Curr Treat Options Allergy (2015) 2:39–53
DOI 10.1007/s40521-014-0037-6

Specific Immunotherapy (L Cox, Section Editor)

# Allergen Immunotherapy Adherence in the Real World: How Bad Is It and How Can It Be Improved?

*Gianenrico Senna, MD*[1,*]
*Marco Caminati, MD*[1]
*Richard F. Lockey, MD*[2]

**Address**
[*,1]Allergy Unit, Verona University and General Hospital, Piazzale Stefani 1, 37126, Verona, Italy
Email: gianenrico.senna@ospedaleuniverona.it
[2]Division of Allergy and Immunology, Department of Internal Medicine, University of South Florida College of Medicine, C/o V.A. Medical Center, 13000 Bruce B. Downs Blvd (111D), Tampa, FL 33612, USA

Published online: 3 December 2014


This article is part of the Topical Collection on *Specific Immunotherapy*

**Keywords** Adherence · Allergen immunotherapy · Allergic rhinitis · Allergic asthma · Chronic disease

## Opinion Statement

Allergen immunotherapy (AIT) is the only available causal treatment for allergic respiratory diseases; however, data demonstrate a high discontinuation rate for both subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT). The complex mechanism of action of allergen immunotherapy (AIT) includes an interaction of innate and adaptive immune processes, resulting in immune tolerance, as illustrated by a decrease in specific immunoglobulin (Ig)-E, an increase in specific IgG1 and IgG4, and inhibition of inflammation involving mast cells, basophils, and eosinophils. This induction of immune tolerance leads to a significant improvement in symptoms and decreased medication scores. A 3- to 5-year course of AIT is required to obtain this disease-modifying effect, which substantially differentiates AIT frompharmacologic treatment. A carry-over effect can persist for up to 12 years. Furthermore, AIT may prevent the onset of asthma in patients with allergic rhinitis, as well as decreasing the onset of new sensitizations to inhalant allergens. Several meta-analyses and controlled studies, involving adult and pediatric subjects, have indicated that both sublingual immunotherapy (SLIT) and subcutaneous immunotherapy (SCIT) are relatively safe, effective, and well tolerated. AIT may also have a positive impact on the cost to the healthcare system, as evidence indicates the

cost–benefit of such treatment. Adherence to AIT is crucial for a positive clinical outcome and non-adherence represents a major drawback for such therapy. It actually concerns not only AIT but also various pharmacologic treatments for allergic respiratory diseases, as well as for other chronic illnesses. The issue of non-adherence is an emerging and worldwide problem for chronic diseases and could be an important factor responsible for an overall decrease in treatment efficacy and increased rates of hospitalization, morbidity, and mortality. This review provides an overview of the different reasons that may account for the low adherence rate for AIT. Some of these reasons can be related to the patient's age when they begin such therapy, the allergic disease being treated, and questions about the efficacy, costs, inconvenience, and safety of AIT. Well-structured educational programs,especially by healthcare professionals, the print media, and the Internet, are needed to improve adherence to AIT.

## Introduction

"Drugs don't work in patients who don't take them." This simple admonition by C. Everett Koop, MD, US Surgeon General from 1982 to 1989, perfectly summarizes the problem of nonadherence to medications. The term "adherence", which is preferred to the word "compliance", implies a willingness of the patient to follow medical treatment prescribed by a physician or other healthcare professional [1]. The issue of nonadherence is an emerging and worldwide problem for various chronic diseases and is one of several factors responsible for an overall decrease in treatment efficacy and increased hospitalizations, morbidity, and mortality. The latter causes an increased adverse burden, not only for patients and their families but also in terms of the added costs to the healthcare system [1]. The rates of discontinuation of treatment are between 20 and 40 % for acute diseases and between 30 and 60 % for chronic diseases, and increase to 80 % for preventive therapy [2]. The impact of such discontinuation is even more dramatic if it is considered that "increasing the effectiveness of adherence intervention may have a far greater impact on the health of the population than any improvement in specific medical treatments", as stated by R. Brian Haynes [3]. The exponential increase in the number of scientific papers on this subject during the last 10 years supports the advocacy of this statement (Fig. 1). This trend concerns most chronic diseases, including respiratory allergic diseases. Adherence is also an important part of a new pharmaceutical or medical research project. For example, a dropout rate over 50 % undermines the results of randomized controlled trials (RCTs), making it necessary to increase the sample size fivefold to retain the appropriate power to properly interpret study results [4]. Real-life experiences in research confirm the critical role of adherence. For example, it is estimated that every year, 89,000 premature deaths in the USA are due to lack of adherence by patients who have essential hypertension [5]. At the same time, the cost due to lack of adherence is estimated to be US$100 billion per year for unnecessary hospitalizations [1–6].

Nonadherence is related to many different factors, including the social and cultural background of the patient. Illness-related factors are also important, such as treatment, which involves a schedule of how and when a medication is to be taken, its costs and side effects, and the physician–patient relationship experience as it concerns the patient's expectations to improve their health. These factors are complex and variable [7], and all affect adherence.

Allergic asthma and rhinitis are common diseases with a significant socioeconomic burden, due to both direct (medications and physician visits) and indirect (loss of productivity/working day) costs. The current worldwide prevalence of allergic rhinitis in adults is 10 to 30 %, and in children it is up to 37 % in some Western countries [8]. Respiratory allergy and other chronic diseases have similar medication treatment discontinuation rates [9]. Table 1 summarizes data about adherence to treatment for common chronic diseases [10–16].

Adherence represents the most critical issue for AIT as a treatment modality for allergic rhinitis. It significantly reduces the clinical symptoms and concomitant drug use, as demonstrated in RCTs and meta-analyses [17, 18••]. A 3- to 4-year course of AIT is necessary to obtain a carry-over effect after its discontinuation [19–21], as well as to reduce the risk of developing asthma [22, 23] and new allergen sensitizations [24, 25].

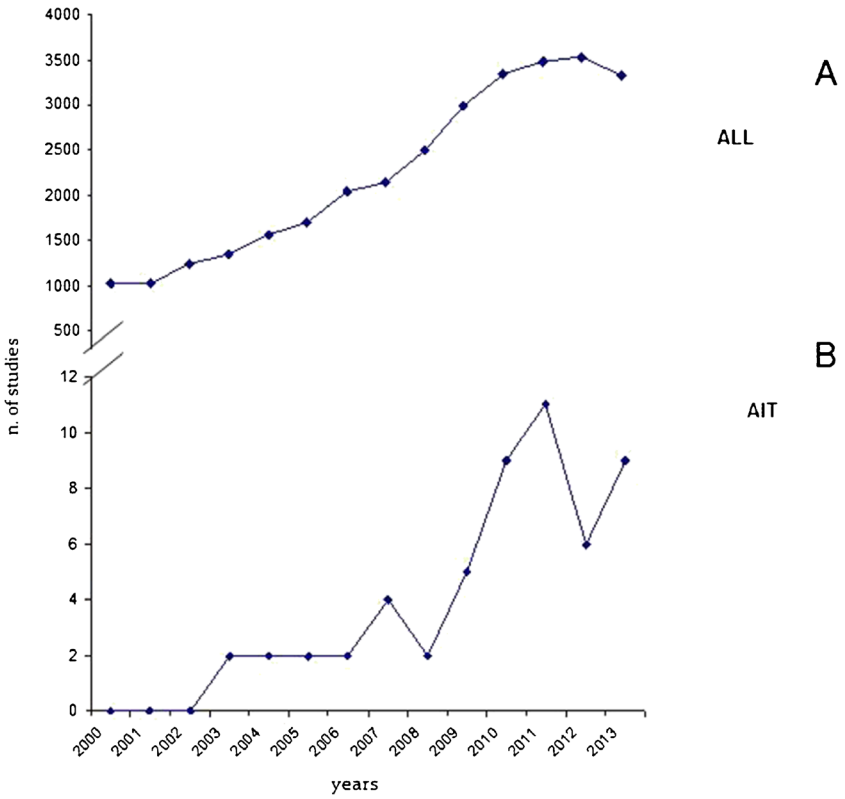


**Fig. 1.** Number of studies on adherence published since 2000, according to PubMed, for chronic illnesses (A) and allergen immunotherapy [AIT] (B) [personal research].

The purpose of this paper is to review the available literature about adherence to AIT in order to identify the potential reasons for discontinuation and to evaluate and implement new strategies to improve adherence. A short comparative overview of other common chronic diseases is included.

## Adherence to AIT: current data

The adherence rate for individual patients is usually reported as the percentage of the prescribed doses of a medication actually taken over a specified period [1]. However, adherence evaluation is not yet standardized. In fact, though many methods and tools have been proposed, each provides some advantages and disadvantages, and none are considered the gold standard. The available approaches can be best divided into three categories [9]:

1. Subjective assessment, based on the reported medication consumption, is obtained by the patient, physician, or other healthcare professional. This is simple and inexpensive, but its feasibility is limited by the potential patient's unwillingness to admit poor adherence. Moreover, interpretation of the data, collected by means of questionnaires, is not always practicable.
2. Objective measures can be obtained by counting the number of injections given or drops or tablets consumed, by analyzing pharmacy record refills or by using electronic devices for monitoring medication consumption. The

**Table 1. Treatment adherence in common chronic conditions**

| Publication | Disease | Treatment adherence rate (%) | Reasons for nonadherence | Strategies for improving adherence |
|---|---|---|---|---|
| Shingler et al., 2014 [10] | Cancer | 20–88 | Adverse events, patient beliefs, inadequate knowledge, disease progression, long treatment duration, and regimen complexity | Understanding of patient preference and home administration |
| Chowdhury et al., 2013 [11]; Kronish and Ye, 2013 [12] | Cardiovascular diseases | 4.9–93.3 | Adverse events, costs, uncertainty about effectiveness, concerns about medications, psychological disorders, polypharmacy, and inaccurate knowledge | Enhanced counseling and education, simplification of regimen and reminders (phone/e-mail/text messages), and collaboration with other healthcare professionals |
| de Achaval and Suarez-Almazor, 2010 [13] | Rheumatoid arthritis | 11–92 | Uncertainty about effectiveness, concerns about medications, psychological disorders, regimen complexity, poor knowledge, costs, patients' beliefs, polypharmacy, and low socioeconomic and educational status | Reminders (phone/ e-mail/text messages) and enhanced counseling and education |
| Vervloet et al., 2011 [14] | Diabetes | 35–95 | Polypharmacy, regimen complexity, poor knowledge, and low socioeconomic and educational status | Enhanced counseling and education, simplification of regimen and reminders (phone/e-mail/SMS), and collaboration with other healthcare professionals |
| Sumino and Cabana, 2013 [15] | Asthma | 30–70 | Uncertainty about effectiveness, concerns about medications, psychological disorders, polypharmacy, and inaccurate knowledge | Enhanced counseling and education, simplification of regimen, reminders (phone/e-mail/text messages), smartphone apps, and collaboration with other healthcare professionals |
| Restrepo et al., 2008 [16] | COPD | 40–90 | Uncertainty about effectiveness, concerns about medications, psychological disorders, polypharmacy, inadequate | Enhanced counselling, monitoring and feedback about inhaler use through electronic medication delivery |

**Table 1.** (Continued)

| Publication | Disease | Treatment adherence rate (%) | Reasons for nonadherence | Strategies for improving adherence |
|---|---|---|---|---|
| | | | knowledge, disease progression, long treatment duration, and regimen complexity | devices, and collaboration with pharmacists and primary care |

*COPD* chronic obstructive pulmonary disease, *SMS* short message service

disadvantage of pill counts is that all missing pills are considered consumed, whether or not they truly are consumed. This method is less reliable over time. Electronic devices probably give more accurate information, but, till now, they have been too expensive for practical use.

3. A more objective approach consists of measuring the presence or the amount of medication or its metabolites in the blood or urine. This method is available only for selected medications, e.g., digoxin and theophylline, as well as antiepileptic medications. For patients with asthma on regular oral steroids, evaluation of serum cortisol and exhaled nitric oxide can also be useful.

Besides these technical limitations, a major methodological drawback concerning adherence studies is the immediate bias related to the patient's awareness of the study outcome [1]. Data from controlled studies are partially biased, as the patients are strictly followed and observed. Furthermore, at times, nonadherent patients are dropped from the study and therefore not included in the final results. More reliable data are derived from real-life studies.

There is no consensus about an acceptable adherence rate; however, many investigators consider an adherence rate of greater than 80 % to be adequate for some large trials [1, 18••].

SCIT and SLIT adherence rates have been investigated in several studies [9, 26–40, 41••]. As illustrated in Table 2 [28–40, 41••, 42] and Table 3 [43–52, 53•, 54], adherence is generally poor, although it is broadly represented for both routes of administration. A greater number of studies on SLIT versus SCIT report an adherence rate (defined as the proportion of the scheduled doses actually taken by the patient) of >80 % (Table 4) [28–40, 41••, 42–52, 53•, 54]. However, the SCIT studies include an overall larger population, and six out of 15 lasted for more than 3 years—the necessary time to achieve optimal success from AIT. In contrast, the follow-up studies with SLIT are considerably shorter, lasting longer than 3 years only in one study.

Three studies directly compare the adherence rates between SLIT and SCIT and demonstrate conflicting results. An Italian 3-year pediatric study, involving 1,886 patients, reported a significantly greater number of children on SLIT who prematurely discontinued the treatment, compared with those treated with SCIT (22 % versus 11 %, $P$ <0.005) [35]. A retrospective American 3-year follow-up study reported similar discontinuation rates between SLIT (41 %) and SCIT (45 %) [39]. A poor adherence rate was reported in a large Dutch study, published in 2013, with the discontinuation rate being significantly lower in the SLIT group than in the SCIT group (93 % versus 77 %, $P$ <0.001) [41••].

**Table 2. Treatment adherence in subcutaneous immunotherapy (SCIT) studies**

| Publication | Study population (*n*) | Age group | Follow-up duration | Adherence rate (%) | Reasons for nonadherence |
|---|---|---|---|---|---|
| Cohn and Pizzi, 1993 [28] | 217 | Adults | 4 years | 50 | Inconvenience and clinical efficacy |
| Lower et al., 1993 [29] | 315 | Children | 4 years | 56 | Non-private funding of treatment |
| Tinkelman et al., 1995 [30] | 3,349 | Children, adults | 1 ;years | 65 | Inconvenience |
| Ruiz et al., 1997 [31] | 247 | Adults | 18 months | 62 | Clinical efficacy and costs |
| Donahue et al., 1999 [32] | 603 | Children, adults | 4 years | 33 | Young patient age |
| Rhodes, 1999 [33] | 1,033 | Adults | 3 years | 88 | Inconvenience |
| More and Hagan, 2002 [34] | 381 | Children, adults | 3 years | 77 | Inconvenience |
| Pajno et al., 2005 [35] | 1,886 | Children | 3 years | 89 | Costs |
| Hommers et al., 2007 [36] | 296 | Adults | Not specified | 66 | Lack of efficacy |
| Hankin et al., 2008 [37] | 520 | Children | 3 years | 47 (1st year)<br>16 (3rd year) | Lowest adherence among Hispanics |
| Mahesh et al., 2010 [38] | 100 | Adults | Not specified | 58 | Not reported |
| Hsu and Reisacher, 2012 [39] | 139 | Adults | 4 years | 55 | Inconvenience |
| Guenechea-Sola et al., 2014 [40] | 156 | Adults | 5 years | 63 | Psychiatric diseases; young patient age |
| Kiel et al., 2013 [41••] | 2,796 | Adults | 3 years | 23 | Prescription issued by general practitioners; young patient age (adolescents) |
| Silva et al., 2014 [42] | 122 | Children, adults | 4 years | 54 | Costs |

Adherence data also can be derived from market sources. According to sales data provided by two of the main Italian allergen extract manufacturers, more than 50 % of subjects discontinue SLIT treatment within 1 year and only 13 % are still on treatment after 3 years [55]. Likewise, a German study reports that 49 % and 64 % of patients did not renew their SLIT and SCIT allergen vaccine prescriptions for grass immunotherapy, respectively, within 2 years [56].

Finally, the widespread heterogeneity of the results of studies may account for the conflicting results and the impossibility of drawing definite conclusions. One reason is that published studies thus far have been carried out in different populations and countries, and patients have been treated with different allergen vaccines with different treatment schedules. In addition, the methods to measure the adherence rate were dissimilar from study to study, e.g., retrospective, prospective, and cross-sectional [18••].

## Reasons for discontinuation of treatment

The delivery route of AIT does not seem to substantially affect treatment adherence. In fact, the overall analysis of published studies does not highlight

**Table 3. Treatment adherence in sublingual immunotherapy (SLIT) studies**

| Publication | Study population (*n*) | Age group | Follow-up duration | Adherence rate (%) | Reasons for nonadherence |
|---|---|---|---|---|---|
| Marogna et al., 2004 [43] | 319 | Adults | 3 years | 85 | Local tolerability |
| Lombardi et al., 2004 [44] | 86 | Adults | 18 months | 79–97 | Forgetfulness in taking SLIT |
| Pajno et al., 2005 [35] | 806 | Children | 3 years | 79 | Costs |
| Passalacqua et al., 2006 [45] | 443 | Adults | 6 months | 76 | Local tolerability |
| Passalacqua et al., 2007 [46] | 71 | Children | 6 months | 85 | Not reported |
| Cadario et al., 2008 [47] | 40 | Adults | 1 years | 65 | Not reported |
| Roder et al., 2008 [48] | 154 | Adults | 2 years | 77 | Local tolerability |
| Chang et al., 2009 [49] | 142 | Adults/children | 6 months | 69 | Local tolerability |
| Jansen et al., 2009 [50] | 91 | Adults | 6 months | 95 | Not reported |
| Ott et al., 2009 [51] | 183 | Adults/children | 2 years | 91 | Not reported |
| Vita et al., 2010 [52] | 300 | Children | 2 years | 30–76 | Not reported |
| Hsu and Reisacher, 2012 [39] | 139 | Adults | 4 years | 59 | Costs |
| Pajno et al., 2012 [53•] | 150 | Children | 2 years | 54 | Local tolerability |
| Kiel et al., 2013 [41••] | 3,690 | Adults | 3 years | 7 | Young patient age |
| Trebuchon et al., 2014 [54] | 736 | Children | 2 years | 86 | Not reported |

significant differences between SLIT and SCIT, even if univocal results are not easy to collect, because of methodical differences [18••]. Even though the reasons for nonadherence are similar for the two routes of AIT, the relevance of single causes was somewhat different forSLIT versus SCIT (Table 5) [28–40, 41••, 42–52, 53•, 54]. These results could be focused in order to selectively improve the adherence to AIT. Reasons for discontinuation can be divided roughly into two categories:

## Causes related to the patient

The age of the patient has a minimal effect on adherence for both SLIT and SCIT. However, some SCIT studies report a slightly higher discontinuation rate in the younger [33, 48] versus older age group [33, 34, 40]. Likewise, a few studies

**Table 4. Comparison between subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) studies**

| | SCIT studies | SLIT studies |
|---|---|---|
| Number of studies | 15 | 15 |
| Study population (*n*) | 12,160 | 7,050 |
| Age groups evaluated | 8 adult, 4 pediatric, 3 mixed | 8 adult, 6 pediatric, 2 mixed |
| Adherence rate >80 % | 2 studies | 5 studies |
| Follow up duration >3 years | 11 studies | 2 studies |
| Overall adherence rate (%; range) | 23–88 | 7–97 |
| Pediatric adherence rate (%; range) | 16–89 | 30–86 |
| Adult adherence rate (%; range) | 23–88 | 7–97 |

**Table 5. Reasons for discontinuation negatively affecting adherence to allergen immunotherapy (AIT), rate reported, and relevance of single reasons**

| Reasons for discontinuation | SCIT | | SLIT | |
|---|---|---|---|---|
| | Reported prevalence (%) | Relevance | Reported prevalence (%) | Relevance |
| Related to the patient | | | | |
| Age | Not reported | Not relevant | Not reported | Not relevant |
| Disease | Not reported" | Not relevant | Not reported | Not relevant |
| Perceived lack of treatment efficacy | 2–13 | Not relevant | 5–50 | Fairly relevant |
| Related to the treatment | | | | |
| Safety | 1–16 | Fairly relevant | Not reported | Not relevant |
| Tolerability | 4 | Not relevant | 8–33 | Relevant |
| Inconvenience | 11–66 | Relevant | 7–18 | Not relevant |
| Costs | 4–40 | Relevant | 8–60 | Relevant |

SCIT subcutaneous immunotherapy, SLIT sublingual immunotherapy

observe that males are more compliant than females when treated with SCIT [29]. According to one study patients suffering from both asthma and rhinitis were more likely to continue SCIT than patients with only one disease [32]. The severity of the disease apparently does not affect adherence, as reported in two SLIT studies [45, 48]. Accordingly, a 2013 study of patients with fire ant allergy, which can be a life-threatening condition, unexpectedly reported a lower adherence rate in patients who had experienced a more severe systemic allergic reaction [57]. Other causes responsible for poor adherence have occasionally been observed, e.g., subjects having nonallergic parents; concomitant food allergy; psychiatric disorders; and Hispanic ethnicity [37]. Low socioeconomic status has also been associated with a reduced rate of adherence to AIT [37].

## Causes related to treatment

Treatment-related factors represent a crucial aspect of adherence to AIT and provide a good opportunity for interventions to improve AIT tolerability.

AIT-related severe adverse reactions are rare, in particular for SLIT, but also for SCIT, which has a low rate of severe reactions, unless the SCIT is not properly administered under optimal conditions [29, 34]. Local side effects, e.g., itching and swelling of the oral pharynx, crucially influence SLIT adherence [39, 45, 46, 53•, 54, 58]. Five out of 15 studies report that local discomfort, particularly in the oral pharynx, is a major cause of SLIT discontinuation in adults and children (Table 3). Though data from RCTs are not completely applicable to real life, in particular when measuring adherence, a systematic review performed on controlled SLIT studies showed that poor oral pharyngeal tolerability was the only significant factor negatively affecting adherence to SLIT [59•].

Alternative sites for SLIT administration could be considered to reduce these local oral pharyngeal side effects. For example, one study demonstrates a lower density of mast cells and an larger number of Langerhans cells, with potent antigen uptake capability, in the vestibulum of the oral mucosa versus the sublingual mucosa [60]. Additionally, although it is considered a trivial issue, the taste of an allergen vaccine can affect its tolerability. In fact, it has been

suggested that the adherence rate to nasal glucocorticoids primarily depends on the taste, smell, and aftertaste of the solution, being inversely related to the intensity of its sensorial impact [61].

With SCIT, local reactions to an injection are only occasionally related to SCIT discontinuation [29]. Inconvenience is more related to SCIT, e.g., the need for regular injections, distance from the hospital or clinic to receive regular injections, and loss of working time [28, 29, 33]. The use of shorter AIT schedules seems to improve the compliance rate [28, 30] in comparison with the more time-consuming traditional treatment schedules [28–30]. Some studies of SLIT suggest that a shorter pre-coseasonal schedule for seasonal allergic rhinitis achieves better adherence than a perennial regimen, although the result does not reach statistical significance [35, 47]. Where AIT is administered may also affect adherence. Tinkelman et al. reported that a significantly larger number of patients stopped the treatment when it was carried out by the office of a different physician than the one who had prescribed such therapy (35 % versus 11 %) [30].

Costs are a common drawback for both AIT routes of administration [29, 31, 34, 39, 45, 46, 49, 62]. An Italian study shows that costs are responsible for SLIT discontinuation over time. In fact, a significantly larger number of patients whose costs were fully reimbursed by the national healthcare system were still on treatment after 3 years, compared with those who were partially reimbursed or had to pay the full cost for their treatment [55]. Conversely, Lower et al. found that patients with non-private insurance were more likely to discontinue SCIT [29]. De Olano and Twose examined the influence of the European financial crisis on AIT prescriptions. A significant decrease was observed only for treatment of seasonal allergies, whereas the sales of allergen vaccines for perennial allergies remained substantially unchanged. In the meantime, prices of vaccines increased for both SCIT (+25 %) and SLIT (+17.8 %) [63].

The clinical outcome of the treatment can affect adherence. For example, lack of efficacy is more frequently reported as a reason for discontinuation in SLIT studies [35, 39, 49, 53•, 54] than in SCIT studies [29, 31]. It is also a main reason for switching from SLIT to SCIT, as reported by Pajno et al. [64]. Perception of lack of efficacy, according to an Italian survey, also was considered the most important cause of AIT discontinuation by allergists [65]. Paradoxically, a rapid clinical improvement following a short course of AIT can negatively affect adherence [29, 31, 34].

Finally, the duration of treatment is a factor affecting adherence. Patients who had a longer treatment period were more compliant then those who had shorter treatment, and patient satisfaction was related to better adherence [66].

## Strategies for improving adherence to AIT

Successful adherence should be based on multiple steps and long-term strategies, whereas a single tool or intervention usually produces a temporary effect. Implementation of such long-term strategies is expensive and needs financial support. Although expenses for such interventions are relevant, they would not exceed the costs of nonadherence to AIT [41••], which is a cost-effective

treatment in the long term [67, 68]. Every single approach is discussed separately in this review, but keep in mind that only a combination of strategies can be successful.

## Educational plans

Education remains the cornerstone of adherence improvement and has successfully impacted outcomes for chronic diseases such as diabetes mellitus [69, 70], essential hypertension [71], depression [72, 73], tuberculosis [74], and human immunodeficiency virus (HIV) [75] disease. Such programs not only increase the adherence to treatment but also result in better control of the disease, as well as reducing the social costs.

Structured educational programs for allergic rhinitis have increased pharmacologic therapy compliance and improved clinical outcomes [76]. Successful educational interventions are also reported in asthma management [77]. However, education about AIT is scarcely addressed. Inadequate knowledge about AIT on the part of patients was reported in a study in the USA, which indicated that 39 % of treated patients expected a complete resolution of their symptoms, and four out of ten were unaware of the need for long-term treatment [78]. Likewise, 33 % of the SCIT patients were completely unaware of the possibility of such therapy inducing a systemic allergic reaction. Patients who more recently began AIT had better knowledge of their therapy than those on long-term treatment, which suggests the need for regular re-education of patients on such therapy.

Education as a method to increase AIT adherence has been investigated. Two groups of patients were compared in a small pilot study, one of which received only detailed instructions about SLIT self-administration, whereas the other attended a short educational course about treatment outcomes. Potential side effects and problems related to the use of SLIT were also discussed. A lower dropout rate was observed after 1 year in the "educated" group versus the group that received only detailed instructions about SLIT self-administration [79]. An educational plan and regular phone calls to remind patients about follow-up appointments, versus provision of only minimal instructions to a control group, was carried out in another SLIT study. The first group achieved a significantly higher adherence rate than did the latter. It is important to note that the first month of treatment in this study was identified as the more important period, with the highest rate of discontinuation [80].

Effective patient–physician communication for improving adherence is based on five components: (1) the willingness of the patient to share a therapeutic plan; (2) open discussion and evaluation of the available options; (3) information about the pros and cons of the treatment modality; (4) a balanced conversation between the physician and the patient; and (5) a dedicated proper amount of time for the visit [81].

Patients remember approximately 60 % of what is said to them during such a discussion, so it is usually better to be redundant, particularly with the first part of the discussion [82].

To be effective, physicians should be trained to optimize the time for education during a consultation. In fact during routine visits, it is difficult to arrange a structured educational program. Other healthcare professionals, such as nurses and other paramedics, are crucial in organizing such an

educational plan. Pharmacists may also be helpful in improving adherence to AIT [69].

Technological innovations and social media have improved the possibility to obtain and share information across all areas of medicine during the past several years.

Electronic devices, such as tablet computers and social media (e.g., Twitter, YouTube, online networks) have been included as part of the educational plan for patients undergoing AIT [83, 84]. Even so, the scientific literature provides little information about how such interventions affect patient outcomes. Future studies should use these types of media to address this subject and to identify how they can be used in educational programs to improve adherence.

### Regular and arranged assessments

Regular follow-up visits can increase the adherence of patients, as well as reinforcing their education. An Italian study highlights a correlation between the number of yearly follow-up visits and the rate of adherence to SLIT [52]. Regular assessment is necessary for this form of AIT, as it is self-managed by the patient at home, using convenient schedules. However, SCIT is administered by a physician in an office setting at regular intervals, usually monthly, after the patient reaches the maintenance dose. However, rush and cluster schedules have become more popular, reducing the patient's inconvenience because of decreased visits to a hospital or clinic for vaccine administration. A shorter administration schedule also reduces the time for regular follow-up visits. Data comparing adherence to cluster and traditional SCIT schedules are lacking.

### Electronic devices

Technological innovations are significantly affecting the management of chronic diseases. Many different devices have been developed to permit self-management. They usually provide the patient with immediate feedback about their disease status and remind them about the appropriate treatment schedule [85]. Some asthma and rhinitis modules exist, but, until now, few of them have been developed specifically for AIT [50, 86–90]. Those that have seem to positively impact adherence to AIT, though further studies should explore how these interventions affect patient outcomes and what kinds of patients (i.e., age and disease status) could really benefit from the use of electronic devices.

## Conclusions

The rate of adherence to AIT, as compared with treatment adherence in other chronic diseases, such as diabetes mellitus, essential hypertension, bronchial asthma, and COPD, is relatively good. However, these illnesses are considered more life threatening than allergic rhinitis, which is generally regarded as a less severe disease, not deserving costly and time-consuming treatment. Therefore, a first step may be to change this erroneous concept, emphasizing the potential consequences of this disease, i.e., poor quality of life, as well as the potential associated complications, such as acute and chronic sinusitis, worsening asthma, and sleep apnea.

Education is a cornerstone of any strategy to increase adherence, but it cannot be limited to a routine visit to the allergist. Education has to be shared by other healthcare professionals and be an essential part of any structured strategy. It has to be based on a plain and incisive message for patients and the general population. The news media and Internet can be very helpful in education and reinforcing this information. Likewise, general practitioners have to be involved and play a key role in any long-term treatment, especially with AIT.

There are practical and technical means by which increased adherence can occur—first, by shortening the SCIT build-up phase with accelerated schedules, thereby reducing the inconvenience of recurring visits to receive injections. Likewise, adopting patient-friendly routine schedules for the administration of SLIT would be beneficial. Costs should be kept as reasonable as possible, although they are more difficult to control.

## Compliance with Ethics Guidelines

**Conflict of Interest**

Gianenrico Senna declare that he has no conflict of interest.
Marco Caminati declare that he has no conflict of interest.
Richard F. Lockey declare that he has no conflict of interest.

**Human and Animal Rights and Informed Consent**

This article does not contain any studies with human or animal subjects performed by any of the authors.

## References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance


1. Osterberg L, Blashke T. Adherence to medication. N Engl J Med. 2005;353:487–93.
2. Christensen AJ. Patient adherence to medical treatment regimens: bridging the gap between behavioural science and biomedicine. Current Perspectives in Psychology series. New Haven: Yale University Press; 2004.
3. Sabatè E, editor. Adherence to long term therapies: evidence for action. Geneva: World Health Organization; 2003.
4. Reisacher WR, Visaya JM. Patient adherence to allergy immunotherapy. Curr Opin Otolaryngol Head Neck Surg. 2013;21:256–62.
5. Cutler DM, Long G, Berndt ER, et al. The value of antihypertensive drugs: a perspective of medical innovation. Health Aff (Millwood). 2007;26:97–110.
6. Cutler DM, Everett W. Thinking outside the pillbox. Medication adherence as a priority for Health Care Reform. N Engl J Med. 2010;362:1553–5.
7. Di Matteo M. Variations on patient's adherence to medical recommendations: a quantitative review of 50 years of research. Med Care. 2004;42:200–9.
8. Pawankar R, Canonica GW, Casale T, Lockey RF, editors. The World Allergy Organization white book on allergy. Milwaukee: World Allergy Organization; 2011.
9. Passalacqua G, Baiardini I, Senna G, Canonica GW. Adherence to pharmacological treatment and specific immunotherapy in allergic rhinitis. Clin Exp Allergy. 2013;43:22–8.
10. Shingler SL, Bennett BM, Cramer JA, Towse A, Twelves C, Lloyd AJ. Treatment preference, adherence and outcomes in patients with cancer: literature review and

development of a theoretical model. Curr Med Res Opin. 2014;29:1–13.
11. Chowdhury R, Khan H, Heydon E, Shroufi A, Fahimi S, Moore C, et al. Adherence to cardiovascular therapy: a meta-analysis of prevalence and clinical consequences. Eur Heart J. 2013;34(38):2940–8.
12. Kronish IM, Ye S. Adherence to cardiovascular medications: lessons learned and future directions. Prog Cardiovasc Dis. 2013;55(6):590–600.
13. de Achaval S, Suarez-Almazor ME. Treatment adherence to disease-modifying antirheumatic drugs in patients with rheumatoid arthritis and systemic lupus erythematosus. Int J Clin Rheumtol. 2010;5(3):313–26.
14. Vervloet M, van Dijk L, Santen-Reestman J, van Vlijmen B, Bouvy ML, de Bakker DH. Improving medication adherence in diabetes type 2 patients through real time medication monitoring: a randomised controlled trial to evaluate the effect of monitoring patients' medication use combined with short message service (SMS) reminders. BMC Health Serv Res. 2011;11:5.
15. Sumino K, Cabana MD. Medication adherence in asthma patients. Curr Opin Pulm Med. 2013;19(1):49–53.
16. Restrepo RD, Alvarez MT, Wittnebel LD, Sorenson H, Wettstein R, Vines DL, et al. Medication adherence issues in patients treated for COPD. Int J Chron Obstruct Pulm Dis. 2008;3(3):371–84.
17. Bousquet J, Lockey R, Mallion HJ. World Health Organization position paper. Allergen immunotherapy: therapeutical vaccines for allergic diseases. Allergy. 1998;53(Suppl):1–33.
18.•• Cox L, Hankin C, Lockey R. Allergen immunotherapy adherence and delivery route: location does not matter. J Allergy Clin Immunol Pract. 2014;2:156–60.

This recent expert commentary explores the impact of the administration route on adherence, clarifying a key aspect of AIT product choice in clinical practice.

19. Eng PA, Borer-Reinhold M, Heijnen JA, Gnehm HP. Twelve year follow-up after discontinuation of preseasonal grass pollen immunotherapy in children. Allergy. 2006;61:198–201.
20. Durham SR, Emmiger W, Kapp A, Colombo G, De Monchy JC, Rak S, et al. Long term clinical efficacy in grass-pollen induced conjunctivitis after treatment with SQ-standardized grass allergy immunotherapy tablet. J Allergy Clin Immunol. 2010;125:131–7.
21. Durham SR, Emmiger W, Kapp A, De Monchy JC, Rak S, Scadding GK, et al. SQ-standardized sublingual grass immunotherapy confirmation of disease modification 2 years after 3 years of treatment in a randomized trial. J Allergy Clin Immunol. 2012;129:717–25.
22. Jacobsen L, Niggemann B, Dreborg S, Ferdousi HA, Halken S, Host A, et al. Specific immunotherapy has a long-term preventive effect on seasonal and perennial asthma: 10 year follow-up on the PAT study. Allergy. 2007;62:493–8.
23. Polosa R, Li Gotti F, Mangano G, Paolino G, Mastruzzo C, Vancheri C, et al. Effect of immunotherapy on asthma progression, BHR and sputum eosinophils in allergic rhinitis. Allergy. 2004;59:1224–8.
24. Des Roches A, Paradis L, Menardo JL, Bouges S, Daures JP, Bousquet J. Immunotherapy with a standardized *Dermatophagoides pteronyssinus* extract IV. Specific immunotherapy prevents the onset of new sensitization in children. J Allergy Clin Immunol. 1997;99:450–3.
25. Pajno GB, Barberio G, De Luca F, Morabito L, Parmiani S. Prevention of new sensitizations in asthmatic children monosensitized to house dust mite by specific immunotherapy: a six year follow up study. Clin Exp Allergy. 2001;31:1392–7.
26. Cox L, Wallace D. Specific allergy immunotherapy for allergic rhinitis: subcutaneous and sublingual. Immunol Allergy Clin N Am. 2011;31(3):561–99.
27. Plaza V, Ramos Barbon B, Munoz AM, et al. Exhaled nitric oxide fraction as an add on to ACQ 7 for not well controlled asthma. PLos One. 2013;8:e77085.
28. Cohn JR, Pizzi A. Determinants of patient compliance with allergen immunotherapy. J Allergy Clin Immunol. 1993;91:734–7.
29. Lower T, Hensy J, Mandik L, Janosky J, Friday Jr GA. Compliance with allergen immunotherapy. Ann Allergy. 1993;70:480–2.
30. Tinkelman D, Smith F, Cole 3rd WD, Slik HJ. Compliance with an allergen immunotherapy regimen. Ann Allergy Asthma Immunol. 1995;74:241–6.
31. Ruiz FJ, Jimenez A, Cocoletzi J, Duran E. Compliance with and abandonment of immunotherapy. Rev Alerg Mex. 1997;44:42–4.
32. Donahue JG, Greineder DK, Connor-Lacke L, Canning CF, Platt R. Utilization and cost of immunotherapy for allergic asthma and rhinitis. Ann Allergy Asthma Immunol. 1999;82:339–47.
33. Rhodes BJ. Patient dropouts before completion of optimal dose, multiple allergen immunotherapy. Ann Allergy Asthma Immunol. 1999;82:281–6.
34. More DR, Hagan LL. Factors affecting compliance with allergy immunotherapy at a military medical center. Ann Allergy Asthma Immunol. 2002;88:391–4.
35. Pajno GB, Vita D, Caminiti L, Arrigo T, Lombardo F, Incorvaia C, et al. Children's compliance with allergen immunotherapy according to administration routes. J Allergy Clin Immunol. 2005;116:1380–1.
36. Hommers L, Ellert U, Scheidt-Nave C, et al. Factors contributing to conductance and outcome of specific immunotherapy: data from Germany National Health Interview and Examination Survey. Eur J Public Health. 2007;17:278–84.
37. Hankin CS, Cox L, Land D, et al. Allergy immunotherapy among Medicaid enrolled children with allergic rhinitis: patterns of care, resource use, and costs. J Allergy Clin Immunol. 2008;121:227–32.
38. Mahesh PA, Vadanthan PH, Amrutha DH, et al. Factors associated with non-adherence to specific

immunotherapy in management of respiratory allergy. Indian J Chest Dis Allied Sci. 2010;52:91–5.
39. Hsu NM, Reisacher WR. A comparison attrition rates in patients undergoing sublingual immunotherapy vs subcutaneous immunotherapy. Int Forum Allergy Rhinol. 2012;2:280–4.
40. Guenechea-Sola M, Hariri SR, Galoosian A, Yusin JF. A retrospective review of veterans' adherence to allergen immunotherapy over 10 years. Ann Allergy Asthma Immunol. 2014;112:71–82.
41.•• Kiel M, Roder F. Gerth van Wjik et al. Real-life compliance and persistence among users of subcutaneous and sublingual immunotherapy. J Allergy Clin Immunol. 2013;132:353–60.

This paper provides very recent data on the topic and investigates the potential determinants of compliance with treatment in the complex daily clinical practice setting.

42. Silva D, Pereira A, Santos N, Placido JL. Costs of treatment affect compliance to specific subcutaneous immunotherapy. Eur Ann Allergy Clin Immunol. 2014;46:87–94.
43. Marogna M, Spadolini I, Massolo A, Canonica GW, Passalacqua G. Randomized controlled open study of SLIT for respiratory allergy in real life: clinical efficacy and more. Allergy. 2004;59:1205–10.
44. Lombardi C, Gani F, Landi M, Falagiani P, Bruno G, Canonica GW, et al. Quantitative assessment of the adherence to sublingual immunotherapy. J Allergy Clin Immunol. 2004;113:1219–20.
45. Passalacqua G, Musarra A, Pecora S, Amoroso S, Antonicelli L, Cadario G, et al. Quantitative assessment of the compliance with once-daily sublingual immunotherapy regimen in real life (EASY Project: Evaluation of a Novel SLIT Formulation During a Year). J Allergy Clin Immunol. 2006;117:946–8.
46. Passalacqua G, Musarra A, Pecora S, Amoroso S, Antonicelli L, Cadario G, et al. Quantitative assessment of the compliance with once-daily sublingual immunotherapy children (EASY Project: Evaluation of a Novel SLIT Formulation During a Year). Pediatr Allergy Immunol. 2007;18:58–62.
47. Cadario G, Ciprandi G, Di Cara G, et al. Comparison between continuous or intermittent schedules of sublingual immunotherapy for house dust mites: effects on compliance, patient's satisfaction, quality of life and safety. Int J Immunopharmacol. 2008;21:471–3.
48. Roder E, Berger MY, de Groot H, ven Wijk RG. Sublingual immunotherapy in youngsters: adherence in a randomized clinical trial. Clin Exp Allergy. 2008;38:1659–67.
49. Chang H, Han DH, Mo JH, et al. Early compliance and efficacy of sublingual immunotherapy in patients with allergic rhinitis to house dust mite. Clin Exp Otorhinolaryngol. 2009;2:136–40.
50. Jansen A, Andersen KF, Brüning H. Evaluation of a compliance device in a subgroup of adult patients receiving specific immunotherapy with grass allergen tablets (Grazax) in a randomized open-label, controlled study: an a priori subgroup analysis. Clin Ther. 2009;31(2):321–7.
51. Ott H, Sieber J, Breheler R, et al. Efficacy of grass pollen immunotherapy for three consecutive seasons and after cessation of treatment. The ECRIT study. Allergy. 2009;64:179–86.
52. Vita D, Caminiti L, Ruggeri P, Pajno G. Sublingual immunotherapy: adherence based on timing and monitoring control visits. Allergy. 2010;65:668–9.
53.• Pajno G, Caminiti L, Crisafulli G, et al. Adherence to sublingual immunotherapy in preschool children. Pediatr Allergy Immunol. 2012;23:688–9.

This paper highlights the determinants that may affect treatment adherence in the pediatric population and that should be specifically addressed in clinical practice in order to improve patients' adherence.

54. Trebuchon F, Lheritier-Barrand M, David M, Demoli P. Characteristics and management of sublingual allergen immunotherapy in children with allergic rhinitis and asthma induced by house dust mite allergens. Clin Transl Allergy. 2014;4:15.
55. Senna G, Lombardi C, Canonica GW, Passalacqua G. How adherent to sublingual immunotherapy prescriptions are patients? The manufacturer's view point. J Allergy Clin Immunol. 2010;126:668–9.
56. Sieber J, De Geest S, Sahah-Hosseini K, Mosges R. Medication persistence with long term, specific grass pollen immunotherapy measured by renewal prescription rate. Curr Med Res Opin. 2011;27:855–61.
57. Stokes SC, Quinn JM, Sacha JJ, White KM. Adherence to imported fire ant subcutaneous immunotherapy. Ann Allergy Asthma Immunol. 2013;110:165–7.
58. Senna G, Caminati M, Canonica GW. Safety and tolerability of sublingual immunotherapy in clinical trials and real life. Curr Opin Allergy Clin Immunol. 2013;13:656–62.
59.• Makatsory M, Scadding GW, Lombardo C, et al. Drop outs in sublingual allergen immunotherapy trials: a systematic review. Allergy. 2014;69:571–80.

This extensive recent analysis of adherence rate in SLIT clinical trials provides a complete evaluation of reasons for dropout, which are not only important in the planning of clinical studies but are also relevant for adherence to immunotherapy in daily clinical practice.

60. Allam JP, Stojanovoski G, Fredrichs G, et al. Distribution of Langerhans cells and mast cells within the human oral mucosa: new application for sites of allergens in sublingual immunotherapies. Allergy. 2008;63:720–7.
61. Mahadevia PJ, Shas S, Leibman C, Kleinman L, et al. Patient's preference for sensory attributes of intranasal corticosteroids and willingness to adhere to prescribed therapy for allergic rhinitis: a conjoint analysis. Ann Allergy Asthma Immunol. 2004;93:345–50.
62. Pajno GB, Caminiti L, Crisafulli G, et al. Direct comparison between continuous and coseasonal regimen for sublingual immunotherapy in children with grass allergy. Pediatr Allergy Immunol. 2011;22:803–7.

63. de Olano DG, Twose IA. Adherence to immunotherapy in time of financial crisis. Ann Allergy Asthma Immunol. 2013;110:466–8.
64. Pajno G, Caminiti L, Passalacqua G. Changing the route of immunotherapy administration: an 18 year survey in pediatric patients with allergic rhinitis and asthma. Allergy Asthma Proc. 2013;34:523–6.
65. Passalacqua G, Frati F, Puccinelli P, et al. Adherence to sublingual immunotherapy. The allergists' viewpoint. Allergy. 2009;64:1795–6.
66. Marti E, Sanchez-Salguero C, Scorza E, Alberto Garcia M. Longer treatment duration with SLIT leads to higher patient's satisfaction and clinical improvement. Outcomes of the SAMITES study. Clinical Transl Allergy. 2013; (Suppl 2):P12.
67. Cox L, Calderon M, Pfaar O. Subcutaneous allergen immunotherapy for allergic disease: examining efficacy, safety, and cost/effectiveness of current and novel formulations. Immunotherapy. 2012;4:601–14.
68. Nesser S, Vestenbaek U, Beriot-Mathiot A, Poulsen PB. Cost-effectiveness of specific immunotherapy with Grazax in allergic rhinitis co-existing with asthma. Allergy. 2008;63:1624–9.
69. Odegard PS, Carpinito G, Christensen DB. Medication adherence program: adherence program and interventions in type 2 diabetes. J Am Pharm Assoc. 2013;53:267–72.
70. Marsh RJ, Rhode H, Zwarenstein M, Rollnick S, et al. Effectiveness of a group of diabetes education programme in under-served communities in South Africa: a pragmatic cluster randomized trial. Diabet Med. 2014;31:987–93.
71. Ogedegbe G, Chaplin W, Schoenthaler A, et al. A practice based trial on motivation interviewing and adherence in hypertensive African Americans. Am J Hypertens. 2008;21:1137–43.
72. Bultman DC, Svarstad BL. Effects of physician communication style on client medication beliefs and adherence with antidepressant treatment. Patient Educ Couns. 2000;40:173–85.
73. Bull SA, Xu XH, Hunkeler EM, et al. Discontinuation use and switching of antidepressant: influence of patient-physician communication. JAMA. 2002;288:1403–9.
74. Albino S, Tabb KM, Requena D, Egoavil M, Pineros-Leano MF, Zunt JR, et al. Perceptions and acceptability of short message services technology to improve treatment adherence amongst tuberculosis patients in Peru: a Focus Group study. PLoS One. 2014;9(5):e95770.
75. Gao X, Nau DP, Rosenbluth SA, Scott V, Woodward C. The relationship of disease severity, health beliefs and medication adherence among HIV patients. AIDS Care. 2000;12(4):387–98.
76. Gani F, Pozzi E, Crivellaro MA, et al. The role of patient's training in the management of seasonal allergic rhinitis. Allergy. 2001;56:65–8.
77. Brown R, Bratton SL, Cabana MD, Kaciroti N, Clark NM. Physician asthma education program improves outcomes for children of low-income families. Chest. 2004;126:369–74.
78. Sade K, Berkun Y, Dolev Z, Shalit M, Kivity S. Knowledge and expectations of patients receiving aeroallergen immunotherapy. Ann Allergy Asthma Immunol. 2003;91:444–8.
79. Incorvaia C, Rapetti A, Scurati S, Puccinelli P, Capece M, Frati F. Importance of patient's education in favouring compliance with sublingual immunotherapy. Allergy. 2010;65:1341–2.
80. Savi E, Peveri S, Senna G, Passalacqua G. Causes of SLIT discontinuation and strategies to improve the adherence: a pragmatic approach. Allergy. 2013;68:1193–5.
81. Britten N. Patient's expectations of consultations. BMJ. 2004;328:416–7.
82. Cushing A, Metclafe R. Optimizing medicines management: from compliance to concordance. Ther Clin Risk Manag. 2007;3:1047–58.
83. Panahi S, Watson J, Patridge H. Social media and physicians: exploring the benefits and challenges. Health Informatics J. 2014;18. doi:10.1177/1460458214540907.
84. Fenny N, Wolf R, Dimov V. Rapid growth of Twitter use by allergists and immunologists for professional purposes [abstract]. Ann Allergy Asthma Immunol. 2012;109(5 Suppl):A125.
85. Nickels A, Dimov V. Innovations in technology: social media and mobile technology in the care of adolescents with asthma. Curr Allergy Asthma Rep. 2012;12(6):607–12.
86. Tripodi S, Comberiati P, Di Rienzo Businco A. A web-based tool for improving adherence to sublingual immunotherapy. Pediatr Allergy Immunol. 2014;25(6):611–2.
87. EMR System, Electronic Medical Records (EMR) Software, EHR Software [http://www.allergyehr.com].
88. ModuleMD Healthcare Solutions – (EMR and EHR) | Medical Billing | Practice Management | Revenue Management | Meaningful Use | ModuleMD WISE-TOUCH [http://www.modulemd.com].
89. Mountainside Software, Inc. | Integrated software solutions for physicians and their medical practice [http://www.mountainsidesoftware.com].
90. Rosch Visionary Systems - Home [http://www.roschvisionary.com].