

Solving the Problem of Nonadherence to Immunotherapy



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KEYWORDS

- Allergen immunotherapy • Adherence • Patient-centered care
- Shared decision making • Motivational interviewing

KEY POINTS

- Fewer than one-half of patients complete a course of allergen immunotherapy.
- Very little research has been conducted to address nonadherence to immunotherapy.
- Communication models including patient-centered care, shared decision making, and motivation interviewing can be used to help improve immunotherapy adherence.
- Sensitivity to health literacy, language, and cultural differences are also important to improved immunotherapy adherence.

INTRODUCTION

Allergen immunotherapy (AIT) is an effective form of therapy to treat subjects with allergic rhinoconjunctivitis, allergic asthma, stinging insect hypersensitivity, and atopic eczema. It involves the gradual administration of increasing doses of the causative allergens, for example, inhalant allergens for allergic rhinoconjunctivitis, asthma, and atopic eczema and stinging insect venom allergens for individuals allergic to Hymenoptera or stinging insects. Whereas conventional vaccination, for example, tetanus or diphtheria, initiate and boost the immunologic memory and thereby protect against these diseases, AIT decreases established immune responses mediated by immunoglobulin (Ig)E and allergen-specific memory T cells through a gradual and controlled exposure to the offending allergens.¹

Subcutaneous immunotherapy (SCIT) has been used to treat allergic diseases for over a century; however, it was not a universally accepted form of therapy until the end of the 20th century when the World Health Organization (WHO) sponsored a

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treatise on AIT entitled “WHO Position Paper, Allergen Immunotherapy: Therapeutic Vaccines for Allergic Diseases.” This treatise summarized the scientific evidence for such therapy and broadened its appeal to physicians and subjects who suffer from these diseases throughout the world.²

New forms of AIT, particularly sublingual immunotherapy (SLIT), now complement SCIT. However, as with any form of therapy, efficacy depends on appropriate diagnosis, selection, and education of patients who suffer from these diseases. Many subjects who begin a course of either SCIT or SLIT for a variety of different reasons do not complete or continue these forms of therapy.

ADHERENCE TO ALLERGEN IMMUNOTHERAPY

Despite the clinical value of AIT, patient adherence is often very low. Reports of AIT adherence rates have varied greatly. For example, a review of 12 studies (6 SCIT, 5 SLIT, and 1 nasal immunotherapy) reported adherence rates ranging from 27% to 97%.³ Variance in reported adherence likely reflects differing methodologies used to measure adherence. AIT clinical trials that rely on self-report data record unrealistically high adherence rates for reasons that include the implied obligation of patients to use their medication in the trial setting and inaccuracy of diary card data. Further, the adherence of clinical trial dropouts is frequently omitted from the reported data, thus further inflating an artificially high adherence rate. The consequence of these factors creates a distorted picture of actual adherence in clinical settings. For example, diary card trials have reported mean SLIT adherence rates of 87%,³ 99%,⁴ 90%⁵ and 80%.⁶ Self-report by means other than diary card is similarly subject to exaggeration. Of 71 families of SLIT-treated children interviewed by telephone, 84% reported adherence of greater than 75% at 6 months, again with no objective confirmation.⁷ Despite seeming to be more objective, chart review studies fare only slightly better because they still rely on patient self-report.^{5,6} Objective, methodologically sound measurement of adherence has often been absent from AIT trials. However, informative data emerge in asthma trials that have clearly demonstrated the inaccuracy of patient self-report when compared with objective adherence measures. In the final year of the 4-year Childhood Asthma Management Program clinical trial, patients on average took only 52% of their controller medication (as measured by returned medication), while reporting 91% adherence on diary cards (**Fig. 1**).⁸ In a 4-month study of 104 children with asthma, inhaled corticosteroid adherence measured by an electronic

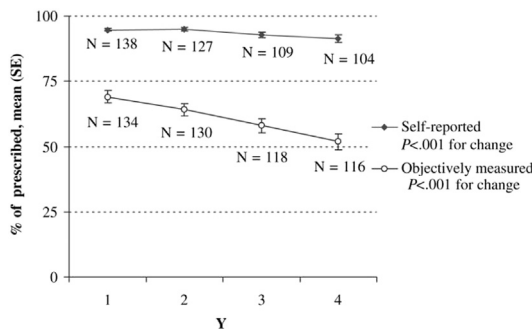


Fig. 1. Objective and self-reported adherence to asthma controller medication. SE, standard error. (From Krishnan J, Bender B, Wamboldt F, et al. Adherence to inhaled corticosteroids: an ancillary study of the childhood asthma management program clinical trial. *J Allergy Clin Immunol* 2012;129:112–8; with permission.)

device attached to their inhaler was contrasted with 1 of 3 forms of self-report: diary card, in-person interview, or computer interview. Adherence was significantly overreported in all self-report conditions; one-half of families exaggerated their adherence by more than 25% and one-third reported perfect adherence when no medication was taken.⁹

Pharmacy database studies reporting on AIT refill rates provide more objective data that do not rely on patient self-reports or estimates from physicians and other health care professional (PHCP). When a patient stops filling their medication, they have clearly abandoned that treatment. Although refill data are not reliable in short-term intervals, when used to evaluate adherence over a year or more, they provide insightful information. Adherence measurements by refill data correlate well with electronic tracking devices.^{10–13} A large pharmacy refill database has shown that 53% to 56% of SLIT and SCIT patients discontinued treatment in year 1 and 84% to 87% by years 3 to 4 (Fig. 2).¹⁴ In a side-by-side comparison of 6486 immunotherapy patients, 77% of those on SCIT and 93% of those on SLIT discontinued treatment before reaching 3 years.¹⁵ Another study of SCIT and SLIT treatment termination revealed that attrition from SCIT was markedly higher in the first 2 months of treatment and SLIT attrition increased after 2 months; over 24 months, the overall rates of attrition approached 50% for both forms of AIT (Fig. 3).¹⁶

COST VERSUS BENEFIT

Most allergy treatments, such as intranasal corticosteroids and antihistamines, provide short-term benefit as long as they are used. Patterns of use often depend on current symptoms, and discussions of nonadherence are less relevant because these medications are largely dictated by the patient's perceived need for relief. In contrast, AIT is intended to modify the underlying immune system response and hence benefit follows only from persistent long-term use. Modest symptom relief may be received with a year of treatment, but maximum, lasting benefit is obtained with at least 3 years of treatment.¹⁷ Collective evidence indicates that persistence is equally problematic for both SCIT and SLIT. The assessment of cost versus benefit must, therefore, take into account the loss of any benefit resulting from early termination of therapy. A large retrospective analysis of pharmacy data in The Netherlands indicated that only 23% of SCIT patients and 7% of SLIT patients completed a full 3 years of

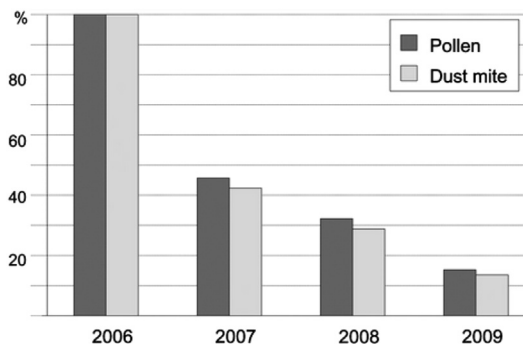


Fig. 2. Proportion of patients continuing sublingual immunotherapy. (From Senna G, Lombardi C, Canonica G, et al. How adherent to sublingual immunotherapy prescriptions are patients? the manufacturers' viewpoint. *J Allergy Clin Immunol* 2010;126:668–9; with permission.)

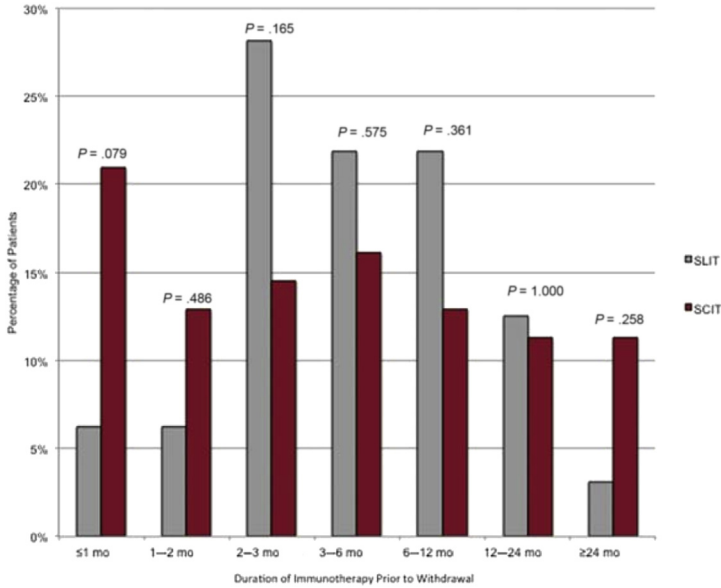


Fig. 3. Duration of sublingual immunotherapy (SLIT) and subcutaneous immunotherapy (SCIT). (From Hsu N, Reisacher W. A comparison of attrition rates in patients undergoing sublingual immunotherapy vs subcutaneous immunotherapy. *Int Forum Allergy Rhinol* 2012;2(4):280–4; with permission.)

treatment, representing a \$4000 cost per nonpersistent patient that was “largely misspent.”¹⁵ To establish a satisfactory cost versus benefit balance with an effective treatment, it becomes particularly important that PHCPs be equipped to identify patients most likely to commit to and benefit from a full course of AIT and to engage communication tools to maximize adherence.

IDENTIFYING PATIENTS LIKELY TO BE NONADHERENT

Multiple studies have documented an association between AIT nonadherence and patient characteristics that include younger age,^{18,19} lower socioeconomic status,²⁰ government insurance,^{21,22} minority race,^{23,24} and cost.³ A primary reason for subjects discontinuing SCIT is the inconvenience of receiving injections,^{3,25} because injections cannot be administered at home. A physician well-versed and competent in treating a systemic allergic reaction must be present because SCIT can induce a systemic allergic reaction and even cause death.²⁶ Other patient-reported reasons for SCIT and SLIT nonadherence summarized in a review of more than 25 studies included concurrent illness, perceived ineffectiveness, symptom improvement, change in residence or clinic, adverse reaction, systemic reaction, local reaction, inconvenience, and cost or lack of insurance (Table 1).²⁵ Somewhat unexpectedly, adherence to SLIT seems to be even more problematic than adherence with SCIT. Although SLIT maintains a strong safety profile and can be administered at home, the primary reason given by patients for SLIT discontinuation and/or nonadherence was an “inability to take medication according to schedule and/or non-compliance.” Other reasons were “time-consuming and/or inconvenience, not effective, concurrent illness and/or medical condition, adverse effects, cost.”²⁵

Table 1**Patient-reported reasons for discontinuation of allergen immunotherapy**

Subcutaneous Immunotherapy	Sublingual Immunotherapy
Inconvenience	Inability to take medication according to schedule and/or forgetting and/or noncompliance
Concurrent illness	Time consuming and/or inconvenient
Not effective	Not effective
Symptoms improved	Concurrent illness and/or medical condition
Changed residence or clinic	Adverse effects
Adverse reaction	Cost
Systemic reaction	—
Local reaction	—

From Cox L, Hankin C, Lockey R. Allergy immunotherapy adherence and delivery route: location does not matter. *J Allergy Clin Immunol Pract* 2014;2(2):156–60; with permission.

COMMUNICATION STRATEGIES TO MAXIMIZE ADHERENCE TO ALLERGEN IMMUNOTHERAPY

PHCPs can adopt brief, effective, evidence-based strategies to improve AIT adherence. Randomized trials of interventions to improve AIT adherence are in process; until these data are available, interventions directed at other health conditions including asthma can be applied to AIT. The key elements of an effective AIT adherence intervention plan come from studies of patient-centered care, shared decision making, and motivational interviewing.

Patient-Centered Care

Patient-centered care is a model for care in which PHCPs create partnerships with patients and their family members. The Institute of Medicine strongly endorses this model, emphasizing the importance of “providing care that is respectful of and responsive to individual patient preferences, needs, and values, and ensuring that patient values guide all clinical decisions.”²⁷ Guided by the principles of patient-centered care, PHCPs focus on establishing a caring relationship from the first meeting with the patient. Trust is more likely to develop when the PHCP is warm and friendly, demonstrates genuine interest in the patient's problem, and does not seem to be rushed. In patient-centered care, the PHCP listens carefully to the patient, allows sufficient time for the patient to share their primary concerns and what they hope to accomplish in the visit, verifies to be sure that the PHCP has correctly understood the patient, and addresses the patient's concerns during the visit.²⁸ Clinic barriers that interfere with patient-centered care include time pressures that produce a need to move quickly through the encounter, and in turn an increasing tendency to speak rapidly and decrease listening time. When PHCPs listen carefully to patients and are supportive, understanding, and nonjudgmental, patients express greater satisfaction and are more likely to be adherent to treatment.^{29–31}

Motivational Interviewing

In its original format, motivational interviewing, although effective, is impractical for most PHCPs. Programs to decrease alcohol consumption or improve physical activity³² or medication adherence^{33–35} have required 1 to 5 hours of motivational interviewing to accomplish changes in patient behavior. Few primary care PHCPs or

specialists have the luxury of time to allow this degree of patient interaction. Nonetheless, recent work has developed time- and resource-efficient approaches to motivational interviewing that can enhance patient motivation and adherence.^{36,37} Two specific motivational interviewing techniques that can be used to improve AIT adherence are (1) asking open-ended questions and (2) reflective listening. Open-ended questions cannot be answered “yes” or “no” and allow the patient to express their concerns and expectations regarding this visit. Reflective listening includes summarizing back to the patient what the PHCP has heard from the patient to ensure a correct understanding of the patient’s perspective and preferences. Motivational interviewing strategies have proven effective in improving asthma adherence³⁸ and may be similarly applied to patients with allergic disorders.

Shared Decision Making

Strategies of patient-centered care and motivational interviewing integrate well with shared decision making. All 3 concepts embrace the importance of communicating effectively, listening closely, and respecting patient concerns and wishes. All 3 strategies avoid lecturing patients or imparting the expectation that PHCPs will be disappointed if the patient does not comply with the PHCP’s recommendations. Shared decision making builds on strong listening skills by providing a guideline for choosing treatments. This communication strategy includes attempts to increase concordance about treatment choices and goals, leads to higher adherence in patients with asthma,³⁹ and is well-suited to PHCP–patient discussions regarding AIT. When using shared decision making, the PHCP is deferring some control over treatment decisions to the patient. Differences in patient and PHCP goals and patient expectations must be discussed and resolved before the treatment plan is finalized.⁴⁰ To reach this point, the PHCP must make sure that the patient has an adequate understanding of the illness and treatment options. Hence, patient education becomes an important step in creating a patient–PHCP partnership. Patients differ significantly in the degree to which they want or understand detailed information. Therefore, sensitivity to health literacy, language, cultural differences, and desire for choices are essential in PHCP–patient communication.⁴¹ Information about health, illness, and treatment should be delivered in clear language and at a pace that seems to be comfortable to each patient. One-size-fits-all education often leaves many patients dissatisfied. The principles of adult learning, established decades ago⁴² continue to be helpful guides and include (1) assessing the person’s knowledge of a topic before teaching, (2) progressing from simple to complex, (3) encouraging questions and discussion, (4) repeating and reinforcing new information, and (5) practicing new skills (eg, the correct self-administration of a inhaler or tablet medication).

SUMMARY AND FUTURE CONSIDERATIONS

AIT is an effective therapy that can improve allergic response by modifying the underlying disease. However, many patients are nonadherent with AIT regardless of the mode of delivery, including SLIT. Medication refill studies reveal that barely 10% of patients complete a full 3-year course of AIT, and one-half of patients quit taking AIT in the first year. PHCP teams can improve AIT adherence by (1) appropriately diagnosing and selecting patients likely to benefit, (2) avoiding prescribing AIT prematurely to patients not yet ready to commit to treatment, (3) providing sufficient education about the treatment, and (4) using effective communication strategies to motivate and activate patients toward greater adherence. Evidence-based communication strategies are drawn from patient-centered care, motivational interviewing,

and shared decision making. Collectively, the key strategies from these include (1) establishing trust, (2) working diligently to understand patient concerns and priorities, (3) taking sufficient time, and (4) involving the patient in decisions regarding whether and when to initiate AIT. Sensitivity to health literacy, language, cultural differences, and a desire for choices are essential to this PHCP–patient communication. Using these strategies, PHCP teams can enhance both AIT adherence and consequent benefit to patients.

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