Meta-analyses of the efficacy of pharmacotherapies and sublingual allergy immunotherapy tablets for allergic rhinitis in adults and children*

Eli O. Meltzer[1], Dana Wallace[2], Howard S. Friedman[3], Prakash Navaratnam[3], Erin P. Scott[4], Hendrik Nolte[5]

[1] Allergy and Asthma Medical Group & Research Center, University of California School of Medicine, San Diego, CA, USA
[2] Nova Southeastern Allopathic Medical School, Davie, FL, USA
[3] DataMed Solutions, New York, NY, USA
[4] Scott Medical Communications, Tyler, TX, USA
[5] ALK-Abelló, Bedminster, NJ, USA

Rhinology 59: 5, 422 - 433, 2021
https://doi.org/10.4193/Rhin21.054

***Received for publication:**
February 3, 2021
Accepted: July 31, 2021

Abstract

Background: Treatment options for seasonal and perennial allergic rhinitis (SAR/PAR) include pharmacotherapies and allergy immunotherapy. These meta-analyses evaluated the efficacy of pharmacotherapies and sublingual immunotherapy tablets (SLIT-tablets) versus placebo on nasal symptoms associated with SAR and PAR.

Methods: Randomized, double-blind, placebo-controlled trials were identified from systematic PubMED/EMBASE searches through 7/18/2019 (PROSPERO protocol CRD42018105632). The primary outcome was mean numerical difference in total nasal symptom score (TNSS; 0-12) between active treatment and placebo at the end of the assessment period. Random-effects meta-analyses estimated the mean difference for each medication group weighted by the inverse of the trial variance. Publication bias assessments and sensitivity analyses were conducted.

Results: Rescue symptom-relieving pharmacotherapy was prohibited in most pharmacotherapy trials but was allowed in all SLIT-tablet trials. For adult/adolescent SAR, the mean numerical difference (95% CI) in TNSS versus placebo was: intranasal corticosteroids (INCS)=1.38 (1.18, 1.58; 39 trials); combination intranasal antihistamine/INCS=1.34 (1.15, 1.54; 4 trials); intranasal antihistamines=0.72 (0.56, 0.89; 13 trials); oral antihistamine=0.62 (0.35, 0.90; 18 trials); SLIT-tablets=0.57 (0.41, 0.73; 4 trials); and montelukast=0.48 (0.36, 0.60; 10 trials). For adult/adolescent PAR, mean difference in TNSS versus placebo (95% CI) was: INCS=0.82 (0.66, 0.97; 14 trials); SLIT-tablets=0.65 (0.42, 0.88; 3 trials); and oral antihistamine=0.27 (0.11, 0.42; 3 trials). The number of eligible trials limited meta-analyses for pediatric SAR/PAR.

Conclusions: All treatments significantly improved nasal symptoms versus placebo. SLIT-tablets provided improvement in TNSS despite access to rescue symptom-relieving pharmacotherapy. Extensive trial heterogeneity and strong indications of publication bias preclude the comparison of treatment effects among treatment classes.

Key words: glucocorticoids, histamine antagonists, montelukast, rhinitis, allergic, sublingual immunotherapy

Introduction

Allergic rhinitis (AR) has a substantial impact on patients' health-related quality of life [1, 2]. The nasal symptoms (congestion, sneezing, itching, rhinorrhea) of AR have been shown to be associated with substantial morbidity including sleep impairment and reduction in work and school productivity [3, 4]. Current treatment options for seasonal AR (SAR) and perennial AR (PAR) are primarily pharmacotherapy (including, second-generation oral or intranasal antihistamines, decongestants, intranasal corticosteroids [INCS], leukotriene receptor antagonists [LTRA]) and allergy immunotherapy (AIT) [5-7]. AIT is available in various formulations, of which sublingual immunotherapy (SLIT)-tablets are the most rigorously studied.

A small number of the pharmacotherapy trials have included

active comparators from other treatment classes, but because there are many pharmacotherapy options for AR, there are little direct head-to-head data comparing efficacy among all the various treatment classes. Furthermore, there have been no head-to-head trials designed to directly compare the efficacy of pharmacotherapy and SLIT-tablets, partially due to the need for long-term SLIT-tablet trials to allow rescue symptom-relieving pharmacotherapy use in both placebo and active treatment groups. Thus, comparisons between the effects of all the treatment classes can only be done indirectly. Two previous meta-analyses compared the treatment effects of SLIT-tablets, oral antihistamines, INCS, and LTRA but were limited in that one analysis only included single products from varying pharmacological classes and the other analysis only included patients with SAR [8, 9]. Furthermore, neither meta-analyses reported results for children with AR.

The objective of these meta-analyses was to systematically evaluate the efficacy of pharmacotherapy and SLIT-tablets versus placebo on nasal symptoms associated with adult/adolescent and pediatric SAR and PAR.

Materials and methods

The protocol for these meta-analyses was registered and can be accessed in PROSPERO (CRD42018105632). These meta-analyses were conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [10].

Trial eligibility criteria

Randomized, double-blind, placebo-controlled trials that evaluated the efficacy of pharmacotherapies and SLIT-tablets for SAR or PAR in adults/adolescents and/or children were included in these analyses. Nasal provocation, environmental exposure unit, and cross-over trials were excluded. Additional trial eligibility criteria were the evaluation of US Food and Drug Administration (FDA)-approved doses (Supplemental Table E1), minimum pharmacotherapy assessment period of 2 weeks for SAR, and minimum pharmacotherapy assessment period of 4 weeks for PAR. There was no limit on assessment periods for the SLIT-tablet trials since AIT requires several weeks of treatment before an effect is observed and trials last months, rather than weeks. A reported efficacy variable of total nasal symptom score (TNSS) defined as the sum or average of scores for sneezing, rhinorrhea (or nasal discharge), congestion (or blocked nose), and nasal itching, or any combination of these symptoms scored on any scale was required for eligibility. The TNSS had to be reported in tables, figures, or text in such a way that actual average daily sum score at the end of the primary assessment period could be directly used or calculated (ie, trials solely reporting graphical results that would require estimating of scores were excluded). Pharmacotherapies included in the analyses were those approved by the US FDA for the treatment of AR and which, in the opinion of the authors, are commonly currently used and well-studied. The specific pharmacotherapies that were included were second-generation oral antihistamines (cetirizine, desloratadine, fexofenadine, levocetirizine, loratadine), intranasal antihistamines (azelastine, olopatadine), oral leukotriene receptor antagonists (montelukast), INCS (aqueous or aerosol beclomethasone dipropionate, budesonide, ciclesonide, fluticasone propionate, fluticasone furoate, mometasone furoate, triamcinolone acetonide), combination intranasal antihistamines/INCS (azelastine/fluticasone), and combination oral antihistamines/decongestants (cetirizine/pseudoephedrine, desloratadine/pseudoephedrine, fexofenadine/pseudoephedrine, loratadine/pseudoephedrine). Trials evaluating only first-generation antihistamines were excluded because of limited availability of published randomized, double-blind placebo-controlled trials and because they are no longer recommended as first-line therapy due to their side effect profile. SLIT-tablet trials were limited to those evaluating products approved by the FDA for the treatment of AR, which at the writing of this analysis limits the products to those for grass (Grastek®, Oralair®), ragweed (Ragwitek®), and house dust mite (Odactra™) allergies.

Systematic searches and data collection process

PubMED/MEDLINE and EMBASE databases were searched for relevant trials. Searches were limited up to July 18, 2019 and English-only publications. EMBASE searches were limited to May 18, 2016 through May 18, 2018. The search strings used are defined in the Supplemental Material.

Records identified during the database searches were initially reviewed in duplicate by EPS and an independent reviewer for inclusion based on the specified criteria using the title and abstract. In the case of discrepancies, a third reviewer provided resolution. Full texts of the initially identified potential articles were then reviewed by EPS and an independent reviewer for determination of final trial inclusion and data extraction.

Data from identified trials that met all the inclusion criteria were entered into an Excel spreadsheet by EPS. HSF conducted quality checks of the data extraction. The primary data elements extracted from the articles and used as inputs in the meta-analyses were the placebo and active treatment(s) TNSS at the end of the primary assessment period, along with the corresponding sample sizes and other trial information. TNSS could have been scored on any scale and include any number of symptoms. In cases where symptom scores were reported as instantaneous and reflective, or as 12 hour and 24 hours, whichever measurement was defined in the trial as the primary endpoint was the measurement captured. Where multiple time points were assessed, the time point defined for the primary endpoint was captured. In situations where multiple doses were evaluated, the dose that was FDA-approved and which showed the greatest efficacy was

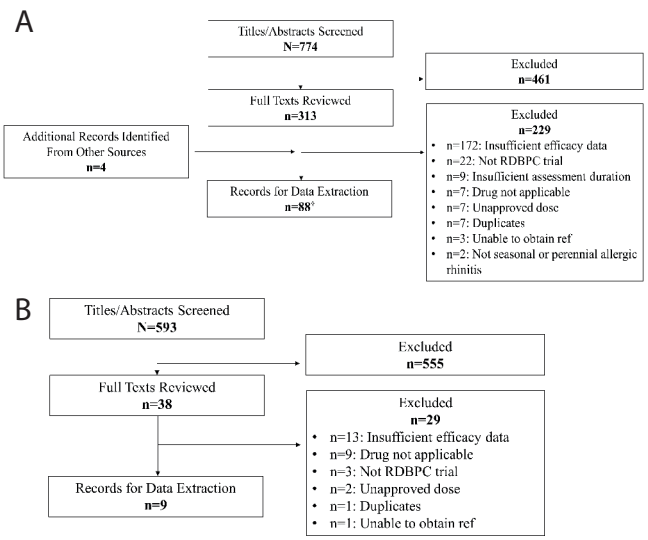


Figure 1. Trial selection for A) pharmacotherapies and B) sublingual immunotherapy (SLIT)-tablets. †12 trials evaluated more than one medication included in the analysis. RDBPC, randomised, double-blind placebo-controlled.

the dose used for the meta-analyses.

Risk of bias and heterogeneity assessment

Potential biases in the individual studies were assessed by the Cochrane Risk of Bias tool by EPS [11]. Modifications and definitions for subjective assessment of the bias domains (ie, attrition bias, etc.) were followed as described by Liu et al. [12]. Bias in each category was assigned as "low", "probably no", or "probably yes". Publication biases across trials for each treatment class were assessed visually by funnel plots and statistically by Egger's test. Heterogeneity among the pooled trials was assessed by I^2 and the Cochran's Q-test. Additional details for assessment of publication bias and heterogeneity are described in the Supplemental Material.

Data synthesis

Trials were categorized into assessment of therapy for adult/adolescent SAR, adult/adolescent PAR, pediatric SAR, and pediatric PAR groups. Adult/adolescent trials were defined as those that included subjects aged 12 years and older. In the few trials that included both children and adults, the results were analyzed in the adult/adolescent group. The main outcome evaluated in each meta-analysis was the mean numerical difference in average daily sum TNSS between placebo and active treatment at the end of the primary assessment period. Particularly in the pharmacotherapy trials, TNSS was often reported as change from baseline, in which case the final score at the end of the assessment period was calculated using baseline data. All TNSS data were converted to reflect the average daily sum on a scale of 0 to 12. When trials reported TNSS scores that could not be converted to the 0 to 12 scale, there was an attempt to obtain usable data from the corresponding authors. If usable data were not obtained, the trial was excluded. When standard deviations were not reported, a hierarchy of methods for imputation was used in line with published best practices (see Supplemental Material).

Meta-analyses were conducted using fixed effects and random effects modeling. The overall effect size and corresponding 95% CI for each of the pharmacotherapy classes and SLIT-tablets in the adult/adolescent SAR, adult/adolescent PAR, pediatric SAR, and pediatric PAR categories were calculated. Heterogeneity tests indicated significant heterogeneity among the trials within the treatment classes. Thus, only the results of the random effects modeling are reported. Random-effects meta-analyses estimated the mean difference for each medication group weighted by the inverse of the trial variance. Cook's test was conducted to identify trials that heavily influenced the analysis results. Sensitivity analyses removing the heavy-influencing trials did not notably alter the effect sizes. Meta-analyses were performed using R Studio Version 1.0.136 and the Metafor package version 1.9-7.

AIT trials allow the use of rescue symptom-relieving pharmacotherapy in both active and placebo groups, which leads to lower symptoms scores in placebo than would be expected with a true placebo. To address this issue, reporting the impact on symptoms (with or without medication scores) as the percentage improvement relative to placebo is advocated by professional allergy societies and AIT experts [13, 14]. In an effort to put the results into a context that more closely matches typical SLIT-tablet trial reporting, the percentage relative improvement versus placebo was calculated for each treatment class by dividing the meta-analytic weighted treatment difference by the placebo TNSS ([active treatment-placebo]/placebo) x 100%).

Results

From the pharmacotherapy searches, 774 records were screened and 461 records were excluded before full-text review. Of the 313 full-texts reviewed, 88 records were ultimately used for data extraction (Figure 1A). For the SLIT-tablet searches, 593 records were screened and 555 records were excluded before full-text review. Of the 38 full-texts reviewed, 9 records were used for data extraction (Figure 1B). The primary reason for record exclusion in all therapy classes was insufficient reporting of usable TNSS data. The greatest number of eligible trials were in the INCS medication class (Table 1). Characteristics of the trials used in the meta-analysis are shown in Supplemental Tables E2- E5.

Treatment effects for adult/adolescent SAR

All treatment classes demonstrated a significant improvement in nasal symptoms associated with adult/adolescent SAR vs placebo (Table 1). Forest plots for each medication class show that

Table 1. Treatment effects of pharmacotherapies and allergy immunotherapies for adult/adolescent SAR, adult/adolescent PAR, pediatric SAR, and pediatric PAR.

Adult/adolescent SAR	INCS	Oral antihistamine	Intranasal antihistamine	Montelukast	Combo antihistamine/ decongestant	Combo intranasal antihistamine/INCS	SLIT-tablets
Number of trials	39	18	13	10	1	4	4
Number of subjects	10,456	6774	5034	5091	274	2009	2965
Active TNSS EOT, mean	5.20	6.10	7.01	6.76	4.16	6.66	1.95
Placebo TNSS EOT, mean	6.58	6.73	7.73	7.24	5.52	8.00	2.52
Mean numerical EOT difference (95% CI)	1.38 (1.18, 1.58)	0.62 (0.35, 0.90)	0.72 (0.56, 0.89)	0.48 (0.36, 0.60)	1.36 (0.69, 2.03)	1.34 (1.15, 1.54)	0.57 (0.41, 0.73)
Improvement vs placebo, % (range)	26.5% (5.8%, 66.7%	10.2% (-5.4%, 31.9%)	9.3% (4.5%, 19.3%)	6.6% (3.1%, 25.4%)	24.6%	16.8% (15.2%, 20.0%)	22.7% (14.8%, 26.1%)
Adult/adolescent PAR	**INCS**	**Oral antihistamine**	**Intranasal antihistamine**	**Montelukast**	**Combo antihistamine /decongestant**	**Combo intranasal antihistamine /INCS**	**SLIT-tablets**
Number of trials	14	3	0	1	0	0	3
Number of subjects	5073	2049	0	1992	0	0	2771
Active TNSS EOT, mean	5.24	5.82	-	6.68	-	-	3.27
Placebo TNSS EOT, mean	6.06	6.08	-	7.00	-	-	3.92
Mean numerical EOT difference (95% CI)	0.82 (0.66, 0.97)	0.27 (0.11, 0.42)	-	0.32 (0.14, 0.50)	-	-	0.65 (0.42, 0.88)
Improvement vs placebo, % (range)	13.5% (8.9%, 35.9%)	4.4% (1.9%, 6.5%)	-	4.6%	-	-	16.6% (15.5%, 18.5%)
Ped SAR	**INCS**	**Oral antihistamine**	**Intranasal antihistamine**	**Montelukast**	**Combo antihistamine / decongestant**	**Combo intranasal antihistamine /INCS**	**SLIT-tablets**
Number of trials	5	0	1	1	0	1	2
Number of subjects	1157	0	944	57	0	304	519
Active TNSS EOT, mean	5.83	-	6.70	4.32	-	7.35	2.30
Placebo TNSS EOT, mean	6.55	-	7.20	5.88	-	7.55	2.84
Mean numerical EOT difference (95% CI)	0.72 (0.44, 1.00)	-	0.50 (0.22, 0.78)	1.56 (0.12, 3.00)	-	0.20 (-0.28, 0.68)	0.53 (0.19, 0.87)
Improvement vs placebo, % (range)	11.0% (8.9%, 18.5%)	-	6.9%	26.5%	-	2.6%	19.8% (16.4%, 23.1%)
Ped PAR	**INCS**	**Oral antihistamine**	**Intranasal antihistamine**	**Montelukast**	**Combo antihistamine /decongestant**	**Combo intranasal antihistamine /INCS**	**SLIT-tablets**
Number of trials	5	0	0	0	0	0	0
Number of subjects	1967	0	0	0	0	0	0
Active TNSS EOT, mean	4.88	-	-	-	-	-	-
Placebo TNSS EOT, mean	5.50	-	-	-	-	-	-
Mean numerical EOT difference (95% CI)	0.62 (0.41, 0.83)	-	-	-	-	-	-
Improvement vs placebo, % (range)	11.2% (7.3%, 25.0%)	-	-	-	-	-	-

EOT, end of treatment; INCS, intranasal corticosteroids; PAR, perennial allergic rhinitis; SAR, seasonal allergic rhinitis; SLIT, sublingual immunotherapy; TNSS, total nasal symptom score.

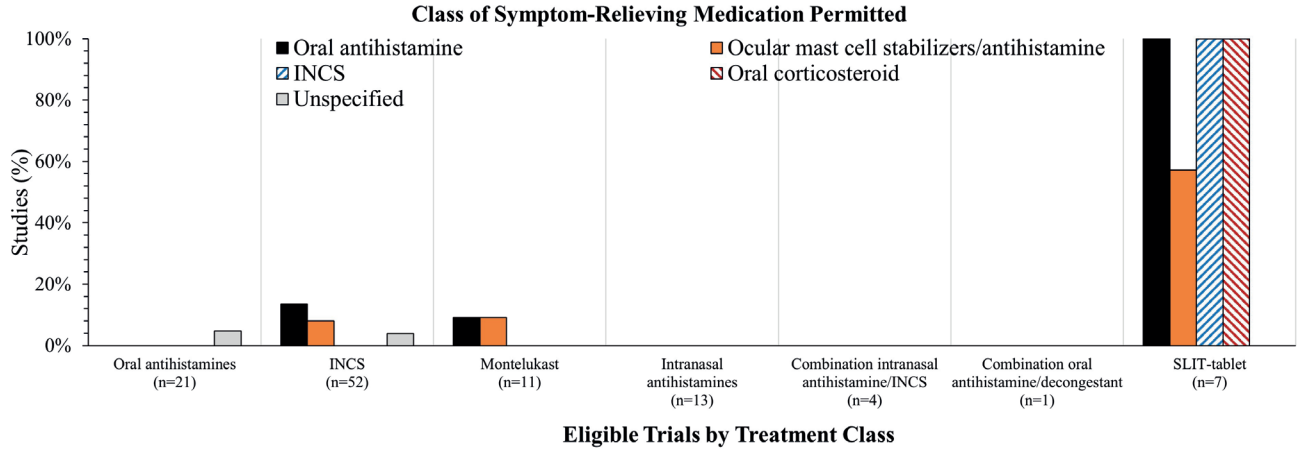


Figure 2. Proportion of all eligible trials (adult/adolescent and pediatric) addressing seasonal and perennial allergic rhinitis with trial designs permitting the use of symptom-relieving medication. Allowed use of symptom-relieving medication was undocumented in 19 of the pharmacotherapy trials.

most individual trials demonstrated a significant improvement in TNSS with active treatment versus placebo (see Supplemental Figures E1A-F) [15-79]. The mean difference in TNSS versus placebo (95% CI) in the analyzed medication classes was: INCS=1.38 (1.18, 1.58); combination intranasal antihistamine/INCS=1.34 (1.15, 1.54); intranasal antihistamines=0.72 (0.56, 0.89); oral antihistamines=0.62 (0.35, 0.90); SLIT-tablets=0.57 (0.41, 0.73); and montelukast=0.48 (0.36, 0.60). Although excluded from the meta-analysis, in the one eligible trial for combination oral antihistamine/decongestant, the mean difference (95% CI) in TNSS versus placebo was 1.36 (0.69, 2.03) [80].

Rescue symptom-relieving pharmacotherapy use was allowed in active and placebo groups in 8 of the 72 pharmacotherapy trials for adult SAR that reported this information (undocumented in 13 pharmacotherapy trials) and all of the SLIT-tablet trials (Supplemental Tables E2 and E4).

Treatment effects for adult/adolescent PAR

All treatment classes demonstrated a significant improvement in nasal symptoms associated with adult/adolescent PAR vs placebo (Table 1). The treatment effect of the pharmacotherapies on nasal symptoms appears to be less for adult/adolescent PAR compared with SAR (Table 1). Forest plots for each medication class show that most individual trials demonstrated a significant improvement in TNSS with active treatment versus placebo (see Supplemental Figures E2A-C) [81-103]. The mean difference in TNSS versus placebo (95% CI) was: INCS=0.82 (0.66, 0.97; 14 trials); SLIT-tablets=0.65 (0.42, 0.88; 3 trials); and oral antihistamines=0.27 (0.11, 0.42; 3 trials). Although excluded from the meta-analysis, in the one eligible trial for montelukast, the mean difference (95% CI) in TNSS versus placebo was 0.32 (0.14, 0.50) [104]. There were no eligible trials of intranasal antihistamines, combination intranasal antihistamines/INCS, or combination oral antihistamine/decongestant identified for adult/adolescent PAR.

Rescue symptom-relieving pharmacotherapy use was allowed in active and placebo groups in 3 of the 14 pharmacotherapy trials for adult/adolescent PAR that reported this information (undocumented in 4 pharmacotherapy trials) and all of the SLIT-tablet trials (Supplemental Tables E2 and E4).

Treatment effects for pediatric SAR and PAR

The number of pediatric SAR and PAR trials eligible for meta-analyses was limited. For pediatric SAR there were 5 INCS trials and 2 SLIT-tablet trials identified (Table 1) [105-111]. Three of the 5 INCS trials had 95% CI for the mean difference that crossed zero, indicating the treatment difference was not significant from placebo (Supplemental Figure E3A). Forest plots for the 2 pediatric SAR SLIT-tablet trials show that both trials demonstrated a significant improvement in TNSS with active treatment versus placebo (Supplemental Figure E3B). The overall mean difference in TNSS versus placebo (95% CI) for INCS was 0.72 (0.44, 1.00) and for SLIT-tablets was 0.53 (0.19, 0.87). The mean differences (95% CI) in TNSS versus placebo in the one eligible trial each for intranasal antihistamine and combination intranasal antihistamine/INCS for pediatric SAR were 0.50 (0.22, 0.78) and 0.20 (−0.28, 0.68), respectively [112, 113]. For the one identified eligible trial of montelukast for pediatric SAR [114], the small sample size (n=57), unusually low placebo effect, and large 95% CI makes the TNSS mean difference of 1.56 (95% CI, 0.12, 3.00) very questionable, especially when compared with the findings in all other montelukast studies as reported above.

For pediatric PAR, the only eligible trials identified were 5 INCS trials (Table 1) [115-119]. Two of these 5 INCS trials had 95% CI for

the mean difference that crossed zero, indicating the treatment difference was not significant from placebo (Supplemental Figure E3C). However, the overall mean difference in TNSS versus placebo (95% CI) for INCS was 0.62 (0.41, 0.83).
Symptom-relieving pharmacotherapy use was allowed in active and placebo groups in 3 of the 7 pharmacotherapy pediatric SAR trials and 3 of the 4 pediatric PAR trials that reported this information (undocumented in 1 pharmacotherapy pediatric SAR trial and 1 pediatric PAR trial) (Supplemental Tables E3 and E5). Symptom-relieving pharmacotherapy use was allowed in active and placebo groups in both of the SLIT-tablet pediatric SAR trials.

Percentage relative improvement versus placebo

Using the percentage relative improvement in TNSS versus placebo resulted in a different pattern of efficacy ranking than the pattern observed when comparing mean numerical differences (Table 1). SLIT-tablets demonstrated a similar percentage improvement to that of INCS. Pharmacotherapies assessed by differences in percentage improvement again appear to have less of a treatment effect in adult/adolescent PAR compared with adult/adolescent SAR (Table 1).

Bias and heterogeneity assessment

Selection and performance bias were considered "probably yes" for a large number of the trials. This potential bias was primarily due to lack of reporting for specific randomization and blinding procedures.
There was considerable heterogeneity among trials in disease severity, trial duration, and symptom-relieving medication use (Figure 2). Based on the I^2 value and Q-tests, the INCS and oral antihistamine adult/adolescent SAR trials exhibited significant and high heterogeneity; intranasal antihistamine adult/adolescent SAR trials exhibited significant and medium heterogeneity. Because of the limited sample size, it is likely that the Q-tests were underpowered for most of the other analyses.
A significant publication bias based on the Egger's test was noted for the INCS and intranasal antihistamine adult/adolescent SAR trials and for the INCS adult/adolescent PAR trials. Funnel plots for INCS and oral antihistamines in adult/adolescent trials indicate a strong tendency toward publication of trials with positive outcomes (see Supplemental Figures E4A-D). As with the heterogeneity tests, the Egger's test was likely underpowered for most of the other analyses that had small sample sizes (<10 trials).

Discussion

These meta-analyses were conducted to systematically evaluate the efficacy of pharmacotherapy and SLIT-tablets versus placebo in the treatment of adult/adolescent and pediatric SAR and PAR, using the most widely reported endpoint, the TNSS (a score based on self-reported nasal symptoms). Despite extensive, careful analyses, the results were not sufficient to make definitive comparative efficacy conclusions among AR treatment classes, emphasizing the need for direct head-to-head trials. In general, all the treatment classes analyzed resulted in a significant improvement in nasal symptoms versus placebo for adult/adolescent SAR and adult/adolescent PAR. The largest improvement in TNSS for any pharmacotherapy was observed with INCS used alone or in combination with intranasal antihistamines. SLIT-tablets also provided clinically meaningful improvements in TNSS despite concomitant rescue symptom-relieving medication use, which was permitted in all SLIT-tablet trials. Although this is the first meta-analyses that has attempted to compare AR pharmacotherapies for SAR and PAR in both adult/adolescent and pediatric populations, the number of eligible trials limited the ability to conduct meta-analyses for pediatric SAR and PAR.
Two other meta-analyses have previously compared pharmacotherapies and SLIT-tablets for SAR, but these previous meta-analyses had some limitations. A meta-analysis by Devillier et al. [8], examined effect sizes with INCS, oral antihistamines, montelukast, and combination intranasal antihistamine/INCS and grass SLIT-tablets, for SAR, but did not make a distinction in their analysis between total symptom scores that contained ocular symptoms and total nasal symptom scores. A meta-analysis by Durham et al. [9], examined TNSS effect sizes with INCS, oral antihistamine, and montelukast and SLIT-tablets for adult SAR and PAR, but the analyzed trials were limited to a single manufacturer and one specific formulation within each pharmacotherapy class (e.g., mometasone furoate and desloratadine). Neither of the previous meta-analyses evaluated the treatment effect on children specifically.
TNSS was selected as the primary endpoint for these meta-analyses although the TNSS for AR trials has never been standardized or validated. Nevertheless, TNSS is the endpoint recommended by the FDA and other regulatory agencies for AR trials and an initial feasibility review revealed that TNSS was the most commonly reported primary endpoint in pharmacotherapy trials. The TNSS was also available in many of the SLIT-tablet trials. In the SLIT-tablet trials, the TNSS was most often reported as an individual component of the combined symptom and medication score. The combined symptom and medication score is considered a more recent and clinically meaningful endpoint from the perspective of the FDA and other regulatory agencies and is the most commonly reported endpoint in SLIT-tablet trials. However, it is not an endpoint that is used in pharmacotherapy trials, thus, TNSS was chosen as the best outcome for these meta-analyses. A major limitation of these meta-analyses was the number of trials ineligible for inclusion because of insufficient TNSS reporting. To be eligible for the meta-analyses, the TNSS had to be reported in such a way that actual scores at the end of the primary assessment period could be directly

used or calculated, not simply in a graph without numeric labels or values in the text. The largest number of eligible trials for the meta-analyses were for adult/adolescent SAR. The lack of eligible trials made meta-analyses among treatment classes underpowered for adult/adolescent PAR, and few analyses were able to be conducted for pediatric SAR and PAR. Comparisons of treatment effects across a small number of trials may be impacted by low power, and the conclusions drawn from these comparisons may be subject to misinterpretation.

Most of the pharmacotherapy trials eligible for the current meta-analyses reported TNSS as a change from baseline. Because of the nature of SLIT-tablet trial design, baseline TNSS was not available for seasonal SLIT-tablet trials. Therefore, TNSS at end of assessment was the only feasible time point. The pharmacotherapy trials that only reported a change from baseline required a calculation using baseline values to convert to the primary measure of TNSS at end of assessment. Thus, a "basement effect" may also impact comparisons versus placebo among the treatment classes. This is best illustrated in the results for the combination intranasal antihistamine/INCS trials versus the INCS trials. The percentage improvement relative to placebo was only 16.8% with combination treatment compared with 26.5% for INCS alone. This result is contrary to what is expected since the individual combination treatment trials showed a significantly better effect on TNSS symptoms versus INCS monotherapy controls [46, 47]. The average baseline TNSS scores in the combination treatment were approximately 1.5 points (out of max of 12) higher than the average baseline in the INCS trials. As a theoretical exercise, when the end of treatment TNSS scores for the combination trials were recalculated using the average baseline scores from the INCS trials, the percentage improvement with combination treatment increased to 22%, indicating a basement effect. On the other hand, low placebo TNSS scores, as seen in the SLIT-tablet trials, create a "ceiling effect" in which there is little room to demonstrate improvement.

The substantial difference in the permitted use of rescue symptom-relieving medication between pharmacotherapy and SLIT-tablet trials for subjects receiving active treatment or placebo is one of the largest potential sources of confounding when comparing SLIT-tablet treatment effects versus pharmacotherapy. As a result of rescue symptom-relieving medication use, reported symptom responses in both active and placebo groups may be lower, masking differences between the groups. To address this issue, SLIT-tablet trials usually report the impact on symptoms (with or without medication scores) as the percentage improvement relative to placebo (aka, the relative clinical impact [RCI]). When using the percentage improvement relative to placebo in the current meta-analyses, the pattern of efficacy for adult/adolescent SAR changed from the pattern observed with the mean numerical difference. This may explain the conflicting results for the effect of SLIT-tablets for adult/adolescent SAR, which is notably lower than INCS based on mean numerical difference (0.57 vs 1.38) but is comparable with INCS when based on percentage change relative to placebo (22.7% vs 26.5%).

Significant heterogeneity was detected for the INCS, oral antihistamine, and intranasal antihistamine adult/adolescent SAR trials. Heterogeneity between pharmacotherapy and SLIT-tablet trials in regards to trial duration, population disease severity, and allowed rescue symptom-relieving medication use was acknowledged in both the previous meta-analyses [8, 9]. Some of the heterogeneity among trials in the current analyses could potentially have been addressed by conducting subgroup analyses of trials with similar trial durations or that treated the same allergen, etc. However, the overall small numbers of eligible identified trials for most of the treatment classes would preclude any meaningful analysis for most subgroups.

Publication bias is a well-known confounder and can lead to overestimation of a drug's efficacy. Funnel plots indicated significant publication bias towards trials with positive outcomes for INCS and oral antihistamines in adults/adolescents but were underpowered for those analyses that had less than 10 trials.

Lastly, these analyses were limited to pharmacotherapies approved and available in the US. Other pharmacotherapies are available in other countries. A meta-analysis of SCIT trials compared with pharmacotherapy would be of interest, however, there is substantial heterogeneity among the SCIT trials and most are relatively small (<150 patients total) compared with the large populations evaluated in the SLIT-tablet trials. Thus, meta-analyses of SCIT trials compared with pharmacotherapy would have even more limitations than the current analyses; the current analyses were therefore limited to SLIT-tablets.

Conclusion

In summary, all treatments significantly improved nasal symptoms versus placebo for adult/adolescent SAR and adult/adolescent PAR. Analyses of treatments for pediatric SAR and PAR were limited by the small number of eligible trials and additional well controlled trials in this population are needed. Major limitations including, but not limited to, high heterogeneity within each treatment class, differential use of rescue symptom-relieving medication between treatment classes, and strong evidence of publication bias do not permit indirect comparisons among treatment classes. The value of future meta-analyses comparing effects of different treatments for SAR and PAR are questionable in the absence of well-designed head-to-head trials. The lack of comparative efficacy information among treatment classes emphasizes the importance of shared decision making in the management of AR.

Acknowledgements

Medical writing and editorial assistance were provided by Erin P. Scott, PhD, of Scott Medical Communications, LLC. This assis-

tance was supported by ALK-Abelló, Hørsholm, Denmark.

Authorship contribution

All authors contributed to the development of the selection criteria, search strategy, and outcomes assessment. EPS designed and conducted the searches and data extraction and wrote the first draft of the manuscript. EOM, DW, and HN provided clinical expertise. PN and HF provided statistical expertise and conducted the statistical analyses. All authors provided critical review of the manuscript and approved for submission for publication.

Conflict of interest

E.O. Meltzer has served as a consultant or speaker for ALK-Abelló, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, GossamerBio, Merck, Mylan, Optinose and Sanofi/Regeneron. D. Wallace has served as consultant or speaker for ALK-Abelló, Sanofi/Regeneron, OpiNose, Mylan, and Kaleo. H.S. Friedman and P. Navaratnam are employees of DataMed Solutions, LLC, which provides consulting services to ALK-Abelló, Hørsholm, Denmark. E.P. Scott is an employee of Scott Medical Communications, LLC, which provides medical writing services to ALK-Abelló, Hørsholm, Denmark. H. Nolte is an employee of ALK-Abelló.

Financial disclosure

These meta-analyses were funded by ALK-Abelló, Hørsholm, Denmark. The sponsor (ALK-Abelló) provided clinical expertise in the development of the protocol, interpretation of the data, and was involved in development of the report. All authors agreed to submission of the report for publication.

References

1. Bousquet PJ, Demoly P, Devillier P, Mesbah K, Bousquet J. Impact of allergic rhinitis symptoms on quality of life in primary care. Int Arch Allergy Immunol. 2013; 160: 393-400.
2. Meltzer EO, Farrar JR, Sennett C. Findings from an Online Survey Assessing the Burden and Management of Seasonal Allergic Rhinoconjunctivitis in US Patients. J Allergy Clin Immunol Pract. 2017; 5: 779-89 e6.
3. Bielory L, Skoner DP, Blaiss MS, et al. Ocular and nasal allergy symptom burden in America: the Allergies, Immunotherapy, and RhinoconjunctivitiS (AIRS) surveys. Allergy Asthma Proc. 2014; 35: 211-8.
4. Meltzer EO, Nathan R, Derebery J, et al. Sleep, quality of life, and productivity impact of nasal symptoms in the United States: findings from the Burden of Rhinitis in America survey. Allergy Asthma Proc. 2009; 30: 244-54.
5. Bousquet J, Khaltaev N, Cruz AA, et al. Allergic Rhinitis and Its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). Allergy. 2008; 63: 8-160.
6. Brożek JL, Bousquet J, Agache I, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines-2016 revision. J Allergy Clin Immunol. 2017; 140: 950-8.
7. Wise SK, Lin SY, Toskala E, et al. International Consensus Statement on Allergy and Rhinology: Allergic Rhinitis. Int Forum Allergy Rhinol. 2018; 8: 108-352.
8. Devillier P, Dreyfus JF, Demoly P, Calderon MA. A meta-analysis of sublingual allergen immunotherapy and pharmacotherapy in pollen-induced seasonal allergic rhinoconjunctivitis. BMC Med. 2014; 12: 71.
9. Durham SR, Creticos PS, Nelson HS, et al. Treatment Effect of Sublingual Immunotherapy Tablets and Pharmacotherapies for Seasonal and Perennial Allergic Rhinitis: Pooled Analyses. J Allergy Clin Immunol. 2016; 138: 1081-8.
10. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009; 6: e1000097.
11. The Cochrane Collaboration's tool for assessing risk of bias. In: Higgins J, Green Se, editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5102011.
12. Liu G, Zhou X, Chen J, Liu F. Oral Antihistamines Alone vs in Combination with Leukotriene Receptor Antagonists for Allergic Rhinitis: A Meta-analysis. Otolaryngol Head Neck Surg. 2018; 158: 450-8.
13. Bousquet J, Schunemann HJ, Bousquet PJ, et al. How to design and evaluate randomized controlled trials in immunotherapy for allergic rhinitis: an ARIA-GA(2) LEN statement. Allergy. 2011; 66: 765-74.
14. Nelson HS, Calderon MA, Bernstein DI, et al. Allergen Immunotherapy Clinical Trial Outcomes and Design: Working Toward Harmonization of Methods and Principles. Curr Allergy Asthma Rep. 2017; 17: 18.
15. Andrews CP, Martin BG, Jacobs RL, et al. Fluticasone furoate nasal spray is more effective than fexofenadine for nighttime symptoms of seasonal allergy. Allergy Asthma Proc. 2009; 30: 128-38.
16. Bronsky EA, Aaronson DW, Berkowitz RB, et al. Dose ranging study of mometasone furoate (Nasonex) in seasonal allergic rhinitis. Ann Allergy Asthma Immunol. 1997; 79: 51-6.
17. Bronsky EA, Dockhorn RJ, Meltzer EO, et al. Fluticasone propionate aqueous nasal spray compared with terfenadine tablets in the treatment of seasonal allergic rhinitis. J Allergy Clin Immunol. 1996; 97: 915-21.
18. Creticos P, Fireman P, Settipane G, Bernstein D, Casale T, Schwartz H. Intranasal budesonide aqueous pump spray (Rhinocort Aqua) for the treatment of seasonal allergic rhinitis. Rhinocort Aqua Study Group. Allergy Asthma Proc. 1998; 19: 285-94.
19. Di Lorenzo G, Gervasi F, Drago A, et al. Comparison of the effects of fluticasone propionate, aqueous nasal spray and levocabastine on inflammatory cells in nasal lavage and clinical activity during the pollen season in seasonal rhinitics. Clin Exp Allergy. 1999; 29: 1367-77.
20. Di Lorenzo G, Pacor ML, Pellitteri ME, et al. Randomized placebo-controlled trial comparing fluticasone aqueous nasal spray in mono-therapy, fluticasone plus cetirizine, fluticasone plus montelukast and cetirizine plus montelukast for seasonal allergic rhinitis. Clin Exp Allergy. 2004; 34: 259-67.
21. Dykewicz MS, Kaiser HB, Nathan RA, et al. Fluticasone propionate aqueous nasal spray improves nasal symptoms of seasonal allergic rhinitis when used as needed (prn). Ann Allergy Asthma Immunol. 2003; 91: 44-8.
22. Findlay S, Huber F, Garcia J, Huang L. Efficacy of once-a-day intranasal administration of triamcinolone acetonide in patients with seasonal allergic rhinitis. Ann Allergy. 1992; 68: 228-32.
23. Fokkens WJ, Jogi R, Reinartz S, et al. Once daily fluticasone furoate nasal spray is effective in seasonal allergic rhinitis caused by grass pollen. Allergy. 2007; 62: 1078-84.
24. Ford LB, Matz J, Hankinson T, Prillaman B, Georges G. A comparison of fluticasone propionate nasal spray and cetirizine in ragweed fall seasonal allergic rhinitis. Allergy Asthma Proc. 2015; 36: 313-9.
25. Graft D, Aaronson D, Chervinsky P, et al. A placebo- and active-controlled randomized trial of prophylactic treatment of seasonal allergic rhinitis with mometasone furoate aqueous nasal spray. J Allergy Clin Immunol. 1996; 98: 724-31.
26. Jacobs R, Martin B, Hampel F, Toler W, Ellsworth A, Philpot E. Effectiveness of fluticasone furoate 110 microg once daily in the treatment of nasal and ocular symptoms of seasonal allergic rhinitis in adults and adolescents sensitized to mountain cedar pollen. Curr Med Res Opin. 2009; 25: 1393-401.
27. Kaiser HB, Naclerio RM, Given J, Toler TN, Ellsworth A, Philpot EE. Fluticasone furoate

nasal spray: a single treatment option for the symptoms of seasonal allergic rhinitis. J Allergy Clin Immunol. 2007; 119: 1430-7.
28. Mansfield LE, Posey CR. Daytime sleepiness and cognitive performance improve in seasonal allergic rhinitis treated with intranasal fluticasone propionate. Allergy Asthma Proc. 2007; 28: 226-9.
29. Martin BG, Ratner PH, Hampel FC, et al. Optimal dose selection of fluticasone furoate nasal spray for the treatment of seasonal allergic rhinitis in adults and adolescents. Allergy Asthma Proc. 2007; 28: 216-25.
30. Meltzer EO, Jalowayski AA, Orgel HA, Harris AG. Subjective and objective assessments in patients with seasonal allergic rhinitis: effects of therapy with mometasone furoate nasal spray. J Allergy Clin Immunol. 1998; 102: 39-49.
31. Meltzer EO, Shekar T, Teper AA. Mometasone furoate nasal spray for moderate-to-severe nasal congestion in subjects with seasonal allergic rhinitis. Allergy Asthma Proc. 2011; 32: 159-67.
32. Munk ZM, Gross GN, Hampel FC, Jr., Ratner PH. Preseasonal, once daily triamcinolone acetonide nasal aerosol for seasonal allergic rhinitis. Ann Allergy Asthma Immunol. 1997; 78: 325-31.
33. Munk ZM, LaForce C, Furst JA, Simpson B, Feiss G, Smith JA. Efficacy and safety of triamcinolone acetonide aqueous nasal spray in patients with seasonal allergic rhinitis. Ann Allergy Asthma Immunol. 1996; 77: 277-81.
34. Okubo K, Nakashima M, Miyake N, Komatsubara M, Okuda M. Comparison of fluticasone furoate and fluticasone propionate for the treatment of Japanese cedar pollinosis. Allergy Asthma Proc. 2009; 30: 84-94.
35. Prenner BM, Lanier BQ, Bernstein DI, Shekar T, Teper A. Mometasone furoate nasal spray reduces the ocular symptoms of seasonal allergic rhinitis. J Allergy Clin Immunol. 2010; 125: 1247-53.e5.
36. Raphael GD, Berger WE, Prenner BM, Finn AF, Jr., Kelley L, Tantry SK. Efficacy, safety, and optimal dose selection of beclomethasone dipropionate nasal aerosol for seasonal allergic rhinitis in adolescents and adults. Curr Med Res Opin. 2013; 29: 1329-40.
37. Ratner PH, van Bavel JH, Martin BG, et al. A comparison of the efficacy of fluticasone propionate aqueous nasal spray and loratadine, alone and in combination, for the treatment of seasonal allergic rhinitis. J Fam Pract. 1998; 47: 118-25.
38. Ratner PH, Wingertzahn MA, van Bavel JH, Hampel F, Darken PF, Shah T. Efficacy and safety of ciclesonide nasal spray for the treatment of seasonal allergic rhinitis. J Allergy Clin Immunol. 2006; 118: 1142-8.
39. Rosenthal R, Berger W, Bronsky E, et al. Tri-Nasal triamcinolone acetonide nasal spray 200 and 400 micrograms qd versus placebo and Nasacort triamcinolone acetonide nasal aerosol 440 micrograms qd in patients suffering from seasonal allergic rhinitis during the grass season. Am J Rhinol. 1998; 12: 427-33.
40. Schenkel E, Newman KB. Therapeutic equivalence of triamcinolone acetonide hydrofluoroalkane and chlorofluorocarbon nasal inhalers in patients with seasonal allergic rhinitis. Am J Rhinol Allergy. 2013; 27: 109-12.
41. Steensen H, Lindqvist N. Treatment of grass pollen-induced hay fever with intranasal budesonide. A double-blind clinical comparison between budesonide and placebo. Allergy. 1981; 36: 245-9.
42. Stern MA, Dahl R, Nielsen LP, Pedersen B, Schrewelius C. A comparison of aqueous suspensions of budesonide nasal spray (128 micrograms and 256 micrograms once daily) and fluticasone propionate nasal spray (200 micrograms once daily) in the treatment of adult patients with seasonal allergic rhinitis. Am J Rhinol. 1997; 11: 323-30.
43. Tinkelman D, Falliers C, Gross G, et al. Multicenter evaluation of triamcinolone acetonide nasal aerosol in the treatment of adult patients with seasonal allergic rhinitis. Ann Allergy. 1990; 64: 234-40.
44. van Bavel JH, Ratner PH, Amar NJ, et al. Efficacy and safety of once-daily treatment with beclomethasone dipropionate nasal aerosol in subjects with seasonal allergic rhinitis. Allergy Asthma Proc. 2012; 33: 386-96.
45. Anolik R. Clinical benefits of combination treatment with mometasone furoate nasal spray and loratadine vs monotherapy with mometasone furoate in the treatment of seasonal allergic rhinitis. Ann Allergy Asthma Immunol. 2008; 100: 264-71.
46. Carr W, Bernstein J, Lieberman P, et al. A novel intranasal therapy of azelastine with fluticasone for the treatment of allergic rhinitis. J Allergy Clin Immunol. 2012; 129: 1282-9.e10.
47. Hampel FC, Ratner PH, Van Bavel J, et al. Double-blind, placebo-controlled study of azelastine and fluticasone in a single nasal spray delivery device. Ann Allergy Asthma Immunol. 2010; 105: 168-73.
48. Pullerits T, Praks L, Ristioja V, Lotvall J. Comparison of a nasal glucocorticoid, antileukotriene, and a combination of antileukotriene and antihistamine in the treatment of seasonal allergic rhinitis. J Allergy Clin Immunol. 2002; 109: 949-55.
49. Berger WE, White MV. Efficacy of azelastine nasal spray in patients with an unsatisfactory response to loratadine. Ann Allergy Asthma Immunol. 2003; 91: 205-11.
50. Demoly P, Dreyfus I, Dhivert-Donnadieu H, Mesbah K. Desloratadine for the treatment of cypress pollen-induced allergic rhinitis. Ann Allergy Asthma Immunol. 2009; 103: 260-6.
51. Dockhorn RJ, Bergner A, Connell JT, et al. Safety and efficacy of loratadine (Sch-29851): a new non-sedating antihistamine in seasonal allergic rhinitis. Ann Allergy. 1987; 58: 407-11.
52. Hampel F, Jr., Howland W, 3rd, Van Bavel J, Ratner P. A randomized, double-blind, placebo-controlled study comparing the efficacy and safety of ebastine (20 mg and 10 mg) to loratadine 10 mg once daily in the treatment of seasonal allergic rhinitis. J Investig Allergol Clin Immunol. 2004; 14: 56-63.
53. Kuna P, Bachert C, Nowacki Z, et al. Efficacy and safety of bilastine 20 mg compared with cetirizine 10 mg and placebo for the symptomatic treatment of seasonal allergic rhinitis: a randomized, double-blind, parallel-group study. Clin Exp Allergy. 2009; 39: 1338-47.
54. Lu S, Malice MP, Dass SB, Reiss TF. Clinical studies of combination montelukast and loratadine in patients with seasonal allergic rhinitis. J Asthma. 2009; 46: 878-83.
55. Meltzer EO, Malmstrom K, Lu S, et al. Concomitant montelukast and loratadine as treatment for seasonal allergic rhinitis: a randomized, placebo-controlled clinical trial. J Allergy Clin Immunol. 2000; 105: 917-22.
56. Pradalier A, Neukirch C, Dreyfus I, Devillier P. Desloratadine improves quality of life and symptom severity in patients with allergic rhinitis. Allergy. 2007; 62: 1331-4.
57. Skassa-Brociek W, Bousquet J, Montes F, et al. Double-blind placebo-controlled study of loratadine, mequitazine, and placebo in the symptomatic treatment of seasonal allergic rhinitis. J Allergy Clin Immunol. 1988; 81: 725-30.
58. Nayak AS, Philip G, Lu S, Malice MP, Reiss TF. Efficacy and tolerability of montelukast alone or in combination with loratadine in seasonal allergic rhinitis: a multicenter, randomized, double-blind, placebo-controlled trial performed in the fall. Ann Allergy Asthma Immunol. 2002; 88: 592-600.
59. Philip G, Malmstrom K, Hampel FC, et al. Montelukast for treating seasonal allergic rhinitis: a randomized, double-blind, placebo-controlled trial performed in the spring. Clin Exp Allergy. 2002; 32: 1020-8.
60. van Adelsberg J, Philip G, LaForce CF, et al. Randomized controlled trial evaluating the clinical benefit of montelukast for treating spring seasonal allergic rhinitis. Ann Allergy Asthma Immunol. 2003; 90: 214-22.
61. Bernstein JA, Prenner B, Ferguson BJ, Portnoy J, Wheeler WJ, Sacks HJ. Double-blind, placebo-controlled trial of reformulated azelastine nasal spray in patients with seasonal allergic rhinitis. Am J Rhinol Allergy. 2009; 23: 512-7.
62. Howland WC, Amar NJ, Wheeler W, Sacks H. Efficacy and safety of azelastine 0.15% nasal spray administered once daily in patients with allergy to Texas mountain cedar pollen. Int Forum Allergy Rhinol. 2011; 1: 275-9.
63. LaForce CF, Corren J, Wheeler WJ, Berger WE. Efficacy of azelastine nasal spray in seasonal allergic rhinitis patients who remain symptomatic after treatment with fexofena-

dine. Ann Allergy Asthma Immunol. 2004; 93: 154-9.
64. Lumry W, Prenner B, Corren J, Wheeler W. Efficacy and safety of azelastine nasal spray at a dose of 1 spray per nostril twice daily. Ann Allergy Asthma Immunol. 2007; 99: 267-72.
65. Shah S, Berger W, Lumry W, La Force C, Wheeler W, Sacks H. Efficacy and safety of azelastine 0.15% nasal spray and azelastine 0.10% nasal spray in patients with seasonal allergic rhinitis. Allergy Asthma Proc. 2009; 30: 628-33.
66. Shah SR, Nayak A, Ratner P, Roland P, Michael Wall G. Effects of olopatadine hydrochloride nasal spray 0.6% in the treatment of seasonal allergic rhinitis: a phase III, multicenter, randomized, double-blind, active- and placebo-controlled study in adolescents and adults. Clin Ther. 2009; 31: 99-107.
67. van Bavel J, Howland WC, Amar NJ, Wheeler W, Sacks H. Efficacy and safety of azelastine 0.15% nasal spray administered once daily in subjects with seasonal allergic rhinitis. Allergy Asthma Proc. 2009; 30: 512-8.
68. Okubo K, Baba K. Therapeutic effect of montelukast, a cysteinyl leukotriene receptor 1 antagonist, on Japanese patients with seasonal allergic rhinitis. Allergol Int. 2008; 57: 247-55.
69. Philip G, Nayak AS, Berger WE, et al. The effect of montelukast on rhinitis symptoms in patients with asthma and seasonal allergic rhinitis. Curr Med Res Opin. 2004; 20: 1549-58.
70. van Adelsberg J, Philip G, Pedinoff AJ, et al. Montelukast improves symptoms of seasonal allergic rhinitis over a 4-week treatment period. Allergy. 2003; 58: 1268-76.
71. Charpin D, Gouitaa M, Dron-Gonzalvez M, et al. Immunotherapy with an aluminum hydroxide-adsorbed Juniperus ashei foreign pollen extract in seasonal indigenous cypress pollen rhinoconjunctivitis. A double-blind, placebo-controlled study. Int Arch Allergy Immunol. 2007; 143: 83-91.
72. Ferrer M, Burches E, Pelaez A, et al. Double-blind, placebo-controlled study of immunotherapy with Parietaria judaica: clinical efficacy and tolerance. J Investig Allergol Clin Immunol. 2005; 15: 283-92.
73. Frew AJ, Powell RJ, Corrigan CJ, Durham SR. Efficacy and safety of specific immunotherapy with SQ allergen extract in treatment-resistant seasonal allergic rhinoconjunctivitis. J Allergy Clin Immunol. 2006; 117: 319-25.
74. Varney VA, Gaga M, Frew AJ, Aber VR, Kay AB, Durham SR. Usefulness of immunotherapy in patients with severe summer hay fever uncontrolled by antiallergic drugs. BMJ 1991; 302: 265-9.
75. Zenner HP, Baumgarten C, Rasp G, et al. Short-term immunotherapy: a prospective, randomized, double-blind, placebo-controlled multicenter study of molecular standardized grass and rye allergens in patients with grass pollen-induced allergic rhinitis. J Allergy Clin Immunol. 1997; 100: 23-9.
76. Creticos PS, Maloney J, Bernstein DI, et al. Randomized controlled trial of a ragweed allergy immunotherapy tablet in North American and European adults. J Allergy Clin Immunol. 2013; 131: 1342-9 e6.
77. Dahl R, Kapp A, Colombo G, et al. Efficacy and safety of sublingual immunotherapy with grass allergen tablets for seasonal allergic rhinoconjunctivitis. J Allergy Clin Immunol. 2006; 118: 434-40.
78. Maloney J, Bernstein DI, Nelson H, et al. Efficacy and safety of grass sublingual immunotherapy tablet, MK-7243: a large randomized controlled trial. Ann Allergy Asthma Immunol. 2014; 112: 146-53.e2.
79. Nelson HS, Nolte H, Creticos P, Maloney J, Wu J, Bernstein DI. Efficacy and safety of timothy grass allergy immunotherapy tablet treatment in North American adults. J Allergy Clin Immunol. 2011; 127: 72-80 e2.
80. Nathan RA, Finn AF, Jr., LaForce C, et al. Comparison of cetirizine-pseudoephedrine and placebo in patients with seasonal allergic rhinitis and concomitant mild-to-moderate asthma: randomized, double-blind study. Ann Allergy Asthma Immunol. 2006; 97: 389-96.
81. Bende M, Carrillo T, Vona I, da Castel-Branco MG, Arheden L. A randomized comparison of the effects of budesonide and mometasone furoate aqueous nasal sprays on nasal peak flow rate and symptoms in perennial allergic rhinitis. Ann Allergy Asthma Immunol. 2002; 88: 617-23.
82. Chervinsky P, Kunjibettu S, Miller DL, et al. Long-term safety and efficacy of intranasal ciclesonide in adult and adolescent patients with perennial allergic rhinitis. Ann Allergy Asthma Immunol. 2007; 99: 69-76.
83. Given JT, Cheema AS, Dreykluft T, et al. Fluticasone furoate nasal spray is effective and well tolerated for perennial allergic rhinitis in adolescents and adults. Am J Rhinol Allergy. 2010; 24: 444-50.
84. Kivisaari E, Baker RC, Price MJ. Comparison of once daily fluticasone propionate aqueous nasal spray with once daily budesonide reservoir powder device in patients with perennial rhinitis. Clin Exp Allergy. 2001; 31: 855-63.
85. Kobayashi RH, Beaucher WN, Koepke JW, et al. Triamcinolone acetonide aqueous nasal spray for the treatment of patients with perennial allergic rhinitis: a multicenter, randomized, double-blind, placebo-controlled study. Clin Ther. 1995; 17: 503-13.
86. Meltzer EO. Clinical and antiinflammatory effects of intranasal budesonide aqueous pump spray in the treatment of perennial allergic rhinitis. Ann Allergy Asthma Immunol. 1998; 81: 128-34.
87. Meltzer EO, Jacobs RL, LaForce CF, Kelley CL, Dunbar SA, Tantry SK. Safety and efficacy of once-daily treatment with beclomethasone dipropionate nasal aerosol in subjects with perennial allergic rhinitis. Allergy Asthma Proc. 2012; 33: 249-57.
88. Meltzer EO, Kunjibettu S, Hall N, et al. Efficacy and safety of ciclesonide, 200 microg once daily, for the treatment of perennial allergic rhinitis. Ann Allergy Asthma Immunol. 2007; 98: 175-81.
89. Mohar D, Berger WE, Laforce C, et al. Efficacy and tolerability study of ciclesonide nasal aerosol in patients with perennial allergic rhinitis. Allergy Asthma Proc. 2012; 33: 19-26.
90. Nathan RA, Berger W, Yang W, et al. Effect of once-daily fluticasone furoate nasal spray on nasal symptoms in adults and adolescents with perennial allergic rhinitis. Ann Allergy Asthma Immunol. 2008; 100: 497-505.
91. Spector S, Bronsky E, Chervinsky P, et al. Multicenter, double-blind, placebo-controlled trial of triamcinolone acetonide nasal aerosol in the treatment of perennial allergic rhinitis. Ann Allergy. 1990; 64: 300-5.
92. Vasar M, Houle PA, Douglass JA, et al. Fluticasone furoate nasal spray: effective monotherapy for symptoms of perennial allergic rhinitis in adults/adolescents. Allergy Asthma Proc. 2008; 29: 313-21.
93. Weinstein SF, Andrews CP, Shah SR, et al. Long-term efficacy and safety of once-daily treatment with beclomethasone dipropionate nasal aerosol. Allergy Asthma Proc. 2014; 35: 323-31.
94. Freche C, Leynadier F, Horak F, et al. Mizolastine provides effective symptom relief in patients suffering from perennial allergic rhinitis: a double-blind, placebo-controlled study versus loratadine. Ann Allergy Asthma Immunol. 2002; 89: 304-10.
95. Holmberg K, Tonnel AB, Dreyfus I, et al. Desloratadine relieves nasal congestion and improves quality-of-life in persistent allergic rhinitis. Allergy. 2009; 64: 1663-70.
96. Kim K, Sussman G, Hebert J, Lumry W, Lutsky B, Gates D. Desloratadine therapy for symptoms associated with perennial allergic rhinitis. Ann Allergy Asthma Immunol. 2006; 96: 460-5.
97. Garcia-Robaina JC, Sanchez I, de la Torre F, Fernandez-Caldas E, Casanovas M. Successful management of mite-allergic asthma with modified extracts of Dermatophagoides pteronyssinus and Dermatophagoides farinae in a double-blind, placebo-controlled study. J Allergy Clin Immunol. 2006; 118: 1026-32.
98. McHugh SM, Lavelle B, Kemeny DM, Patel S, Ewan PW. A placebo-controlled trial of immunotherapy with two extracts of Dermatophagoides pteronyssinus in allergic rhinitis, comparing clinical outcome with changes in antigen-specific IgE, IgG, and IgG subclasses. J Allergy Clin Immunol. 1990; 86: 521-31.
99. Riechelmann H, Schmutzhard J, van der Werf JF, Distler A, Kleinjans HA. Efficacy and safety of a glutaraldehyde-modified house dust mite extract in allergic rhinitis. Am J Rhinol Allergy. 2010; 24: e104-9.
100. Varney VA, Tabbah K, Mavroleon G, Frew AJ. Usefulness of specific immunotherapy in

patients with severe perennial allergic rhinitis induced by house dust mite: a double-blind, randomized, placebo-controlled trial. Clin Exp Allergy. 2003; 33: 1076-82.
101. Demoly P, Emminger W, Rehm D, Backer V, Tommerup L, Kleine-Tebbe J. Effective treatment of house dust mite-induced allergic rhinitis with 2 doses of the SQ HDM SLIT-tablet: Results from a randomized double-blind, placebo-controlled phase III trial. J Allergy Clin Immunol 2016; 137: 444-51.
102. Nolte H, Bernstein DI, Nelson HS, et al. Efficacy of house dust mite SLIT-tablet in North American adolescents and adults in a randomized, placebo-controlled trial. J Allergy Clin Immunol. 2016; 138: 1631-8.
103. Okubo K, Masuyama K, Imai T, et al. Efficacy and safety of the SQ house dust mite sublingual immunotherapy tablet in Japanese adults and adolescents with house dust mite-induced allergic rhinitis. J Allergy Clin Immunol. 2017; 139: 1840-8.e10.
104. Patel P, Philip G, Yang W, et al. Randomized, double-blind, placebo-controlled study of montelukast for treating perennial allergic rhinitis. Ann Allergy Asthma Immunol. 2005; 95: 551-7.
105. Agertoft L, Wolthers OD, Fuglsang G, Pedersen S. Nasal powder administration of budesonide for seasonal rhinitis in children and adolescents. Pediatr Allergy Immunol. 1993; 4: 152-6.
106. Banov CH, Silvers WS, Green AW, et al. Placebo-controlled, double-blind study of the efficacy and safety of triamcinolone acetonide aerosol nasal inhaler in pediatric patients with seasonal allergic rhinitis. Clin Ther. 1996; 18: 265-72.
107. Georges G, Kim KT, Ratner P, Segall N, Qiu C. Effect of intranasal triamcinolone acetonide on basal hypothalamic-pituitary-adrenal axis function in children with allergic rhinitis. Allergy Asthma Proc. 2014; 35: 163-70.
108. Meltzer EO, Lee J, Tripathy I, Lim J, Ellsworth A, Philpot E. Efficacy and safety of once-daily fluticasone furoate nasal spray in children with seasonal allergic rhinitis treated for 2 wk. Pediatr Allergy Immunol. 2009; 20: 279-86.
109. Storms WW, Segall N, Mansfield LE, et al. Efficacy and safety of beclomethasone dipropionate nasal aerosol in pediatric patients with seasonal allergic rhinitis. Ann Allergy Asthma Immunol. 2013; 111: 408-14.e1.
110. Bufe A, Eberle P, Franke-Beckmann E, et al. Safety and efficacy in children of an SQ-standardized grass allergen tablet for sublingual immunotherapy. J Allergy Clin Immunol. 2009; 123: 167-73 e7.
111. Halken S, Agertoft L, Seidenberg J, et al. Five-grass pollen 300IR SLIT tablets: efficacy and safety in children and adolescents. Pediatr Allergy Immunol. 2010; 21: 970-6.
112. Berger W, Meltzer EO, Amar N, et al. Efficacy of MP-AzeFlu in children with seasonal allergic rhinitis: Importance of paediatric symptom assessment. Pediatr Allergy Immunol. 2016; 27: 126-33.
113. Meltzer EO, Blaiss M, Fairchild CJ. Comprehensive report of olopatadine 0.6% nasal spray as treatment for children with seasonal allergic rhinitis. Allergy Asthma Proc. 2011; 32: 213-20.
114. Razi C, Bakirtas A, Harmanci K, Turktas I, Erbas D. Effect of montelukast on symptoms and exhaled nitric oxide levels in 7- to 14-year-old children with seasonal allergic rhinitis. Ann Allergy Asthma Immunol. 2006; 97: 767-74.
115. Baena-Cagnani CE, Patel P. Efficacy and long-term safety of mometasone furoate nasal spray in children with perennial allergic rhinitis. Curr Med Res Opin. 2010; 26: 2047-55.
116. Berger WE, Jacobs RL, Amar NJ, Tantry SK, Li J, Small CJ. Efficacy and safety of beclomethasone dipropionate nasal aerosol in children with perennial allergic rhinitis. Ann Allergy Asthma Immunol. 2015; 115: 130-6.
117. Fokkens WJ, Cserhati E, dos Santos JM, et al. Budesonide aqueous nasal spray is an effective treatment in children with perennial allergic rhinitis, with an onset of action within 12 hours. Ann Allergy Asthma Immunol. 2002; 89: 279-84.
118. Maspero JF, Rosenblut A, Finn A, Jr., Lim J, Wu W, Philpot E. Safety and efficacy of fluticasone furoate in pediatric patients with perennial allergic rhinitis. Otolaryngol Head Neck Surg. 2008; 138: 30-7.
119. Weinstein S, Qaqundah P, Georges G, Nayak A. Efficacy and safety of triamcinolone acetonide aqueous nasal spray in children aged 2 to 5 years with perennial allergic rhinitis: a randomized, double-blind, placebo-controlled study with an open-label extension. Ann Allergy Asthma Immunol. 2009; 102: 339-47.

Hendrik Nolte, MD, PhD
ALK
US Highway 135 Route 202/206
Bedminster NJ 07921
USA

Tel: (+1) 516 767 1800
E-mail: Hendrik.nolte@alk.net

This manuscript contains online supplementary material

SUPPLEMENTARY MATERIAL

Methods

Search strings used in database searches

The search string used to identify pharmacotherapy trials was: Allergic rhinitis[MeSH] AND (cetirizine[TIAB] OR loratadine[TIAB] OR desloratadine[TIAB] OR levocetirizine [TIAB] OR fexofenadine [TIAB] OR azelastine[TIAB] OR olopatadine[TIAB] OR Montelukast[TIAB] OR beclomethasone[TIAB] OR budesonide[TIAB] OR ciclesonide[TIAB] OR fluticasone[TIAB] OR mometasone[TIAB] OR triamcinolone[TIAB] OR pseudoephedrine[TIAB]) AND placebo[TIAB] NOT "review".
The search string used to identify SLIT-tablet trials was: (immunotherapy[MeSH] OR desensitization, immunologic[MeSH]) AND (allergic rhinitis[MeSH] OR rhinoconjunctivitis) AND placebo[TIAB] NOT "review".

Publication bias and heterogeneity assessment

Publication biases across trials for each treatment class were assessed visually by funnel plots depicting the mean numerical difference in TNSS for each trial between active treatment and placebo on the x-axis and the standard error on the y-axis. Symmetric funnels (centered around the estimated mean effect size from the meta-analysis model) were viewed as evidence that publication bias was unlikely, whereas asymmetric funnels indicated a potential relationship between the effect size estimate (x-axis) and study precision (y-axis). The Egger's test was used to statistically assess publication bias across trials, which requires a P >0.05 to reject the null hypothesis that the intercept is equal to zero in the population of studies being evaluated, indicating no publication bias. The Egger's test is sensitive to the number of studies being evaluated and requires that there be at least 10 trials in order to robustly indicate if publication bias exists [1].
An assessment of heterogeneity among the pooled trials was conducted. Both I^2 (the ratio of the total heterogeneity divided by the total variability) and the Cochran's Q-test were computed. Interpretation of the I^2 was guided by I^2 of <40%, 40%-60%, and >60%, representing low, medium, and high heterogeneity, respectively. A Q-test with a p-value <0.1 indicated high heterogeneity[1].

Imputation methods for standard deviations

When standard deviations (SD) were not reported in the trial publications for use in the meta-analysis, a hierarchy of methods for imputation was used.

Step 1: When there was sufficient information reported on the end of assessment values (p-values, t-stat, interquartile range [IQR], etc), then that information was used to compute the SD of the end of assessment directly by algebraic recalculation as previously described [2]. When algebraic recalculation was not possible, then approximation methods such as IQR were used. When algebraic recalculation or approximation methods were not possible and there was a sufficient number of studies to develop a sense for the distribution of the SD, then a prognostic method was used to impute the missing values [3].

Step 2: When there was insufficient information about the SD of the end of assessment values but there was sufficient information on the change from baseline, the hierarchy of methods in Step 1 was used to develop an estimate of the SD of the change from baseline for the active treatment and placebo.

Step 3: Then the estimated SD of the change from baseline for the active treatment and placebo was used to estimate the SD of the end of assessment values for active treatment and placebo based on the formula for error propagation previously described [2].

Change in active treatment (X) = End of Assessment active treatment (A) – Baseline Value active treatment (B)

$$Var(X)=Var(A)+Var(B) – corr*SD(A)SD(B)$$

The correlation was imputed from the other trials that had complete data.

Step 4: In situations where there was no information on the SD/var Baseline, an assumption was made that Var Baseline = Var End of Assessment. This resulted in:

$$Var\ (X) = Var\ (A)(2\text{-}corr)$$

$$SD\ (A) = sqrt(Var\ X/(2\text{-}corr))$$

Table E1. Doses evaluated based on US Food and Drug Administration-approval. Doses are total daily dose.

Product	Evaluated dose	
	Aged ≥12 y	Aged <12 y
INCS		
Beclomethasone dipropionate	160-320 mcg	80 mcg
Budesonide	64-256 mcg	64-128 mcg
Ciclesonide	74-200 mcg	200 mcg
Fluticasone propionate	100-200 mcg	100-200 mcg
Fluticasone furoate	55-110 mcg	55-110 mcg
Mometasone furoate	200 mcg	100 mcg
Triamcinolone acetonide	110-220 mcg	110-220 mcg
Oral antihistamines		
Cetirizine	5-10 mg	2.5-10 mg
Loratadine	10 mg	5-10 mg
Desloratadine	5 mg	1-2.5 mg
Levocetirizine	2.5-5 mg	1.25-2.5 mg
Fexofenadine	180 mg	30-60 mg
Intranasal antihistamines		
Azelastine	548-1644 mcg (0.1%-0.15%; 1-2 sprays per nostril BID)	548-822 mcg (0.1%-0.15%; 1 spray per nostril BID)
Olopatadine	5320 mcg (2 sprays per nostril BID)	2660 mcg (1 spray per nostril BID)
Intranasal antihistamine/INCS		
Azelastine/fluticasone	548mcg/200 mcg	548mcg/200 mcg
Oral LTRA		
Montelukast	10 mg	4-5 mg
Oral antihistamines/decongestants		
Cetirizine/pseudoephedrine	5-10 mg/120-240 mg	Not approved
Loratadine/pseudoephedrine	5-10 mg/120-240 mg	Not approved
Desloratadine/pseudoephedrine	2.5-5 mg/120-240 mg	Not approved
Fexofenadine/pseudoephedrine	60-180 mg/120-240 mg	Not approved
SLIT-tablets		
Timothy grass tablet	2,800 BAU (75,000 SQ-T)	2,800 BAU (75,000 SQ-T)
5-grass tablet	300 IR	300 IR
Ragweed tablet	12 Amb a 1-U	Not approved
House dust mite tablet	12 SQ-HDM	Not approved

BID, twice-daily; INCS, intranasal corticosteroid; LTRA, leukotriene receptor antagonist.

Table E2. Pharmacotherapy trials in adults/adolescents included in the meta-analysis. *Trial also included children (<12 y).

Author, Year	Allergy Type	Product, Daily Dose	Rescue Symptom-relieving Medication	Number Treated
Oral antihistamines				
Andrews et al, 2009, study 1[4]	Seasonal	Fexofenadine, 180 mg	no	Active: 311, Placebo: 313
Andrews et al, 2009, study 2[4]	Seasonal	Fexofenadine, 180 mg	no	Active: 227, Placebo: 229
Anolik et al, 2008[5]	Seasonal	Loratadine, 10 mg	Allowed but unspecified	Active: 181, Placebo: 176
Berger et al, 2003[6]	Seasonal	Desloratadine, 5 mg	Undocumented	Active: 111, Placebo: 111
Demoly et al, 2009[7]	Seasonal	Desloratadine, 5 mg	no	Active: 118, Placebo: 115
Dockhorn et al, 1987[8]	Seasonal	Loratadine, 10 mg	no	Active: 108, Placebo: 107
Ford et al, 2015[9]	Seasonal	Cetirizine, 10 mg	Undocumented	Active: 170, Placebo: 171
Hampel et al, 2004[10]	Seasonal	Loratadine, 10 mg	no	Active: 189, Placebo: 186
Kuna et al, 2009[11]	Seasonal	Cetirizine, 10 mg	no	Active: 227, Placebo: 225
Lu et al, 2009, study 1[12]	Seasonal	Loratadine, 10 mg	no	Active: 116, Placebo: 57
Lu et al, 2009, study 2[12]	Seasonal	Loratadine, 10 mg	no	Active: 164, Placebo: 54
Meltzer et al, 2000[13]	Seasonal	Loratadine, 10 mg	no	Active: 92, Placebo: 91
Nayak et al, 2002[14]	Seasonal	Loratadine, 10 mg	no	Active: 301, Placebo: 149
Philip et al, 2002[15]	Seasonal	Loratadine, 10 mg	no	Active: 602, Placebo: 352
Pradalier et al, 2007[16]	Seasonal	Desloratadine, 5 mg	no	Active: 234, Placebo: 249
Ratner et al, 1998[17]	Seasonal	Loratadine, 10 mg	no	Active: 150, Placebo: 150
Skassa-Brociek et al, 1988[18]	Seasonal	Loratadine, 10 mg	no	Active: 22, Placebo: 24
Van Adelsberg et al, 2003[19]	Seasonal	Loratadine, 10 mg	no	Active: 171, Placebo: 521
Freche et al, 2002[20]	Perennial	Loratadine, 10 mg	no	Active: 140, Placebo: 146
Holmberg et al, 2009[21]	Perennial	Desloratadine, 5 mg	no	Active: 293, Placebo: 291
Kim et al, 2006[22]	Perennial	Desloratadine, 5 mg	no	Active: 591, Placebo: 588
INCS				
Andrews et al, 2009[4]	Seasonal	Fluticasone furoate, 110 mcg	no	Active: 224 Placebo: 229
Anolik et al, 2008[5]	Seasonal	Mometasone, 200 mcg	Allowed but unspecified	Active: 176 Placebo: 176
Bronsky et al, 1997[23]	Seasonal	Mometasone, 200 mcg	no	Active: 96 Placebo: 95
Bronsky et al, 1996[24]	Seasonal	Fluticasone propionate, 200 mcg	no	Active: 117 Placebo: 115
Carr et al, 2012, Study 1[25]	Seasonal	Fluticasone propionate, 200 mcg	no	Active: 207 Placebo: 209
Carr et al, 2012, study 2[25]	Seasonal	Fluticasone propionate, 200 mcg	no	Active: 189 Placebo: 200
Carr et al, 2012, study 3[25]	Seasonal	Fluticasone propionate, 200 mcg	no	Active: 450 Placebo: 448
Creticos et al, 1998[26]*	Seasonal	Budesonide, 128 mcg	Chlorpheniramine maleate 4 mg tablets	Active: 83 Placebo: 83
Di Lorenzo et al, 1999[27]	Seasonal	Fluticasone propionate, 200 mcg	Undocumented	Active: 8 Placebo: 8
Di Lorenzo et al, 2004[28]	Seasonal	Fluticasone propionate, 200 mcg	Undocumented	Active: 20 Placebo: 20
Dykewicz et al, 2003[29]	Seasonal	Fluticasone propionate, 200 mcg	no	Active: 122 Placebo: 119
Findlay et al, 1992[30]	Seasonal	Triamcinolone, 220 mcg	Undocumented	Active:79 Placebo: 75
Fokkens et al, 2007[31]	Seasonal	Fluticasone furoate, 110 mcg	no	Active: 141 Placebo: 144
Ford et al, 2015[9]	Seasonal	Fluticasone propionate, 200 mcg	Undocumented	Active: 170 Placebo: 171
Graft et al, 1996[32]	Seasonal	Mometasone, 200 mcg	no	Active: 114 Placebo: 104
Graft et al, 1996[32]	Seasonal	Beclomethasone, 336 mcg	no	Active: 112 Placebo: 104
Hampel et al, 2010[33]	Seasonal	Fluticasone propionate, 200 mcg	no	Active: 151 Placebo: 151
Jacobs et al, 2009[34]	Seasonal	Fluticasone furoate, 110 mcg	no	Active: 152 Placebo: 150
Kaiser et al, 2007[35]	Seasonal	Fluticasone furoate, 110 mcg	no	Active: 151 Placebo: 148
Mansfield et al, 2007[36]	Seasonal	Fluticasone propionate, 200 mcg	Undocumented	Active: 16 Placebo: 16
Martin et al, 2007[37]	Seasonal	Fluticasone furoate, 110 mcg	no	Active: 127 Placebo: 128

next page

Author, Year	Allergy Type	Product, Daily Dose	Rescue Symptom-relieving Medication	Number Treated
Meltzer et al, 1998[38]	Seasonal	Mometasone, 200 mcg	no	Active: 85 Placebo: 43
Meltzer et al, 2011[39]	Seasonal	Mometasone, 200 mcg	Undocumented	Active: 344 Placebo: 340
Munk et al, 1997[40]	Seasonal	Triamcinolone, 220 mcg	no	Active: 56 Placebo: 56
Munk et al, 1996[41]	Seasonal	Triamcinolone, 220 mcg	no	Active: 70 Placebo: 70
Okubo et al, 2009[42]	Seasonal	Fluticasone furoate, 110 mcg	no	Active: 147 Placebo: 70
Prenner et al, 2010[43]	Seasonal	Mometasone, 200 mcg	no	Active: 220 Placebo: 209
Pullerits et al, 2002[44]	Seasonal	Fluticasone propionate, 200 mcg	cromoglycate eyedrops; loratadine tablets	Active: 13 Placebo: 18
Raphael et al, 2013[45]	Seasonal	Beclomethasone, 320 mcg	no	Active: 122 Placebo: 123
Ratner et al, 1998[17]	Seasonal	Fluticasone propionate, 200 mcg	no	Active: 150 Placebo: 150
Ratner et al, 2006[46]	Seasonal	Ciclesonide, 200 mcg	Undocumented	Active: 164 Placebo: 163
Rosenthal et al, 1998[47]	Seasonal	Triamcinolone, 200 mcg	Undocumented	Active: 94 Placebo: 96
Schenkel et al, 2013[48]	Seasonal	Triamcinolone, 110 mcg	no	Active: 107 Placebo: 111
Steensen et al, 1981[49]	Seasonal	Budesonide, 200 mcg	dexchlorpheniramine maleate 2 mg; antazolinhydrochloride eyedrops	Active: 14 Placebo: 12
Stern et al, 1997[50]	Seasonal	Budesonide, 256 mcg	terfenadine 60 mg QD/BID; disodium cromoglycate eye drops 20 mg/ml, 1-8 drops/d	Active: 182 Placebo: 59
Stern et al, 1997[50]	Seasonal	Fluticasone propionate, 200 mcg	terfenadine 60 mg QD/BID; disodium cromoglycate eye drops 20 mg/ml, 1-8 drops/d	Active: 180 Placebo: 59
Tinkelman et al, 1990[51]	Seasonal	Triamcinolone, 110 mcg	no	Active: 81 Placebo: 87
Van Bavel et al, 2012[52]	Seasonal	Beclomethasone, 320 mcg	no	Active: 167 Placebo: 171
Bende et al, 2002[53]	Perennial	Budesonide, 256 mcg	loratadine 10 mg QD	Active: 107 Placebo: 114
Bende et al, 2002[53]	Perennial	Mometasone, 200 mcg	loratadine 10 mg QD	Active: 106 Placebo: 114
Chervinsky et al, 2007[54]	Perennial	Ciclesonide, 200 mcg	Undocumented	Active: 441 Placebo: 222
Given et al, 2010[55]	Perennial	Fluticasone furoate, 110 mcg	no	Active: 160 Placebo: 155
Kivisaari et al, 2001[56]	Perennial	Fluticasone propionate, 200 mcg	Undocumented	Active: 110 Placebo: 108
Kobayashi et al, 1995[57]	Perennial	Triamcinolone, 220 mcg	no	Active: 88 Placebo: 90
Meltzer et al, 1998[58]*	Perennial	Budesonide, 256 mcg	Undocumented	Active: 96 Placebo: 97
Meltzer et al, 2012[59]	Perennial	Beclomethasone, 320 mcg	no	Active: 232 Placebo: 234
Meltzer et al, 2007[60]	Perennial	Ciclesonide, 200 mcg	Undocumented	Active: 238 Placebo: 233
Mohar et al, 2012[61]	Perennial	Ciclesonide, 148 mcg	no	Active: 505 Placebo: 307
Nathan et al, 2008[62]	Perennial	Fluticasone furoate, 110 mcg	no	Active: 149 Placebo: 153
Spector et al, 1990[63]	Perennial	Triamcinolone, 100 mcg	no	Active: 94 Placebo: 94
Vasar et al, 2008[64]	Perennial	Fluticasone furoate, 110 mcg	no	Active: 151 Placebo: 151
Weinstein et al, 2014[65]	Perennial	Beclomethasone, 320 mcg	Allowed but unspecified	Active: 414 Placebo: 110
Montelukast				
Lu et al, 2009, study 1[12]	Seasonal	Montelukast, 10 mg	no	Active: 112 Placebo: 57
Lu et al, 2009, study 2[12]	Seasonal	Montelukast, 10 mg	no	Active: 103 Placebo: 54
Meltzer et al, 2000[13]	Seasonal	Montelukast, 10 mg	no	Active: 95 Placebo: 91
Nayak et al, 2002[14]	Seasonal	Montelukast, 10 mg	no	Active: 155 Placebo: 149
Okubo et al, 2008[66]	Seasonal	Montelukast, 10 mg	Undocumented	Active: 310 Placebo: 314
Philip et al, 2002[15]	Seasonal	Montelukast, 10 mg	no	Active: 348 Placebo: 352
Philip et al, 2004[67]	Seasonal	Montelukast, 10 mg	no	Active: 415 Placebo: 416
Pullerits et al, 2002[44]	Seasonal	Montelukast, 10 mg	cromoglycate eyedrops; loratadine tablets	Active: 16 Placebo: 18

next page

Author, Year	Allergy Type	Product, Daily Dose	Rescue Symptom-relieving Medication	Number Treated
Van Adelsberg et al, 2003[68]	Seasonal	Montelukast, 10 mg	no	Active: 448 Placebo: 451
Van Adelsberg et al, 2003[19]	Seasonal	Montelukast, 10 mg	no	Active: 522 Placebo: 521
Patel et al, 2005[69]	Perennial	Montelukast, 10 mg	no	Active: 1002 Placebo: 990
Intranasal antihistamines				
Berger et al, 2003[6]	Seasonal	Azelastine, 548 mcg	Undocumented	Active: 108 Placebo: 111
Bernstein et al, 2009[70]	Seasonal	Azelastine, 548 mcg	no	Active: 146 Placebo: 138
Carr et al, 2012, study 1[25]	Seasonal	Azelastine, 548 mcg	no	Active: 208 Placebo: 209
Carr et al, 2012, study 2[25]	Seasonal	Azelastine, 548 mcg	no	Active: 194 Placebo: 200
Carr et al, 2012, study 3[25]	Seasonal	Azelastine, 548 mcg	no	Active: 445 Placebo: 448
Hampel et al, 2010[33]	Seasonal	Azelastine, 548 mcg	no	Active: 152 Placebo: 151
Howland et al, 2011[71]	Seasonal	Azelastine, 822 mcg	no	Active: 251 Placebo: 254
LaForce et al, 2004[72]	Seasonal	Azelastine, 548 mcg	no	Active: 112 Placebo: 111
Lumry et al, 2007, study 1[73]	Seasonal	Azelastine, 548 mcg	no	Active: 139 Placebo: 141
Lumry et al, 2007, study 2[73]	Seasonal	Azelastine, 548 mcg	no	Active: 137 Placebo: 137
Shah et al, 2009[74]	Seasonal	Azelastine, 822 mcg	no	Active: 177 Placebo: 177
Shah et al, 2009[75]	Seasonal	Olopatadine, 5320 mcg	Undocumented	Active: 180 Placebo: 176
Van Bavel et al, 2009[76]	Seasonal	Azelastine, 822 mcg	no	Active: 266 Placebo: 266
Combination intranasal antihistamine/INCS				
Carr et al, 2012, study 1[25]	Seasonal	Azelastine + fluticasone propionate, 548 mcg/200 mcg	no	Active: 207 Placebo: 209
Carr et al, 2012, study 2[25]	Seasonal	Azelastine + fluticasone propionate, 548 mcg/200 mcg	no	Active: 193 Placebo: 200
Carr et al, 2012, study 3[25]	Seasonal	Azelastine + fluticasone propionate, 548 mcg/200 mcg	no	Active: 448 Placebo: 448
Hampel et al, 2010[33]	Seasonal	Azelastine + fluticasone propionate, 548 mcg/200 mcg	no	Active: 153 Placebo: 151
Combination oral antihistamine/decongestant				
Nathan et al, 2006[77]	Seasonal	Cetirizine + pseudoephedrine, 5 mg/120 mg	no	Active: 139 Placebo: 135

BID, twice-daily; INCS, intranasal corticosteroid; QD, once-daily.

Table E3. Pharmacotherapy trials in children included in the meta-analysis.

Author, Year	Allergy Type	Product, Daily Dose	Rescue Symptom-relieving Medication	Number Treated
Oral antihistamines				
No eligible studies				
INCS				
Agertoft et al, 1993[78]	Seasonal	Budesonide, 400 mcg	terfenadine 60 mg tablets	Active: 27 Placebo: 29
Banov et al, 1996[79]	Seasonal	Triamcinalone, 220 mcg	no	Active: 58 Placebo: 58
Georges et al, 2014[80]	Seasonal	Triamcinalone, 110/220 mcg	loratadine 5 mg/mL syrup	Active: 69 Placebo: 71
Meltzer et al, 2009[81]	Seasonal	Fluticasone furoate, 110 mcg	subjects aged 6–11 yr did not receive rescue symptom-relieving medication; subjects aged 2 to <6 yr were provided loratadine 1 mg/ml syrup	Active: 184 Placebo: 186
Storms et al, 2013[82]	Seasonal	Beclomethasone, 160 mcg	no	Active: 241 Placebo: 234
Baena-Cagna et al, 2010[83]	Perennial	Mometasone, 100 mcg	Undocumented	Active: 190 Placebo: 191
Berger et al, 2015[84]	Perennial	Beclomethasone, 80 mcg	subjects aged 4-5 yr: loratadine 5 mg tablet or 5 mL (1 mg/mL) syrup QD; subjects aged 6-11 yr: loratadine 10 mg tablet or 10 mL (1 mg/mL) syrup QD during first 6 weeks	Active: 362 Placebo: 185
Fokkens et al, 2002[85]	Perennial	Budesonide, 128 mcg	cetirizine 10 mg QD	Active: 100 Placebo: 102
Maspero et al, 2008[86]	Perennial	Fluticasone furoate, 110 mcg	no	Active: 185 Placebo: 188
Weinstein et al, 2009[87]	Perennial	Triamcinolone, 110 mcg	loratadine syrup 5 mg QD	Active: 231 Placebo: 233
Montelukast				
Razi et al, 2006[88]	Seasonal	Montelukast, 5 mg	no	Active: 29 Placebo: 28
Intranasal antihistamines				
Meltzer et al, 2011[89]	Seasonal	Olopatadine, 2660 mcg	no	Active: 471 Placebo: 473
Combination intranasal antihistamine/INCS				
Berger et al, 2016[90]	Seasonal	Azelastine + fluticasone propionate, 548 mcg/200 mcg	Undocumented	Active: 152 Placebo: 152
Combination oral antihistamine/decongestant				
No eligible studies				

INCS, intranasal corticosteroid; QD, once-daily.

next page

Table E4. Sublingual immunotherapy tablet trials in adults/adolescents included in the meta-analysis. *Trial also included children (≥5 y).

Author, Year	Allergy Type	Product	Induction Dose Range	Maintenance Dose	Allergen Content	Rescue Symptom-relieving Medication	Number Treated
Creticos et al, 2013[91]	Seasonal	ragweed SLIT-tablet (Ragwitek)	12 Amb a 1-U	12 Amb a 1-U	NA	loratadine 10 mg tablet QD; olopatadine HCl 0.1% ophthalmic solution; mometasone furoate nasal spray 50 mcg; prednisone 5 mg tablet	Active: 194 Placebo: 198
Dahl et al, 2006[92]	Seasonal	Tim grass SLIT-tablet (Grastek)	75,000 SQ-T	75,000 SQ-T	75,000 SQ-T=15 mcg Phl p 5	desloratadine 5 mg QD; budesonide nasal spray 32 mcg (max 2 puffs per nostril BID); prednisone 5 mg tablet (max 50 mg/day)	Active: 316 Placebo: 318
Maloney et al, 2014[93]*	Seasonal	Tim grass SLIT-tablet (Grastek)	75,000 SQ-T	75,000 SQ-T	75,000 SQ-T=15 mcg Phl p 5	oral antihistamines (unspecified); ocular antihistamines (unspecified); intranasal corticosteroids (unspecified); oral corticosteroids (unspecified)	Active: 752 Placebo: 749
Nelson et al, 2011[94]	Seasonal	Tim grass SLIT-tablet (Grastek)	75,000 SQ-T	75,000 SQ-T	75,000 SQ-T=15 mcg Phl p 5	loratadine 10 mg tablet QD; olopatadine HCl 0.1% ophthalmic solution (max 1 drop in the affected eye BID); mometasone furoate nasal spray 50 mcg (max 2 sprays in each nostril QD); prednisone 5 mg tablet (day 1, 1 mg/kg/d, maximum of 50 mg/d; day 21, 0.5 mg/kg/d, maximum of 25 mg/d)	Active: 213 Placebo: 225
Demoly et al, 2016[95]	Perennial	HDM SLIT-tablet (Odactra)	12 SQ-HDM	12 SQ-HDM	NA	desloratadine 5 mg QD or budesonide 64 mcg (max dose 2 puffs per nostril QD); azelastine 0.05%, or lodoxamide tromethamine 0.1% [in Croatia only], none [in Serbia only] (max 2 drops per eye QD)	Active: 318 Placebo: 338
Nolte et al, 2016[96]	Perennial	HDM SLIT-tablet (Odactra)	12 SQ-HDM	12 SQ-HDM	12 SQ-HDM=15 mcg group 1 and 15 mcg group 2	loratadine 10 mg tablet QD; mometasone nasal spray 50 mcg (max 2 sprays per nostril QD); olopatadine hydrochloride, 0.1% (max 1 drop per eye BID)	Active: 741 Placebo: 741
Okubo et al, 2017[97]	Perennial	HDM SLIT-tablet (Odactra)	12 SQ-HDM	12 SQ-HDM	NA	antihistamine tablets (unspecified); eye drops (unspecified); or nasal steroids (unspecified)	Active: 314 Placebo: 319

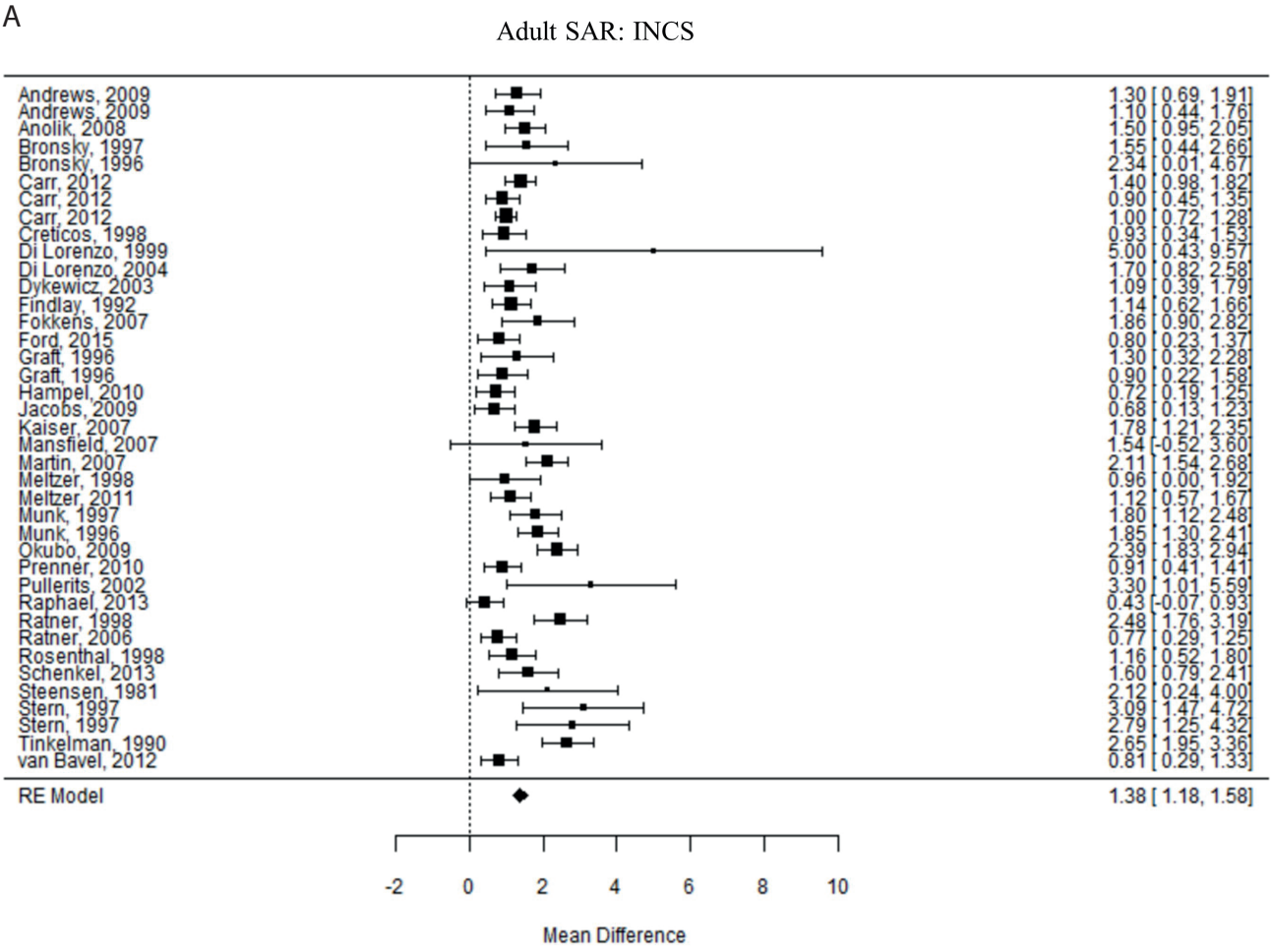
BID, twice-daily; IR, arbitrary index of reactivity; HDM, house dust mite; QD, daily; SLIT, sublingual immunotherapy; SQ, a method of standardisation of biological potency, major allergen content, and complexity of the allergen extract.

Table E5. Sublingual immunotherapy tablet trials in children included in the meta-analysis.

Author, Year	Allergy Type	Product	Induction Dose Range	Maintenance Dose	Allergen Content	Rescue Symptom-relieving Medication	Number Treated
Bufe et al, 2009[98]	Seasonal	Tim grass SLIT-tablet (Grastek)	75,000 SQ-T	75,000 SQ-T	75,000 SQ-T=15 mcg Phl p 5	loratadine tablets; levocabastine eye drops; budesonide nasal spray; salbutamol spray; fluticasone inhaler; and prednisolone tablets	Active: 126 Placebo: 127
Halken et al, 2010[99]	Seasonal	5 grass SLIT-tablet (Oralair)	100 IR-300 IR	300 IR	300 IR=20 mcg group 5 allergens	antihistamine (unspecified); intranasal corticosteroid (unspecified); oral corticosteroid (unspecified)	Active: 131 Placebo: 135

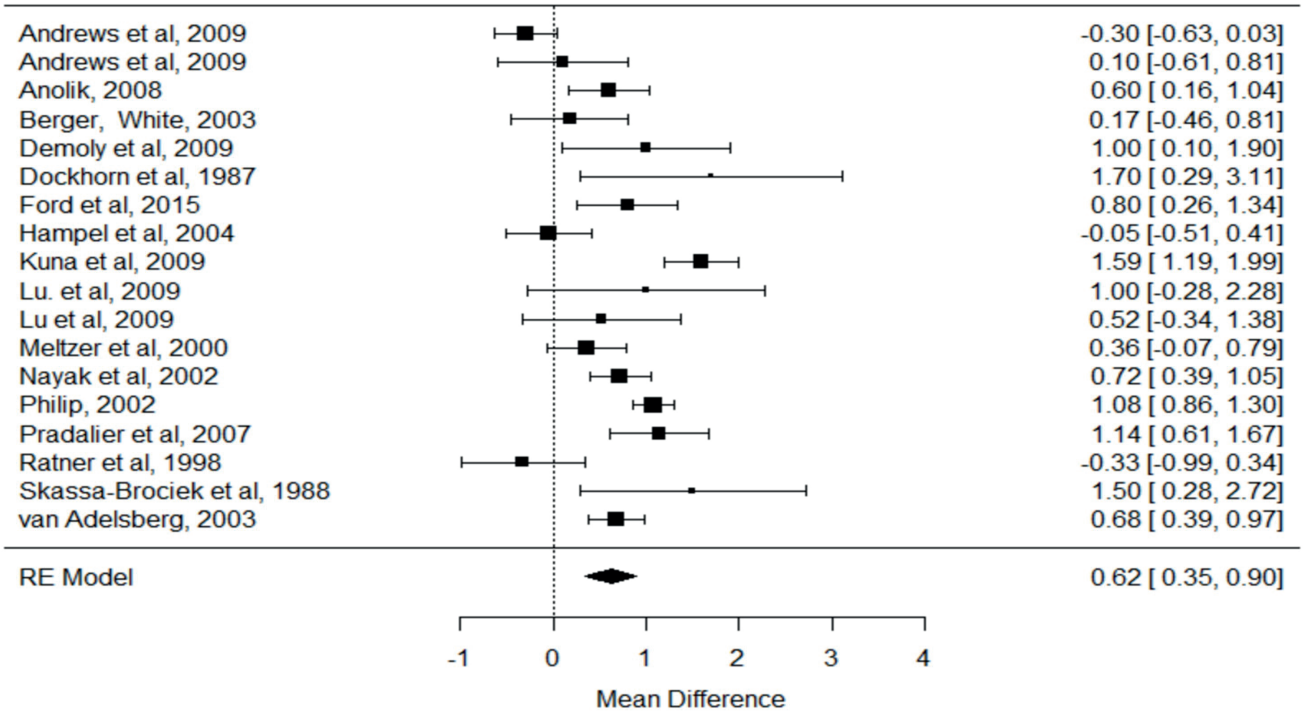
IR, arbitrary index of reactivity; SLIT, sublingual immunotherapy; SQ, a method of standardisation of biological potency, major allergen content, and complexity of the allergen extract.

Figure E1. Mean difference from placebo in total nasal symptom score in adult/adolescent seasonal allergic rhinitis (SAR) for A) INCS, B) oral antihistamines, C) intranasal antihistamines, D) montelukast, E) combination intranasal antihistamines/INCS, and F) SLIT-tablets. INCS, intranasal corticosteroids; SLIT, sublingual immunotherapy.



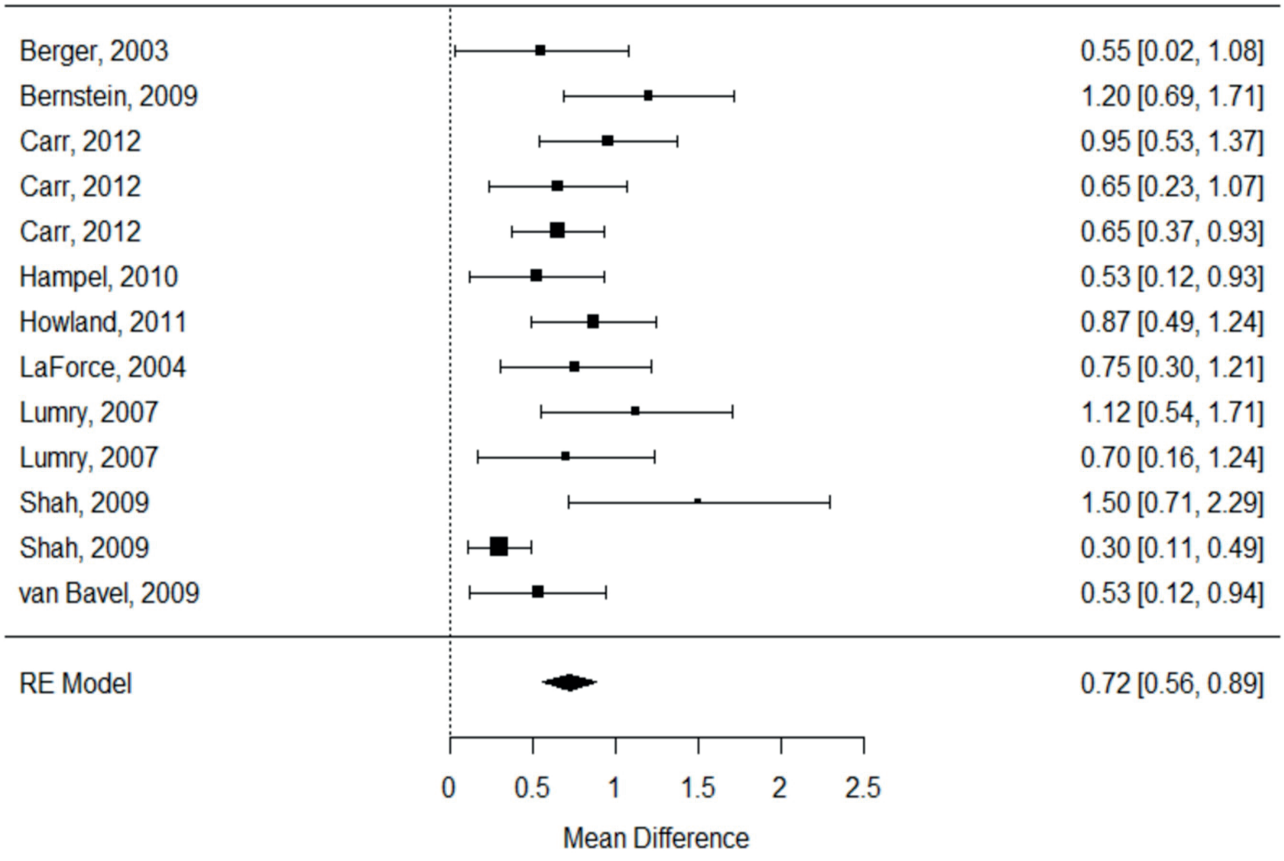
B

Adult SAR: Oral Antihistamines



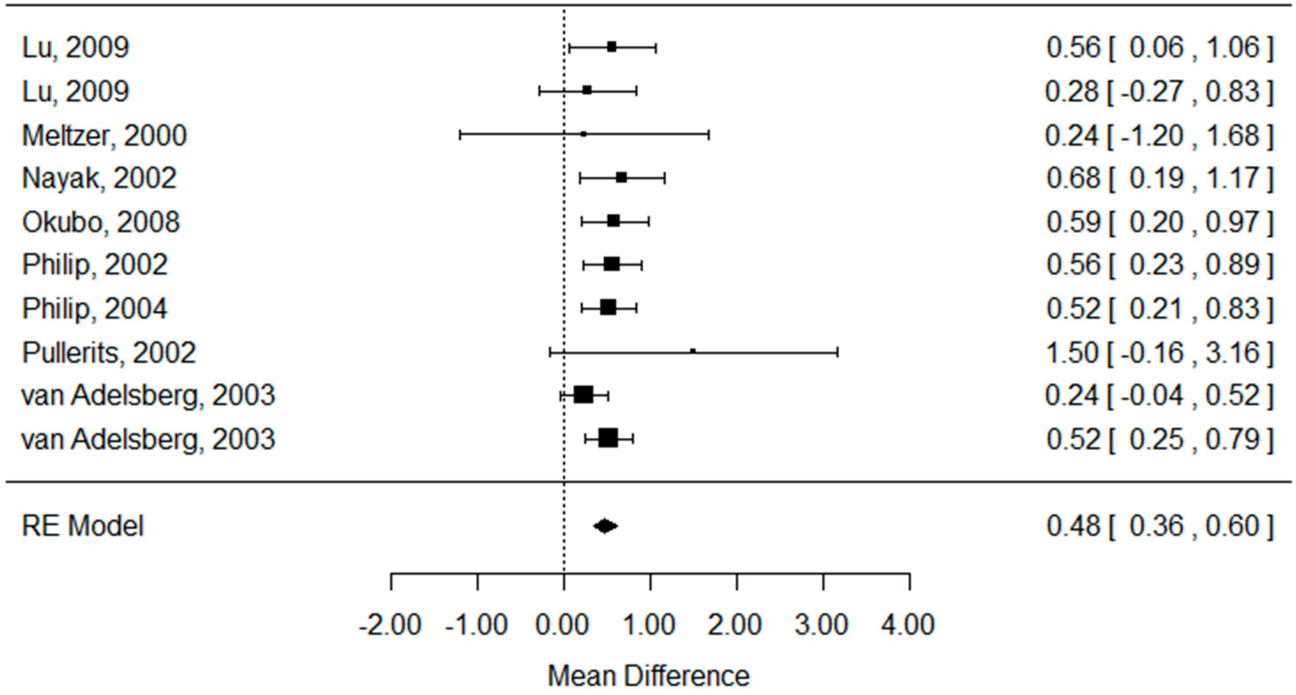
C

Adult SAR: Intranasal Antihistamines



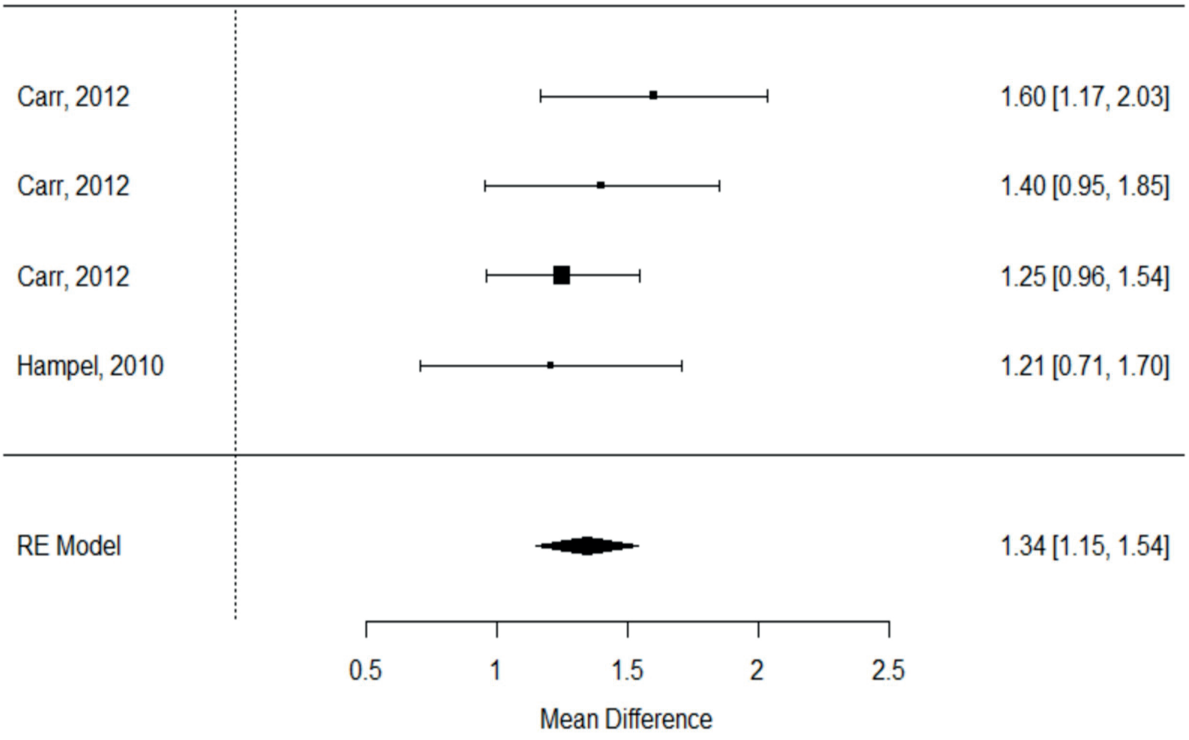
D

Adult SAR: Montelukast



E

Adult SAR: Combo Intranasal Antihistamines/INCS



F

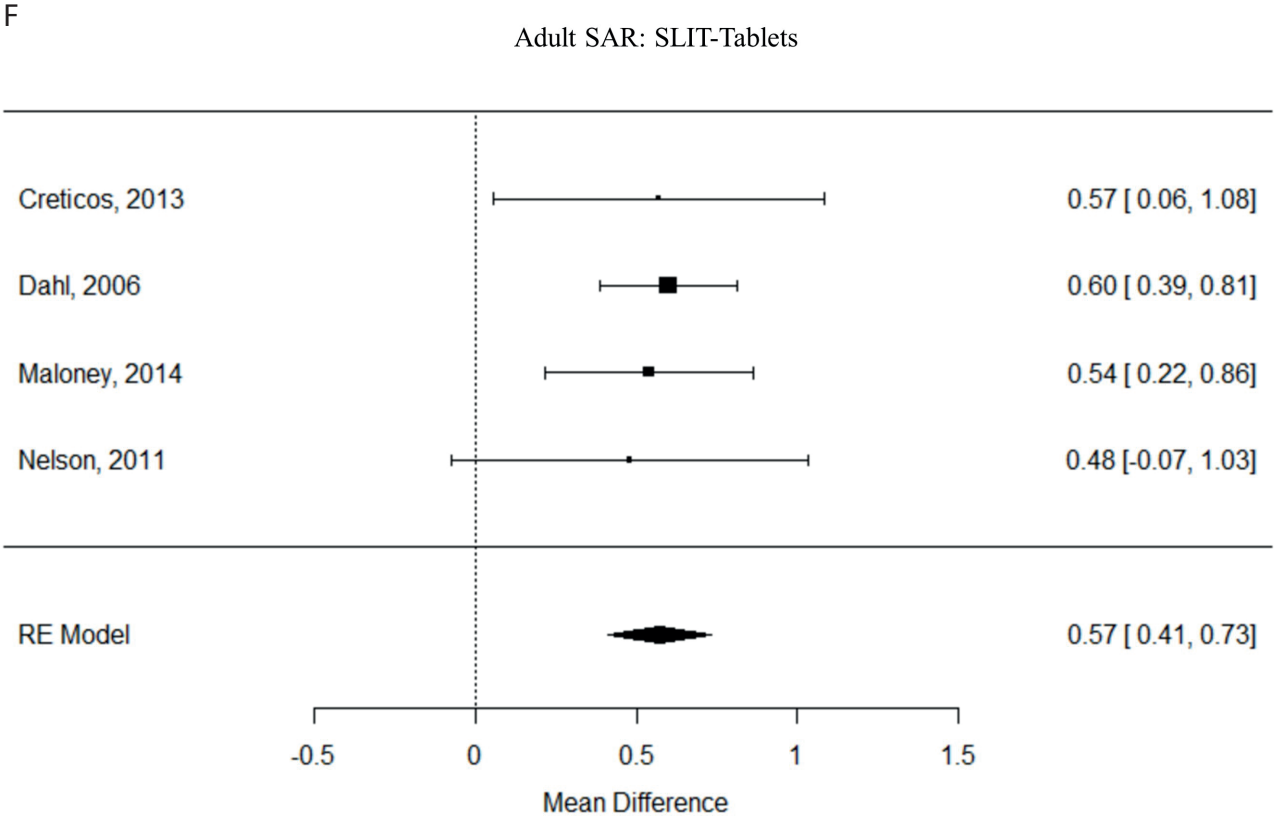
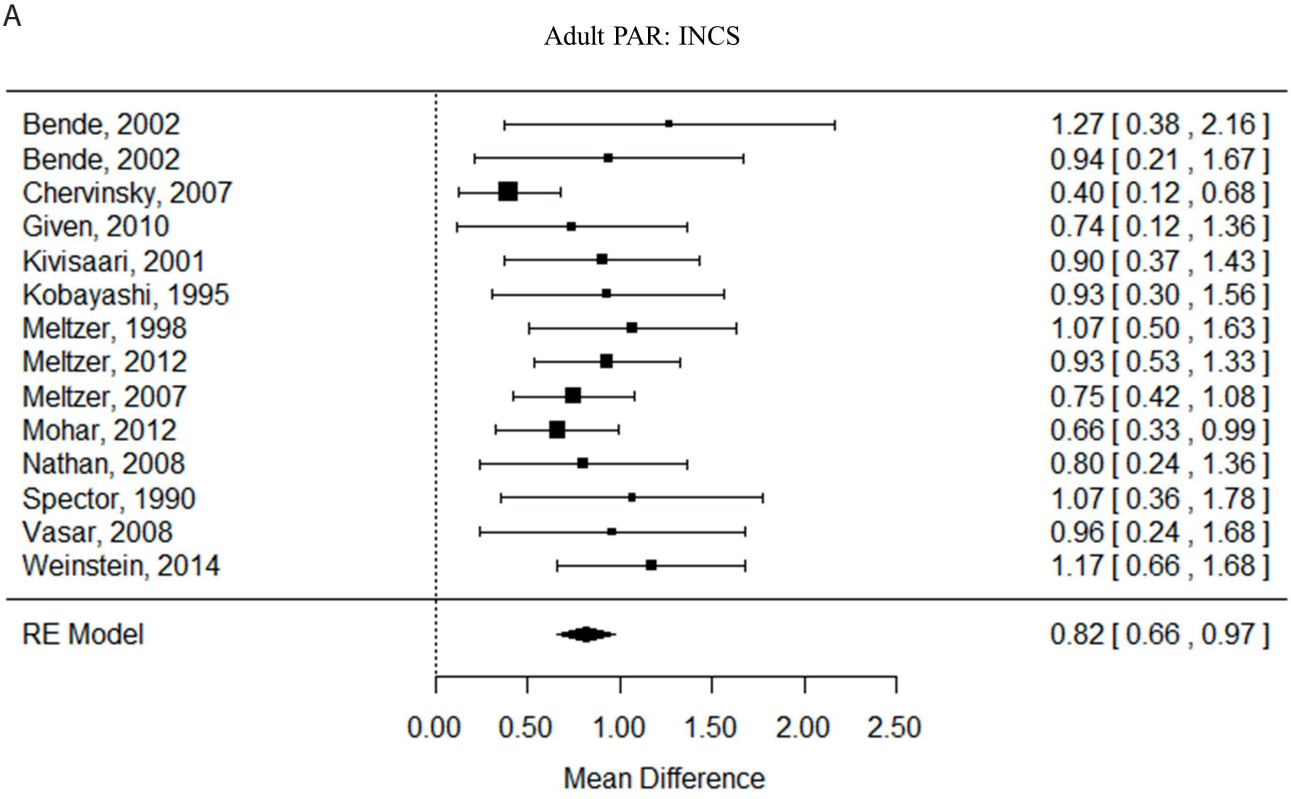
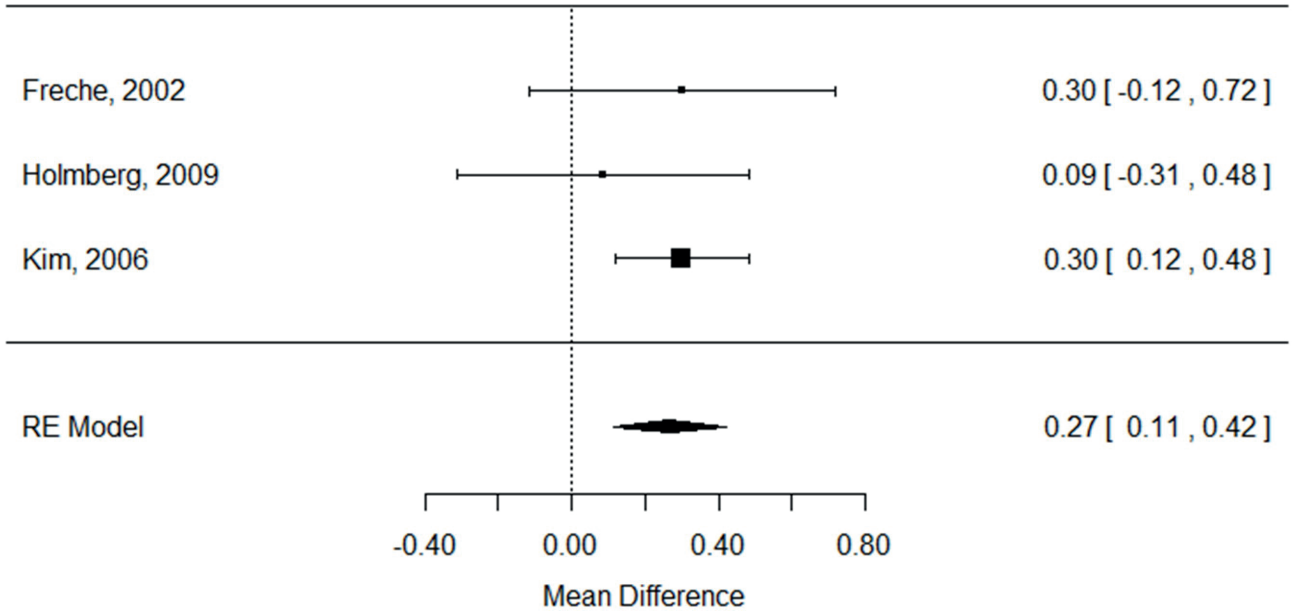

Adult SAR: SLIT-Tablets
Creticos, 2013
0.57 [0.06, 1.08]
Dahl, 2006
0.60 [0.39, 0.81]
Maloney, 2014
0.54 [0.22, 0.86]
Nelson, 2011
0.48 [-0.07, 1.03]
RE Model
0.57 [0.41, 0.73]
-0.5
0
0.5
1
1.5
Mean Difference

Figure E2. Mean difference from placebo in total nasal symptom score in adult/adolescent perennial allergic rhinitis (PAR) for A) INCS, B) oral antihistamines, and C) SLIT-tablets. INCS, intranasal corticosteroids; SLIT, sublingual immunotherapy.

A



B



C

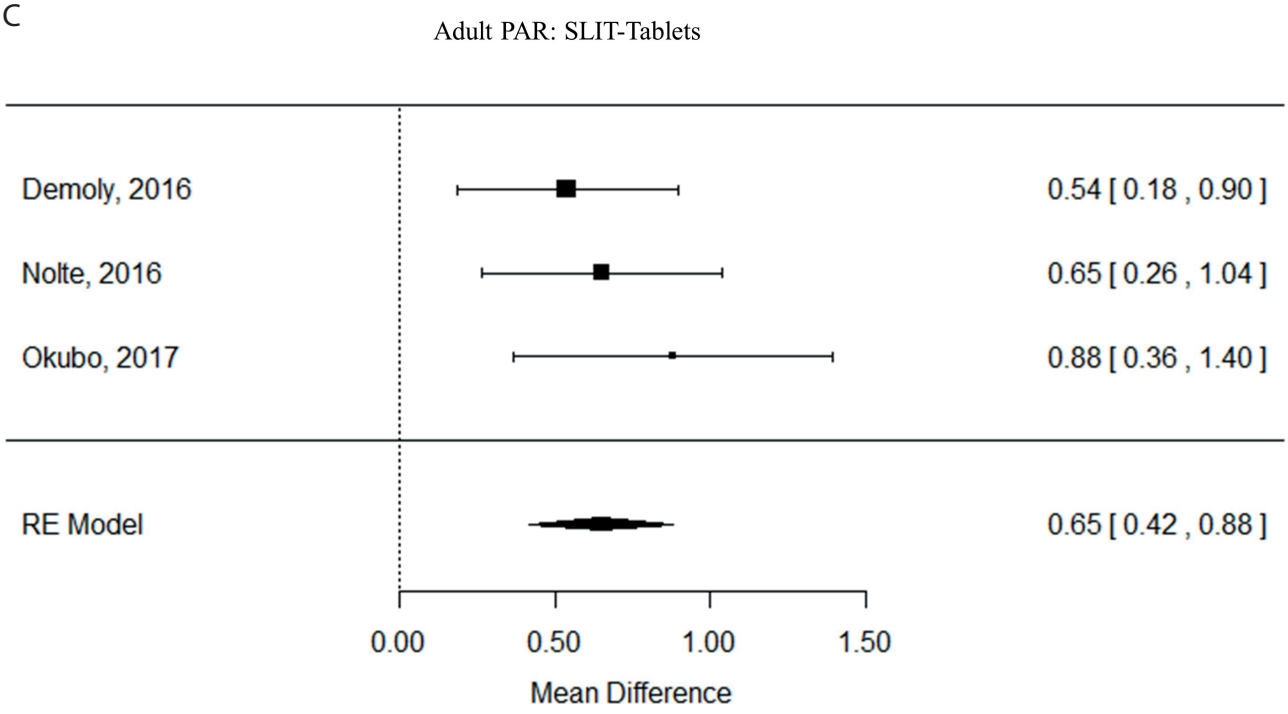
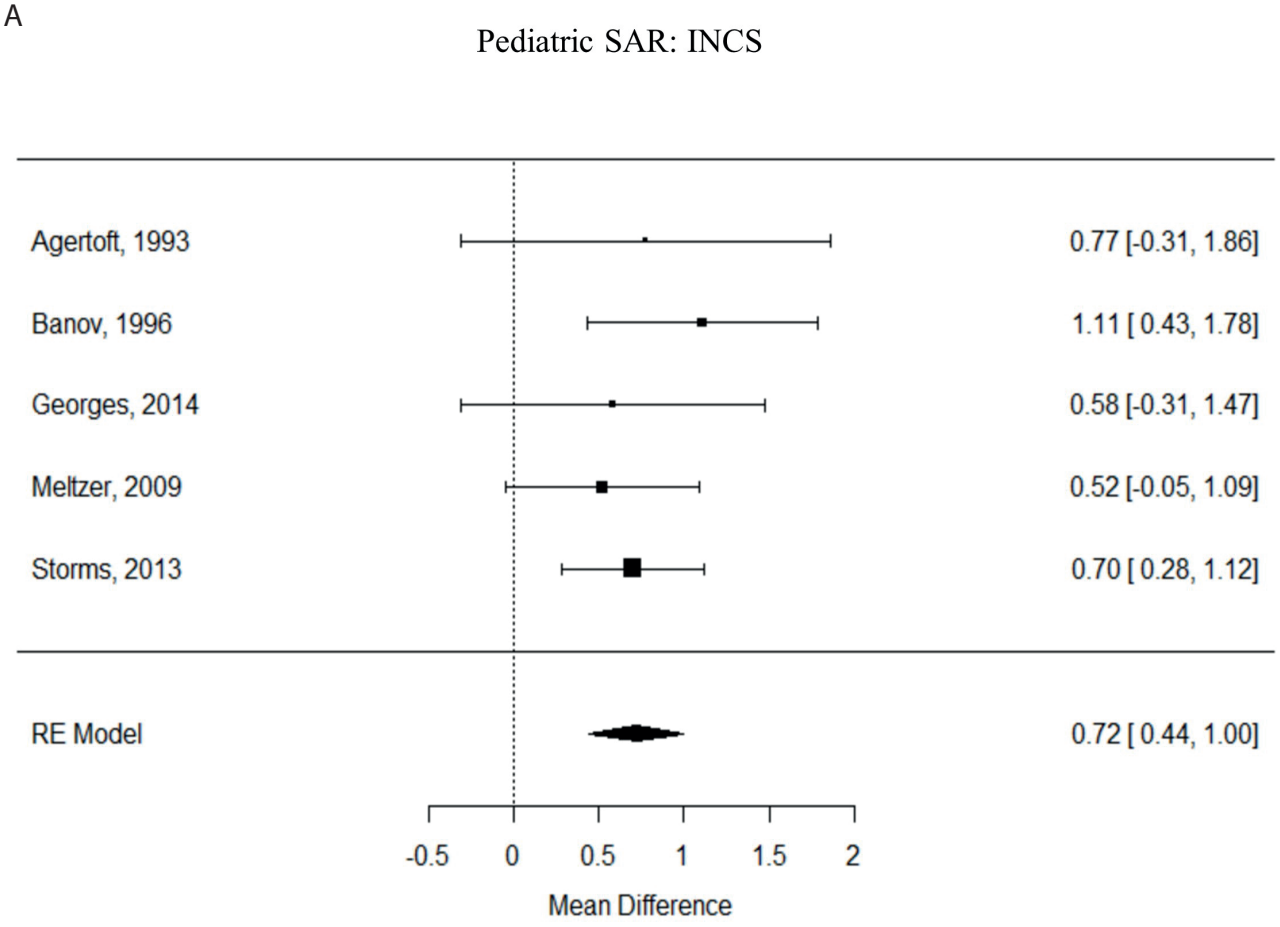
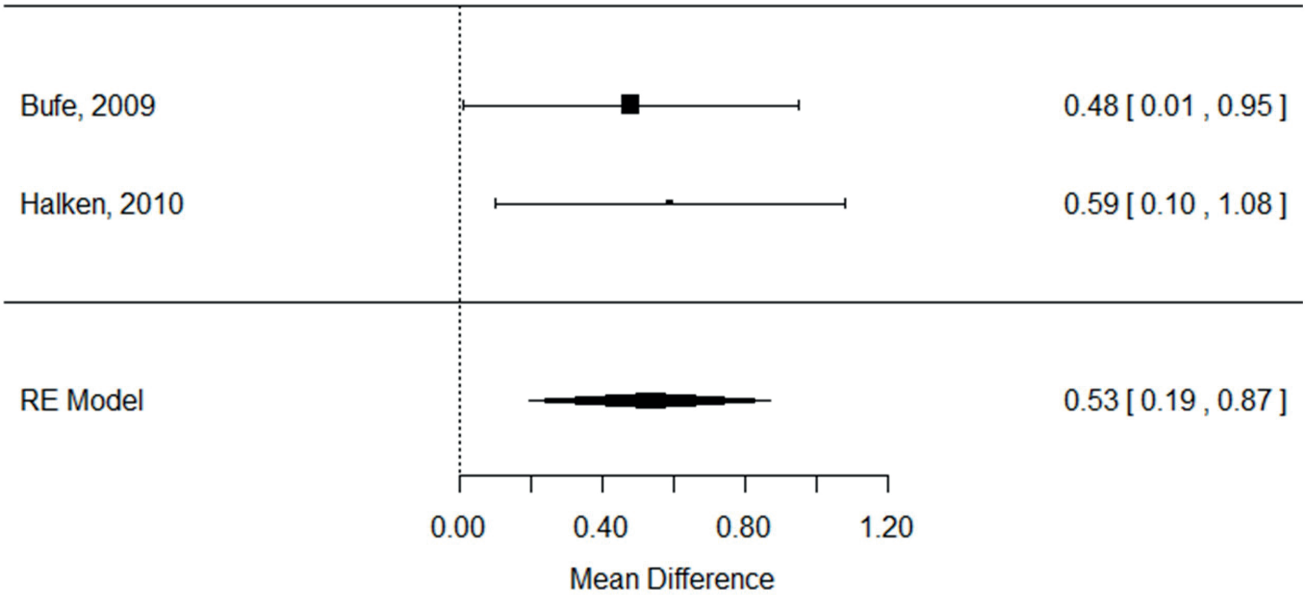

Adult PAR: SLIT-Tablets
Demoly, 2016
0.54 [0.18 , 0.90]
Nolte, 2016
0.65 [0.26 , 1.04]
Okubo, 2017
0.88 [0.36 , 1.40]
RE Model
0.65 [0.42 , 0.88]
0.00
0.50
1.00
1.50
Mean Difference

Figure E3. Mean difference from placebo in total nasal symptom score in pediatric A) INCS SAR, B) SLIT-tablet SAR, and C) INCS PAR trials. INCS, intranasal corticosteroids; PAR, perennial allergic rhinitis; SAR, seasonal allergic rhinitis; SLIT, sublingual immunotherapy.

A



B



C

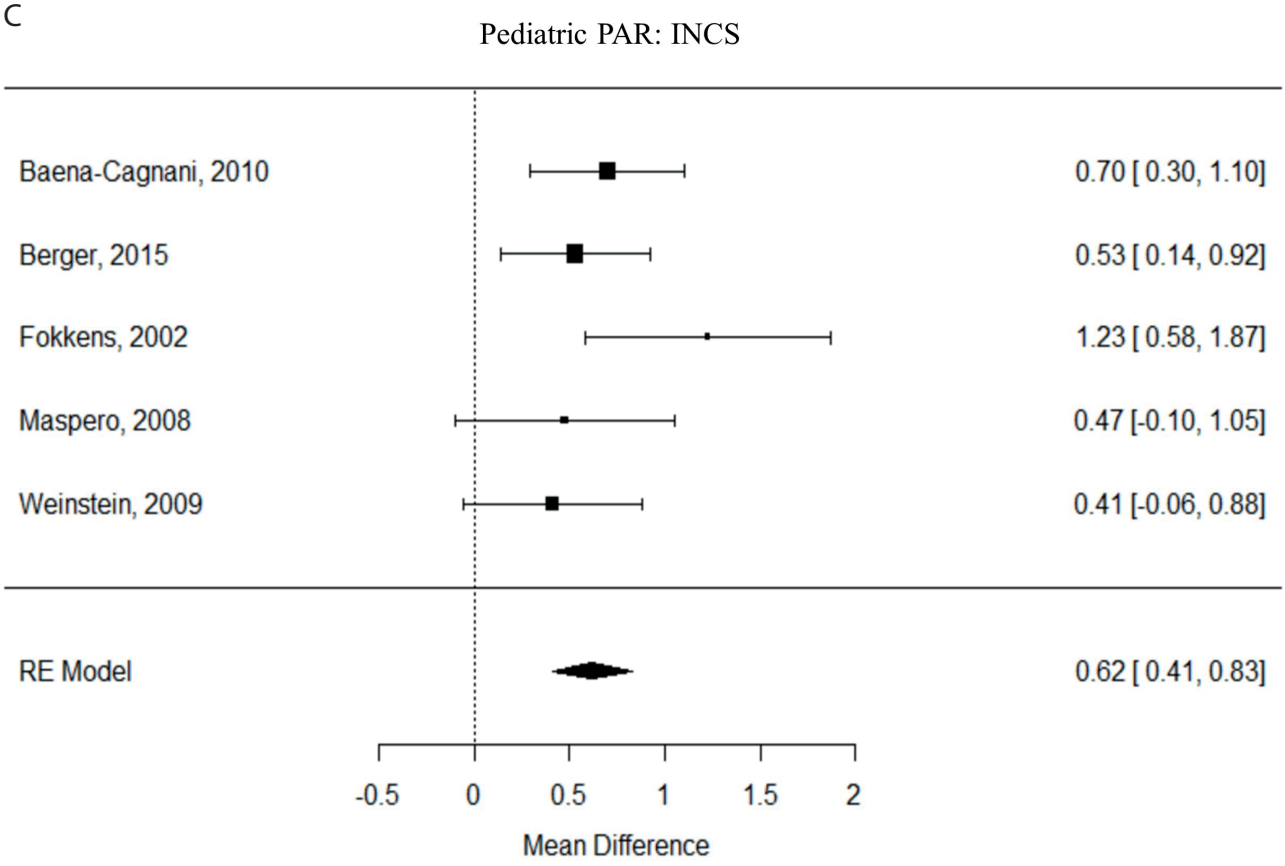
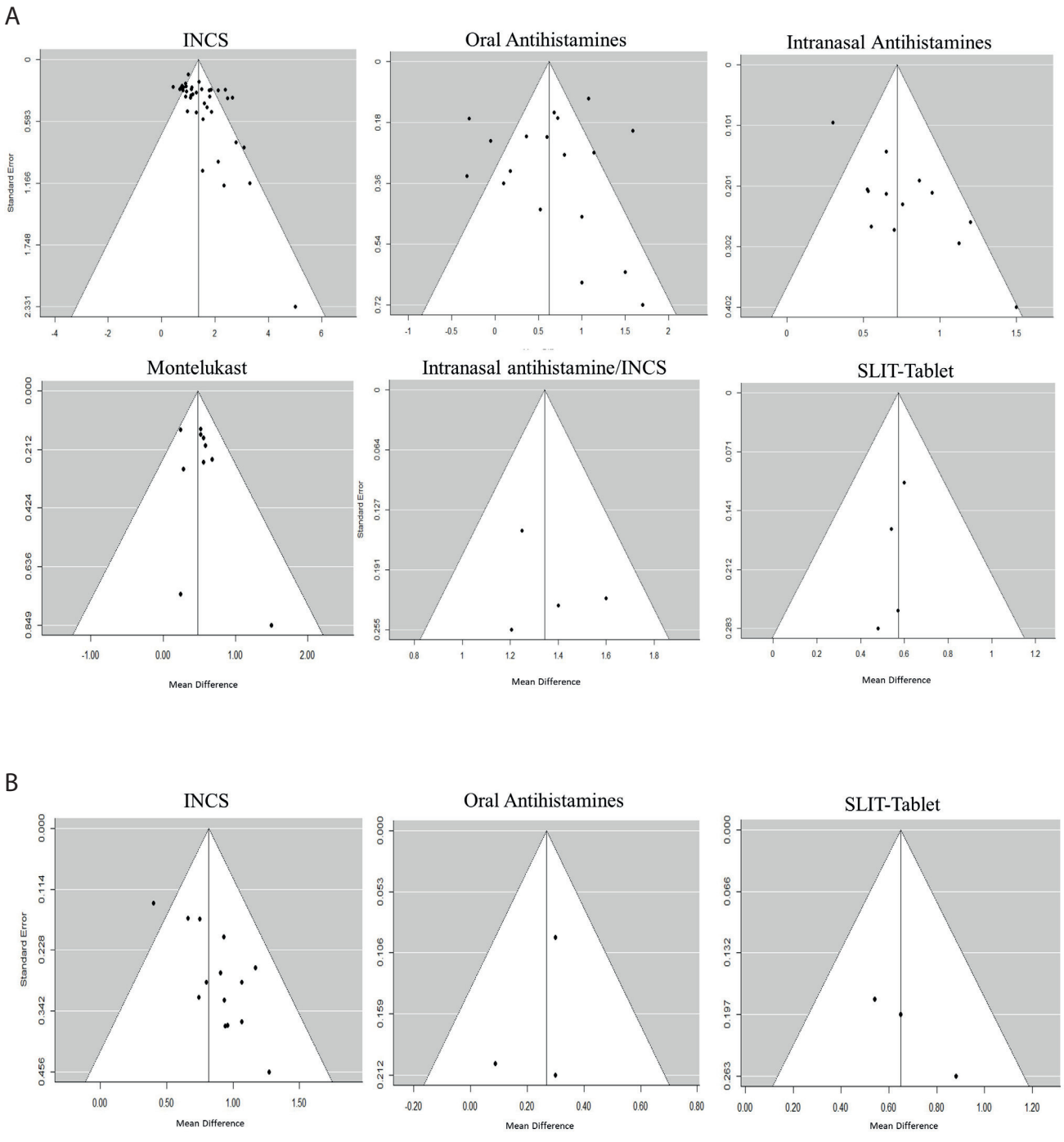
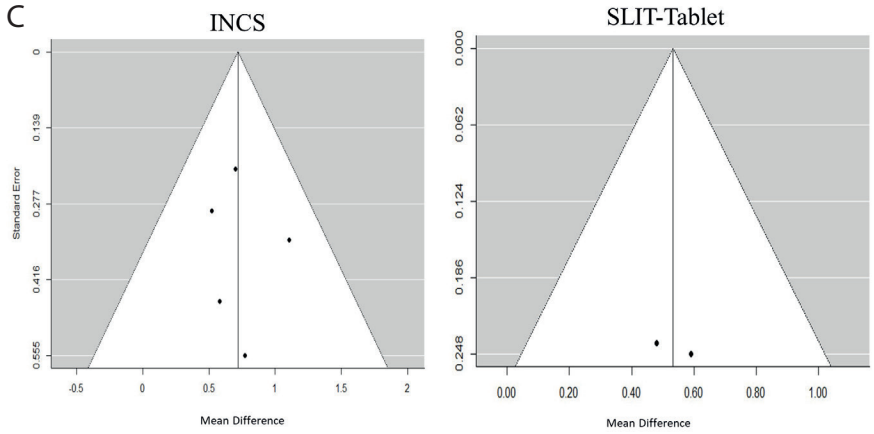

Pediatric PAR: INCS
Baena-Cagnani, 2010
0.70 [0.30, 1.10]
Berger, 2015
0.53 [0.14, 0.92]
Fokkens, 2002
1.23 [0.58, 1.87]
Maspero, 2008
0.47 [-0.10, 1.05]
Weinstein, 2009
0.41 [-0.06, 0.88]
RE Model
0.62 [0.41, 0.83]
-0.5
0
0.5
1
1.5
2
Mean Difference

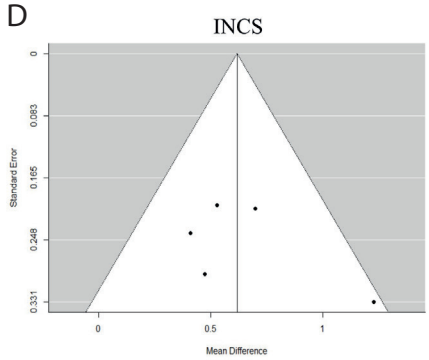
Figure E4. Funnel plots of medication classes for A) adult/adolescent seasonal allergic rhinitis, B) adult/adolescent perennial allergic rhinitis, C) pediatric seasonal allergic rhinitis, and D) pediatric perennial allergic rhinitis trials. Asymmetric plots indicate publication bias. INCS, intranasal corticosteroids; SLIT, sublingual immunotherapy.



C


INCS
SLIT-Tablet
Standard Error
0
0.139
0.277
0.416
0.555
-0.5
0
0.5
1
1.5
2
Mean Difference
0.000
0.062
0.124
0.186
0.248
0.00
0.20
0.40
0.60
0.80
1.00
Mean Difference

D


INCS
Standard Error
0
0.083
0.165
0.248
0.331
0
0.5
1
Mean Difference

References

1. Liu G, Zhou X, Chen J, Liu F. Oral Antihistamines Alone vs in Combination with Leukotriene Receptor Antagonists for Allergic Rhinitis: A Meta-analysis. Otolaryngol Head Neck Surg. 2018;158(3):450-458.
2. Higgins J, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]: The Cochrane Collaboration; 2011. Higgins J, Green S, eds.
3. Ma J, Liu W, Hunter A, Zhang W. Performing meta-analysis with incomplete statistical information in clinical trials. BMC Medical Research Methodology. 2008;8(1):56.
4. Andrews CP, Martin BG, Jacobs RL, et al. Fluticasone furoate nasal spray is more effective than fexofenadine for nighttime symptoms of seasonal allergy. Allergy Asthma Proc. 2009;30(2):128-138.
5. Anolik R. Clinical benefits of combination treatment with mometasone furoate nasal spray and loratadine vs monotherapy with mometasone furoate in the treatment of seasonal allergic rhinitis. Ann Allergy Asthma Immunol. 2008;100(3):264-271.
6. Berger WE, White MV. Efficacy of azelastine nasal spray in patients with an unsatisfactory response to loratadine. Ann Allergy Asthma Immunol. 2003;91(2):205-211.
7. Demoly P, Dreyfus I, Dhivert-Donnadieu H, Mesbah K. Desloratadine for the treatment of cypress pollen-induced allergic rhinitis. Ann Allergy Asthma Immunol. 2009;103(3):260-266.
8. Dockhorn RJ, Bergner A, Connell JT, et al. Safety and efficacy of loratadine (Sch-29851): a new non-sedating antihistamine in seasonal allergic rhinitis. Ann Allergy. 1987;58(6):407-411.
9. Ford LB, Matz J, Hankinson T, Prillaman B, Georges G. A comparison of fluticasone propionate nasal spray and cetirizine in ragweed fall seasonal allergic rhinitis. Allergy Asthma Proc. 2015;36(4):313-319.
10. Hampel F, Jr., Howland W, 3rd, Van Bavel J, Ratner P. A randomized, double-blind, placebo-controlled study comparing the efficacy and safety of ebastine (20 mg and 10 mg) to loratadine 10 mg once daily in the treatment of seasonal allergic rhinitis. J Investig Allergol Clin Immunol. 2004;14(1):56-63.
11. Kuna P, Bachert C, Nowacki Z, et al. Efficacy and safety of bilastine 20 mg compared with cetirizine 10 mg and placebo for the symptomatic treatment of seasonal allergic rhinitis: a randomized, double-blind, parallel-group study. Clin Exp Allergy. 2009;39(9):1338-1347.
12. Lu S, Malice MP, Dass SB, Reiss TF. Clinical studies of combination montelukast and loratadine in patients with seasonal allergic rhinitis. J Asthma. 2009;46(9):878-883.
13. Meltzer EO, Malmstrom K, Lu S, et al. Concomitant montelukast and loratadine as treatment for seasonal allergic rhinitis: a randomized, placebo-controlled clinical trial. J Allergy Clin Immunol. 2000;105(5):917-922.
14. Nayak AS, Philip G, Lu S, Malice MP, Reiss TF. Efficacy and tolerability of montelukast alone or in combination with loratadine in seasonal allergic rhinitis: a multicenter, randomized, double-blind, placebo-controlled trial performed in the fall. Ann Allergy Asthma Immunol. 2002;88(6):592-600.
15. Philip G, Malmstrom K, Hampel FC, et al. Montelukast for treating seasonal allergic rhinitis: a randomized, double-blind, placebo-controlled trial performed in the spring. Clin Exp Allergy. 2002;32(7):1020-1028.
16. Pradalier A, Neukirch C, Dreyfus I, Devillier P. Desloratadine improves quality of life and symptom severity in patients with allergic rhinitis. Allergy. 2007;62(11):1331-1334.
17. Ratner PH, van Bavel JH, Martin BG, et al. A comparison of the efficacy of fluticasone propionate aqueous nasal spray and loratadine, alone and in combination, for the treatment of seasonal allergic rhinitis. J Fam Pract. 1998;47(2):118-125.
18. Skassa-Brociek W, Bousquet J, Montes F, et al. Double-blind placebo-controlled study of loratadine, mequitazine, and placebo in the symptomatic treatment of seasonal allergic rhinitis. J Allergy Clin Immunol. 1988;81(4):725-730.
19. van Adelsberg J, Philip G, LaForce CF, et al. Randomized controlled trial evaluating the clinical benefit of montelukast for treating spring seasonal allergic rhinitis. Ann Allergy Asthma Immunol. 2003;90(2):214-222.
20. Freche C, Leynadier F, Horak F, et al. Mizolastine provides effective symptom relief in patients suffering from perennial allergic rhinitis: a double-blind, placebo-controlled study versus loratadine. Ann Allergy Asthma Immunol. 2002;89(3):304-310.
21. Holmberg K, Tonnel AB, Dreyfus I, et al. Desloratadine relieves nasal congestion and improves quality-of-life in persistent allergic rhinitis. Allergy. 2009;64(11):1663-1670.
22. Kim K, Sussman G, Hebert J, et al. Desloratadine therapy for symptoms associated with perennial allergic rhinitis. Ann Allergy Asthma Immunol. 2006;96(3):460-465.
23. Bronsky EA, Aaronson DW, Berkowitz RB, et al. Dose ranging study of mometasone furoate (Nasonex) in seasonal allergic rhinitis. Ann Allergy Asthma Immunol. 1997;79(1):51-56.
24. Bronsky EA, Dockhorn RJ, Meltzer EO, et al. Fluticasone propionate aqueous nasal spray compared with terfenadine tablets in the treatment of seasonal allergic rhinitis. J Allergy Clin Immunol. 1996;97(4):915-921.
25. Carr W, Bernstein J, Lieberman P, et al. A novel intranasal therapy of azelastine with fluticasone for the treatment of allergic rhinitis. J Allergy Clin Immunol. 2012;129(5):1282-1289.e1210.
26. Creticos P, Fireman P, Settipane G, et al. Intranasal budesonide aqueous pump spray (Rhinocort Aqua) for the treatment of seasonal allergic rhinitis. Rhinocort Aqua Study Group. Allergy Asthma Proc. 1998;19(5):285-294.
27. Di Lorenzo G, Gervasi F, Drago A, et al. Comparison of the effects of fluticasone propionate, aqueous nasal spray and levocabastine on inflammatory cells in nasal lavage and clinical activity during the pollen season in seasonal rhinitics. Clin Exp Allergy. 1999;29(10):1367-1377.
28. Di Lorenzo G, Pacor ML, Pellitteri ME, et al. Randomized placebo-controlled trial comparing fluticasone aqueous nasal spray in mono-therapy, fluticasone plus cetirizine, fluticasone plus montelukast and cetirizine plus montelukast for seasonal allergic rhinitis. Clin Exp Allergy. 2004;34(2):259-267.
29. Dykewicz MS, Kaiser HB, Nathan RA, et al. Fluticasone propionate aqueous nasal spray improves nasal symptoms of seasonal allergic rhinitis when used as needed (prn). Ann Allergy Asthma Immunol. 2003;91(1):44-48.
30. Findlay S, Huber F, Garcia J, Huang L. Efficacy of once-a-day intranasal administration of triamcinolone acetonide in patients with seasonal allergic rhinitis. Ann Allergy. 1992;68(3):228-232.
31. Fokkens WJ, Jogi R, Reinartz S, et al. Once daily fluticasone furoate nasal spray is effective in seasonal allergic rhinitis caused by grass pollen. Allergy. 2007;62(9):1078-1084.
32. Graft D, Aaronson D, Chervinsky P, et al. A placebo- and active-controlled randomized trial of prophylactic treatment of seasonal allergic rhinitis with mometasone furoate aqueous nasal spray. J Allergy Clin Immunol. 1996;98(4):724-731.
33. Hampel FC, Ratner PH, Van Bavel J, et al. Double-blind, placebo-controlled study of azelastine and fluticasone in a single nasal spray delivery device. Ann Allergy Asthma Immunol. 2010;105(2):168-173.
34. Jacobs R, Martin B, Hampel F, et al. Effectiveness of fluticasone furoate 110 microg once daily in the treatment of nasal and ocular symptoms of seasonal allergic rhinitis in adults and adolescents sensitized to mountain cedar pollen. Curr Med Res Opin. 2009;25(6):1393-1401.
35. Kaiser HB, Naclerio RM, Given J, et al. Fluticasone furoate nasal spray: a single treatment option for the symptoms of seasonal allergic rhinitis. J Allergy Clin Immunol. 2007;119(6):1430-1437.
36. Mansfield LE, Posey CR. Daytime sleepiness and cognitive performance improve in seasonal allergic rhinitis treated with intranasal fluticasone propionate. Allergy Asthma Proc. 2007;28(2):226-229.
37. Martin BG, Ratner PH, Hampel FC, et al. Optimal dose selection of fluticasone furoate nasal spray for the treatment of seasonal allergic rhinitis in adults and adolescents. Allergy Asthma Proc. 2007;28(2):216-225.
38. Meltzer EO, Jalowayski AA, Orgel HA, Harris AG. Subjective and objective assessments in patients with seasonal allergic rhinitis: effects of therapy with mometasone furoate nasal spray. J Allergy Clin Immunol.

1998;102(1):39-49.
39. Meltzer EO, Shekar T, Teper AA. Mometasone furoate nasal spray for moderate-to-severe nasal congestion in subjects with seasonal allergic rhinitis. Allergy Asthma Proc. 2011;32(2):159-167.
40. Munk ZM, Gross GN, Hampel FC, Jr., Ratner PH. Preseasonal, once daily triamcinolone acetonide nasal aerosol for seasonal allergic rhinitis. Ann Allergy Asthma Immunol. 1997;78(3):325-331.
41. Munk ZM, LaForce C, Furst JA, et al. Efficacy and safety of triamcinolone acetonide aqueous nasal spray in patients with seasonal allergic rhinitis. Ann Allergy Asthma Immunol. 1996;77(4):277-281.
42. Okubo K, Nakashima M, Miyake N, Komatsubara M, Okuda M. Comparison of fluticasone furoate and fluticasone propionate for the treatment of Japanese cedar pollinosis. Allergy Asthma Proc. 2009;30(1):84-94.
43. Prenner BM, Lanier BQ, Bernstein DI, Shekar T, Teper A. Mometasone furoate nasal spray reduces the ocular symptoms of seasonal allergic rhinitis. J Allergy Clin Immunol. 2010;125(6):1247-1253.e1245.
44. Pullerits T, Praks L, Ristioja V, Lotvall J. Comparison of a nasal glucocorticoid, antileukotriene, and a combination of antileukotriene and antihistamine in the treatment of seasonal allergic rhinitis. J Allergy Clin Immunol. 2002;109(6):949-955.
45. Raphael GD, Berger WE, Prenner BM, et al. Efficacy, safety, and optimal dose selection of beclomethasone dipropionate nasal aerosol for seasonal allergic rhinitis in adolescents and adults. Curr Med Res Opin. 2013;29(10):1329-1340.
46. Ratner PH, Wingertzahn MA, van Bavel JH, et al. Efficacy and safety of ciclesonide nasal spray for the treatment of seasonal allergic rhinitis. J Allergy Clin Immunol. 2006;118(5):1142-1148.
47. Rosenthal R, Berger W, Bronsky E, et al. Tri-Nasal triamcinolone acetonide nasal spray 200 and 400 micrograms qd versus placebo and Nasacort triamcinolone acetonide nasal aerosol 440 micrograms qd in patients suffering from seasonal allergic rhinitis during the grass season. Am J Rhinol. 1998;12(6):427-433.
48. Schenkel E, Newman KB. Therapeutic equivalence of triamcinolone acetonide hydrofluoroalkane and chlorofluorocarbon nasal inhalers in patients with seasonal allergic rhinitis. Am J Rhinol Allergy. 2013;27(2):109-112.
49. Steensen H, Lindqvist N. Treatment of grass pollen-induced hay fever with intranasal budesonide. A double-blind clinical comparison between budesonide and placebo. Allergy. 1981;36(4):245-249.
50. Stern MA, Dahl R, Nielsen LP, Pedersen B, Schrewelius C. A comparison of aqueous suspensions of budesonide nasal spray (128 micrograms and 256 micrograms once daily) and fluticasone propionate nasal spray (200 micrograms once daily) in the treatment of adult patients with seasonal allergic rhinitis. Am J Rhinol. 1997;11(4):323-330.
51. Tinkelman D, Falliers C, Gross G, et al. Multicenter evaluation of triamcinolone acetonide nasal aerosol in the treatment of adult patients with seasonal allergic rhinitis. Ann Allergy. 1990;64(2 Pt 2):234-240.
52. van Bavel JH, Ratner PH, Amar NJ, et al. Efficacy and safety of once-daily treatment with beclomethasone dipropionate nasal aerosol in subjects with seasonal allergic rhinitis. Allergy Asthma Proc. 2012;33(5):386-396.
53. Bende M, Carrillo T, Vona I, da Castel-Branco MG, Arheden L. A randomized comparison of the effects of budesonide and mometasone furoate aqueous nasal sprays on nasal peak flow rate and symptoms in perennial allergic rhinitis. Ann Allergy Asthma Immunol. 2002;88(6):617-623.
54. Chervinsky P, Kunjibettu S, Miller DL, et al. Long-term safety and efficacy of intranasal ciclesonide in adult and adolescent patients with perennial allergic rhinitis. Ann Allergy Asthma Immunol. 2007;99(1):69-76.
55. Given JT, Cheema AS, Dreykluft T, et al. Fluticasone furoate nasal spray is effective and well tolerated for perennial allergic rhinitis in adolescents and adults. Am J Rhinol Allergy. 2010;24(6):444-450.
56. Kivisaari E, Baker RC, Price MJ. Comparison of once daily fluticasone propionate aqueous nasal spray with once daily budesonide reservoir powder device in patients with perennial rhinitis. Clin Exp Allergy. 2001;31(6):855-863.
57. Kobayashi RH, Beaucher WN, Koepke JW, et al. Triamcinolone acetonide aqueous nasal spray for the treatment of patients with perennial allergic rhinitis: a multicenter, randomized, double-blind, placebo-controlled study. Clin Ther. 1995;17(3):503-513.
58. Meltzer EO. Clinical and antiinflammatory effects of intranasal budesonide aqueous pump spray in the treatment of perennial allergic rhinitis. Ann Allergy Asthma Immunol. 1998;81(2):128-134.
59. Meltzer EO, Jacobs RL, LaForce CF, et al. Safety and efficacy of once-daily treatment with beclomethasone dipropionate nasal aerosol in subjects with perennial allergic rhinitis. Allergy Asthma Proc. 2012;33(3):249-257.
60. Meltzer EO, Kunjibettu S, Hall N, et al. Efficacy and safety of ciclesonide, 200 microg once daily, for the treatment of perennial allergic rhinitis. Ann Allergy Asthma Immunol. 2007;98(2):175-181.
61. Mohar D, Berger WE, Laforce C, et al. Efficacy and tolerability study of ciclesonide nasal aerosol in patients with perennial allergic rhinitis. Allergy Asthma Proc. 2012;33(1):19-26.
62. Nathan RA, Berger W, Yang W, et al. Effect of once-daily fluticasone furoate nasal spray on nasal symptoms in adults and adolescents with perennial allergic rhinitis. Ann Allergy Asthma Immunol. 2008;100(5):497-505.
63. Spector S, Bronsky E, Chervinsky P, et al. Multicenter, double-blind, placebo-controlled trial of triamcinolone acetonide nasal aerosol in the treatment of perennial allergic rhinitis. Ann Allergy. 1990;64(3):300-305.
64. Vasar M, Houle PA, Douglass JA, et al. Fluticasone furoate nasal spray: effective monotherapy for symptoms of perennial allergic rhinitis in adults/adolescents. Allergy Asthma Proc. 2008;29(3):313-321.
65. Weinstein SF, Andrews CP, Shah SR, et al. Long-term efficacy and safety of once-daily treatment with beclomethasone dipropionate nasal aerosol. Allergy Asthma Proc. 2014;35(4):323-331.
66. Okubo K, Baba K. Therapeutic effect of montelukast, a cysteinyl leukotriene receptor 1 antagonist, on Japanese patients with seasonal allergic rhinitis. Allergol Int. 2008;57(3):247-255.
67. Philip G, Nayak AS, Berger WE, et al. The effect of montelukast on rhinitis symptoms in patients with asthma and seasonal allergic rhinitis. Curr Med Res Opin. 2004;20(10):1549-1558.
68. van Adelsberg J, Philip G, Pedinoff AJ, et al. Montelukast improves symptoms of seasonal allergic rhinitis over a 4-week treatment period. Allergy. 2003;58(12):1268-1276.
69. Patel P, Philip G, Yang W, et al. Randomized, double-blind, placebo-controlled study of montelukast for treating perennial allergic rhinitis. Ann Allergy Asthma Immunol. 2005;95(6):551-557.
70. Bernstein JA, Prenner B, Ferguson BJ, et al. Double-blind, placebo-controlled trial of reformulated azelastine nasal spray in patients with seasonal allergic rhinitis. Am J Rhinol Allergy. 2009;23(5):512-517.
71. Howland WC, Amar NJ, Wheeler W, Sacks H. Efficacy and safety of azelastine 0.15% nasal spray administered once daily in patients with allergy to Texas mountain cedar pollen. Int Forum Allergy Rhinol. 2011;1(4):275-279.
72. LaForce CF, Corren J, Wheeler WJ, Berger WE. Efficacy of azelastine nasal spray in seasonal allergic rhinitis patients who remain symptomatic after treatment with fexofenadine. Ann Allergy Asthma Immunol. 2004;93(2):154-159.
73. Lumry W, Prenner B, Corren J, Wheeler W. Efficacy and safety of azelastine nasal spray at a dose of 1 spray per nostril twice daily. Ann Allergy Asthma Immunol. 2007;99(3):267-272.
74. Shah S, Berger W, Lumry W, et al. Efficacy and safety of azelastine 0.15% nasal spray and azelastine 0.10% nasal spray in patients with seasonal allergic rhinitis. Allergy Asthma Proc. 2009;30(6):628-633.
75. Shah SR, Nayak A, Ratner P, Roland P, Michael Wall G. Effects of olopatadine hydrochloride nasal spray 0.6% in the treatment of seasonal allergic rhinitis: a phase III, multicenter, randomized, dou-

ble-blind, active- and placebo-controlled study in adolescents and adults. Clin Ther. 2009;31(1):99-107.
76. van Bavel J, Howland WC, Amar NJ, Wheeler W, Sacks H. Efficacy and safety of azelastine 0.15% nasal spray administered once daily in subjects with seasonal allergic rhinitis. Allergy Asthma Proc. 2009;30(5):512-518.
77. Nathan RA, Finn AF, Jr., LaForce C, et al. Comparison of cetirizine-pseudoephedrine and placebo in patients with seasonal allergic rhinitis and concomitant mild-to-moderate asthma: randomized, double-blind study. Ann Allergy Asthma Immunol. 2006;97(3):389-396.
78. Agertoft L, Wolthers OD, Fuglsang G, Pedersen S. Nasal powder administration of budesonide for seasonal rhinitis in children and adolescents. Pediatr Allergy Immunol. 1993;4(3):152-156.
79. Banov CH, Silvers WS, Green AW, et al. Placebo-controlled, double-blind study of the efficacy and safety of triamcinolone acetonide aerosol nasal inhaler in pediatric patients with seasonal allergic rhinitis. Clin Ther. 1996;18(2):265-272.
80. Georges G, Kim KT, Ratner P, Segall N, Qiu C. Effect of intranasal triamcinolone acetonide on basal hypothalamic-pituitary-adrenal axis function in children with allergic rhinitis. Allergy Asthma Proc. 2014;35(2):163-170.
81. Meltzer EO, Lee J, Tripathy I, et al. Efficacy and safety of once-daily fluticasone furoate nasal spray in children with seasonal allergic rhinitis treated for 2 wk. Pediatr Allergy Immunol. 2009;20(3):279-286.
82. Storms WW, Segall N, Mansfield LE, et al. Efficacy and safety of beclomethasone dipropionate nasal aerosol in pediatric patients with seasonal allergic rhinitis. Ann Allergy Asthma Immunol. 2013;111(5):408-414.e401.
83. Baena-Cagnani CE, Patel P. Efficacy and long-term safety of mometasone furoate nasal spray in children with perennial allergic rhinitis. Curr Med Res Opin. 2010;26(9):2047-2055.
84. Berger WE, Jacobs RL, Amar NJ, et al. Efficacy and safety of beclomethasone dipropionate nasal aerosol in children with perennial allergic rhinitis. Ann Allergy Asthma Immunol. 2015;115(2):130-136.
85. Fokkens WJ, Cserhati E, dos Santos JM, et al. Budesonide aqueous nasal spray is an effective treatment in children with perennial allergic rhinitis, with an onset of action within 12 hours. Ann Allergy Asthma Immunol. 2002;89(3):279-284.
86. Maspero JF, Rosenblut A, Finn A, Jr., et al. Safety and efficacy of fluticasone furoate in pediatric patients with perennial allergic rhinitis. Otolaryngol Head Neck Surg. 2008;138(1):30-37.
87. Weinstein S, Qaqundah P, Georges G, Nayak A. Efficacy and safety of triamcinolone acetonide aqueous nasal spray in children aged 2 to 5 years with perennial allergic rhinitis: a randomized, double-blind, placebo-controlled study with an open-label extension. Ann Allergy Asthma Immunol. 2009;102(4):339-347.
88. Razi C, Bakirtas A, Harmanci K, Turktas I, Erbas D. Effect of montelukast on symptoms and exhaled nitric oxide levels in 7- to 14-year-old children with seasonal allergic rhinitis. Ann Allergy Asthma Immunol. 2006;97(6):767-774.
89. Meltzer EO, Blaiss M, Fairchild CJ. Comprehensive report of olopatadine 0.6% nasal spray as treatment for children with seasonal allergic rhinitis. Allergy Asthma Proc. 2011;32(3):213-220.
90. Berger W, Meltzer EO, Amar N, et al. Efficacy of MP-AzeFlu in children with seasonal allergic rhinitis: Importance of paediatric symptom assessment. Pediatr Allergy Immunol. 2016;27(2):126-133.
91. Creticos PS, Maloney J, Bernstein DI, et al. Randomized controlled trial of a ragweed allergy immunotherapy tablet in North American and European adults. J Allergy Clin Immunol. 2013;131(5):1342-1349 e1346.
92. Dahl R, Kapp A, Colombo G, et al. Efficacy and safety of sublingual immunotherapy with grass allergen tablets for seasonal allergic rhinoconjunctivitis. J Allergy Clin Immunol. 2006;118(2):434-440.
93. Maloney J, Bernstein DI, Nelson H, et al. Efficacy and safety of grass sublingual immunotherapy tablet, MK-7243: a large randomized controlled trial. Ann Allergy Asthma Immunol. 2014;112(2):146-153. e142.
94. Nelson HS, Nolte H, Creticos P, et al. Efficacy and safety of timothy grass allergy immunotherapy tablet treatment in North American adults. J Allergy Clin Immunol. 2011;127(1):72-80 e72.
95. Demoly P, Emminger W, Rehm D, et al. Effective treatment of house dust mite-induced allergic rhinitis with 2 doses of the SQ HDM SLIT-tablet: Results from a randomized double-blind, placebo-controlled phase III trial. J Allergy Clin Immunol 2016;137(2):444-451.
96. Nolte H, Bernstein DI, Nelson HS, et al. Efficacy of house dust mite SLIT-tablet in North American adolescents and adults in a randomized, placebo-controlled trial. J Allergy Clin Immunol. 2016;138(6):1631-1638.
97. Okubo K, Masuyama K, Imai T, et al. Efficacy and safety of the SQ house dust mite sublingual immunotherapy tablet in Japanese adults and adolescents with house dust mite-induced allergic rhinitis. J Allergy Clin Immunol. 2017;139(6):1840-1848.e1810.
98. Bufe A, Eberle P, Franke-Beckmann E, et al. Safety and efficacy in children of an SQ-standardized grass allergen tablet for sublingual immunotherapy. J Allergy Clin Immunol. 2009;123(1):167-173 e167.
99. Halken S, Agertoft L, Seidenberg J, et al. Five-grass pollen 300IR SLIT tablets: efficacy and safety in children and adolescents. Pediatr Allergy Immunol. 2010;21(6):970-976.