

REVIEW

Long-term adherence to sublingual therapy: literature review and suggestions for management strategies based on patients' needs and preferences

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Summary

Sublingual immunotherapy (SLIT) is an at-home, self-administered, long-term therapy. As with other chronic diseases, patient adherence is a prerequisite for the success of SLIT. Its ease of intake and convenience should ensure adequate patient compliance; however, a recent post-marketing manufacturers' survey has shown a very high rate of discontinuation. The available literature on patient adherence to SLIT is reviewed in the present article. Great differences exist between controlled studies, which show a satisfactory adherence rate, and long-term real-life studies, which show poor compliance with SLIT. Remarkable divergence in the weight placed on different reasons for SLIT discontinuation is reported in the various studies. The main reasons for withdrawal are analysed and discussed. Data from placebo-controlled studies demonstrate that adherence depends less on the patient's perception of the inefficacy of therapy or other causes than on the patient's motivation, that is the patient's decision to participate in the trial and to meet the researcher's expectations. The enrolment of patients who agree to enter a blind, placebo-controlled trial is conceptually similar to a concordance process. Concordance is a consultation process that aims to establish a therapeutic alliance between the physician and patient and to bring about agreement on a therapeutic programme. Concordance is based on the patient's beliefs and needs and implies actions that support the patient's adherence. Suggestions are given for a SLIT management strategy based on the concordance process and designed to integrate the patient's viewpoints into treatment-related decisions and to meet patients' preferences and their health-system-related needs.

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Introduction

Allergen immunotherapy is a keystone of allergic respiratory disease management because it is the only treatment that can act on disease causes to modify the natural progression of the allergy and offer long-lasting efficacy of symptoms reduction [1].

Subcutaneous immunotherapy (SCIT) has long been the only available conventional allergy therapy. Because SCIT is directly administered by allergists, compliance was taken for granted. However, some studies showed poor compliance in approximately 50% of cases, and compliance was even worse (84%) over a 3-year course [2–4]. Inconvenience was the most important reason for withdrawal.

Sublingual immunotherapy (SLIT) represents an effective alternative to subcutaneous immunotherapy. Efficacy

has been established in a number of clinical trials and meta-analyses, and the safety profile is very satisfactory [1]. SLIT is widely used in clinical practice (at least in European countries).

SLIT is an at-home, self-administered, long-term therapy. The regular intake of scheduled doses for an extended time (at least 3 years) is mandatory to produce appreciable outcomes [1]. For this reason, as for other chronic diseases, the patient's adherence is a prerequisite for the success of immunotherapy. Convenience and ease of intake should ensure adequate patient compliance.

The purpose of this study was to assess long-term compliance with SLIT based on a literature review, to discuss the main factors that can influence adherence in real life, and to suggest an intervention strategy to enhance long-term adherence to/compliance with SLIT.

Methods

The available literature on the topic was searched on the MEDLINE database using the research terms 'sublingual immunotherapy', 'SLIT', and 'allergen-specific immunotherapy', each separately paired with 'compliance' or 'adherence' (i.e. SLIT AND compliance; SLIT AND adherence) and a selection date range of 2000.01.01–2013.12.31.

Articles were considered if they reported useful data about SLIT adherence/compliance and information on the main causes of non-compliance and discontinuation. The bibliographies of chosen articles were also considered. Studies with an excessively small sample (<60 patients) were discarded.

Controlled prospective studies on the efficacy and safety of SLIT starting with, but not limited to, those listed in the main SLIT position papers and meta-analyses were reviewed for further information.

Compliance, adherence, and concordance

The terms *adherence* and *compliance* are often used synonymously, but they have significant conceptual differences, which can influence the patient's behaviour regarding a given physician's prescription or a therapeutic programme.

Compliance describes the extent to which a patient follows physician's advice and prescriptions [5, 6]. Given that definition, compliance implies that the physician has an authoritative role in the physician/patient relationship and that the patient is obligated to follow the doctor's orders. As a consequence, non-compliance could express a patient's inability to understand or comply with prescriptions or a therapeutic programme.

Adherence describes the extent to which a patient agrees to give his/her consent and to follow physician's advice and prescriptions [5, 6].

The term 'adherence' highlights the concept that, within the physician/patient relationship, the patient has the right to decide whether to accept the doctor's directives and that patients should not be blamed for non-adherence.

Strong emphasis has been placed on the need to differentiate adherence from compliance; however, ultimately, adherence simply adds to the compliance concept the need for the patient to agree to the physician's recommendations. Clear information is essential for obtaining agreement, but it is not enough to guarantee adherence.

Adherence to a long-term therapy is simultaneously influenced by several factors, which include social and economic factors, characteristics of the disease and the disease therapy, factors related to the healthcare team

and system/organisation, and patient-related factors. To ensure satisfactory adherence to therapies, it is necessary to solve problems related to each of these factors [5, 6].

A long-term therapeutic programme requires strong motivation, especially when the benefits are not obvious to the patient and when treatment could interfere with life and work habits. The patient's and the doctor's viewpoints can diverge regarding the valuation of a treatment's risks and benefits and its impact on quality of life. Therefore, negotiation is necessary to reach a shared decision.

Concordance defines a consultation process that aims to establish a therapeutic alliance between physician and patient to help them agree on a therapeutic programme that considers the patient's beliefs and needs [7]. Concordance does not refer to the patient's behaviour in terms of compliance/adherence. Concordance describes actions that support the patient's adherence and is synonymous with patient-centred care.

In other words, patients will not be asked to conform to the healthcare service's organisation; rather, the service team will strive to organise its activities according to the patient's needs.

Compliance with/adherence to sublingual immunotherapy

Adherence is currently the preferred term; however, as a rule in the literature on the topic and consequently in the present review, adherence and compliance are used synonymously.

Non-compliance with immunotherapy can be described as the rate of withdrawal. However, because SLIT is self-managed at home without direct medical supervision, it entails a risk of incorrect or irregular use. As a consequence, non-compliance can also be defined as the inconsistent intake of scheduled doses.

Compliance or adherence can be assessed using direct or indirect methods. Directly observed therapy is impractical in real life, and no methods for measuring vaccine levels in the blood or other biological specimens are available. Structured questionnaires, medication diaries, dose counts (leftover tablets/vials or drops), and the reorder interval for prescriptions are indirect measurement methods. Such measurements are simple, inexpensive, and easy to perform but are easily manipulated by patients.

There are no standard, approved methods for assessing adherence, and various measurement techniques are used. For this reason, it is difficult to compare the results of published studies. The consumption of at least 80% of the prescribed doses is generally accepted as good compliance, but self-reported medication intake is frequently overestimated [8, 9].

Other shortcomings in clinical trials should also be considered. As they approach the date of control visits, patients often resume regular intake of the drugs and continue it during the days that follow (the so-called white-coat effect) [10]. Moreover, the patients' awareness that adherence is the trial's aim introduces an intrinsic, significant bias in prospective studies.

Compliance in terms of regular dose intake

A small number of clinical studies have specifically addressed SLIT compliance/adherence, mainly in terms of the regular dose intake.

Three real-life surveys, which used the same methodological approach, involved a total population of 600 people (71 children) [11–13]. The patients, unaware that they were being observed, were asked to count their remaining doses during random, unscheduled phone calls. Asking the patient to count on demand should avoid an overestimation of adherence in self-reporting. The resulting SLIT adherence values were satisfactory, ranging from 77 to 97%.

A randomised, controlled study of 319 adults that was designed to investigate adherence (along with other primary endpoints) showed an adherence rate of 72% [14].

The impact of an electronic reminder device with a programmable acoustic alarm on SLIT compliance was evaluated in 261 adult patients with grass-pollen allergies. The resulting compliance rates were 83% in both randomised parallel groups [15]. In a previous study using the same electronic device in a subgroup of 91 adult patients (already enrolled in a multi-centre, open-label European trial), the mean rate of treatment compliance was 95%, but no control data were reported, and only 46% of the patients reported that the compliance device made it easier to remember to take their tablets regularly [16].

In a recent retrospective study of 1289 patients (551 children) based on data collected from the medical files of a randomly selected sample of specialists, physician-rate compliance was good or very good in 88% of the patients. In this study, compliance was not clearly defined, and it is noteworthy that no significant differences in the compliance rate were reported between patients who completed the treatment course (95.6%) and those who discontinued (84.1%) [17]. However, the study results are most likely biased by shortcomings in the patient selection criteria and data reporting.

Data on compliance, defined as the regular intake of scheduled vaccine doses, can also be drawn from some controlled prospective studies that are not specifically designed to assess compliance.

In a 2-year randomised placebo-controlled study that primarily aimed to evaluate SLIT efficacy, adherence to

medication intake was assessed in 154 children who completed the study [18]. The adherence rate was 77%, with no significant difference between the verum treatment group (82%) and the placebo group (72%). The overlap between calculated adherence and self-reported adherence was 78% during the overall study period, but it was near complete (97–100%) among adherent participants and very poor (3–12%) among the non-adherent (drop-out) children [18].

Similar results were found in a previous 1-year study of 30 children. Based on the patients' diaries, regular intake of sublingual therapy was found for all of the children who completed the study, with minor irregularities (missed doses <8% of the total amount or dosing mistakes) for one-third of the cases. These figures were identical for the active and placebo groups [19].

In a 3-year randomised placebo-controlled study of 213 adult and child patients with grass allergies, compliance ranged from 88 to 91%, with no specified difference between verum and placebo [20].

Further information can be obtained from the 'big trials', large studies performed to evaluate the safety and efficacy of SLIT for grass allergies in a dissolving-tablet formulation.

In a multi-centre, double-blind, randomised, parallel-group, placebo-controlled trial involving 855 adult patients taking three different doses of an allergen, adherence ranged from 94 to 98%, with no differences among the various groups [21]. To investigate the sustained efficacy of SLIT, the trial was extended to cover 3 years of daily treatment for 257 subjects. The compliance with the assigned treatment regimen during the last treatment year was 91%, with no difference between the active and placebo groups [22].

Two analogous trials were conducted with paediatric populations. Two hundred and seventy-eight children were enrolled in one study. The compliance rate was 95% in the placebo group and 94% in the active group [23]. The mean compliance was 93% in the second study, which included 253 paediatric patients, and there was no difference between the active and placebo groups [24].

In a recent randomised controlled trial of a ragweed allergy immunotherapy tablet, 784 adult patients were randomly assigned to once-daily treatment with three different doses of the allergen or a placebo. Compliance ranged from 92 to 94%, with no differences between groups [25].

Compliance as withdrawal rate

In some clinical trials, SLIT compliance was evaluated in terms of the withdrawal rate.

A 2-year, randomised, double-blind, placebo-controlled study on SLIT for house-dust mite allergies

included 72 adult and paediatric patients [26]. In this study, the regular intake of the scheduled vaccine doses was not specifically checked, and control visits were planned at the end of the first- and second-therapy years. Compliance was not satisfactory. The withdrawal rate was significantly greater in the placebo group (61%) than in the active group (30%). Perceived inefficacy was the main cause of discontinuation. In the active treatment group, 21.6% of the patients discontinued therapy because of lack of efficacy, compared with 39.5% in the placebo group. This difference is not statistically significant, but it indicates a trend towards better compliance in the active treatment group because of the efficacy of immunotherapy [26].

In a similar 3-year trial of 97 children using grass-pollen SLIT, the withdrawal rate was 23% (32% by admitted non-compliance), with no difference between the active and placebo groups [27]. In both studies, compliance was not clearly defined.

Eight hundred and six children who received SLIT either in a hospital setting or in a private medical office were followed for a 3-year period. The discontinuation rate was 21.5%. Costs (36%), followed by perceived inefficacy (25%), were the main causes of discontinuation. No significant differences were found between patients who were followed in hospital (87.2%) or in private practice (81.7%) [28]. In a further study of 100 preschool children aged 4–6 years who were followed for a 2-year period, the withdrawal rate was between 32 (for the 4- to 5-year-old group) and 26% (for the 5- to 6-year-old group) [29].

One hundred and ten asthmatic children were randomised in a double-blind, placebo-controlled, six-month study on the efficacy and tolerability of house-dust mite SLIT. The withdrawal rate was 12%, with no difference between the active and placebo groups. Perceived inefficacy was a cause of discontinuation only in the active group [30].

In a similar double-blind, 18-month-long, placebo-controlled trial performed with 111 asthmatic children to assess the efficacy of house-dust mite SLIT, the withdrawal rate was 17%, with no differences between the active treatment and placebo groups. The main cause of discontinuation was non-compliance with therapy [31].

To assess efficacy and safety, 112 Korean children with allergic rhinitis who began taking house-dust mites SLIT were followed for 1 year. Substantial improvement in symptoms was seen within the first 6 months. The withdrawal rate was 21%. Adverse events and perceived inefficacy (both 33%), followed by non-compliance with therapy, were the main causes of discontinuation [32].

In the previously quoted study by Roder et al. [18], the causes of early SLIT discontinuation were clearly detailed. The withdrawal rate was 24%. The main cause

was non-compliance (52%), defined as the inability to take the medication according to schedule (for a half of the cases, this occurred along with the inability to complete the diary card); there was no difference between the verum and placebo groups. Eighty percent of the dropouts reported forgetting doses, compared with 37% of those who completed the follow-up. This study demonstrates in detail that patients who completed the fixed follow-up period take almost all of their scheduled doses and vice versa: patients with frequent oversights or an inability to take vaccine doses according to schedule in all probability will withdraw from SLIT.

To evaluate the safety and efficacy of house-dust mite SLIT in elderly patients (over 60 years of age) with allergic rhinitis, 108 patients were enrolled in a 3-year, double-blind study to receive either active treatment or placebo. Non-compliance was the main cause of discontinuation (12%), with no differences between the two groups [33].

In the previously mentioned 'big trials' [21–25], the mean percentage of discontinuation ranged from 4 to 22%, with non-significant differences between the active and placebo groups. In these studies, side-effects were the most commonly cited cause of withdrawal.

A multi-centre, double-blind, placebo-controlled European trial has been conducted to assess the efficacy and safety of two doses of house-dust mite sublingual tablets over 1 year of treatment in 509 adult patients. The withdrawal rate was 10% in the placebo group and 19% in the treatment group; the treatment group had a significantly higher withdrawal rate because of a higher incidence of adverse events. No significant group differences were found for the other causes of discontinuation, including perceived inefficacy [34].

A non-controlled observational study that aimed to assess compliance with SLIT in 142 Korean patients, which can be seen as a real-life study, reported a drop-out rate of 31%, which is relatively high compared with other studies [35]. The main reasons for discontinuation were admitted non-compliance, defined as the inability to take medication according to scheduled doses (28%), followed by ineffectiveness. (22%)

The possibility of a trend of a higher attrition rate in real life compared with controlled studies was confirmed by a retrospective study of 217 patients taking SCIT (139) and SLIT (78) over a 4-year period [36]. In this study, the SLIT withdrawal rate was 41%. Concerns about efficacy, followed by cost, were the major motivations for withdrawal. No statistically significant difference in the discontinuation rate was found compared with a group of patients on SCIT, but the SCIT patients withdrew earlier (within the first 6 months) than the SLIT patients did (up to 12 months) [36].

Limited, inadequate SLIT compliance in real life seems definitively confirmed by the post-marketing surveys, which show a very high rate of discontinuation.

Published data concerning the Italian market show sales declines of approximately 55% in the first year, 75% in the second year, and up to 85% in the third year after the initial prescription [37]. This finding means that only 15 to 20% of SLIT patients were persisting with therapy at 3 years.

A real-life retrospective study based on a nationwide drug-dispensing database (6486 adult Dutch patients: 3690 SLIT and 2796 SCIT patients) shows SLIT withdrawal rates of 62% in the first year and 93% in the third year. The corresponding figures for SCIT were 20 and 77%, respectively, which were significantly lower. This finding means that only 7% of SLIT patients were continuing therapy at 3 years. The median time of discontinuation was 1.7 years for SCIT and 0.6 years for SLIT [38].

Available data on the SLIT withdrawal rate from the studies considered here, together with the details about the observation time, scheduled visit interval and the main causes of discontinuation, are summarised in the Table 1.

General considerations

Controlled trials and real-life studies are not comparable, and there are important differences in methods for assessing adherence. As a consequence, the different studies show remarkable divergence in the weight given to different reasons for discontinuing SLIT. (Tab 1) However, it is still possible to draw some general conclusions:

- 1 In all of the controlled studies, compliance was satisfactory both in terms of therapy throughout the planned time and the regular intake of scheduled doses.
- 2 In general, the more frequent the control visits and the more firm the patients' involvement were, the better adherence was. This was also true for the randomised, double-blind, placebo-controlled studies. Therefore, infrequent monitoring of treatment might be a drawback to be considered.
- 3 In observational studies, SLIT compliance results were less satisfactory. Although almost all of these studies were biased by periodical control visits and by the various methods used to assess compliance, the differences in compliance rate compared with randomised, double-blind, placebo-controlled trials are significant if the results of short-term studies are not considered (Mann–Whitney *U*-test, $P < 0.01$).
- 4 In the only retrospective, real-life study with no intervention for the considered population, the attrition rate was remarkably high and quite similar to

the discontinuation rate reported in the post-marketing survey.

- 5 Compliance seems very satisfactory during the early months because the majority of SLIT patients tend to withdraw later, up to 12 months after their treatment begins. Studies on SLIT compliance should be extended over at least 1 year, ideally for three or 5 years, to evaluate compliance in a reliable way.
- 6 Patients who complete the follow-up period show a regular intake of scheduled doses, unlike patients who discontinue therapy. In general, SLIT withdrawal implies an inconsistent intake of scheduled vaccine doses and vice versa.
- 7 In placebo-controlled studies, there are no significant differences in adherence between the active and placebo groups. Adherence proved to be determined less by patients' perceptions of the inefficacy of therapy or other causes than by the patient's motivation, that is the patient's decision to participate in the trial and to meet their agreement with the researchers.

Comment on the main causes of withdrawal and the concordance process

There is a general agreement that the patient's perception of or belief in the inefficacy or poor efficacy of any therapy is most likely the most important influence on adherence. This is also the case for SLIT. In a questionnaire study administered to a sample of randomly selected, 54% ranked the perception of clinical efficacy as the primary cause of discontinuation, and 78% ranked it as one of the three main causes of discontinuation [39].

Immunotherapy is not a relief medication; rather, it is a long-term therapy with results that are not expected in a short time. Consequently, patients may believe that SLIT is ineffective and therefore unnecessary. Efforts should be made to address patients' unrealistic expectations of quick improvement of symptoms. Patients must receive correct instruction and information about SLIT and the time required to achieve the expected results.

The literature data on patient withdrawal from vaccine immunotherapy because of perceived inefficacy show great variability (Table 1), but in double-blind, placebo-controlled studies, there are no significant differences in discontinuation rates between active and placebo groups. This finding indicates that the perception of poor efficacy (which is very probable among placebo-treated patients) can be overcome by the patient's motivation to complete the fixed course for SLIT.

The allergist should monitor the evolution of allergic disease during immunotherapy to verify the outcomes, possibly using functional examinations and other evidence to address the patient's perception and to increase

Table 1. Studies of sublingual immunotherapy adherence

Reference [n]	Nr/A	Visits	F-up	Ad (%)	Withdrawal cause (%)	Notes
Guez [22]	72/A, C	1, 12, 24 Ms	2 Ys	54	I = 64; NC = 25; O = 11	Withdrawal rate was greater in the placebo group (40%) than in the active group (22%), but not significant
Lombardi [11]	86/A, C	ND	4–12 Ms	97	ND (?)	Compliance was of 97% calculated as total number of taken tablets /expected for all together the patients. 11 patients (13%) reported occasionally omitted dose because illness, forgetfulness or work
Marogna [14]	319/A	1 /Ys	3 Ys	85	I = 19; NC = 15; SE = 10; O = 56	Others refer to unclear “protocol deviation”. Compliance was also calculated as taken doses/expected and resulted >80% for 72%, from 60 to 80% for 18%, and <60% for 10% of the patients
Rolinck-Werninghaus [27]	97/C	4 /Ys	3 Ys	77	NC = 32; I = 13; SE = 13; O = 42	Compliance not clear defined, multiple entries for premature discontinuation
Pajno [28]	806/C	4 Ms	3 Ys	78	C = 36; I = 25; T = 18; O = 21	
Durham [22]	855/A	3, 4 Ws	4–6 Ms	92	SE = 40; NC = 15; I = 6; O = 39	Figures are data not unbundled from placebo arms (see article full-text for details)
Niu [30]	110/C	2 Ws	6 Ms	88	I = 23; NC = 15; O = 62	NC refers to withdrawn consent. Perceived inefficacy was cause of discontinuation only in the active group
Passalacqua [12]	443/A, C	3, 6 Ms	6 Ms	94	SE = 33; C = 7; O = 60	Adherence computed as taken doses/expected was of 77% (3 months) and 88% (6 months)
Passalacqua [13]	71/C	3 Ms	6 Ms	93	C = 80; SE = 20	In this study adherence computed as taken doses/expected was of 85%
Pham-Thi [31]	111/C	2 Ms	18 Ms	83	NC = 32; SE = 16; I = 5; O = 47	Others are: lost to follow-up or wish to end the study
Roder [18]	204/C	6 Ws	2 Ys	76	NC = 52; SE = 28; O = 20	Adherence computed as taken doses/expected was of 82% in verum treatment group and 72% in placebo group
Wahn [23]	278/C	1 Ms	8 Ms	96	SE = 75; NC = 17; O = 8	Withdrawal, mainly because of SE, was higher in active group with no significant difference
Bufe [24]	253/C	2 Ms	4–8 Ms	92	SE = 32; NC = 26; O = 42	
Chang [35]	142/A, C	ND	6–13 Ms	69	NC = 28; I = 22; SE = 14; O = 36	
Durham [22]	257/A	6 Ms	3 Ys	85	SE = 4; I = 2; O = 94	
Pajno [29]	100/C	3 Ms	2 Ys	71	T = 27; SE = 21; I = 14; O = 38	Data on children ≤4 yrs, biased for children's refusal or problem in keeping sublingual doses, have been omitted
Alesina [15]	261/A	2, 12, 24 Ws	1 Yr	81	ND	Study aimed to test compliance with and without Memozax. No significant difference found. Adherence computed as taken doses/expected was >90%
Bozek [33]	108/E	ND	3/Yr	88	NC = 46; New D = 39; O = 15	New D = Occurrence of a new disease (besides those stable and well controlled at the beginning of the study)
Hsu [36]	139/A, C	ND	3 Ys	59	I = 50; C = 38; SE = 12; O = 10	
Trebuschon [17]	1289/A, C	2, 6 Ms	3–5 Ys	73	NC = 32; I = 25; SE = 8; O = 35	Compliance rated by physician was of 88%. Others are non mentioned causes of discontinuation
Park [32]	112/C	5/Ys	1 Ys	79	SE = 33; I = 33; NC = 21; O = 13	
Creticos [25]	784/A	4/Ys	13 Ms	78	SE = 28; NC = 15; O = 57	Adherence computed as taken doses/ expected was ≥92% in all groups
Bergmann [34]	509/A	6/Ys	1 Ys	84	SE = 51; NC = 27; I = 1; O = 21	Withdrawal was significantly greater in active groups for higher incidence of SE. NC refers to withdrawal consent or investigators' request

Nr, number of patients; A, age; A, adults, C, children, E, elderly; Visits, scheduled or estimated visit intervals; F-up, follow-up: Ws, weeks, Ms, months, Ys, years, ND, not done/applicable; Ad, adherence (%); Causes: C, costs, I, inefficacy, T, time waste, SE, side-effects, NC, non-compliance, O, other.

their confidence in SLIT's efficacy. A monitoring program with periodical controls can multiply the opportunities for communication and interaction with the healthcare team and can be a powerful tool to strengthen patients' motivations and encourage patients to continue vaccine therapy even if they do not perceive any benefits. The good SLIT adherence found in controlled studies is evidently also the result of regular monitoring of the enrolled patients because monitoring visits and educational programmes have been proven to improve SLIT adherence [40–42].

However, the typical allergic patient is a young man/woman who works full-time or is a student. When proposing regular SLIT follow-up, efforts should be made to avoid wasting the patient's time, which could interfere with their day-to-day life. As a matter of fact, retirees and family members show much better compliance than patients who are working [43].

Tolerability is most likely the second factor that affects adherence. In fact, 66% of practicing allergists ranked tolerability as one of the three main reasons for SLIT withdrawal [39]. Data in the literature show wide variability in withdrawal because of tolerability, ranging from 0 to 30% (for studies with discontinuation rates of 15% or greater) (Table 1).

The safety profile of SLIT is very good. Side-effects are usually mild and limited to local reactions in the mouth and/or the gastrointestinal tract. However, patients' concerns about potential harmful adverse events are one of the major reasons for treatment discontinuation. Clear information and reassurances about ordinary adverse reactions, although essential, are not enough to prevent unnecessary withdrawal [5]. It is common for patients' perceptions of side-effects to differ greatly according to their own psychology and abstract representations of the symptoms and their possible consequences.

Patients' concerns should be addressed via counselling and/or direct supervision. When necessary, the manufacturer-recommended immunotherapy programme should be modified to improve tolerability and minimise side-effects. In effect, the rate of withdrawal is proportionally lower in controlled studies compared with epidemiological observations. In other words, the more regular the clinical survey of SLIT is, the lower the number of patients' discontinuations.

Education about self-management is crucial, but SLIT management should not be completely delegated to the patient and his or her general practitioner. Such a management model could generate disappointment and vaccine discontinuation if therapy-related problems begin. In our survey based on direct interviews (unpublished data), the vast majority of patients stated that allergy vaccine management should be the exclusive domain of the allergists.

According to some authors, the main cause of withdrawal was the high cost of therapy. This opinion is shared by most Italian allergists. As a result of a previously quoted study, 34% of the polled specialists ranked cost as the primary cause of discontinuation, and 98% ranked it as one of the three main causes [33]. This belief was debunked by the post-marketing survey, which demonstrated that the discontinuation rate was similar in all Italian regions, irrespective of reimbursement modalities (full, partial, or no reimbursed) [37]. Immunotherapy is reimbursed by insurance companies in the Netherlands. Nevertheless, SLIT (and SCIT) long-term adherence rate are impressively low, and higher socio-economic status showed a significant time-dependent relationship with premature discontinuation [38].

The high cost of medicines and care is consistently reported as an important reason for non-adherence in developing countries. In developed countries, economic burden alone does not predict cost-related non-adherence, but higher medication costs increase the risk, and low income is positively correlated with poor adherence [5, 44]. In a recent survey, only 20% of the studied population reported some form of cost-related non-adherence, but a number of non-cost factors influenced the patients' behaviour [45].

Other prospective factors affecting adherence are usually deemed to be of secondary importance, but their role is most likely underestimated.

Inconvenience related to the daily intake of doses could be an important cause of non-compliance. Modification of current schedules to meet patient's preferences regarding their work and life habits can facilitate compliance. In some cases, an intermittent schedule led to better compliance compared with the usual continuous schedule [46].

Patients' education, as a rule, is not considered to be related to adherence. However, it is not clear what allergists mean by an educational programme. Patients' education is not meant to refer to the necessary, standard instructions regarding SLIT; rather, it refers to an educational process designed to efficiently influence the patient's behaviours and help the patient become an enlightened manager of his or her treatment programme. Of course, educational programmes are among the most challenging and time-consuming services a clinician provides.

In conclusion, a number of factors can affect SLIT adherence. Some of these factors are patient-related others can be attributed to the characteristics of the disease and its treatment. However, healthcare-system-related factors and service delivery can also have great influence on patients' behaviour and on their ability to adhere to vaccine immunotherapy. Consequently, a management strategy that can address these problems systematically is needed.

Suggestions for overcoming non-adherence-related problems

Non-adherence to treatment recommendations for a chronic disease that requires self-administered therapy is a major problem in medical practice, regardless of the disease and the availability of health resources. On average, only a half of patients suffering from the most common chronic diseases (such as hypertension, diabetes and asthma) adhere to their established long-term therapy, but non-adherence peaks of approximately eighty percent have been observed in some studies [6].

SLIT is an at-home, self-administered, long-term therapy whose outcomes are neither immediately observed nor easily measurable. For this reason, the risks of drop-out or patients' loss are even greater than those of other treatment methods.

Adherence and compliance both essentially refer to the patient's medicine-taking behaviours. As a consequence, both terms focus on patient-related factors, strengthening the traditional misconception that non-adherence is a patient-driven problem and neglecting or underestimating the role of providers and health-system-related determinants.

There is strong evidence that adherence is determined by the interaction of a number of factors that can be gathered along five dimensions: [6]

1 Patient-related factors.

This factor set refers to the patient's preferences and viewpoints regarding treatment-related decisions and personal needs. Such factors include adequate knowledge about the disease; the patient's beliefs about the severity

of the disease; the patient's perceptions about health risks and concerns about progressive worsening and complications; information and expectations about therapy outcomes; concerns about adverse reactions to or side-effects of therapy; self-management abilities; and the treatment's impact on the patient's quality of life.

2 Socio-economic factors.

Some factors, such as educational level, occupational status, living conditions and social network, costs of therapy and medical supervision, distance from the treatment centre, wastes of time, and the loss of work hours, can have a significant effect on adherence.

However, socio-economic status does not consistently prove to be an independent predictor of adherence. The healthcare organisation and the relationship between the patient and the healthcare team are far more important [6].

3 Healthcare organisation- and healthcare-team-related factors.

The patients' confidence in and good relationship with his or her healthcare providers are key factors in improving adherence. Educational programmes in self-management, exhaustive information about the therapeutic plan and its expected outcomes/benefits, systems to educate patients and provide regular follow-up and the availability of specialised providers are other important factors that enhance long-term adherence.

4 Condition-related factors

The progression and worsening of the disease and its symptoms, the availability of effective treatments, the onset of complications, health risks, physical and/or

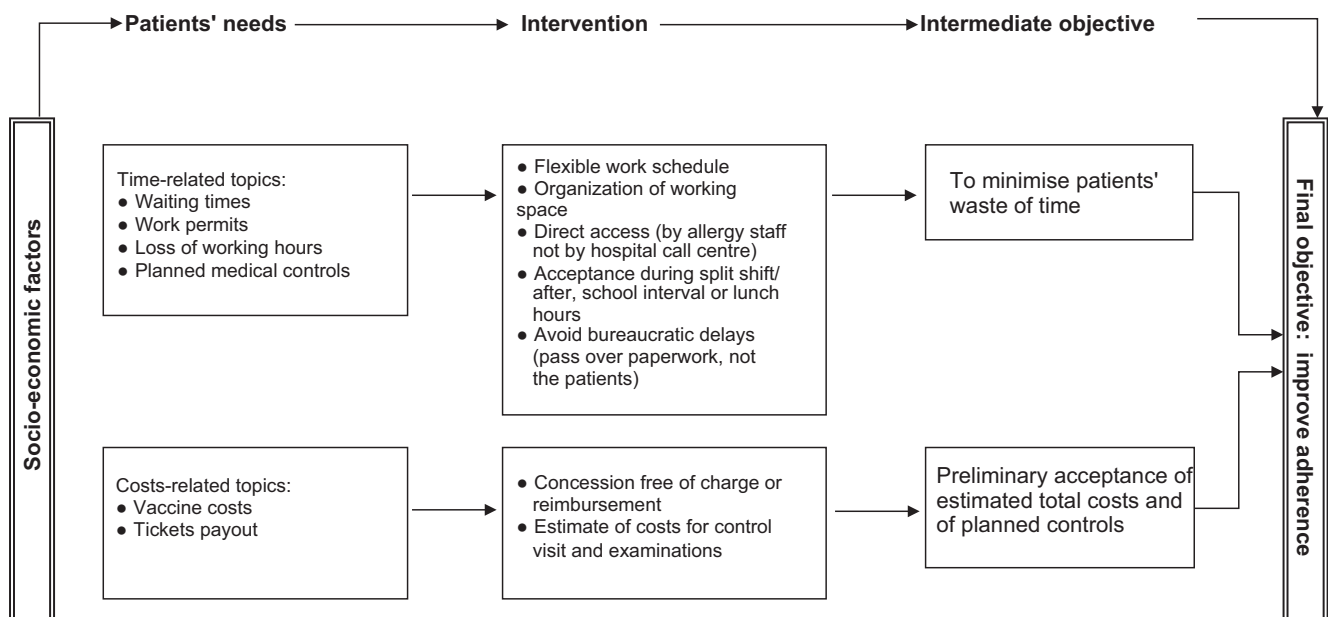


Fig. 1. Breakdown of the interventions to target patients' relevant needs and intermediate objectives: socio-economic factors.

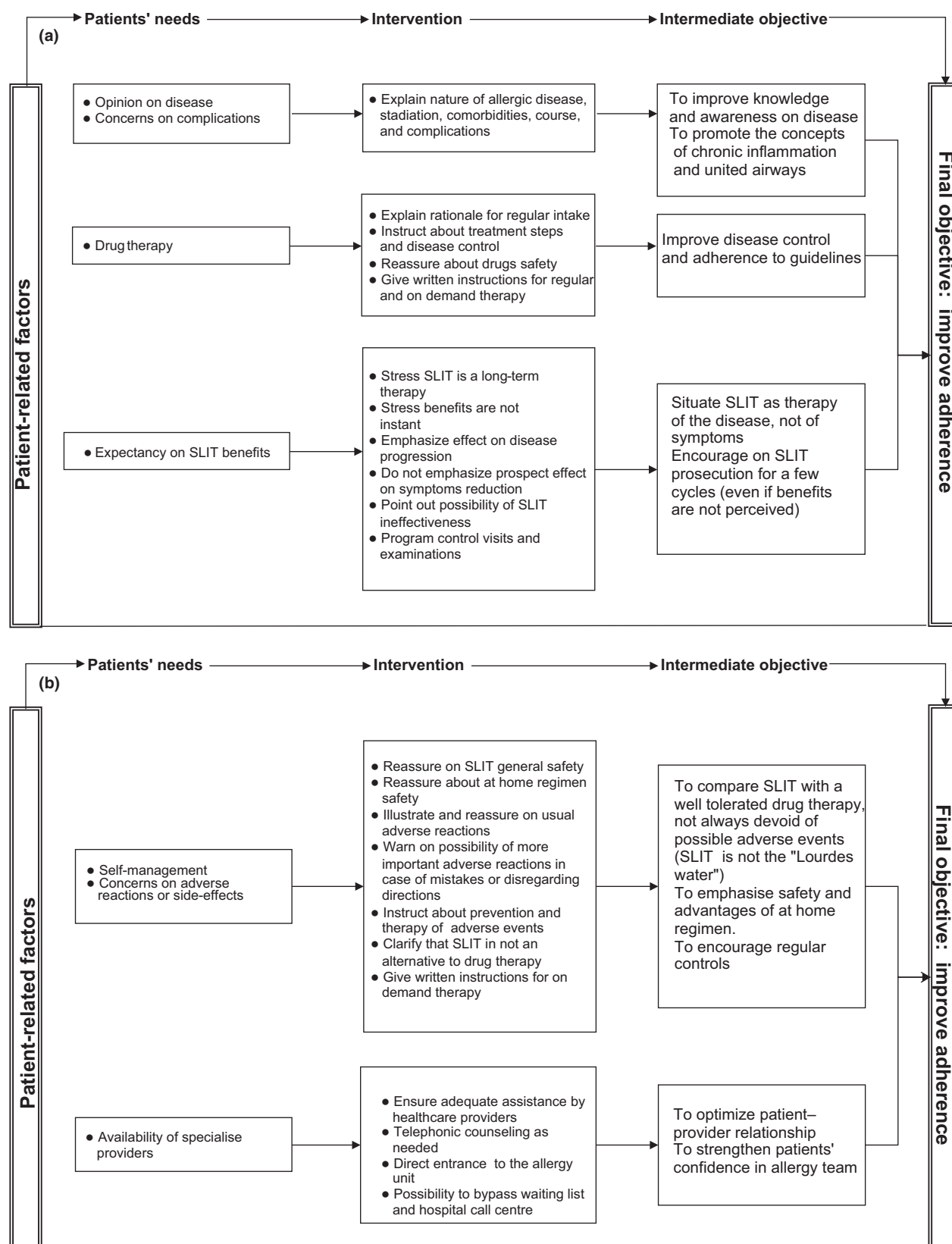


Fig. 2. (a) Breakdown of the interventions to target patients' relevant needs and intermediate objectives: patient-related factors. (b) Breakdown of the interventions to target patients' relevant needs and intermediate objectives: patient-related factors.

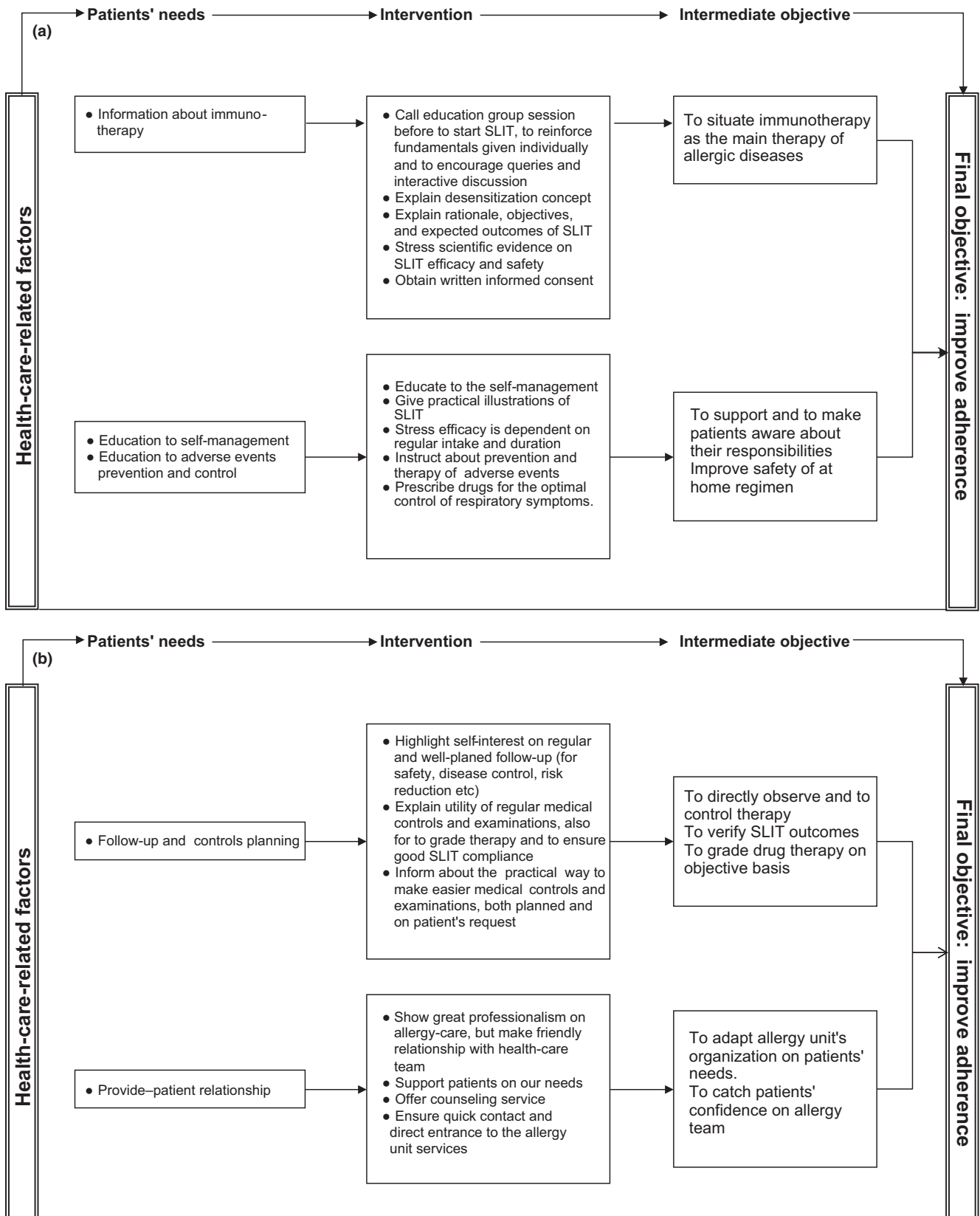


Fig. 3. (a) Breakdown of the interventions to target patients' relevant needs and intermediate objectives: healthcare-related factors. (b) Breakdown of the interventions to target patients' relevant needs and intermediate objectives: healthcare-related factors.

psychological impairments, and comorbidities are important modifiers of adherence.

5 Therapy-related factors

The complexity of the medical regimen, the duration of treatment, failures and frequent changes of therapy, the patient's perceptions of improvements or ineffectiveness, and the occurrence of side-effects, and the availability of medical support to address them are other significant factors affecting adherence.

World-wide experiences with actions to improve adherence to major chronic disease treatments have proven that targeting a single dimension (usually patient-related factors) is ineffective. All five dimensions should be considered for an effective intervention programme, and health professionals should execute a systematic process to assess all the potential barriers to adherence [6].

The concordance process could be an effective method for understanding and addressing possible causes of non-adherence. Concordance refers to a consultation process between equals in which physician and patient establish a therapeutic partnership to accomplish a therapeutic programme. To achieve concordance, the healthcare team should interact with patients to remove traditional barriers to adherence [5–7]. Moreover, and of primary importance, healthcare organisations should support the needs and preferences of patients to make the treatment as convenient as possible and to tailor it to each patient's lifestyle. The concordance process implies that physicians will make efforts to know and analyse patients' needs, preferences, and viewpoints and give patients effective and satisfactory responses both at the clinical and organisational levels.

Starting with the experience and knowledge gained from actions taken to address non-compliance with treatments for major chronic diseases [6] and from the analysis of the main causes of non-compliance found in the present literature review, we provide suggestions for a management strategy to improve long-term adherence to SLIT. A plan of action based on patient's needs and preferences is shown in some breakdowns of the three interacting domains of adherence (socio-economic, patient, and healthcare-related factors; Figs 1–3). These domains include conditions and therapy-related factors, which do

not outweigh the common factors affecting adherence, but modify their influence [6].

There is strong evidence that provider and health-system-related determinants are as important as patient-related factors in influencing long-term therapy adherence. These factors support a healthcare environment in which patients and their needs and preferences play an active role. If patients' needs and preferences are not elicited and taken into account, they can become frustrated, which leads to poor therapy adherence [5]. It is mandatory to gain patients' confidence. 'Patients need to be supported, not blamed' should be the clinician's slogan [6].

Patient-related, socio-economic, and health-service-related factors interact in a dynamic process that influences adherence. These factors are generally time varying. For this reason, a solid partnership should be established, and patients should be supported throughout SLIT treatment by a well-planned and shared follow-up programme.

Data from placebo-controlled studies demonstrate that adherence depends less on patients' perceptions of the inefficacy of therapy or other causes than on patients' motivation, that is the patient's decision to participate in the trial and honour the agreement undertaken with the researchers.

The enrolment of patients who agree to participate in a blind, placebo-controlled trial is conceptually similar to a concordance process.

The concordance process has never been assessed in clinical trials on allergen immunotherapy. The effectiveness of the proposed management strategy should be validated in real life. However, it is reasonable to assume that the clinical use of a concordance approach, which should be planned by each healthcare team in its own specific healthcare system and socio-economic context, could be the best way to understand and obviate SLIT adherence problems.

Conflict of interest

The author has no conflict of interest to declare.

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