacy of standardized SLIT in patient sensitized to *Alternaria***

**N=27 (14-42 years)**
N=15 SLIT (cum dose 60 µg of Alt a 1)
N=12 placebo

**Mean (SD) symptom scores reduced in active group (182 [67] vs 315 [115], P=.02) Medication scores significant reduction in active**

**Results favored SLIT for symptom reduction and medication scores only in active group. Cum 60 µg Alt a 1 = 6 µg per month – considered low dose**

**Small sample size**
Short length of study
Difficult in recruitment due to strict inclusion criteria
<table>
<thead>
<tr>
<th>Creticos, P. S., Esch, R. E., Couroux, P., Gentile, D., D’Angelo, P., Whitlow, B., ... Coyne, T. C. (2014). Randomized, double-blind, placebo-controlled trial of standardized ragweed sublingual allergen immunotherapy liquid (RW-SAIL) extract in subjects with ragweed-related allergic rhinoconjunctivitis.</th>
<th>N=218 RW-SAIL N=211 placebo</th>
<th>Only 1 maintenance dose was used. A dose-ranging study would be necessary to see if efficacy could be improved.</th>
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<td>(2010). Sublingual immunotherapy for Alternaria-induced allergic rhinitis: a randomized placebo-controlled trial</td>
<td>group (P=.02) Mean (SD) diameter of wheal increased vs baseline (10.9 [3.4] vs 8.7 [3] mm) 1 patient has oral itching and conjunctivitis in active group with spontaneous resolution</td>
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<td>allergy to <em>Alternaria</em> 10 months of SLIT or placebo</td>
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<td>Creticos, P. S., Esch, R. E., Couroux, P., Gentile, D., D’Angelo, P., Whitlow, B., ... Coyne, T. C. (2014). Randomized, double-blind, placebo-controlled trial of standardized ragweed sublingual allergen immunotherapy liquid (RW-SAIL) extract in subjects with ragweed-related allergic rhinoconjunctivitis.</td>
<td>N=218 RW-SAIL N=211 placebo</td>
<td>Only 1 maintenance dose was used. A dose-ranging study would be necessary to see if efficacy could be improved.</td>
</tr>
<tr>
<td>(2010). Sublingual immunotherapy for Alternaria-induced allergic rhinitis: a randomized placebo-controlled trial</td>
<td>group (P=.02) Mean (SD) diameter of wheal increased vs baseline (10.9 [3.4] vs 8.7 [3] mm) 1 patient has oral itching and conjunctivitis in active group with spontaneous resolution</td>
<td>Only 1 maintenance dose was used. A dose-ranging study would be necessary to see if efficacy could be improved.</td>
</tr>
<tr>
<td>(2010). Sublingual immunotherapy for Alternaria-induced allergic rhinitis: a randomized placebo-controlled trial</td>
<td>allergy to <em>Alternaria</em> 10 months of SLIT or placebo</td>
<td>Only 1 maintenance dose was used. A dose-ranging study would be necessary to see if efficacy could be improved.</td>
</tr>
<tr>
<td>al-liquid immunotherapy for allergic conjunctivitis</td>
<td>The primary end point was subject-assessed total combined daily rhinoconjunctivitis symptom and medication scores (TCS)</td>
<td>unctivitis (ARC)</td>
</tr>
<tr>
<td>-------------------------------------------------</td>
<td>-------------------------------------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>De Bot, C. A., Moed, H., Berger, M. Y., Roder, E., Hop, W. C., De Groot, H., ... Van der Wouden, J. C. (2012). Sublingual Randomized DBPC trial SLIT in children 6-18 yrs. old with HDM allergic rhinitis for 2 years. Maintenance dosing after escalation 20 drops twice weekly (1 mL or 700 BU) Der p 1, Der f 1</td>
<td>Investigate if SLIT for dust-mite allergic children is safe and effective in primary care</td>
<td>N=257 N=251 safety population N=226 ITT population N=185 PP (per protocol) population</td>
</tr>
<tr>
<td>Immunotherapy not effective in house dust mite-allergic children in primary care</td>
<td>Immunity not effective in house dust mite-allergic children in primary care</td>
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<td>Immunotherapy not effective in house dust mite-allergic children in primary care</td>
</tr>
<tr>
<td>Eifan, A. O., Akkoc, T., Yildiz, A., Keles, S., Ozdemir, C., Bahceciler, N. N., &amp; Barlan, I. B. (2010). Clinical efficacy and immunological mechanisms of sublingual and subcutaneous immunotherapy in asthmatic/rhinitis children sensitized to house dust mite (HDM).</td>
<td>Compare SLIT, SCIT &amp; pharmacology in relation to clinical efficacy &amp; immunological mechanisms in asthma/rhinitis children sensitized to house dust mite (HDM)</td>
<td>N=48 children (5-10 years old)</td>
</tr>
<tr>
<td>Single center, prospective, randomized, controlled, open labelled, 3 parallel group trial Symptom, medication, &amp; VAS evaluated for 12 months</td>
<td>Symptom, medication, &amp; VAS evaluated for 12 months</td>
<td>N=48 children (5-10 years old)</td>
</tr>
<tr>
<td>No AE’s with SLIT. 2 AE’s with SCIT</td>
<td>SCIT &amp; SLIT demonstrated clinical improvement over pharmacotherapy in asthma/rhinitis children with HDM</td>
<td>No difference in SCIT &amp; SLIT – equally effective in controlling severity of disease</td>
</tr>
<tr>
<td>SLIT had greater reduction in medication usage than SCIT</td>
<td>SLIT had greater reduction in medication usage than SCIT</td>
<td>SLIT had greater reduction in medication usage than SCIT</td>
</tr>
<tr>
<td>Small sample size increased risk of statistical error II &amp; raised ethical issues without using a placebo</td>
<td>Small sample size increased risk of statistical error II &amp; raised ethical issues without using a placebo</td>
<td>Small sample size increased risk of statistical error II &amp; raised ethical issues without using a placebo</td>
</tr>
<tr>
<td>dust mite: an open randomized controlled trial</td>
<td>Fujimura, T., Yonekura, S., Horiguchi, S., Taniguchi, Y., Saito, A., Yasueda, H., ... Okamoto, Y. (2011). Increase of regulator T cells and the ratio of specific IgE to total IgE are candidates for response monitoring or prognostic biomarkers in 2-year sublingual immunotherapy (SLIT)</td>
<td>Randomized, DBPC clinical trial Japanese Cedar in Japan (Cry j 1) 2000 JAU extract contains 1.5-4.2 µg of Cry j 1 (monthly cum. Dose 8000 JAC/10 µg) Primary endpoints: safety &amp; clinical effects of SLIT &amp; upregulation of iTregs as a response monitoring biomarker Secondary: Carry-over effects, immunologic changes, and biomarkers for positive clinical</td>
</tr>
<tr>
<td><strong>Effects induced by SLIT</strong></td>
<td><strong>Increased iTreg group had increased QOL symptom &amp; QOL total when compared with placebo</strong></td>
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<tr>
<td>For Japanese cedar pollinosis</td>
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<tr>
<td><strong>Makino, Y., Noguchi, E., Takahashi, N., Natsyniti, Y., Kubo, S., Yamada, T.,... Fujieda, S. (2010).</strong> Apolipoprotein A-IV is a candidate target molecule for the treatment of seasonal allergic rhinitis</td>
<td><strong>25 patients randomly categorized into placebo-treated and an active treated group with Japanese Cedar pollen extract (2000 JAU/mL maintenance – 15 µg Cry j 1 and 2 to 5 µg Cry j 2) Precise mechanism of AIT is not well understood. Aim is to identify protein expression signature reflective of AIT</strong></td>
<td></td>
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<tr>
<td>N=25 N=15 actively treated N=9 placebo treated</td>
<td><strong>SMS during peak pollination lower in SLIT group, but not significant (p=.36). No difference in medication scores. QOL SLIT superior to placebo (9.5 ± 8.3 vs 15.9 ± 19.6; P=0.48)</strong></td>
<td></td>
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<tr>
<td><strong>Levels of apoA-IV, complement C4A &amp; transthyretin increased in SLIT group, trend not observed in placebo group. Identified proteins associated with SKIT by 2-DE analysis</strong></td>
<td><strong>Small sample size. 37% of population were polysensitized to other allergens</strong></td>
<td></td>
</tr>
<tr>
<td>Authors</td>
<td>Study Design</td>
<td>compares effects of treatment</td>
</tr>
<tr>
<td>-------------------------</td>
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<td>--------------------------------</td>
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<tr>
<td>Marogna, M., Coombo, F., Spadolini, J., Massolo, A., Berra, D., Zanon, P., ... Passalacqua, G. (2010)</td>
<td>Open randomized controlled, 2 parallel groups trial (ethics committee denied permission to blind the treatments and use a placebo arm)</td>
<td>Moderate persistent asthma due to birch pollen</td>
</tr>
<tr>
<td>Marogna, M., Spadolini, I.,</td>
<td>Open, 2-parallel groups, Randomized</td>
<td>Inhaled budesonide vs SLIT</td>
</tr>
</tbody>
</table>

Endpoints: Seasonal symptoms plus drug intake score, pulmonary function, bronchial hyperresponsiveness, nasal eosinophils.
<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Study Design</th>
<th>Intervention</th>
<th>N</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Massolo, A., Berra, D., Zanon, P., Chiodini, E., ... Passalacqua, G. (2009).</td>
<td>Long-term comparison of sublingual immunotherapy vs inhaled budesonide in patients with mild persistent asthma due to grass pollen</td>
<td>SLIT for up to 5 years</td>
<td>N=26</td>
<td>Improvement in the SLIT group compared with budesonide group. Improved nasal symptoms not appreciated by inhaled budesonide. SLIT produces greater benefit over solely inhaled budesonide in patients with asthma &amp; rhinitis due to grass pollen.</td>
</tr>
<tr>
<td>O’Hehir, R. E., Gardner, L. M., De Leon, M. P., Hales, B. J., Biondo, M., Douglass, J. A., ... Sandrini, A. (2009).</td>
<td>Randomized DBPC study of adults with moderate to severe perennial rhinitis to HDM for 12 months.</td>
<td>N=30</td>
<td>SLIT clinical efficacy supported by longitudinal (within groups) improvement in clinical outcomes &amp; decreases in allergen-specific CD4+ T cell proliferation, transient increase in</td>
<td></td>
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<tr>
<td></td>
<td>Perform detailed immunological investigation of SLIT-HDM</td>
<td>HDM, SLIT reduced symptom score (P&lt;0.05) and total asthma score (P&lt;0.01)</td>
<td>N=15</td>
<td>SLIT produces greater benefit over solely inhaled budesonide in patients with asthma &amp; rhinitis due to grass pollen.</td>
</tr>
</tbody>
</table>

(Ethics committee denied permission to blind and use a placebo group due to length of study) Build up to 10,000 RU/mL grass pollen Cum. Annual dose 70 µg Phl p 1

Budesonide 800 µg

Improved nasal symptoms not appreciated by inhaled budesonide. SLIT produces greater benefit over solely inhaled budesonide in patients with asthma & rhinitis due to grass pollen. |

No double blind

Parameters evaluated at 3 & 5 years—missing information

Some authors have financial relationships or board membership with pharmaceutical co.
### House dust mite sublingual immunotherapy: The role for transforming growth factor-b and functional regulatory T cells

<table>
<thead>
<tr>
<th>Ott, H., Sieber, J., Brehler, R., Folster-Hoist, R., Kapp, A., Klimek, L., ... Merk, H. (2009). Efficacy of grass pollen sublingual immunotherapy for three consecutive seasons and after cessation of treatment: the Randomized DBPC study (2:1 randomization) 7.9-64.7 years old with grass pollen allergy, ultra-rush titration</th>
<th>Evaluate the efficacy, carry-over effect and safety of grass pollen SLIT using co-seasonal treatment. Efficacy, safety, &amp; tolerability of Coseasonal ultra-Rush sublingual Immunotherapy (ECRIT)</th>
<th>N=213 (7.9-64.7 years) randomized, but data obtained for 183 patients &amp; diaries for 145 patients – ITT population. N=99 SLIT w/21 µg Phl p 5 (mix cocksfoot or orchard, meadow, perennial rye, sweet vernal &amp; timothy grasses) N=46 placebo</th>
<th>Combined symptom &amp; medication score decreased significantly w/SLIT (P=0.043); magnitude of efficacy 33.9% for symptom with SLIT (P=0.0366); Medication decrease not statistically significant. Efficacy of co-seasonal treatment was demonstrated over 3 years and may be beneficial for those presenting late for treatment. Study applicable to adults and need confirmation before generalization to pediatric population. Study sponsored by allergen extract manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CD4+CD25+FOXP3+/CD127</strong>&lt;sup&gt;+&lt;/sup&gt; <strong>Possible difference between perennial &amp; seasonal allergens</strong></td>
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<tr>
<td>ECRIT study</td>
<td>Phase IV open study to compare the clinical efficacy of a continuous and a co-seasonal SLIT for grass allergy for 3 years in 8-16 year olds with hx of rhinoconjunctivitis / asthma only during grass pollen season in the last 2 years</td>
<td>Year 1: Symptom scores, medication scores, &amp; chest symptoms significantly lower in CON-SLIT than baseline (p=0.001, 0.007, 0.02 respectively)</td>
<td>Continuous treatment with grass pollen SLIT in children with seasonal respiratory allergies was more effective than co-seasonal treatment in the 1st year. Co-seasonal reached similar efficacy in year 2 and equal in 3rd year.</td>
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<td>---------------------------------------------------------------------------------</td>
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<tr>
<td>Pajno, G. B., Caminiti, L., Crisafulli, G., Vita, D., Valenzise, M., De Luca, R., &amp; Passalacqua, G. (2011). Direct comparison between continuous and co-seasonal regimen for sublingual immunotherapy in children with grass allergy: A randomized controlled study</td>
<td>Randomized, open, with two parallel groups (inclusion of placebo group denied by ethics committee due to length of study)</td>
<td>N=80 N= 40 CON-SLIT w/ 300 IR/ml (14 mcg/ml Phl p 5) w/6 day build up then maint of 6 gitts 5 days/wk N=40 COS-SLIT (same dose started on the first days of pollen season (March) until the end of June)</td>
<td>Year 1: Symptom scores, medication scores, &amp; chest symptoms significantly lower in CON-SLIT than baseline (p=0.001, 0.007, 0.02 respectively)</td>
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</tbody>
</table>

| N=80 | Year 1: Symptom scores, medication scores, & chest symptoms significantly lower in CON-SLIT than baseline (p=0.001, 0.007, 0.02 respectively) | No blinding or placebo group | Continuous treatment with grass pollen SLIT in children with seasonal respiratory allergies was more effective than co-seasonal treatment in the 1st year. Co-seasonal reached similar efficacy in year 2 and equal in 3rd year. | No blinding or placebo group |
| N= 40 | Year 1: Symptom scores, medication scores, & chest symptoms significantly lower in CON-SLIT than baseline (p=0.001, 0.007, 0.02 respectively) | No blinding or placebo group | Continuous treatment with grass pollen SLIT in children with seasonal respiratory allergies was more effective than co-seasonal treatment in the 1st year. Co-seasonal reached similar efficacy in year 2 and equal in 3rd year. | No blinding or placebo group |
| CON-SLIT w/ 300 IR/ml (14 mcg/ml Phl p 5) w/6 day build up then maint of 6 gitts 5 days/wk N=40 COS-SLIT (same dose started on the first days of pollen season (March) until the end of June) | Year 1: Symptom scores, medication scores, & chest symptoms significantly lower in CON-SLIT than baseline (p=0.001, 0.007, 0.02 respectively) | No blinding or placebo group | Continuous treatment with grass pollen SLIT in children with seasonal respiratory allergies was more effective than co-seasonal treatment in the 1st year. Co-seasonal reached similar efficacy in year 2 and equal in 3rd year. | No blinding or placebo group |
| COS-SLIT only medication scores was reduced (p=0.05) SMS reduced CON-SLIT 44% COS-SLIT 20% (p=0.04) Symptom scores fell 39% CON-SLIT; 15% COS-SLIT (p=0.02) Medication scores fell 60% CON-SLIT and 18% COS-SLIT (p=0.03) | Year 1: Symptom scores, medication scores, & chest symptoms significantly lower in CON-SLIT than baseline (p=0.001, 0.007, 0.02 respectively) | No blinding or placebo group | Continuous treatment with grass pollen SLIT in children with seasonal respiratory allergies was more effective than co-seasonal treatment in the 1st year. Co-seasonal reached similar efficacy in year 2 and equal in 3rd year. | No blinding or placebo group |

| Year 1: Symptom scores, medication scores, & chest symptoms significantly lower in CON-SLIT than baseline (p=0.001, 0.007, 0.02 respectively) | No blinding or placebo group | Continuous treatment with grass pollen SLIT in children with seasonal respiratory allergies was more effective than co-seasonal treatment in the 1st year. Co-seasonal reached similar efficacy in year 2 and equal in 3rd year. | No blinding or placebo group | Continuous treatment with grass pollen SLIT in children with seasonal respiratory allergies was more effective than co-seasonal treatment in the 1st year. Co-seasonal reached similar efficacy in year 2 and equal in 3rd year. | No blinding or placebo group |
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| Pozzan, M., & Milani, M. (2010). Efficacy of sublingual specific immunotherapy in patients | Randomized, assessor-blinded, parallel group, placebo-controlled 3 year study | Evaluate the efficacy of SLIT treatment – clinical improvement and rescue medication usage in patients | N=52  
N=34  
SLITI with AA one vial/day w/o up-dosing for 3 years  
(Alt a 1 cum monthly dose 3.6 µg/month) | VAS score  
4.7±0.8 SLIT;  
2±1.5 placebo  
(P=0.0002)  
97% clinical improvement in SLIT group; | SLIT with Alternaria alternata efficacious and well tolerated over 3 year course for patients with AA respiratory allergy | The study was not double-blind  
Efficacy was not assessed with validated | Chest symptoms reduced in CON-SLIT 72% and 11% in COS-SLIT (p<0.01)  
Year 2: No significant difference between groups SMS, Medication scores. Symptoms CON-SLIT fell 51%, COS-SLIT 34% (p=0.04)  
Chest symptoms CON-SLIT 88% & 53% COS-SLIT (p=0.05)  
Year 3. No sign diff |
with respiratory allergy to Alternaria alternata: a randomised assessor-blinded, patient-reported outcome, controlled 3-year trial

<table>
<thead>
<tr>
<th>with Alternaria alternata allergy</th>
<th>N=18 control group treated with symptomatic drugs only.</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=18 placebo (p=0.0001) MS significantly decreased 4.3 to 1.7 (p=0.0001) in SLIT group; Increased in control from 3.4 to 4.</td>
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</table>

27% in placebo

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<tbody>
<tr>
<td>Identify a safe and effective maintenance dose range of sublingual standardized glycerinated short ragweed pollen extracts in adults w/ragweed-induced rhinoconjunctivitis</td>
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<tr>
<td>N=115</td>
<td></td>
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<tr>
<td>N=40 placebo (glycerin soln)</td>
<td></td>
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<tr>
<td>N=39 med dose (4.8µg Amb a 1/d)</td>
<td></td>
</tr>
<tr>
<td>N=36 high dose (48 µg Amb a 1/d)</td>
<td></td>
</tr>
<tr>
<td>15% reduction in rhinosinusitis symptom scores (not stat. sign p&gt;.10) Analysis of covariance; symptom scores &amp; medication scores significantly reduced in high-dose group (p≤.05) Analysis of covariance; symptom scores &amp; medication scores significantly reduced in high-dose group (p≤.05)</td>
<td></td>
</tr>
<tr>
<td>Maintenance dosed of 4.8 µg-48 µg Amb a 1/d safe &amp; induce favorable clinical &amp; immunologic changes in ragweed-sensitive subjects. Additional trials are needed to establish efficacy</td>
<td></td>
</tr>
<tr>
<td>90% of study participants had multiple perennial &amp;/or seasonal allergies – symptoms could be caused by other allergens. Well controlled multi-allergen studies in poly-sensitized subjects</td>
<td>symptomatic score</td>
</tr>
<tr>
<td>MM employee of ALK (SLIT manufacturer)</td>
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<tr>
<td>Study</td>
<td>Design</td>
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<td>-------</td>
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<tr>
<td>Stelmach, I., Kaluzinska-Parzyszek, I., Jerynska, J., Stelmach, P., Stelmach, W., &amp; Majak, P. (2011).</td>
<td>Randomized DBPC 2 year prospective trial of 6-18 year olds with grass pollen rhinitis</td>
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</table>
ess of high dose sublingual immunotherapy in children | Randomized DBPC single center trial with birch pollen allergy for 2 years | Evaluate the effects of high dose birch SLIT on birch induced rhinitis and asthma | N=24 N=14 SLIT co-seasonal protocol (cum. 6.9 mcg Bet v 1) N=10 placebo | Significant decrease (p<0.05) in rhinorrhea and nasal obstruction Median asthma days 3rd visit: SLIT 10, Placebo 13; 6th visit: SLIT 2, placebo 7; Birch pollen asthma may be able to step down after prolonged treatment with SLIT birch extract | Small sample size (difficulty finding mono-sensitized adults) Possible non-normal distribution of data due to small sample size |
<table>
<thead>
<tr>
<th>Immunotherapy to induce a stepdown of season asthma: a pilot study</th>
<th>Asthma stepdown 77% in SLIT, 0 in placebo (p=0.05)</th>
<th>No severe AE’s</th>
<th>Dictated nonparametric tests, thus the pilot study status.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study funded by extract manufacturer</td>
<td>Authors with financial ties to extract manufacturer and drug companies</td>
<td>Unable to compare results with other SLIT tablet trials due to the inclusion of a baseline season patient symptom diary.</td>
<td></td>
</tr>
</tbody>
</table>

Wahn, U., Klimek, L., Ploszczuk, A., Adelt, T., Sandner, B., Trebas-Pietras, E., ... SLIT Study Group (2012). High-dose sublingual Randomized DBPC study in children 4-12 years with grass pollen-allergic rhinitis/rhinocconjunctivitis with or w/o bronchial asthma. (Germany & Poland) Efficacy and safety of high-dose SLIT in children allergic to grass pollen N=207 (4-12 years old) N=158 Active group (3600-4800 µg of grass group 5) N=49 placebo Primary outcome: Mean AUC (change of the area under the curve of the symptom-medication score (SMS) from baseline to post 1 pre-co-seasonal treatment period) Daily single-dose aqueous grass pollen SLIT is efficacious and safe in children 4-12 years with allergic rhinitis/rhinocconjunctivitis.
immunotherapy with single-dose aqueous grass pollen extract in children is effective and safe: a double-blind, placebo-controlled study

| Wang, D. H., Chen, L., Li, K. N., Yuan, H., Lu, J. H., & Li, H. (2013). Fast onset of action of sublingual immunotherapy in house dust mite-induced allergic rhinitis: a multicenter, randomized DBPC trial with house dust mite (Dermatophagoides pteronyssinus and Dermatophagoides farina) treated for 6 months. Symptoms, medication, visual analog scale score were recorded. Investigate how quickly AR symptoms will improve with SLIT, potential side effects, common reason for dropout. N=120 patients w/AR symptoms screened (4-60 years) N=60 HDM N=60 placebo. Significant decrease in symptoms between HDM group & placebo was week 14 (p<0.05). No difference in daily medication scores at each visit; HDM meds lower at weeks 7, 9, 10 than placebo. SLIT w/HDM showed a significant improvement in AR symptoms w/onset at 14 weeks & acceptable safety profiles. 20% dropout rate for treatment group; 38% dropout rate for placebo group. SLIT new to China, additional patient education may decrease dropout rates in future guidelines and recommendations. |
| Active - 212.5 Placebo - 97.8 (P=.0040). | Comparative studies show treatment for >12 months demonstrate greater clinical improvement and should be considered in future guidelines and recommendations |
| | | |
multicenter, randomized, double-blind, placebo-controlled trial.

| baseline (P<0.05); no change in placebo group |
| VAS reduction week 14 (P<0.05) & more pronounced at end of trial |

future studies.
### Appendix B

**Date:** March 06, 2015  
**Principal Investigator:** Melissa Leann Ferrell  
**Protocol Number:** 1503719837  
**Protocol Title:** Sublingual Immunotherapy  
**Level of Review:** Exempt  
**Determination:** Approved  

**Documents Reviewed Concurrently:**  
- HSPP Forms/Correspondence: F107 v2014-01_02262015.doc  
- HSPP Forms/Correspondence: IRB  
- F200_Ferrell_SLIT_02262015_revised IRB.doc  
- HSPP Forms/Correspondence: Signature page.pdf  
- Participant Material: Document 1.docx  
- Participant Material: Document 3_Survey Questions.docx

This submission meets the criteria for exemption under 45 CFR 46.101(b).

- The University of Arizona maintains a Federalwide Assurance with the Office for Human Research Protections (FWA #00004218).  
- All research procedures should be conducted in full accordance with all applicable sections of the Investigator Manual.  
- Exempt projects do not have a continuing review requirement.  
- Amendments to exempt projects that change the nature of the project should be submitted to the Human Subjects Protection Program (HSPP) for a new determination. See the Investigator Manual, 'Appendix C Exemptions,' for more information on changes that affect the determination of exemption. Please contact the HSPP to consult on whether the proposed changes need further review.  
- All documents referenced in this submission have been reviewed and approved. Documents are filed with the HSPP Office. If subjects will be consented the approved consent(s) are attached to the approval notification from the HSPP Office.

Your proposal is in compliance with Federalwide Assurance 00004218. This project should be conducted in full accordance with all applicable sections of the IRB Investigators Manual and you should notify the IRB immediately of any proposed changes that affect the protocol. You should report any unanticipated problems involving risks to the participants or others to the IRB.

This project has been reviewed and approved by an IRB Chair or designee.
Faculty Advisor Approval of Data Collection Program Proposal

Instructions: Print this form and fill in your name and the title of your research project. Discuss your project with your faculty advisor and obtain his or her signature indicating that they have reviewed and support your research proposal before submitting it to AANP.

Student Researcher: Melissa Ferrell

Project Title: Sublingual Immunotherapy

I, Kate G. Sheppard (printed name of faculty advisor), have met with the student listed above and reviewed this research proposal with respect to the proposed participants, methods, instruments, and informed consent requirements.

I hereby support this proposal and student seeking approval to purchase a mailing list from AANP.

[Signature]
Faculty Advisor Signature

3/2/2015
Date
AGREEMENT FOR USE OF AANP MAILING LIST

The American Association of Nurse Practitioners (AANP) agrees to grant Melissa Ferrell a non-exclusive and non-transferable license to use a mailing list provided by the American Association of Nurse Practitioners consisting of 500 nurse practitioner members with family, pediatric and or allergy/immunology as main specialty (the "Mailing List") subject to the following terms and conditions:

Melissa Ferrell agrees:

- Neither the Mailing List nor the information contained on the Mailing List will be reproduced or used for any purpose other than the single and exclusive purpose of providing a mailing piece approved in advance by AANP concerning Sublingual Immunotherapy.
- The Mailing List may not be reproduced, sold, resold, or disseminated for or to third parties.
- The Mailing List may be used only for the purpose indicated above, and will be protected from further use by any other group or individual working on Melissa Ferrell’s behalf.
- All copies of the Mailing List will be destroyed within 5 days after the mailing is completed.
- The Mailing List may not be used in connection with any communication which, in the sole opinion of AANP, appears to be deceptive or misleading or which may be unacceptable in content or presentation.
- A hard copy summary of completed research will be submitted to AANP.

To accommodate this arrangement, AANP agrees to supply the Mailing List on a 7-Zip password protected file which will be emailed to Melissa Ferrell.

Melissa Ferrell agrees to remit payment to AANP in the amount of $135.00 representing $.25/name for each name included on the Mailing List. A check, money order or Visa/MasterCard/AMEX payment in the amount of $135.00 must be received and processed by AANP before AANP will release the Mailing List to Melissa Ferrell.

The parties acknowledge that remedies at law may not be adequate to protect AANP’s rights in the event that Melissa Ferrell or his or her employees, vendors breach any duty or provision contained in this agreement. Therefore, the parties agree that in addition to any other remedies at law, AANP shall have the right to injunctive relief in order to enforce its rights under this agreement.

Having read and understood the above items and conditions of this agreement, Melissa Ferrell agrees to assume full responsibility for compliance with this agreement. Any breach of this agreement will subject the undersigned to any or all legal and equitable remedies available to AANP. Noncompliance will disqualify the undersigned from receiving future goods or services from AANP.

If paying with credit card please complete the following and return by fax, or call 512-442-4263 with payment information:

Expiration Date  Melissa L. Ferrell
Name as it appears on Card  Signature of Card Holder

(Name): Melissa Ferrell, FNP-BC
Requester Signature/Title  FNP-BC
Date  3/1/18
Email Address for receipt of attached file: melissa.ferrell@u.arizona.edu

Please return the executed agreement to:
American Association of Nurse Practitioners Administrative Office
ATTN: Research
P.O. Box 12486
AUSTIN, TX 78711

Or return this agreement by fax: 512-442-4263.

Administration: PO Box 12846 • Austin, TX  78711 • Email: admin@aannp.org • Website: aannp.org
Government Affairs: 225 Reineke Lane, Suite 525 • Alexandria, VA  22314 • Email: governmentaffairs@aannp.org
Appendix D

March 10, 2015

Dear Fellow Nurse Practitioner,

I am a Doctor of Nursing Practice (DNP) student at the University of Arizona. For my DNP project, I am looking at the number of nurse practitioners prescribing allergen sublingual immunotherapy and what barriers exist that prevent the use of sublingual immunotherapy as a treatment for allergies and asthma. Because you are nurse practitioner specializing in the area of Family Practice, Pediatrics and/or Allergy/Immunology, I am inviting you to participate in this study by completing the enclosed survey.

The survey should take approximately five minutes to complete and there is no compensation for participation and no known risks. Participation is voluntary and to maintain confidentiality, please keep your survey responses anonymous and answer the questions as honestly as possible. Feel free to skip any questions that you are not comfortable answering and return the completed survey in the provided stamped envelope by March 24, 2015.

Thank you for taking the time to participate in my study. The data collected will provide useful information about number of nurse practitioners prescribing sublingual immunotherapy and what barriers may exist that prevent the use of allergen sublingual immunotherapy in clinical practice. This information will be used to improve the quality and safety of prescribing practices for nurse practitioners using or interested in using sublingual immunotherapy to treat allergies and asthma. This information will be presented as part of my DNP defense, may be submitted to a nursing or allergy/immunology journal or used as part of an educational presentation for nurse practitioners.

Completion of the questionnaire will indicate your willingness to participate in this study. If you desire additional information or have questions, please contact me at (480) 272-0733.

Thanks again for your participation.

Melissa Ferrell, MSN FNP-BC
DNP student
College of Nursing
University of Arizona
melissaferrell7@email.arizona.edu

Please return surveys to: PO BOX 20695
Mesa, AZ 85277
Project Title: Sublingual Immunotherapy

DISCLOSURE FORM
You are being invited to participate in a research study being conducted by the University of Arizona and asked to read this form prior to your participation so that you are aware of potential risks and how the information you may provide will be used. If you decide to take part in the study, your responses will be anonymous. If you decide you do not want to participate, there is no penalty to you, and you will not lose any benefit you normally would have.

WHY IS THIS STUDY BEING DONE?
The purpose of the study is to ascertain how many Nurse Practitioners are utilizing sublingual immunotherapy for allergy treatment in their practice.

WHAT WILL YOU BE ASKED TO DO IN THIS STUDY?
You will be asked to complete a survey of 8 questions, taking approximately 5 minutes of your time.

ARE THERE ANY BENEFITS, COSTS, OR RISKS TO ME?
There may be no direct benefit to you by participating in the study. What researchers find out from this survey may help other healthcare providers learn how many nurse practitioners are utilizing sublingual immunotherapy as a treatment for allergies in their practice. Aside from your time, there are no costs for taking part in the study. Although the researchers have tried to avoid risks, you may feel that some questions are uncomfortable. You do not have to answer any questions that you do not want to answer.

WILL INFORMATION FROM THIS STUDY BE KEPT CONFIDENTIAL?
Information about you will be kept confidential to the extent permitted or required by law. People who have access to your information include the Principal Investigator and advisement committee. Representatives of regulatory agencies such as the Office of Human Research Protections (OHRP) and entities such as the University of Arizona Human Subjects Protection Program may access your records to make sure the study is being run correctly and that information is collected properly. If there are any professional presentations or publications about this study or survey responses, your name, practice name, e-mail address, or postal address will not be in them.

HOW THE FINDING WILL BE USED?
The results of the study will be used for scholarly purposes only. The results from the study will be presented in educational settings and potentially at professional conferences. The results might be published in a professional journal in the field of nursing and/or allergy and immunotherapy.

WHOM CAN I CONTACT FOR MORE INFORMATION?
The Principal Investigator, Melissa L. Ferrell, FNP-BC, can be reached at (480)272-0733 if you have a concern or complaint about this research study. You may also contact the Principal Investigator’s advisor, Kate G. Sheppard, PhD, RN, FNP, PMHNP-BC, FAANP at kbs1@email.arizona.edu. If you want to talk to someone other than the Investigator or advisor, your may call the University of Arizona Human Subjects Protection Program office.
• Local phone number (520) 626-6721
• Website (this can be anonymous: http://www.orcr.arizona.edu)

By returning the survey in the addressed stamped envelope, you acknowledge that you have read this information and agree to participate in this research survey.
Survey Questionnaire

1. In what state do you hold licensure as a nurse practitioner?

2. What is your healthcare specialty?
   a. Family Nurse Practitioner       b. Adult-Gerontology Primary Care
   c. Pediatric Nurse Practitioner    d. Neonatal Nurse Practitioner
   e. Women’s Health Nurse Practitioner f. Certified Nurse Midwife
   g. Certified Registered Nurse Anesthetist
   h. Other ___________________________

3. Do you currently prescribe sublingual immunotherapy for allergic disease in your practice?
   a. Yes       b. No

4. For which patient population do you currently prescribe sublingual immunotherapy? (Circle all that apply)
   a. Patients < 5 years old       b. Patients 5 – 18 years old
   c. Patients 19 – 65 years old    d. Patients > 65 years old
   h. I do not prescribe sublingual immunotherapy

5. What type of allergy testing do you offer in your practice?
   a. Puncture/scratch skin test       b. Intradermal skin test
   c. Serum IgE blood test            d. None – referral to specialist
   e. Other ___________________________

6. What type of sublingual immunotherapy preparation do you use?
   a. Single-allergen (monotherapy)
   b. Allergen-specific formulation based off of allergy test results
   c. Multi-allergen formulation (> 15 allergens)
   d. Sublingual tablets
   e. Other ___________________________
   f. I do not prescribe sublingual immunotherapy

7. Would you consider prescribing sublingual immunotherapy in your practice?
   a. Yes       b. No
   c. I currently prescribe sublingual immunotherapy

8. What are barriers preventing you from prescribing sublingual immunotherapy in your practice?
   a. Sublingual immunotherapy is an “off-label” route of administration
   b. Minimal or no insurance reimbursement
   c. Limited or no knowledge of how to prescribe or initiate sublingual immunotherapy
d. I prefer to refer patients to an allergist for allergy shots

e. None, I currently prescribe sublingual immunotherapy in my practice

f. Other________________________________________________________
References


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