Sublingual immunotherapy for allergic rhinitis (Review)

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This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2008, Issue 4

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TABLE OF CONTENTS

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This record should be cited as:
Wilson DR, Torres Lima M, Durham SR. Sublingual immunotherapy for allergic rhinitis. *Cochrane Database of Systematic Reviews* 2003, Issue 2. Art. No.: CD002893. DOI: 10.1002/14651858.CD002893.

This version first published online: 22 April 2003 in Issue 2, 2003.
Date of most recent substantive amendment: 11 February 2003

ABSTRACT

Background
Allergic rhinitis is a common condition which, at its most severe, can significantly impair quality of life despite optimal treatment with antihistamines and topical nasal corticosteroids. Allergen injection immunotherapy significantly reduces symptoms and medication requirements in allergic rhinitis but its use is limited by the possibility of severe systemic reactions. There has therefore been considerable interest in alternative routes for delivery of allergen immunotherapy, particularly the sublingual route.

Objectives
To evaluate the efficacy of sublingual immunotherapy (SLIT), compared with placebo, for reductions in symptoms and medication requirements.

Search strategy
The Cochrane Controlled Trials Register, MEDLINE (1966 to 2002), EMBASE (1974 to 2002) and SciSearch were searched, up to September 2002, using the terms (Rhin* OR hay fever) AND (immunotherap* OR desensiti*ation) AND (sublingual).

Selection criteria
All studies identified by the searches were assessed by the reviewers to identify randomised controlled trials involving participants with symptoms of allergic rhinitis and proven allergen sensitivity, treated with SLIT or corresponding placebo.

Data collection and analysis
Data from identified studies were abstracted onto a standard extraction sheet and subsequently entered into RevMan 4.1. Analysis was performed by the method of Standardised Mean Differences (SMD) using a random-effects model. P values < 0.05 were considered statistically significant. Subgroup analyses were performed according to the type of allergen administered, the age of participants and the duration of treatment.

Main results
Twenty-two trials involving 979 patients were included. There were six trials of SLIT for house dust mite allergy, five for grass pollen, five for Parietaria, two for olive and one each for ragweed, cat, tree and Cupressus. Five studies enrolled exclusively children. Seventeen studies administered the allergen by sublingual drops subsequently swallowed, three by drops subsequently spat out and two by sublingual tablets. Eight studies involved treatment for less than six months, 10 studies for 6 to 12 months and four studies for greater than 12 months. All included studies were double-blind placebo-controlled trials of parallel group design. Concealment of treatment allocation was considered adequate in all studies and the use of identical placebo preparations was almost universal. There was significant heterogeneity, most likely due to widely differing scoring systems between studies, for most comparisons.

Overall there was a significant reduction in both symptoms (SMD -0.42, 95% confidence interval -0.69 to -0.15; p = 0.002) and medication requirements (SMD -0.43 [-0.63, -0.23]; p = 0.00003) following immunotherapy. Subgroup analyses failed to identify a disproportionate benefit of treatment according to the allergen administered. There was no significant reduction in symptoms and medication scores in those studies involving only children but total numbers of participants were too small to make this a reliable conclusion. Increasing duration of treatment does not clearly increase efficacy. The total dose of allergen administered may be important but insufficient data were available to analyse this factor.

Authors' conclusions
SLIT is a safe treatment which significantly reduces symptoms and medication requirements in allergic rhinitis. The size of this benefit compared to that of other available therapies, particularly injection immunotherapy, is not clear, having been assessed directly in very few studies. Further research is required concentrating on optimising allergen dosage and patient selection.

PLAIN LANGUAGE SUMMARY

Sublingual immunotherapy can relieve allergic rhinitis (including hay fever), although it is not known whether it is as effective as injections or nasal immune treatments

Allergic rhinitis causes a blocked, runny, itching nose and sneezing. It can be caused by an allergic reaction to pollens and moulds (hay fever) or a reaction to house dust mites or pets. It is often relieved by antihistamines or corticosteroids. When these do not provide enough relief, another option is immunotherapy which builds immunity to the allergen causing the reaction. This can be given under the tongue, nasally or by injection. The review of trials found that sublingual (under the tongue) immunotherapy can relieve allergic rhinitis, although there is not enough evidence to compare it with other immunotherapy treatments.

BACKGROUND

Allergic rhinitis is a condition characterised by sneezing, watery nasal discharge, nasal obstruction and itching. It is an increasingly prevalent condition, particularly in the Western world where it affects around 20% of the adult population. Allergic rhinitis is divided into seasonal allergic rhinitis (hay fever) which is triggered by pollens and moulds and perennial allergic rhinitis in which house dust mites and pet dander are the predominant triggers. The spectrum of severity is wide and includes a significant number of sufferers with severe symptoms that are resistant to treatment with usual pharmacotherapy (antihistamines and topical nasal corticosteroids). In such individuals allergen injection immunotherapy is effective in reducing symptoms and medication requirements (Varney 1991; WHO 1998) - effects which persist after withdrawal of treatment (Durham 1999).

Injection immunotherapy involves the weekly injection of incremental doses of allergen extract until a maintenance dose is reached. Maintenance injections are then given monthly for two to three years. The mechanism of action of this form of treatment is not yet fully understood but relevant observations include changes in serum antibody levels (Lichtenstein 1973), reduced sensitivity to allergen injected into the skin or sprayed into the nose (Creticos 1985) and an alteration in the characteristics of T lymphocytes, the key orchestrating cells of the immune response within the nasal mucosa, from an allergic (Th2) profile to a non-allergic (Th1) profile (Durham 1996) suggesting a modulation of the response of the local immune system to allergen. Immunotherapy is therefore the only current treatment which has the potential to modify the disease process.

Injection immunotherapy is not, however, without problems. Injections can be uncomfortable and minor adverse events such as injection site swelling occur frequently. Systemic reactions are uncommon and anaphylaxis is rare but occasional fatalities have been reported (CSM 1986). For these reasons a safer route for the delivery of immunotherapy has been sought. Nasal administration is effective but use may be limited by local side effects (nasal discharge, blockage and sneezing) which is also the case for bronchial administration (wheeze and breathlessness). Studies assessing the oral route have indicated a lack of efficacy, presumably due to failure of absorption of the allergen. Attention has therefore focussed on the sublingual route, in which the allergen extract is held under the tongue to allow absorption through the sublingual mucosa.

Standardised allergen extracts can be administered frequently and to a high cumulative dose via the sublingual region and trials so far have shown few adverse effects prompting widespread use in Southern Europe and by some practitioners in Australia. The latest international guidelines (EAACI 2000) conclude that nasal and sublingual immunotherapy may be a viable alternative to injection immunotherapy but that further studies were needed to determine the most appropriate patients and dosage.

Several trials have been reported recently assessing this form of treatment.

OBJECTIVES

To evaluate the efficacy of sublingual immunotherapy compared with placebo or injection immunotherapy for: -

1. Reductions in symptoms and/or medication requirements during naturally occurring allergic rhinitis.

2. Alteration of immunological markers in blood and immunological markers and allergen sensitivity in target organs (nose, eye, skin).

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

All randomised blinded placebo-controlled clinical trials.

Types of participants

Persons of any age with a history of allergic rhinitis with or without allergic conjunctivitis, with or without asthma, for whom the allergen is identified and patient sensitivity proven by positive skin prick tests or high circulating levels of allergen-specific IgE antibody detected by radioallergosorbent test (RAST). Trials dealing with asthma alone were excluded. Individuals had to have no other clinically relevant allergen sensitivities.

Types of intervention

Immunotherapy delivered by the sublingual route, whether or not the allergen was subsequently swallowed. All appropriate allergens were considered at all doses and all durations of treatment.

Types of outcome measures

PRIMARY

1. Symptom scores however recorded (e.g. daily or weekly symptom diaries, Visual Analogue Scores, overall assessments).
2. Scores referring to concurrent use of anti-allergic medication.

SECONDARY

3. Assessments of allergen sensitivity in eye, nose or skin.
4. Measurements of serum IgE and IgG antibodies.
5. Adverse event reports.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: Cochrane Ear, Nose and Throat Disorders Group methods used in reviews.

Searches (completed in September 2002) were made of the Cochrane Controlled Trials Register, MEDLINE (1966 to 2002), EMBASE (1974 to 2002) and SciSearch by the reviewers using the terms: (Rhin* OR hay fever) AND (immunotherap* OR desensiti*ation) AND (sublingual). Note: rhin* covers rhinitis, rhinopathy, rhinosinusitis and rhinoconjunctivitis.

Abstracts of relevant conferences were searched and other trials were identified through discussion with specialist allergist colleagues and professional acquaintances with an interest in the area to enquire whether they were aware of any unpublished or ongoing trials meeting the selection criteria. Reference lists of recent reviews and published trials were searched.

METHODS OF THE REVIEW

QUALITY ASSESSMENT

Inclusion of studies in the review was decided by discussion between two of the review authors (DRW, SRD) after all of the studies had been read by DRW. Further information was sought from study authors where needed. The selected studies were then further evaluated for methodological quality to select those suitable for meta-analysis.

Each of the suitable reports were read in detail by DRW and relevant details were abstracted on to a standard extraction sheet (covering study type and methodology; number and description of subjects; details of type, dosage and time schedule/duration of intervention; type, timing and measurement method of outcomes). Concealment of allocation and blinding of study participants and investigators was assessed according to the guidelines of The Cochrane Collaboration.

Due to prior familiarity with the content of most studies author names were not removed before assessment.

DATA ANALYSIS

Outcome data, extracted from the included studies, were entered into RevMan 4.1 for statistical analysis. All outcome data analysed were continuous (symptom scores, medication scores, antibody levels) but authors used a wide variety of scoring systems and scales for symptoms (most frequently a daily quantification of nasal, eye and chest symptoms entered on a diary card and subsequently totalled and averaged) and medication use (typically a daily score reflecting use of eye drops, nasal sprays and antihistamine tablets entered on a diary card and subsequently totalled and averaged). Analysis was therefore performed by the method of Standardised Mean Differences, expressing the difference in means between immunotherapy and placebo recipients in units of the pooled standard deviation. Random-effects models were used to obtain summary statistics for the overall efficacy of sublingual immunotherapy, presented as Standardised Mean Differences with 95% Confidence Intervals. Chi-square tests were performed to assess heterogeneity between studies, with a p value < 0.1 indicating significant differences between studies.

The following subgroup comparisons were proposed prior to undertaking the data analysis:

1. Seasonal versus perennial allergens.
2. Children versus adults.
3. Dosage of major allergen (< 5 mcg major allergen versus 5 to 20 mcg versus > 20 mcg: based on WHO guidelines).
4. Duration of immunotherapy (< 6 months versus 6 to 12 months versus > 12 months: in order to cover pre-seasonal, perennial and prolonged treatment).
5. Sublingual spit versus sublingual swallow.

Where appropriate, additional analyses were performed according to subgroup.

DESCRIPTION OF STUDIES

Searches performed according to the protocol identified 78 abstracts of which 48 were immediately considered unsuitable for inclusion (review articles, descriptive studies, other routes of allergen administration). An additional three studies were identified from personal communication. A total of 33 full papers were therefore reviewed of which eight were excluded (not randomised/controlled (four), insufficient information for analysis (three), duplicate study (one)) and three remain pending - awaiting additional information or data from authors.

Twenty-two studies are therefore included in this analysis. The methods, participants, interventions and outcomes of the included studies are listed in the table of characteristics of included studies.

A wide range of allergens were administered in these studies (house dust mite (six), grass (five), Parietaria (five), Olea (two), ragweed, cat, tree, Cupressus (all one)). Five studies enrolled exclusively children. Seventeen studies administered the allergen by sublingual drops subsequently swallowed, three by drops subsequently spat out and two by sublingual tablets.

The duration of maintenance treatment and the period of follow up varied considerably between studies, largely reflecting pre-seasonal, co-seasonal and perennial administration. Using treatment durations identified in the protocol eight studies involved treatment for less than six months, 10 studies for 6 to 12 months and four studies for greater than 12 months.

It was not possible from most of the studies to determine accurately the dose of allergen given in terms of micrograms of major allergen.

METHODOLOGICAL QUALITY

All included studies were double-blind placebo-controlled trials of parallel group design. Concealment of treatment allocation was considered adequate in all studies - based on statements made by the original authors. Blinding of study subjects and investigators was almost universally maintained by use of identical placebo preparations. It should, however, be noted that most investigators reported high levels of minor oral side effects (tingling, itching and swelling beneath the tongue) in actively treated subjects.

RESULTS

SYMPTOM SCORES

All of the included studies reported symptom scores, recorded in patient diaries, as a primary outcome measure. Data obtained in this way are almost always non-parametric and therefore many studies reported results expressed as median values. Strenuous attempts were made to obtain mean (standard deviation) data direct from authors and studies were only included after this data was obtained. One study (Quirino 1996) compared sublingual immunotherapy (SLIT) with injection immunotherapy rather than with placebo and was therefore excluded from the analysis. From the remaining 21 studies, data from 484 immunotherapy recipients and 475 placebo recipients were included. The combined Standardised Mean Difference (SMD) for symptom scores following SLIT was -0.42 (95% confidence interval -0.69 to -0.15 ($p = 0.002$)) indicating a significant reduction in symptoms. There was, however, significant heterogeneity between studies (Chi-Square = 75.36; $p < 0.00001$).

Subgroup Analyses

For studies involving seasonal allergens (n = 14, SLIT subjects 346, placebo subjects 344) combined SMD was -0.30 (-0.53; -0.07, $p = 0.01$). Chi-square was 26.91, $p = 0.013$ indicating significant heterogeneity.

For studies involving perennial allergens (n = 7, SLIT subjects 138, placebo subjects 131) combined SMD was -0.58 (-1.28; 0.12, $p = 0.11$). Chi-square was 30.66, $p < 0.00001$ indicating significant heterogeneity.

Three individual allergens were used in more than two studies:

House dust mite (n = 6, SLIT subjects 118, placebo subjects 110) combined SMD -0.58 (-1.43; 0.27, $p = 0.18$).
Grass (n = 4, SLIT subjects 144, placebo subjects 143) combined SMD -0.37 (-0.74; 0, $p = 0.05$).
Parietaria (n = 5, SLIT subjects 79, placebo subjects 83) combined SMD -0.29 (-0.6; 0.02, $p = 0.07$).

For studies involving adults only (n = 16, SLIT subjects 373, placebo subjects 368) combined SMD was -0.4 (-0.61; -0.18, $p = 0.0003$). Chi-square was 28.17, $p < 0.02$ indicating significant heterogeneity.

For studies involving children only (n = 5, SLIT subjects 111, placebo subjects 107) combined SMD was -0.31 (-1.32; 0.7, $p = 0.5$). Chi-square was 47.16, $p < 0.00001$ indicating significant heterogeneity.

Duration of treatment was divided into three categories:

For treatment duration less than six months (n = 8 SLIT subjects 183, placebo subjects 175) combined SMD was -0.36 (-0.67; 0.06, $p = 0.02$). Chi-square was 12.1, $p = 0.1$ indicating lack of heterogeneity.

For treatment duration 6 to 12 months (n = 9, SLIT subjects 193, placebo subjects 195) combined SMD was -0.21 (-0.54; 0.11, $p = 0.2$). Chi-square was 18.46, $p = 0.02$ indicating significant heterogeneity.

For treatment duration over 12 months (n = 4, SLIT subjects 108, placebo subjects 105) combined SMD was -0.95 (-1.97; 0.06, p = 0.07). Chi-square was 33.31, p < 0.00001 indicating significant heterogeneity.

MEDICATION SCORES

Diary scores reflecting concurrent use of anti-allergic medication were reported in 18 of the 22 studies but the study of Quirino was again excluded. From the 17 remaining studies data from 405 immunotherapy recipients and 398 placebo recipients were included. The combined SMD for medication scores following SLIT was -0.43 (95% confidence interval -0.63 to -0.23) indicating a significant reduction in medication use (p = 0.00003). Again there was significant heterogeneity between studies but this was less marked (Chi-Square = 28.48; p = 0.028).

Subgroup Analyses

For studies involving seasonal allergens (n = 14, SLIT subjects 346, placebo subjects 344) combined SMD was -0.36 (-0.54; -0.18, p = 0.00007). Chi-square was 16.61, p = 0.22 indicating lack of heterogeneity.

For studies involving perennial allergens (n = 3, SLIT subjects 59, placebo subjects 54) combined SMD was -0.85 (-1.93; 0.23, p = 0.12). Chi-square was 10.58, p = 0.005 indicating significant heterogeneity.

For individual allergens used in more than two studies:

House dust mite (n = 3, SLIT subjects 59, placebo subjects 54) combined SMD -0.85 (-1.93; 0.23, p = 0.1).
Grass (n = 4, SLIT subjects 144, placebo subjects 143) combined SMD -0.41 (-0.81; -0.01, p = 0.04).
Parietaria (n = 5, SLIT subjects 79, placebo subjects 83) combined SMD -0.39 (-0.71; -0.08, p = 0.01).

For studies involving adults only (n = 14, SLIT subjects 343, placebo subjects 338) combined SMD was -0.51 (-0.73; -0.29, p < 0.00001). Chi-square was 22.52, p = 0.05 indicating borderline heterogeneity.

For studies involving children only (n = 3, SLIT subjects 62, placebo subjects 60) combined SMD was 0.02 (-0.34; 0.37, p = 0.9). Chi-square was 0.43, p = 0.8 indicating lack of heterogeneity.

For treatment duration less than six months (n = 7 SLIT subjects 163, placebo subjects 154) combined SMD was -0.63 (-1.09; -0.18, p = 0.007). Chi-square was 19, p = 0.004 indicating lack of heterogeneity.

For treatment duration 6 to 12 months (n = 8, SLIT subjects 178, placebo subjects 180) combined SMD was -0.35 (-0.6; -0.1, p = 0.001). Chi-square was 8.62, p = 0.28 indicating lack of heterogeneity.

For treatment duration over 12 months (n = 2, SLIT subjects 64, placebo subjects 64) combined SMD was -0.27 (-0.62; 0.08, p = 0.13). Chi-squared was 0.09, p = 0.76 indicating lack of heterogeneity.

SERUM ANTIBODY LEVELS

Serum levels of Immunoglobulin (Ig)E and/or IgG were measured before and after treatment in 16 of the 21 included studies. In one study there was no placebo comparison and in a further study total, rather than allergen specific levels were assayed. Detailed data were presented in tabular form in only five studies (one study IgG only) and were available directly from authors for a further one study.

For these studies the combined SMD for changes in allergen-specific IgE (n = 6, SLIT subjects 171, placebo subjects 174) was 0.22 (-0.11; 0.55, p = 0.19). Chi-square was 10.51, p = 0.06.

For allergen-specific IgG4 (n = 6, SLIT subjects 190, placebo subjects 191) the combined SMD was 0.6 (-0.11; 1.31, p = 0.1). Chi-square was 51.93, p < 0.00001.

In the remaining eight studies comments in the published text indicate no significant difference between actively-treated and placebo-treated groups for either IgE or IgG in five studies, no significant difference in IgE but significant increases in IgG4 in two studies and no significant change in IgE (IgG4 not assayed) in one study.

ALLERGEN SENSITIVITY

In 14 of the 21 included studies some measure of allergen sensitivity was performed before and after treatment. Thirteen of these were tests of cutaneous sensitivity, either by skin prick testing, titrated skin prick testing or intradermal testing. In addition studies of nasal sensitivity (four) and conjunctival sensitivity (two) were performed infrequently. The wide variation in methodology and the lack of specific data in the published text made meta-analysis of this data impractical.

For skin sensitivity seven studies reported no significant difference between SLIT and placebo groups, in five there were no data or conclusion drawn and in one there was no placebo comparison.

ADVERSE EVENTS

All of the studies included reported a complete absence of systemic side effects. Minor local side effects consisting of itching and swelling of the oral mucosa were reported almost universally but were rarely of significance.

DISCUSSION

This systematic review of sublingually administered allergen immunotherapy (SLIT) has identified 22 randomised controlled trials with sufficient data for inclusion in meta-analysis. Of the 33 studies initially identified and reviewed in detail, eight were

excluded from the analysis, mostly for being open or non-randomised studies although three studies were excluded because insufficient data were available either from the published manuscript or from direct contact with the authors. Studies were identified from searches of the best available citation databases and from direct communication with key investigators in the field. Whilst it is never possible to rule out any effects of publication bias due to the non-publication of studies with negative results it is felt that this is unlikely due to the amount of direct contact the authors have had with the limited number of investigators working in this specialised field.

The methodological quality of the included studies was adequate but this assessment was based on general statements made by the authors of studies in the published text. Most of the papers, particularly those published earlier, do not conform to the CONSORT (1996) guidelines for the publication of randomised controlled trials making the identification of key information regarding randomisation methods and concealment of allocation difficult.

Scores representing symptom severity were recorded in all of the included studies and scores quantifying concurrent medication use were recorded in 17 studies. The meta-analysis of these scores confirms that SLIT can significantly reduce both rhinitis symptoms and the requirement for anti-allergic medication. Some caution is required in this interpretation as there was significant heterogeneity between studies although this is felt likely to result predominantly from the wide variety of scoring systems used across studies. Despite this we feel that it is reasonable to meaningfully combine these results and the consistency, and high degree of statistical significance of the positive treatment effect allows valid conclusions to be drawn.

Some of the observed variability in treatment effects may be explained by variable responses to treatment according to the type of allergen used, the age of subjects studied or the dose and duration of treatment. As these may be significant factors when selecting suitable individuals for future treatment, additional analyses were performed according to these study characteristics. In almost all cases significant heterogeneity existed between studies and, although this may reflect variability in scoring systems as indicated above, it may be due to incompatibility between smaller numbers of included studies and therefore the results of these analyses should be interpreted with great caution. The subgroup analyses do not strongly indicate a disproportionate benefit for SLIT treatment in any particular patient or disease group but a number of possible trends do emerge.

The seven studies (271 subjects) using perennial allergens (house dust mite and cat) appear to show a similar treatment effect to that observed for seasonal allergens (14 studies; 690 subjects) although the latter was statistically significant, probably as a result of the greater number of subjects. Three allergens (house dust mite, grass pollen and Parietaria) were used in more than two studies and were therefore subjected to separate meta-analysis. The six house dust mite studies formed the bulk of the perennial allergen subgroup and results were similar - falling short of statistical significance for both symptom and medication scores. Both grass pollen and Parietaria, however, did show statistically significant effects although numbers of subjects were small. It may, therefore, be the case that SLIT has greater potential in grass and Parietaria sensitive subjects but this is by no means proven by this analysis.

SLIT is a particularly attractive treatment option for children where safety is paramount and outpatient, home-based therapy is clearly preferable. In contrast to the overall effect in adults and children, the treatment effect in children was not significant. These data must be interpreted with great caution as the number of studies assessing only children was small (five; 218 subjects) but this analysis suggests that SLIT is not of particular benefit for allergic rhinitis in children. Removing children-only studies from the overall analysis did not change the outcome suggesting consistent beneficial effects in adults.

Increasing duration of treatment beyond 12 months does appear to increase the treatment effect but the number of studies of this duration was small (four) and the result just failed to reach significance. It is theoretically likely that the total dose of allergen administered is relevant to the efficacy of treatment but unfortunately it was not possible to analyse the data divided according to allergen dosage due to the wide range of allergen preparations used and a paucity of information regarding the dose expressed in micrograms of major allergen.

Selected secondary outcome measures were much more difficult to analyse. Not all studies (only 16 of 21) reported measurement of serum antibodies and the wide variety of methods used to assess skin or target organ sensitivity made combining results unfeasible. For those studies reporting changes in serum antibodies only a small number (six) published data suitable for meta-analysis and therefore much of the interpretation is descriptive but does suggest consistent increases in allergen-specific IgG4 in SLIT recipients.

Importantly none of the studies reported significant side effects during SLIT.

Allergen injection immunotherapy is an extremely effective treatment for seasonal allergic rhinitis that has failed to respond to pharmacological measures, resulting in a 50% reduction in symptom scores and an 80% reduction in medication scores. These effects persist for at least three years after discontinuation of treatment. These benefits do, however, have to be set against the incidence of severe systemic reactions, including occasional fatalities, during injection immunotherapy. This morbidity has resulted in tight regulation of this form of treatment including recommendations that it be restricted to specialist centres and that patients be observed for up to one hour after injections making it time-consuming and expensive.

For these reasons a number of alternative routes for therapeutic allergen presentation have been considered and sublingual admin-

istration has emerged as the most likely to be both acceptable and effective. The potential for home administration and the fact that no systemic reaction has yet been reported make this form of treatment extremely attractive. This review and meta-analysis will lend support to the promotion of this treatment but assessment of the magnitude of the effect is difficult making direct comparison with injection immunotherapy impossible. Two of the included studies compared injection immunotherapy with SLIT directly (one with a further placebo arm) (Mungan 1999; Quirino 1996). These two studies reported similar improvements in symptoms and medication requirements for the two routes of administration.

Injection immunotherapy is felt most likely to exert its effects through modulation of the response of the immune system upon allergen exposure. Giving high doses of allergen systemically results in changes in both the humoral and cellular components of the immune response felt likely to represent a change from a Th2 predominant response dominated by the cytokines IL-4, IL-5 and IL-13, with the eosinophil as the key effector cell and IgE as the responding antibody, to a Th1 response characterised by an absence of eosinophilia and an IgG antibody response. The role of increases in IgG4 antibodies is unclear and indeed they may play no active role, merely acting as a marker of high dose allergen exposure. Where reported in this review IgG4 levels increase following SLIT, much as they do following injection immunotherapy indicating that a similar immunological change may be initiated. Further mechanistic studies are clearly required.

AUTHORS' CONCLUSIONS

Implications for practice

This systematic review and meta-analysis demonstrates the efficacy of SLIT compared with placebo in terms of a reduction in rhinitis symptom scores and anti-allergic medication requirements but does not allow quantification of the treatment effect compared with other available therapies, particularly injection immunotherapy. Only two studies addressed this question directly.

Despite this drawback the results are convincing with consistent findings across a large number of studies including 979 patients. Of particular note is the apparent safety of SLIT confirming its potential for outpatient based treatment, with home administration of allergen, which is increasingly employed in continental Europe.

Implications for research

A number of questions remain to be answered:

1. What is the ideal dose and treatment duration and is this the same for all allergens, seasonal or perennial?

2. What is the magnitude of symptomatic improvement when SLIT is compared directly with injection immunotherapy?

3. Does SLIT result in modification of the immune response and is the effect of treatment long-lasting, persisting after withdrawal of active treatment?

4. Will compliance with daily home treatment for up to two years be as good outside the confines of a controlled trial?

5. The attractive nature of SLIT as a treatment for children with allergic rhinitis, and also asthma, means that further study is warranted in this area despite current lack of evidence regarding efficacy.

POTENTIAL CONFLICT OF INTEREST

The Department of Upper Respiratory Medicine, National Heart & Lung Institute, London, UK, headed by Professor Durham, has received financial support from ALK Abello, Horsholm, Denmark - manufacturers of allergen extracts.

ACKNOWLEDGEMENTS

Grateful thanks are extended to the authors of individual studies who provided additional data to allow meaningful meta-analysis to be performed.

SOURCES OF SUPPORT

External sources of support

- No sources of support supplied

Internal sources of support

- No sources of support supplied

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TABLES

Characteristics of included studies

Study	Andre 2002
Methods	DBPC trial
Participants	55 active (22 m) 55 placebo (23m) Adults
Interventions	7.5 months Sublingual tabs Dose n/s
Outcomes	Diary scores
Notes	Abstract only
Allocation concealment	A – Adequate

Study	Ariano 2001
Methods	DBPC trial
Participants	10 active (5m) 10 placebo (4m) Adults
Interventions	8 months SLIT 250000U RAST
Outcomes	Diary scores Nasal provocation
Notes	
Allocation concealment	A – Adequate

Study	Bahceciler 2001
Methods	DBPC trial
Participants	8 active (4m) 7 placebo (4m) Children
Interventions	5 months SLIT 0.56 mg D.P. 0.98mg D.F.
Outcomes	Diary scores SPT Total IgE
Notes	
Allocation concealment	A – Adequate

Study	Casanovas 1994
Methods	DBPC trial
Participants	9 active (3m)

	6 placebo (1m) Min age 18
Interventions	2 months pre-seasonal SLIT Dose n/s
Outcomes	Diary scores SPT
Notes	
Allocation concealment	A – Adequate

Study	**D'Ambrosio 1996**
Methods	Randomised, uncontrolled trial
Participants	15 active (7m) 15 placebo (5m) Min age 18
Interventions	8 months SLIT 13mcg Parj1
Outcomes	Diary scores Ig
Notes	
Allocation concealment	C – Inadequate

Study	**D'Ambrosio 1999**
Methods	DBPC trial
Participants	14 active (7m) 16 placebo (7m) Adults
Interventions	9 months SLIT 12.77 mcg Parj1
Outcomes	Diary scores Ig
Notes	
Allocation concealment	A – Adequate

Study	**Feliziani 1995**
Methods	DBPC trial
Participants	18 active 16 placebo Adults
Interventions	3 months SLIT Dose n/s
Outcomes	Diary scores
Notes	
Allocation concealment	A – Adequate

Study	**Guez 2000**
Methods	DBPC trial

Characteristics of included studies (*Continued*)

Participants	36 active (14m) 36 placebo (15m) Adults and children
Interventions	24 months SLIT 2.2 mg D.Pt 1.7mg D.f
Outcomes	Diary scores SPT Ig
Notes	
Allocation concealment	A – Adequate

Study	**Hirsch 1997**
Methods	DBPC trial
Participants	15 active (10m) 15 placebo (10m) Children
Interventions	12 months SLIT 570mcg Derp1
Outcomes	Diary Scores SPT
Notes	
Allocation concealment	A – Adequate

Study	**Hordijk 1998**
Methods	DBPC trial
Participants	35 active (14m) 36 placebo (13m) Adults
Interventions	3 months pre-seasonal SLIT Dose n/s
Outcomes	Diary scores Ig
Notes	
Allocation concealment	A – Adequate

Study	**La Rosa 1999**
Methods	DBPC trial
Participants	20 active (13m) 21 placebo (12m) Children
Interventions	24 months SLIT 52.5 mg Parj1
Outcomes	Diary scores Ig SPT Conjunctival

Characteristics of included studies (*Continued*)

Notes	
Allocation concealment	A – Adequate

Study	**Lima 2002**
Methods	DBPC trial
Participants	28 active 28 placebo Adults
Interventions	12-18 months SLIT 900 mcg Phlp5 per month
Outcomes	Diary scores Ig
Notes	
Allocation concealment	A – Adequate

Study	**Mungan 1999**
Methods	DBPC trial SLIT v injection immunotherapy v placebo
Participants	15 active (2m) 11 placebo (1m) 10 injection (4m) Adults
Interventions	65 days SLIT updosing Dose n/s except 100 x injection.
Outcomes	Diary scores SPT Ig
Notes	
Allocation concealment	A – Adequate

Study	**Nelson 1993**
Methods	DBPC trial
Participants	20 active (7m) 21 placebo (6m) Adults
Interventions	105 days SLIT 450-900 Feld1 units
Outcomes	Cat room scores Ig Titrated SPT
Notes	
Allocation concealment	A – Adequate

Study	**Passalacqua 1998**
Methods	DBPC trial
Participants	10 active (3m) 10 placebo (4m)

Characteristics of included studies (*Continued*)

	Adults
Interventions	24 months SLIT Tablets Dose n/s
Outcomes	Diary scores
Notes	
Allocation concealment	A – Adequate

Study	**Passalacqua 1999**
Methods	DBPC trial
Participants	15 active (10m) 15 placebo (3m) Adults
Interventions	6 months SLIT 16 mcg Parj1
Outcomes	Diary scores Nasal challenge
Notes	
Allocation concealment	A – Adequate

Study	**Pradalier 1999**
Methods	DBPC trial
Participants	63 active (29m) 63 placebo (36m) Adults
Interventions	5 months pre-seasonal SLIT 0.935 mg Phlp5
Outcomes	Diary scores SPT Ig
Notes	
Allocation concealment	A – Adequate

Study	**Quirino 1996**
Methods	DBPC trial SLIT v Inj IT Double Dummy
Participants	10 SLIT (5m) 10 Injection (4m) Adults
Interventions	12 months SLIT or injection 510 BU
Outcomes	Diary scores SPT Ig
Notes	
Allocation concealment	B – Unclear

Characteristics of included studies (*Continued*)

Study	**Tari 1990**
Methods	DBPC trial
Participants	34 active 32 placebo Children
Interventions	18 months SLIT 2340 drops of 5BU/ml mcg dose n/s
Outcomes	Diary scores Ig
Notes	
Allocation concealment	A – Adequate

Study	**Troise 1995**
Methods	DBPC trial
Participants	15 active (6m) 16 placebo (6m) Adults
Interventions	10 months SLIT 6.3 mcg Parj1
Outcomes	Diary scores
Notes	
Allocation concealment	A – Adequate

Study	**Voltolini 2001**
Methods	DBPC trial
Participants	15 active (7m) 15 placebo (4m) Adults
Interventions	Rush pre-seasonal & co-seasonal maint. 445 mcg Betv1
Outcomes	Diary scores Ig SPT
Notes	
Allocation concealment	A – Adequate

Study	**Vourdas 1998**
Methods	DBPC trial
Participants	34 active (25m) 32 placebo (24m) Children
Interventions	6 months SLIT per yr for 2 yrs 4.05 mg Olee1
Outcomes	Diary scores SPT
Notes	

Characteristics of excluded studies

Study	Reason for exclusion
Bernardis 1996	Not randomised
Clavel 1998	Insufficient data available for analysis
Feliziani 1993	Not randomised
Gozalo 1997	Not randomised, controlled or blinded
Horak 1998	No symptom data. Not seasonal exposure
Mitsch 1996	Open study
Sabbah 1993	Duplicate study (same as Sabbah 1994)
Sabbah 1994	Insufficient data available for analysis

ANALYSES

Comparison 01. SLIT v placebo - all

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Allergic Rhinitis symptom scores	21	959	Standardised Mean Difference (Random) 95% CI	-0.42 [-0.69, -0.15]
02 Medication scores	17	803	Standardised Mean Difference (Random) 95% CI	-0.43 [-0.63, -0.23]

Comparison 02. SLIT v placebo - seasonal allergen

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Allergic Rhinitis symptom scores	14	690	Standardised Mean Difference (Random) 95% CI	-0.30 [-0.53, -0.07]
02 Medication scores	14	690	Standardised Mean Difference (Random) 95% CI	-0.36 [-0.54, -0.18]

Comparison 03. SLIT v placebo - perennial allergen

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Allergic Rhinitis symptom scores	7	269	Standardised Mean Difference (Random) 95% CI	-0.58 [-1.28, 0.12]
02 Medication scores	3	113	Standardised Mean Difference (Random) 95% CI	-0.85 [-1.93, 0.23]

Comparison 04. SLIT v placebo - adults

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Allergic Rhinitis symptom scores	16	741	Standardised Mean Difference (Random) 95% CI	-0.40 [-0.61, -0.18]
02 Medication scores	14	681	Standardised Mean Difference (Random) 95% CI	-0.51 [-0.73, -0.29]

Comparison 05. SLIT v placebo - children

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Allergic Rhinitis symptom scores	5	218	Standardised Mean Difference (Random) 95% CI	-0.31 [-1.32, 0.70]
02 Medication scores	3	122	Standardised Mean Difference (Random) 95% CI	0.02 [-0.34, 0.37]

Comparison 06. SLIT v placebo - <6months

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Allergic Rhinitis symptom scores	8	358	Standardised Mean Difference (Random) 95% CI	-0.36 [-0.67, -0.06]
02 Medication scores	7	317	Standardised Mean Difference (Random) 95% CI	-0.63 [-1.09, -0.18]

Comparison 07. SLIT v placebo - 6-12 months

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Allergic Rhinitis symptom scores	9	388	Standardised Mean Difference (Random) 95% CI	-0.21 [-0.54, 0.11]
02 Medication scores	8	358	Standardised Mean Difference (Random) 95% CI	-0.35 [-0.60, -0.11]

Comparison 08. SLIT v placebo - >12 months

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Allergic Rhinitis symptom scores	4	213	Standardised Mean Difference (Random) 95% CI	-0.95 [-1.97, 0.06]
02 Medication scores	2	128	Standardised Mean Difference (Random) 95% CI	-0.27 [-0.62, 0.08]

Comparison 09. SLIT v Placebo - Immunoglobulins

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 IgE levels - post treatment	6	345	Standardised Mean Difference (Random) 95% CI	0.22 [-0.11, 0.55]
02 IgG levels - post treatment	6	381	Standardised Mean Difference (Random) 95% CI	0.60 [-0.11, 1.31]

Comparison 10. SLIT v placebo - HDM

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Allergic Rhinitis symptom scores	6	228	Standardised Mean Difference (Random) 95% CI	-0.58 [-1.43, 0.27]
02 Medication scores	3	113	Standardised Mean Difference (Random) 95% CI	-0.85 [-1.93, 0.23]

Comparison 11. SLIT v placebo - Grass pollen

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Allergic Rhinitis symptom scores	4	287	Standardised Mean Difference (Random) 95% CI	-0.37 [-0.74, -0.00]
02 Medication scores	4	287	Standardised Mean Difference (Random) 95% CI	-0.41 [-0.81, -0.01]

Comparison 12. SLIT v placebo - Parietaria

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Allergic Rhinitis symptom scores	5	162	Standardised Mean Difference (Random) 95% CI	-0.29 [-0.60, 0.02]
02 Medication scores	5	162	Standardised Mean Difference (Random) 95% CI	-0.39 [-0.71, -0.08]

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Sublingual; Allergens [*administration & dosage]; Desensitization, Immunologic [*methods]; Randomized Controlled Trials as Topic; Rhinitis, Allergic, Perennial [*therapy]; Rhinitis, Allergic, Seasonal [*therapy]

MeSH check words

Humans

COVER SHEET

Title	Sublingual immunotherapy for allergic rhinitis
Authors	Wilson DR, Torres Lima M, Durham SR
Contribution of author(s)	DUNCAN WILSON: Lead reviewer, protocol development, searching for trials, quality assessment of trials, design of data extraction form, data extraction, data analysis.

	MARCIA TORRES-LIMA: Quality assessment of trials, data extraction, data analysis, input at all other stages of review. STEPHEN DURHAM: Protocol development, input at all other stages of review.
Issue protocol first published	2001/1
Review first published	2003/2
Date of most recent amendment	11 February 2005
Date of most recent SUBSTANTIVE amendment	11 February 2003
What's New	Information not supplied by author
Date new studies sought but none found	Information not supplied by author
Date new studies found but not yet included/excluded	Information not supplied by author
Date new studies found and included/excluded	Information not supplied by author
Date authors' conclusions section amended	Information not supplied by author
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DOI	10.1002/14651858.CD002893
Cochrane Library number	CD002893
Editorial group	Cochrane Ear, Nose and Throat Disorders Group
Editorial group code	HM-ENT

Analysis 01.01. Comparison 01 SLIT v placebo - all, Outcome 01 Allergic Rhinitis symptom scores

Review: Sublingual immunotherapy for allergic rhinitis

Comparison: 01 SLIT v placebo - all

Outcome: 01 Allergic Rhinitis symptom scores

Study	SLIT N	SLIT Mean(SD)	Placebo N	Placebo Mean(SD)	Standardised Mean Difference (Random) 95% CI	Weight (%)	Standardised Mean Difference (Random) 95% CI
Andre 2002	55	3.78 (2.74)	55	3.95 (2.66)		6.1	-0.06 [-0.44, 0.31]
Ariano 2001	10	1.80 (1.75)	10	5.38 (1.57)		3.1	-2.06 [-3.19, -0.93]
Bahceciler 2001	8	0.53 (0.40)	7	0.40 (0.38)		3.4	0.31 [-0.71, 1.34]
Casanovas 1994	9	5.46 (3.56)	6	10.98 (7.10)		3.1	-1.00 [-2.11, 0.12]
D'Ambrosio 1996	15	290.00 (258.00)	15	408.90 (315.35)		4.6	-0.40 [-1.13, 0.32]
D'Ambrosio 1999	14	509.00 (514.20)	16	897.06 (678.20)		4.6	-0.62 [-1.36, 0.12]
Feliziani 1995	18	109.70 (92.46)	16	215.80 (114.20)		4.6	-1.00 [-1.72, -0.28]
Guez 2000	36	2.30 (1.90)	36	3.20 (2.40)		5.7	-0.41 [-0.88, 0.06]
Hirsch 1997	15	0.99 (1.13)	15	0.52 (0.47)		4.6	0.53 [-0.20, 1.26]
Hordijk 1998	35	3.21 (3.05)	36	5.13 (3.60)		5.7	-0.57 [-1.04, -0.09]
La Rosa 1999	20	1.21 (1.66)	21	1.61 (1.56)		5.1	-0.24 [-0.86, 0.37]
Lima 2002	28	2494.00 (2326.00)	28	2465.00 (1537.00)		5.5	0.01 [-0.51, 0.54]
Mungan 1999	15	0.50 (0.45)	11	0.67 (0.58)		4.4	-0.32 [-1.11, 0.46]
Nelson 1993	20	12.15 (8.68)	21	18.67 (13.56)		5.0	-0.56 [-1.18, 0.07]
Passalacqua 1998	10	59.60 (27.80)	9	109.10 (45.70)		3.5	-1.27 [-2.28, -0.26]
Passalacqua 1999	15	189.00 (113.00)	15	191.00 (108.00)		4.6	-0.02 [-0.73, 0.70]
Pradalier 1999	63	2.33 (1.60)	63	2.65 (2.00)		6.2	-0.18 [-0.53, 0.17]
Tari 1990	34	8.00 (1.50)	32	12.00 (2.00)		5.0	-2.25 [-2.87, -1.62]
Troise 1995	15	87.00 (76.00)	16	102.00 (58.00)		4.7	-0.22 [-0.92, 0.49]
Voltolini 2001	15	130.00 (154.00)	15	83.00 (79.00)		4.6	0.37 [-0.35, 1.10]
Vourdas 1998	34	1.38 (2.01)	32	1.07 (1.63)		5.7	0.17 [-0.32, 0.65]
Total (95% CI)	**484**		**475**			**100.0**	**-0.42 [-0.69, -0.15]**

Test for heterogeneity chi-square=75.36 df=20 p=<0.0001 I^2 =73.5%

Test for overall effect z=3.09 p=0.002

Analysis 01.02. Comparison 01 SLIT v placebo - all, Outcome 02 Medication scores

Review: Sublingual immunotherapy for allergic rhinitis

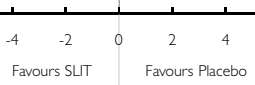
Comparison: 01 SLIT v placebo - all

Outcome: 02 Medication scores

Study	SLIT N	SLIT Mean(SD)	Placebo N	Placebo Mean(SD)	Standardised Mean Difference (Random) 95% CI	Weight (%)	Standardised Mean Difference (Random) 95% CI
Andre 2002	55	3.90 (6.91)	55	8.68 (11.46)		9.6	-0.50 [-0.88, -0.12]
Ariano 2001	10	2.50 (2.10)	10	5.30 (4.90)		3.6	-0.71 [-1.62, 0.20]
Bahceciler 2001	8	1.25 (1.04)	7	1.57 (1.25)		3.1	-0.26 [-1.28, 0.76]
Casanovas 1994	9	1.69 (2.46)	6	2.13 (2.22)		3.0	-0.17 [-1.21, 0.86]
D'Ambrosio 1996	15	59.70 (83.00)	15	68.30 (75.30)		5.1	-0.11 [-0.82, 0.61]
D'Ambrosio 1999	14	48.10 (46.60)	16	124.37 (121.00)		4.8	-0.79 [-1.54, -0.04]
Feliziani 1995	18	24.06 (25.72)	16	75.90 (50.30)		4.8	-1.29 [-2.04, -0.54]
Guez 2000	36	4.10 (5.50)	36	6.10 (6.80)		8.2	-0.32 [-0.79, 0.15]
Hordijk 1998	35	0.16 (0.37)	36	0.31 (0.45)		8.1	-0.36 [-0.83, 0.11]
La Rosa 1999	20	2.28 (3.89)	21	2.36 (3.95)		6.2	-0.02 [-0.63, 0.59]
Lima 2002	28	2334.00 (2616.00)	28	2837.00 (2052.00)		7.3	-0.21 [-0.74, 0.31]
Mungan 1999	15	1.97 (1.40)	11	5.20 (1.60)		3.2	-2.10 [-3.10, -1.11]
Passalacqua 1999	15	42.00 (49.50)	15	83.00 (65.00)		4.9	-0.69 [-1.43, 0.05]
Pradalier 1999	63	1.77 (2.30)	63	2.13 (2.70)		10.1	-0.14 [-0.49, 0.21]
Troise 1995	15	17.00 (21.00)	16	33.00 (33.00)		5.1	-0.56 [-1.28, 0.16]
Voltolini 2001	15	22.00 (30.00)	15	39.00 (34.00)		5.0	-0.52 [-1.25, 0.21]
Vourdas 1998	34	1.77 (3.85)	32	1.39 (3.41)		7.9	0.10 [-0.38, 0.59]
Total (95% CI)	**405**		**398**		◆	**100.0**	**-0.43 [-0.63, -0.23]**

Test for heterogeneity chi-square=28.48 df=16 p=0.03 I^2 =43.8%

Test for overall effect z=4.17 p=0.00003



Analysis 02.01. Comparison 02 SLIT v placebo - seasonal allergen, Outcome 01 Allergic Rhinitis symptom scores

Review: Sublingual immunotherapy for allergic rhinitis

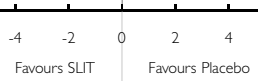
Comparison: 02 SLIT v placebo - seasonal allergen

Outcome: 01 Allergic Rhinitis symptom scores

Study	SLIT N	SLIT Mean(SD)	Placebo N	Placebo Mean(SD)	Standardised Mean Difference (Random) 95% CI	Weight (%)	Standardised Mean Difference (Random) 95% CI
Andre 2002	55	3.78 (2.74)	55	3.95 (2.66)		10.9	-0.06 [-0.44, 0.31]
Ariano 2001	10	1.80 (1.75)	10	5.38 (1.57)		3.3	-2.06 [-3.19, -0.93]
Casanovas 1994	9	5.46 (3.56)	6	10.98 (7.10)		3.4	-1.00 [-2.11, 0.12]
D'Ambrosio 1996	15	290.00 (258.00)	15	408.90 (315.35)		6.1	-0.40 [-1.13, 0.32]
D'Ambrosio 1999	14	509.00 (514.20)	16	897.06 (678.20)		6.0	-0.62 [-1.36, 0.12]
Feliziani 1995	18	109.70 (92.46)	16	215.80 (114.20)		6.2	-1.00 [-1.72, -0.28]
Hordijk 1998	35	3.21 (3.05)	36	5.13 (3.60)		9.3	-0.57 [-1.04, -0.09]
La Rosa 1999	20	1.21 (1.66)	21	1.61 (1.56)		7.3	-0.24 [-0.86, 0.37]
Lima 2002	28	2494.00 (2326.00)	28	2465.00 (1537.00)		8.5	0.01 [-0.51, 0.54]
Passalacqua 1999	15	189.00 (113.00)	15	191.00 (108.00)		6.2	-0.02 [-0.73, 0.70]
Pradalier 1999	63	2.33 (1.60)	63	2.65 (2.00)		11.2	-0.18 [-0.53, 0.17]
Troise 1995	15	87.00 (76.00)	16	102.00 (58.00)		6.3	-0.22 [-0.92, 0.49]
Voltolini 2001	15	130.00 (154.00)	15	83.00 (79.00)		6.1	0.37 [-0.35, 1.10]
Vourdas 1998	34	1.38 (2.01)	32	1.07 (1.63)		9.1	0.17 [-0.32, 0.65]
Total (95% CI)	**346**		**344**			**100.0**	**-0.30 [-0.53, -0.07]**

Test for heterogeneity chi-square=26.91 df=13 p=0.01 I^2 =51.7%

Test for overall effect z=2.51 p=0.01



Analysis 02.02. Comparison 02 SLIT v placebo - seasonal allergen, Outcome 02 Medication scores

Review: Sublingual immunotherapy for allergic rhinitis

Comparison: 02 SLIT v placebo - seasonal allergen

Outcome: 02 Medication scores

Study	SLIT N	SLIT Mean(SD)	Placebo N	Placebo Mean(SD)	Standardised Mean Difference (Random) 95% CI	Weight (%)	Standardised Mean Difference (Random) 95% CI
Andre 2002	55	3.90 (6.91)	55	8.68 (11.46)		13.4	-0.50 [-0.88, -0.12]
Ariano 2001	10	2.50 (2.10)	10	5.30 (4.90)		3.5	-0.71 [-1.62, 0.20]
Casanovas 1994	9	1.69 (2.46)	6	2.13 (2.22)		2.7	-0.17 [-1.21, 0.86]
D'Ambrosio 1996	15	59.70 (83.00)	15	68.30 (75.30)		5.3	-0.11 [-0.82, 0.61]
D'Ambrosio 1999	14	48.10 (46.60)	16	124.37 (121.00)		4.9	-0.79 [-1.54, -0.04]
Feliziani 1995	18	24.06 (25.72)	16	75.90 (50.30)		4.9	-1.29 [-2.04, -0.54]
Hordijk 1998	35	0.16 (0.37)	36	0.31 (0.45)		10.2	-0.36 [-0.83, 0.11]
La Rosa 1999	20	2.28 (3.89)	21	2.36 (3.95)		6.8	-0.02 [-0.63, 0.59]
Lima 2002	28	2334.00 (2616.00)	28	2837.00 (2052.00)		8.6	-0.21 [-0.74, 0.31]
Passalacqua 1999	15	42.00 (49.50)	15	83.00 (65.00)		5.0	-0.69 [-1.43, 0.05]
Pradalier 1999	63	1.77 (2.30)	63	2.13 (2.70)		14.8	-0.14 [-0.49, 0.21]
Troise 1995	15	17.00 (21.00)	16	33.00 (33.00)		5.2	-0.56 [-1.28, 0.16]
Voltolini 2001	15	22.00 (30.00)	15	39.00 (34.00)		5.1	-0.52 [-1.25, 0.21]
Vourdas 1998	34	1.77 (3.85)	32	1.39 (3.41)		9.8	0.10 [-0.38, 0.59]
Total (95% CI)	**346**		**344**		◆	**100.0**	**-0.36 [-0.54, -0.18]**

Test for heterogeneity chi-square=16.61 df=13 p=0.22 I^2 =21.7%

Test for overall effect z=3.96 p=0.00007

Analysis 03.01. Comparison 03 SLIT v placebo - perennial allergen, Outcome 01 Allergic Rhinitis symptom scores

Review: Sublingual immunotherapy for allergic rhinitis

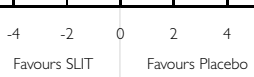
Comparison: 03 SLIT v placebo - perennial allergen

Outcome: 01 Allergic Rhinitis symptom scores

Study	SLIT N	Mean(SD)	Placebo N	Mean(SD)	Standardised Mean Difference (Random) 95% CI	Weight (%)	Standardised Mean Difference (Random) 95% CI
Bahceciler 2001	8	0.53 (0.40)	7	0.40 (0.38)		12.6	0.31 [-0.71, 1.34]
Guez 2000	36	2.30 (1.90)	36	3.20 (2.40)		15.9	-0.41 [-0.88, 0.06]
Hirsch 1997	15	0.99 (1.13)	15	0.52 (0.47)		14.5	0.53 [-0.20, 1.26]
Mungan 1999	15	0.50 (0.45)	11	0.67 (0.58)		14.1	-0.32 [-1.11, 0.46]
Nelson 1993	20	12.15 (8.68)	21	18.67 (13.56)		15.1	-0.56 [-1.18, 0.07]
Passalacqua 1998	10	59.60 (27.80)	9	109.10 (45.70)		12.7	-1.27 [-2.28, -0.26]
Tari 1990	34	8.00 (1.50)	32	12.00 (2.00)		15.1	-2.25 [-2.87, -1.62]
Total (95% CI)	**138**		**131**			**100.0**	**-0.58 [-1.28, 0.12]**

Test for heterogeneity chi-square=41.73 df=6 p=<0.0001 I^2 =85.6%

Test for overall effect z=1.61 p=0.1



Analysis 03.02. Comparison 03 SLIT v placebo - perennial allergen, Outcome 02 Medication scores

Review: Sublingual immunotherapy for allergic rhinitis

Comparison: 03 SLIT v placebo - perennial allergen

Outcome: 02 Medication scores

Study	SLIT N	Mean(SD)	Placebo N	Mean(SD)	Standardised Mean Difference (Random) 95% CI	Weight (%)	Standardised Mean Difference (Random) 95% CI
Bahceciler 2001	8	1.25 (1.04)	7	1.57 (1.25)		30.4	-0.26 [-1.28, 0.76]
Guez 2000	36	4.10 (5.50)	36	6.10 (6.80)		38.7	-0.32 [-0.79, 0.15]
Mungan 1999	15	1.97 (1.40)	11	5.20 (1.60)		30.8	-2.10 [-3.10, -1.11]
Total (95% CI)	**59**		**54**			**100.0**	**-0.85 [-1.93, 0.23]**

Test for heterogeneity chi-square=10.58 df=2 p=0.005 I^2 =81.1%

Test for overall effect z=1.55 p=0.1

Analysis 04.01. Comparison 04 SLIT v placebo - adults, Outcome 01 Allergic Rhinitis symptom scores

Review: Sublingual immunotherapy for allergic rhinitis

Comparison: 04 SLIT v placebo - adults

Outcome: 01 Allergic Rhinitis symptom scores

Study	SLIT N	SLIT Mean(SD)	Placebo N	Placebo Mean(SD)	Standardised Mean Difference (Random) 95% CI	Weight (%)	Standardised Mean Difference (Random) 95% CI
Andre 2002	55	3.78 (2.74)	55	3.95 (2.66)		10.2	-0.06 [-0.44, 0.31]
Ariano 2001	10	1.80 (1.75)	10	5.38 (1.57)		2.9	-2.06 [-3.19, -0.93]
Casanovas 1994	9	5.46 (3.56)	6	10.98 (7.10)		3.0	-1.00 [-2.11, 0.12]
D'Ambrosio 1996	15	290.00 (258.00)	15	408.90 (315.35)		5.5	-0.40 [-1.13, 0.32]
D'Ambrosio 1999	14	509.00 (514.20)	16	897.06 (678.20)		5.4	-0.62 [-1.36, 0.12]
Feliziani 1995	18	109.70 (92.46)	16	215.80 (114.20)		5.6	-1.00 [-1.72, -0.28]
Guez 2000	36	2.30 (1.90)	36	3.20 (2.40)		8.7	-0.41 [-0.88, 0.06]
Hordijk 1998	35	3.21 (3.05)	36	5.13 (3.60)		8.6	-0.57 [-1.04, -0.09]
Lima 2002	28	2494.00 (2326.00)	28	2465.00 (1537.00)		7.9	0.01 [-0.51, 0.54]
Mungan 1999	15	0.50 (0.45)	11	0.67 (0.58)		5.0	-0.32 [-1.11, 0.46]
Nelson 1993	20	12.15 (8.68)	21	18.67 (13.56)		6.6	-0.56 [-1.18, 0.07]
Passalacqua 1998	10	59.60 (27.80)	9	109.10 (45.70)		3.5	-1.27 [-2.28, -0.26]
Passalacqua 1999	15	189.00 (113.00)	15	191.00 (108.00)		5.6	-0.02 [-0.73, 0.70]
Pradalier 1999	63	2.33 (1.60)	63	2.65 (2.00)		10.6	-0.18 [-0.53, 0.17]
Troise 1995	15	87.00 (76.00)	16	102.00 (58.00)		5.7	-0.22 [-0.92, 0.49]
Voltolini 2001	15	130.00 (154.00)	15	83.00 (79.00)		5.5	0.37 [-0.35, 1.10]
Total (95% CI)	**373**		**368**			**100.0**	**-0.40 [-0.61, -0.18]**

Test for heterogeneity chi-square=28.17 df=15 p=0.02 I^2 =46.8%

Test for overall effect z=3.63 p=0.0003

Analysis 04.02. Comparison 04 SLIT v placebo - adults, Outcome 02 Medication scores

Review: Sublingual immunotherapy for allergic rhinitis

Comparison: 04 SLIT v placebo - adults

Outcome: 02 Medication scores

Study	SLIT N	SLIT Mean(SD)	Placebo N	Placebo Mean(SD)	Standardised Mean Difference (Random) 95% CI	Weight (%)	Standardised Mean Difference (Random) 95% CI
Andre 2002	55	3.90 (6.91)	55	8.68 (11.46)		11.8	-0.50 [-0.88, -0.12]
Ariano 2001	10	2.50 (2.10)	10	5.30 (4.90)		4.3	-0.71 [-1.62, 0.20]
Casanovas 1994	9	1.69 (2.46)	6	2.13 (2.22)		3.5	-0.17 [-1.21, 0.86]
D'Ambrosio 1996	15	59.70 (83.00)	15	68.30 (75.30)		6.1	-0.11 [-0.82, 0.61]
D'Ambrosio 1999	14	48.10 (46.60)	16	124.37 (121.00)		5.8	-0.79 [-1.54, -0.04]
Feliziani 1995	18	24.06 (25.72)	16	75.90 (50.30)		5.8	-1.29 [-2.04, -0.54]
Guez 2000	36	4.10 (5.50)	36	6.10 (6.80)		10.0	-0.32 [-0.79, 0.15]
Hordijk 1998	35	0.16 (0.37)	36	0.31 (0.45)		9.9	-0.36 [-0.83, 0.11]
Lima 2002	28	2334.00 (2616.00)	28	2837.00 (2052.00)		8.8	-0.21 [-0.74, 0.31]
Mungan 1999	15	1.97 (1.40)	11	5.20 (1.60)		3.8	-2.10 [-3.10, -1.11]
Passalacqua 1999	15	42.00 (49.50)	15	83.00 (65.00)		5.8	-0.69 [-1.43, 0.05]
Pradalier 1999	63	1.77 (2.30)	63	2.13 (2.70)		12.5	-0.14 [-0.49, 0.21]
Troise 1995	15	17.00 (21.00)	16	33.00 (33.00)		6.1	-0.56 [-1.28, 0.16]
Voltolini 2001	15	22.00 (30.00)	15	39.00 (34.00)		6.0	-0.52 [-1.25, 0.21]
Total (95% CI)	**343**		**338**			**100.0**	**-0.51 [-0.73, -0.29]**

Test for heterogeneity chi-square=22.52 df=13 p=0.05 I^2 =42.3%

Test for overall effect z=4.62 p<0.00001

Analysis 05.01. Comparison 05 SLIT v placebo - children, Outcome 01 Allergic Rhinitis symptom scores

Review: Sublingual immunotherapy for allergic rhinitis

Comparison: 05 SLIT v placebo - children

Outcome: 01 Allergic Rhinitis symptom scores

Study	SLIT N	Mean(SD)	Placebo N	Mean(SD)	Standardised Mean Difference (Random) 95% CI	Weight (%)	Standardised Mean Difference (Random) 95% CI
Bahceciler 2001	8	0.53 (0.40)	7	0.40 (0.38)		18.1	0.31 [-0.71, 1.34]
Hirsch 1997	15	0.99 (1.13)	15	0.52 (0.47)		19.9	0.53 [-0.20, 1.26]
La Rosa 1999	20	1.21 (1.66)	21	1.61 (1.56)		20.5	-0.24 [-0.86, 0.37]
Tari 1990	34	8.00 (1.50)	32	12.00 (2.00)		20.4	-2.25 [-2.87, -1.62]
Vourdas 1998	34	1.38 (2.01)	32	1.07 (1.63)		21.1	0.17 [-0.32, 0.65]
Total (95% CI)	**111**		**107**			**100.0**	**-0.31 [-1.32, 0.70]**

Test for heterogeneity chi-square=47.16 df=4 p=<0.0001 I^2 =91.5%

Test for overall effect z=0.61 p=0.5

Analysis 05.02. Comparison 05 SLIT v placebo - children, Outcome 02 Medication scores

Review: Sublingual immunotherapy for allergic rhinitis

Comparison: 05 SLIT v placebo - children

Outcome: 02 Medication scores

Study	SLIT N	Mean(SD)	Placebo N	Mean(SD)	Standardised Mean Difference (Random) 95% CI	Weight (%)	Standardised Mean Difference (Random) 95% CI
Bahceciler 2001	8	1.25 (1.04)	7	1.57 (1.25)		12.1	-0.26 [-1.28, 0.76]
La Rosa 1999	20	2.28 (3.89)	21	2.36 (3.95)		33.7	-0.02 [-0.63, 0.59]
Vourdas 1998	34	1.77 (3.85)	32	1.39 (3.41)		54.2	0.10 [-0.38, 0.59]
Total (95% CI)	**62**		**60**			**100.0**	**0.02 [-0.34, 0.37]**

Test for heterogeneity chi-square=0.43 df=2 p=0.81 I^2 =0.0%

Test for overall effect z=0.09 p=0.9

Analysis 06.01. Comparison 06 SLIT v placebo - <6months, Outcome 01 Allergic Rhinitis symptom scores

Review: Sublingual immunotherapy for allergic rhinitis

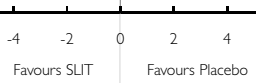
Comparison: 06 SLIT v placebo - <6months

Outcome: 01 Allergic Rhinitis symptom scores

Study	SLIT N	Mean(SD)	Placebo N	Mean(SD)	Standardised Mean Difference (Random) 95% CI	Weight (%)	Standardised Mean Difference (Random) 95% CI
Bahceciler 2001	8	0.53 (0.40)	7	0.40 (0.38)		6.9	0.31 [-0.71, 1.34]
Casanovas 1994	9	5.46 (3.56)	6	10.98 (7.10)		6.0	-1.00 [-2.11, 0.12]
Feliziani 1995	18	109.70 (92.46)	16	215.80 (114.20)		11.4	-1.00 [-1.72, -0.28]
Hordijk 1998	35	3.21 (3.05)	36	5.13 (3.60)		17.9	-0.57 [-1.04, -0.09]
Mungan 1999	15	0.50 (0.45)	11	0.67 (0.58)		10.2	-0.32 [-1.11, 0.46]
Nelson 1993	20	12.15 (8.68)	21	18.67 (13.56)		13.6	-0.56 [-1.18, 0.07]
Pradalier 1999	63	2.33 (1.60)	63	2.65 (2.00)		22.5	-0.18 [-0.53, 0.17]
Voltolini 2001	15	130.00 (154.00)	15	83.00 (79.00)		11.4	0.37 [-0.35, 1.10]
Total (95% CI)	**183**		**175**			**100.0**	**-0.36 [-0.67, -0.06]**

Test for heterogeneity chi-square=12.12 df=7 p=0.10 I^2 =42.2%

Test for overall effect z=2.33 p=0.02



Analysis 06.02. Comparison 06 SLIT v placebo - <6months, Outcome 02 Medication scores

Review: Sublingual immunotherapy for allergic rhinitis

Comparison: 06 SLIT v placebo - <6months

Outcome: 02 Medication scores

Study	SLIT N	Mean(SD)	Placebo N	Mean(SD)	Standardised Mean Difference (Random) 95% CI	Weight (%)	Standardised Mean Difference (Random) 95% CI
Bahceciler 2001	8	1.25 (1.04)	7	1.57 (1.25)		10.7	-0.26 [-1.28, 0.76]
Casanovas 1994	9	1.69 (2.46)	6	2.13 (2.22)		10.6	-0.17 [-1.21, 0.86]
Feliziani 1995	18	24.06 (25.72)	16	75.90 (50.30)		14.3	-1.29 [-2.04, -0.54]
Hordijk 1998	35	0.16 (0.37)	36	0.31 (0.45)		18.5	-0.36 [-0.83, 0.11]
Mungan 1999	15	1.97 (1.40)	11	5.20 (1.60)		11.0	-2.10 [-3.10, -1.11]
Pradalier 1999	63	1.77 (2.30)	63	2.13 (2.70)		20.3	-0.14 [-0.49, 0.21]
Voltolini 2001	15	22.00 (30.00)	15	39.00 (34.00)		14.5	-0.52 [-1.25, 0.21]
Total (95% CI)	**163**		**154**			**100.0**	**-0.63 [-1.09, -0.18]**

Test for heterogeneity chi-square=19.00 df=6 p=0.004 I^2 =68.4%

Test for overall effect z=2.71 p=0.007

Analysis 07.01. Comparison 07 SLIT v placebo - 6-12 months, Outcome 01 Allergic Rhinitis symptom scores

Review: Sublingual immunotherapy for allergic rhinitis

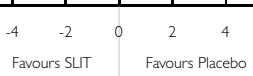
Comparison: 07 SLIT v placebo - 6-12 months

Outcome: 01 Allergic Rhinitis symptom scores

Study	SLIT N	SLIT Mean(SD)	Placebo N	Placebo Mean(SD)	Standardised Mean Difference (Random) 95% CI	Weight (%)	Standardised Mean Difference (Random) 95% CI
Andre 2002	55	3.78 (2.74)	55	3.95 (2.66)		16.4	-0.06 [-0.44, 0.31]
Ariano 2001	10	1.80 (1.75)	10	5.38 (1.57)		5.9	-2.06 [-3.19, -0.93]
D'Ambrosio 1996	15	290.00 (258.00)	15	408.90 (315.35)		10.3	-0.40 [-1.13, 0.32]
D'Ambrosio 1999	14	509.00 (514.20)	16	897.06 (678.20)		10.1	-0.62 [-1.36, 0.12]
Hirsch 1997	15	0.99 (1.13)	15	0.52 (0.47)		10.2	0.53 [-0.20, 1.26]
La Rosa 1999	20	1.21 (1.66)	21	1.61 (1.56)		12.0	-0.24 [-0.86, 0.37]
Passalacqua 1999	15	189.00 (113.00)	15	191.00 (108.00)		10.4	-0.02 [-0.73, 0.70]
Troise 1995	15	87.00 (76.00)	16	102.00 (58.00)		10.5	-0.22 [-0.92, 0.49]
Vourdas 1998	34	1.38 (2.01)	32	1.07 (1.63)		14.3	0.17 [-0.32, 0.65]
Total (95% CI)	**193**		**195**			**100.0**	**-0.21 [-0.54, 0.11]**

Test for heterogeneity chi-square=18.46 df=8 p=0.02 I^2 =56.7%

Test for overall effect z=1.28 p=0.2



Analysis 07.02. Comparison 07 SLIT v placebo - 6-12 months, Outcome 02 Medication scores

Review: Sublingual immunotherapy for allergic rhinitis

Comparison: 07 SLIT v placebo - 6-12 months

Outcome: 02 Medication scores

Study	SLIT N	SLIT Mean(SD)	Placebo N	Placebo Mean(SD)	Standardised Mean Difference (Random) 95% CI	Weight (%)	Standardised Mean Difference (Random) 95% CI
Andre 2002	55	3.90 (6.91)	55	8.68 (11.46)		25.2	-0.50 [-0.88, -0.12]
Ariano 2001	10	2.50 (2.10)	10	5.30 (4.90)		6.4	-0.71 [-1.62, 0.20]
D'Ambrosio 1996	15	59.70 (83.00)	15	68.30 (75.30)		9.7	-0.11 [-0.82, 0.61]
D'Ambrosio 1999	14	48.10 (46.60)	16	124.37 (121.00)		9.0	-0.79 [-1.54, -0.04]
La Rosa 1999	20	2.28 (3.89)	21	2.36 (3.95)		12.6	-0.02 [-0.63, 0.59]
Passalacqua 1999	15	42.00 (49.50)	15	83.00 (65.00)		9.2	-0.69 [-1.43, 0.05]
Troise 1995	15	17.00 (21.00)	16	33.00 (33.00)		9.6	-0.56 [-1.28, 0.16]
Vourdas 1998	34	1.77 (3.85)	32	1.39 (3.41)		18.2	0.10 [-0.38, 0.59]
Total (95% CI)	**178**		**180**			**100.0**	**-0.35 [-0.60, -0.11]**

Test for heterogeneity chi-square=8.62 df=7 p=0.28 I^2 =18.8%

Test for overall effect z=2.88 p=0.004

Analysis 08.01. Comparison 08 SLIT v placebo - >12 months, Outcome 01 Allergic Rhinitis symptom scores

Review: Sublingual immunotherapy for allergic rhinitis

Comparison: 08 SLIT v placebo - >12 months

Outcome: 01 Allergic Rhinitis symptom scores

Study	SLIT N	SLIT Mean(SD)	Placebo N	Placebo Mean(SD)	Standardised Mean Difference (Random) 95% CI	Weight (%)	Standardised Mean Difference (Random) 95% CI
Guez 2000	36	2.30 (1.90)	36	3.20 (2.40)		26.5	-0.41 [-0.88, 0.06]
Lima 2002	28	2494.00 (2326.00)	28	2465.00 (1537.00)		26.1	0.01 [-0.51, 0.54]
Passalacqua 1998	10	59.60 (27.80)	9	109.10 (45.70)		22.0	-1.27 [-2.28, -0.26]
Tari 1990	34	8.00 (1.50)	32	12.00 (2.00)		25.4	-2.25 [-2.87, -1.62]
Total (95% CI)	**108**		**105**			**100.0**	**-0.95 [-1.97, 0.06]**

Test for heterogeneity chi-square=33.31 df=3 p=<0.0001 I^2 =91.0%

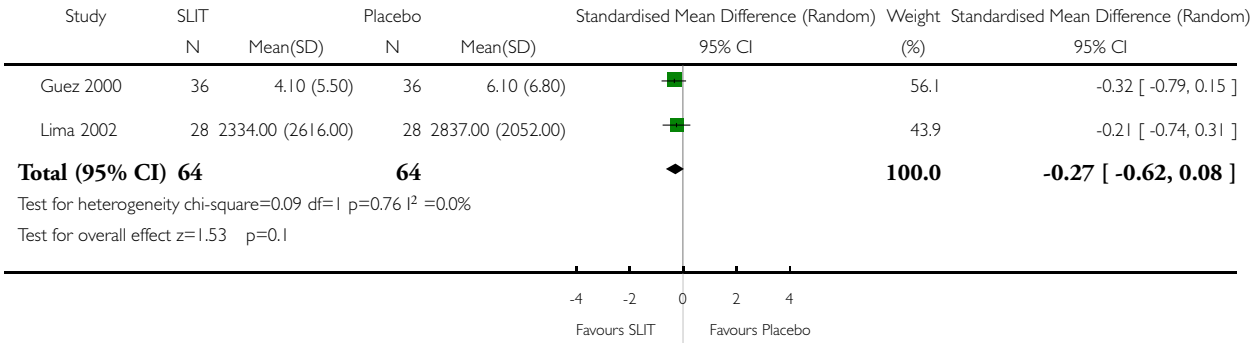
Test for overall effect z=1.84 p=0.07

Analysis 08.02. Comparison 08 SLIT v placebo - >12 months, Outcome 02 Medication scores

Review: Sublingual immunotherapy for allergic rhinitis

Comparison: 08 SLIT v placebo - >12 months

Outcome: 02 Medication scores

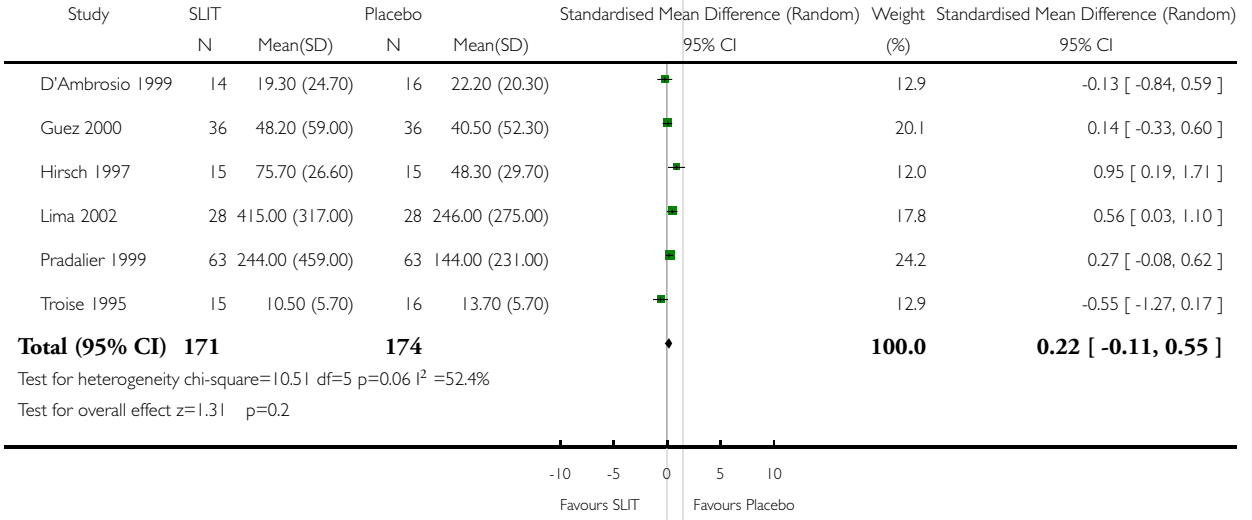


Analysis 09.01. Comparison 09 SLIT v Placebo - Immunoglobulins, Outcome 01 IgE levels - post treatment

Review: Sublingual immunotherapy for allergic rhinitis

Comparison: 09 SLIT v Placebo - Immunoglobulins

Outcome: 01 IgE levels - post treatment



Analysis 09.02. Comparison 09 SLIT v Placebo - Immunoglobulins, Outcome 02 IgG levels - post treatment

Review: Sublingual immunotherapy for allergic rhinitis

Comparison: 09 SLIT v Placebo - Immunoglobulins

Outcome: 02 IgG levels - post treatment

Study	SLIT N	SLIT Mean(SD)	Placebo N	Placebo Mean(SD)	Standardised Mean Difference (Random) 95% CI	Weight (%)	Standardised Mean Difference (Random) 95% CI
D'Ambrosio 1999	14	2.60 (0.40)	16	2.59 (0.70)		15.8	0.02 [-0.70, 0.73]
Guez 2000	36	4.80 (1.80)	36	5.00 (2.30)		17.4	-0.10 [-0.56, 0.37]
Lima 2002	28	8.61 (8.25)	28	2.61 (3.12)		16.9	0.95 [0.39, 1.50]
Pradalier 1999	63	8.70 (10.90)	63	6.80 (4.50)		18.0	0.23 [-0.12, 0.58]
Tari 1990	34	10.71 (3.81)	32	2.78 (2.02)		16.2	2.55 [1.89, 3.21]
Troise 1995	15	28.00 (8.20)	16	28.00 (7.10)		15.9	0.0 [-0.70, 0.70]
Total (95% CI)	**190**		**191**			**100.0**	**0.60 [-0.11, 1.31]**

Test for heterogeneity chi-square=51.93 df=5 p=<0.0001 I^2 =90.4%

Test for overall effect z=1.65 p=0.1

Analysis 10.01. Comparison 10 SLIT v placebo - HDM, Outcome 01 Allergic Rhinitis symptom scores

Review: Sublingual immunotherapy for allergic rhinitis

Comparison: 10 SLIT v placebo - HDM

Outcome: 01 Allergic Rhinitis symptom scores

Study	SLIT N	SLIT Mean(SD)	Placebo N	Placebo Mean(SD)	Standardised Mean Difference (Random) 95% CI	Weight (%)	Standardised Mean Difference (Random) 95% CI
Bahceciler 2001	8	0.53 (0.40)	7	0.40 (0.38)		15.2	0.31 [-0.71, 1.34]
Guez 2000	36	2.30 (1.90)	36	3.20 (2.40)		18.3	-0.41 [-0.88, 0.06]
Hirsch 1997	15	0.99 (1.13)	15	0.52 (0.47)		17.0	0.53 [-0.20, 1.26]
Mungan 1999	15	0.50 (0.45)	11	0.67 (0.58)		16.7	-0.32 [-1.11, 0.46]
Passalacqua 1998	10	59.60 (27.80)	9	109.10 (45.70)		15.3	-1.27 [-2.28, -0.26]
Tari 1990	34	8.00 (1.50)	32	12.00 (2.00)		17.6	-2.25 [-2.87, -1.62]
Total (95% CI)	**118**		**110**			**100.0**	**-0.58 [-1.43, 0.27]**

Test for heterogeneity chi-square=41.67 df=5 p=<0.0001 I^2 =88.0%

Test for overall effect z=1.33 p=0.2

Analysis 10.02. Comparison 10 SLIT v placebo - HDM, Outcome 02 Medication scores

Review: Sublingual immunotherapy for allergic rhinitis

Comparison: 10 SLIT v placebo - HDM

Outcome: 02 Medication scores

Study	SLIT N	Mean(SD)	Placebo N	Mean(SD)	Standardised Mean Difference (Random) 95% CI	Weight (%)	Standardised Mean Difference (Random) 95% CI
Bahceciler 2001	8	1.25 (1.04)	7	1.57 (1.25)		30.4	-0.26 [-1.28, 0.76]
Guez 2000	36	4.10 (5.50)	36	6.10 (6.80)		38.7	-0.32 [-0.79, 0.15]
Mungan 1999	15	1.97 (1.40)	11	5.20 (1.60)		30.8	-2.10 [-3.10, -1.11]
Total (95% CI)	**59**		**54**			**100.0**	**-0.85 [-1.93, 0.23]**

Test for heterogeneity chi-square=10.58 df=2 p=0.005 I^2 =81.1%

Test for overall effect z=1.55 p=0.1

Analysis 11.01. Comparison 11 SLIT v placebo - Grass pollen, Outcome 01 Allergic Rhinitis symptom scores

Review: Sublingual immunotherapy for allergic rhinitis

Comparison: 11 SLIT v placebo - Grass pollen

Outcome: 01 Allergic Rhinitis symptom scores

Study	SLIT N	Mean(SD)	Placebo N	Mean(SD)	Standardised Mean Difference (Random) 95% CI	Weight (%)	Standardised Mean Difference (Random) 95% CI
Feliziani 1995	18	109.70 (92.46)	16	215.80 (114.20)		16.9	-1.00 [-1.72, -0.28]
Hordijk 1998	35	3.21 (3.05)	36	5.13 (3.60)		26.3	-0.57 [-1.04, -0.09]
Lima 2002	28	2494.00 (2326.00)	28	2465.00 (1537.00)		24.1	0.01 [-0.51, 0.54]
Pradalier 1999	63	2.33 (1.60)	63	2.65 (2.00)		32.7	-0.18 [-0.53, 0.17]
Total (95% CI)	**144**		**143**			**100.0**	**-0.37 [-0.74, 0.00]**

Test for heterogeneity chi-square=6.74 df=3 p=0.08 I^2 =55.5%

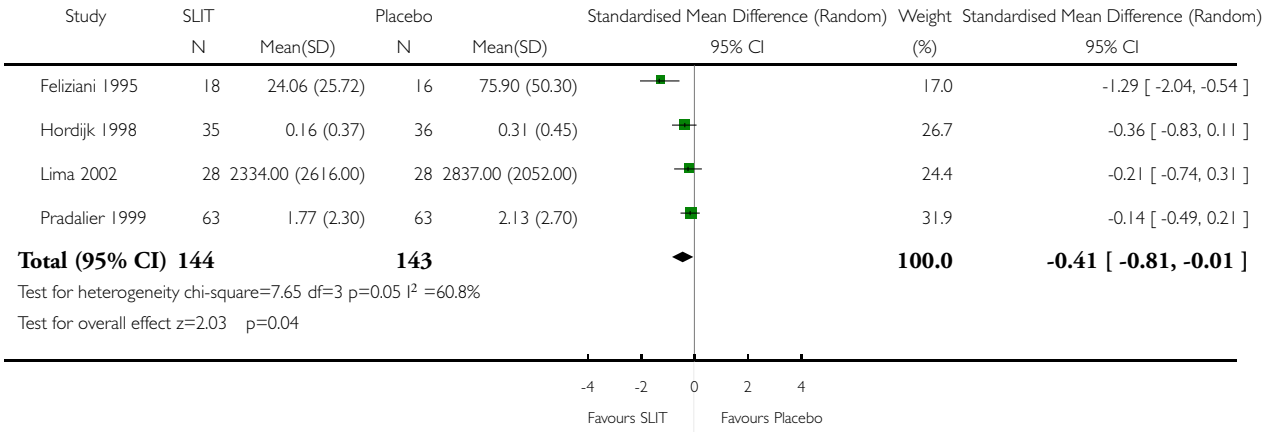
Test for overall effect z=1.97 p=0.05

Analysis 11.02. Comparison 11 SLIT v placebo - Grass pollen, Outcome 02 Medication scores

Review: Sublingual immunotherapy for allergic rhinitis

Comparison: 11 SLIT v placebo - Grass pollen

Outcome: 02 Medication scores

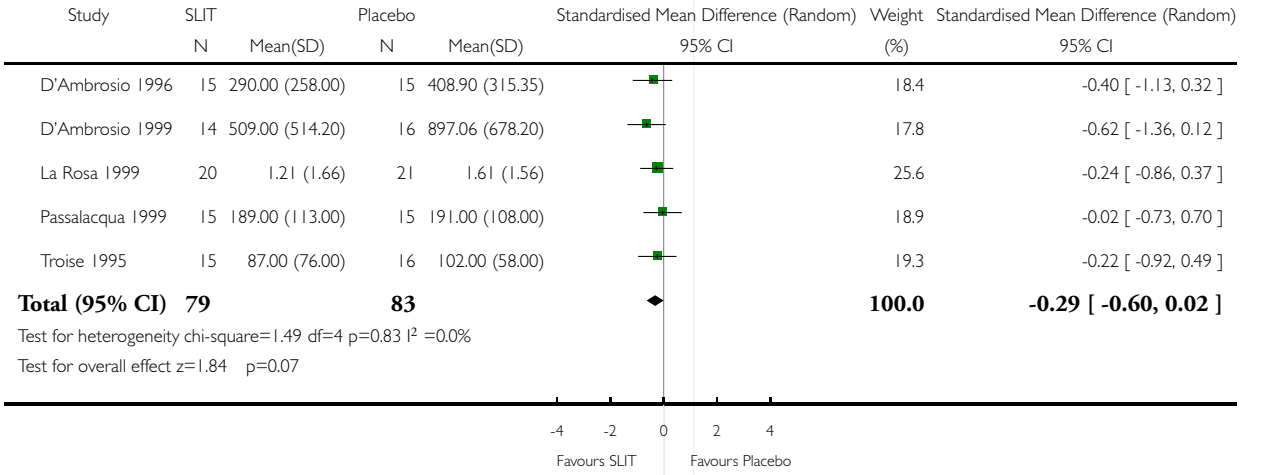


Analysis 12.01. Comparison 12 SLIT v placebo - Parietaria, Outcome 01 Allergic Rhinitis symptom scores

Review: Sublingual immunotherapy for allergic rhinitis

Comparison: 12 SLIT v placebo - Parietaria

Outcome: 01 Allergic Rhinitis symptom scores



Analysis 12.02. Comparison 12 SLIT v placebo - Parietaria, Outcome 02 Medication scores

Review: Sublingual immunotherapy for allergic rhinitis

Comparison: 12 SLIT v placebo - Parietaria

Outcome: 02 Medication scores

Study	SLIT N	SLIT Mean(SD)	Placebo N	Placebo Mean(SD)	Standardised Mean Difference (Random) 95% CI	Weight (%)	Standardised Mean Difference (Random) 95% CI
D'Ambrosio 1996	15	59.70 (83.00)	15	68.30 (75.30)		19.2	-0.11 [-0.82, 0.61]
D'Ambrosio 1999	14	48.10 (46.60)	16	124.37 (121.00)		17.6	-0.79 [-1.54, -0.04]
La Rosa 1999	20	2.28 (3.89)	21	2.36 (3.95)		26.3	-0.02 [-0.63, 0.59]
Passalacqua 1999	15	42.00 (49.50)	15	83.00 (65.00)		18.0	-0.69 [-1.43, 0.05]
Troise 1995	15	17.00 (21.00)	16	33.00 (33.00)		19.0	-0.56 [-1.28, 0.16]
Total (95% CI)	**79**		**83**			**100.0**	**-0.39 [-0.71, -0.08]**

Test for heterogeneity chi-square=3.94 df=4 p=0.41 I^2 =0.0%

Test for overall effect z=2.46 p=0.01