Effective Health Care Program

Comparative Effectiveness Review
Number 120

Treatments for Seasonal Allergic Rhinitis

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This report is based on research conducted by the Blue Cross and Blue Shield Association Technology Evaluation Center Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-2007-10058-I). The findings and conclusions in this document are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new health care technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm.

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an email list to learn about new program products and opportunities for input.

We welcome comments on this systematic review. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

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Key Informants

In designing the study questions, the EPC consulted several Key Informants who represent the end-users of research. The EPC sought Key Informant input on priority areas for research and synthesis. Key Informants are not involved in the analysis of the evidence or the writing of the report. Therefore, in the end, study questions, design, methodological approaches, and/or conclusions do not necessarily represent the views of individual Key Informants.

Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any conflicts of interest.

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Technical Expert Panel

In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

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Peer Reviewers

Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report does not necessarily represent the views of individual reviewers.

Peer Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, Peer Reviewers with potential nonfinancial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

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Treatments for Seasonal Allergic Rhinitis

Structured Abstract

Objectives. This review compared the effectiveness and common adverse events of medication classes used to treat seasonal allergic rhinitis (SAR) in adolescents and adults, in pregnant women, and in children. We sought to compare the following classes of drugs: oral and nasal antihistamines and decongestants; intranasal corticosteroids, mast cell stabilizers (cromolyn), and anticholinergics (ipratropium); oral leukotriene receptor antagonists (montelukast); and nasal saline.

Data sources. We identified English-language studies using a peer-reviewed search strategy. The following databases were searched on July 18, 2012, with no date restrictions: MEDLINE® (PubMed® and Ovid), Embase® (Ovid), Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews, and DARE (Database of Abstracts of Reviews of Effects).

Review methods. We consulted a Technical Expert Panel to identify the treatment comparisons most relevant to patients and providers. Subpopulations of interest were individuals with asthma or eye symptoms. Outcomes of interest were patient-reported symptom scores, quality of life, and adverse events. Inclusion was limited to studies that reported an outcome of interest and directly compared drugs of interest that were approved by the U.S. Food and Drug Administration (FDA). Two independent reviewers performed study selection and data abstraction. Disagreements were resolved by consensus or a third reviewer.

Results. We identified 59 trials that addressed 13 of 22 treatment comparisons of interest for adolescents and adults, 0 of 17 comparisons of interest for pregnant women, and 1 of 21 comparisons of interest for children. Across all comparisons, 20 of 39 drugs FDA approved for the treatment of SAR were studied. For adolescents and adults with SAR, evidence was sufficient to form the following conclusions. For the treatment of nasal symptoms, montelukast (oral leukotriene receptor antagonist) and intranasal corticosteroid were similarly effective (high strength of evidence [SOE]). For the treatment of nasal symptoms and eye symptoms, intranasal corticosteroid, nasal antihistamine, and combination intranasal corticosteroid plus nasal antihistamine were similarly effective (high SOE), and montelukast and oral selective antihistamine were similarly effective (moderate SOE). For improved quality of life, montelukast and oral selective antihistamine were similarly effective (moderate SOE), and combination oral selective antihistamine plus intranasal corticosteroid was superior to oral selective antihistamine alone (low SOE). To avoid insomnia, oral selective antihistamine was superior to oral decongestant and to combination oral selective antihistamine plus oral decongestant (moderate SOE). In patients codiagnosed with SAR and asthma, montelukast was superior to oral selective antihistamine for reduced asthma rescue medication use (moderate SOE). In sensitivity analyses using a lower threshold for minimum clinical effectiveness, combination oral selective antihistamine plus oral decongestant was superior to oral selective antihistamine alone for the treatment of nasal symptoms in adolescents and adults with SAR (moderate SOE). In this population, we did not find evidence that any single treatment was both more effective and had lower risk of harms. Evidence for both effectiveness and harms was insufficient regarding the

comparison between oral selective and oral nonselective antihistamine in children. All effectiveness and harms outcomes were limited by short trial durations.

Conclusions. Several effectiveness comparisons demonstrated similarity of treatments for selected outcomes. For most harms comparisons, the evidence was insufficient. Conclusions were limited by (1) lack of comparative evidence for all drugs within each class and (2) lack of evidence on the magnitude of symptom change that constitutes a minimal clinically important difference.

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Executive Summary

Background

Seasonal allergic rhinitis (SAR), also known as hay fever, is an allergic reaction in the upper airways that occurs when sensitized individuals encounter airborne allergens (typically tree, grass, and weed pollens and some molds). SAR afflicts approximately 10 percent of the U.S. population, or 30 million individuals.[1,2] Although pollen seasons vary across the United States, generally, tree pollens emerge in the spring, grass pollens in the summer, and weed pollens in the fall. Outdoor molds generally are prevalent in the summer and fall. SAR is distinguished from perennial allergic rhinitis (PAR), which is triggered by continuous exposure to house dust mites, animal dander, and other allergens generally found in an individual's indoor environment. Patients may have either SAR or PAR or both (i.e., PAR with seasonal exacerbations). The four defining symptoms of allergic rhinitis are nasal congestion, nasal discharge (rhinorrhea), sneezing, and/or nasal itch. Many patients also experience eye symptoms, such as itching, tearing, and redness.[3] Additional signs of rhinitis include the "allergic salute" (rubbing the hand against the nose in response to itching and rhinorrhea), "allergic shiner" (bruised appearance of the skin under one or both eyes), and "allergic crease" (a wrinkle across the bridge of the nose caused by repeated allergic salute).[4-7] SAR can adversely affect quality of life,[8-10] sleep,[11,12] cognition,[13] emotional life,[14] and work or school performance.[15-17] Treatment improves symptoms and quality of life.

Treatments for SAR include allergen avoidance, pharmacotherapy, and immunotherapy. Although allergen avoidance may be the preferred treatment, for SAR, total allergen avoidance may be an unrealistic approach, as it may require limiting time spent outdoors. Thus, pharmacotherapy is preferable to allergen avoidance for SAR symptom relief. Allergen-specific immunotherapy is the subject of a separate review, also sponsored by the Agency for Healthcare Research and Quality (AHRQ) and posted on the Effective Health Care Web site (www.effectivehealthcare.ahrq.gov/reports/final/cfm).

Six classes of drugs and nasal saline are used to treat SAR.

- *Antihistamines* used to treat allergic rhinitis bind *peripheral* H_1 histamine receptors selectively or nonselectively. Nonselective binding to other receptor types can cause dry mouth, dry eyes, urinary retention, constipation, and tachycardia. Sedation results from the nonselective binding to *central* H_1 receptors. In contrast, selective antihistamines may have reduced incidence of adverse effects.[18] Both selective and nonselective antihistamines interact with drugs that inhibit cytochrome P450 isoenzymes,[4] which may impact patient selection. Two nasal antihistamines—azelastine and olopatadine—are approved by the U.S. Food and Drug Administration (FDA) for the treatment of SAR. Adverse effects of nasal antihistamines may include a bitter aftertaste.
- *Corticosteroids* are potent anti-inflammatory drugs. Intranasal corticosteroids are recommended as first-line treatment for moderate/severe or persistent allergic rhinitis.[5,19] However, their efficacy for the symptom of nasal congestion compared with nasal antihistamine is uncertain,[20,21] particularly in patients with mild allergic rhinitis. For patients with unresponsive symptoms, it is unclear whether adding oral or nasal antihistamine provides any additional benefit. Little is known about cumulative corticosteroid effects in patients who take concomitant oral or inhaled formulations for other diseases. Intranasal corticosteroids do not appear to cause adverse events associated

with systemic absorption (e.g., adrenal suppression, bone fracture among the elderly, and reduced bone growth and height in children). Adverse local effects may include increased intraocular pressure and nasal stinging, burning, bleeding, and dryness. Oral and intramuscular corticosteroids are not reviewed in this report.

- *Decongestants* stimulate the sympathetic nervous system to produce vasoconstriction, which results in decreased nasal swelling and decreased congestion. After several days of nasal decongestant use, rebound congestion (rhinitis medicamentosa) may occur. Other local adverse effects may include nosebleeds, stinging, burning, and dryness. Oral decongestants are used alone and in combination, often with antihistamines. Systemic adverse effects of decongestants may include hypertension, tachycardia, insomnia, headaches, and irritability.[4,22] Decongestants are used with caution, if at all, in patients with diabetes mellitus, ischemic heart disease, unstable hypertension, prostatic hypertrophy, hyperthyroidism, and narrow-angle glaucoma. Oral decongestants are contraindicated with coadministered monoamine oxidase inhibitors and in patients with uncontrolled hypertension or severe coronary artery disease.[23]
- *Ipratropium* nasal spray is an anticholinergic drug approved by the FDA for treating rhinorrhea associated with SAR. Postmarketing experience suggests that there may be some systemic absorption. Cautious use is advised for patients with narrow-angle glaucoma, prostatic hypertrophy, or bladder neck obstruction, particularly if another anticholinergic is coadministered. Local adverse effects may include nosebleeds and nasal and oral dryness.[24]
- Nasal mast cell stabilizers are commonly administered prophylactically, before an allergic reaction is triggered, although as-needed use has been described and may be of benefit. *Cromolyn* is the only mast cell stabilizer approved by the FDA for the treatment of SAR. For prophylaxis, it requires a loading period during which it is applied four times daily for several weeks. Systemic absorption is minimal. Local adverse effects may include nasal irritation, sneezing, and an unpleasant taste.[4,23]
- *Leukotriene receptor antagonists* are oral medications that reduce allergy symptoms by reducing inflammation.[25,26] Montelukast is the only leukotriene receptor antagonist approved by the FDA for the treatment of SAR. Potential adverse effects include upper respiratory tract infection and headache.[23]

Nasal saline has been shown to be beneficial in treating nasal SAR symptoms.[27] Because it is associated with few adverse effects, nasal saline may be particularly well suited for treating SAR symptoms during pregnancy, in children, and in those whose treatment choices are restricted due to comorbidities, such as hypertension and urinary retention.

The optimal treatment of SAR during pregnancy is unknown. Drugs effective before pregnancy may be effective during pregnancy, but their use may be restricted because of concerns about maternal and fetal safety. Preferred treatments are Pregnancy Category B drugs (nasal cromolyn, budesonide, and ipratropium; several oral selective and nonselective antihistamines; and the oral leukotriene receptor antagonist montelukast) commencing in the second trimester, after organogenesis.

Objectives

Although there are multiple guidelines for the treatment of allergic rhinitis,[5,20,28-31] the guidelines are not consistently based on systematic reviews of the literature and often do not

address the treatment of SAR in children and pregnant women. Guidelines generally support the use of intranasal corticosteroids as first-line treatment of moderate/severe SAR. However, agreement is lacking about four other issues of importance to patients and clinicians:

- First-line treatment for mild SAR
- The comparative effectiveness and safety of SAR treatments used in combination with each other for both mild and moderate/severe SAR
- The comparative effectiveness of as-needed use compared with daily dosing
- The comparative effectiveness and harms of SAR treatments for eye symptoms and asthma symptoms that often co-occur with SAR

This review addresses the four issues above. The scope of this review is comparisons across pharmacologic classes. With input from the Technical Expert Panel (TEP), we chose to focus on across-class comparisons because this is the first question that patients, clinicians, and other decisionmakers face. Although there may be differences among drugs within the same class, previous comparative effectiveness reviews in allergic rhinitis[5,20,29,32-38] have found insufficient evidence to support superior effectiveness of any single drug within a drug class. A direct consequence of the decision to conduct across-class comparisons is the inability to compare individual drugs across studies. Additionally, limited conclusions can be drawn about drug classes that are poorly represented by the drugs studied. To our knowledge, methodological approaches for meta-analysis of class comparisons based on studies of single within-class treatment comparisons have not been published.

Key Questions

Key Question 1. What is the comparative effectiveness of pharmacologic treatments, alone or in combination with each other, for adults and adolescents (≥12 years of age) with mild or with moderate/severe SAR?

a. How does effectiveness vary with long-term (months) or short-term (weeks) use?
b. How does effectiveness vary with intermittent or continuous use?
c. For those with symptoms of allergic conjunctivitis, does pharmacologic treatment of SAR provide relief of eye symptoms (itching, tearing)?
d. For those codiagnosed with asthma, does pharmacologic treatment of SAR provide asthma symptom relief?

Key Question 2. What are the comparative adverse effects of pharmacologic treatments for SAR for adults and adolescents (≥12 years of age)?

a. How do adverse effects vary with long-term (months) and short-term (weeks) use?
b. How do adverse effects vary with intermittent or continuous use?

Key Question 3. For the subpopulation of pregnant women, what are the comparative effectiveness and comparative adverse effects of pharmacologic treatments, alone or in combination with each other, for mild and for moderate/severe SAR?

a. How do effectiveness and adverse effects vary with long-term (months) or short-term (weeks) use?
b. How do effectiveness and adverse effects vary with intermittent or continuous use?

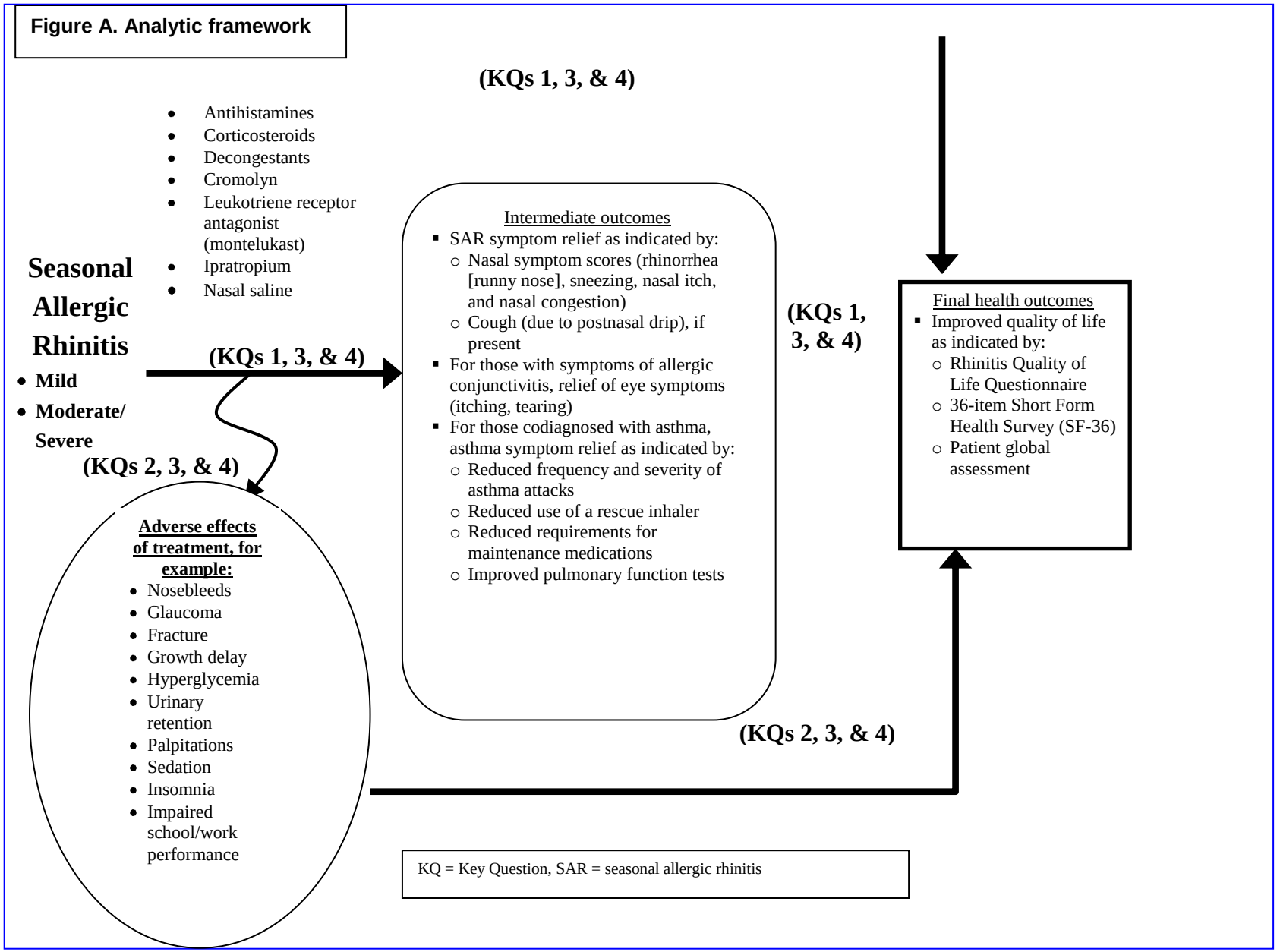
Key Question 4. For the subpopulation of children (<12 years of age), what are the comparative effectiveness and comparative adverse effects of pharmacologic treatments, alone or in combination with each other, for mild and for moderate/severe SAR?

a. How do effectiveness and adverse effects vary with long-term (months) or short-term (weeks) use?
b. How do effectiveness and adverse effects vary with intermittent or continuous use?

Analytic Framework

The analytic framework for this report is presented in Figure A. The figure depicts the Key Questions (KQs) in relation to SAR treatments, adverse effects, and outcomes. The six drug classes of SAR treatments and nasal saline may produce intermediate outcomes such as relief of rhinitis symptoms and, if present, eye and asthma symptoms. Treatments also may result in improved quality of life, the final health outcome. Adverse events may occur at any point after treatment is received and may impact quality of life directly.

Figure A. Analytic framework



Methods

Input From Stakeholders

We formulated the population, intervention, comparator, outcome, timing, setting (PICOTS) conceptual framework and KQs during a topic refinement stage. Key Informants were patients, providers (allergists, a pediatric pulmonologist, pharmacists, otorhinolaryngologists, and family physicians), and payers. Their input was sought to identify important clinical and methodological issues pertinent to the review. We developed a research protocol with input of a TEP. The protocol followed the methods outlined in the AHRQ "Methods Guide for Effectiveness and Comparative Effectiveness Reviews" (Methods Guide).[39] The public was invited to provide comments on the KQs.

Data Sources and Selection

We developed a peer-reviewed search strategy and searched the following databases: MEDLINE® (PubMed® and Ovid), Embase® (Ovid), and the Cochrane Central Register of Controlled Trials (CENTRAL). For systematic reviews, the databases searched were the Cochrane Database of Systematic Reviews, Database of Abstracts and Reviews of Effects (DARE), and the Health Technology Assessment (HTA) databases of the United Kingdom's Centre for Reviews and Dissemination. Articles were limited to those published in the English language, based on technical expert advice that the majority of the literature on this topic is published in English. The databases were searched on July 18, 2012, with no date restrictions. We searched the FDA Web site, electronic conference abstracts of relevant professional organizations, and clinical trial registries for gray literature. Scientific information packets provided by product manufacturers were evaluated to identify unpublished trials that met inclusion criteria.

We sought expert guidance to identify the drug class comparisons most relevant for treatment decisionmaking. A total of 60 treatment comparisons were identified for all three patient populations. For all comparisons, the highest quality evidence was sought. Head-to-head randomized controlled trials (RCTs) were preferred, due to potential bias introduced in uncontrolled or noncomparative studies by the subjective reporting of both efficacy outcomes and harms in SAR research. For comparisons with sparse data from RCTs, we sought nonrandomized trials and comparative observational studies that controlled for confounders and were blinded.

Two reviewers screened abstracts and full-text reports, with conflicts resolved by consensus or a third reviewer. Selection criteria included: disease limited to SAR or results for patients with SAR reported separately, direct head-to-head comparison of interest of FDA-approved drugs from different drug classes, outcomes include patient-reported symptom scores and/or validated quality-of-life instruments, and minimum 2-week duration. Selective and nonselective antihistamine (based on specificity for peripheral H_1 receptors) and different routes of administration (oral or nasal) were considered different classes for this purpose.

Data Abstraction and Quality Assessment

Comparative effectiveness and harms data from included studies were abstracted into an electronic database by two team members. We reconciled discrepancies during daily team

discussions. Extracted information included general trial characteristics, baseline characteristics of trial participants, eligibility criteria, interventions, outcome measures and their method of ascertainment, and results of each predefined outcome.

The quality of individual RCTs was assessed using the United States Preventive Services Task Force (USPSTF)[40] criteria, in accordance with the AHRQ Methods Guide.[39] Two reviewers independently assigned quality ratings of good, fair, or poor. Discordant ratings were resolved with input from a third reviewer. Particular care was taken to ascertain whether patients were properly blinded to treatment because all outcomes of interest were patient reported. Open-label trials and trials in which patient blinding was deemed inadequate received a quality rating of poor.

The quality of harms reporting was assessed using the USPSTF rating, with specific attention to both patient and assessor blinding, and the McMaster Quality Assessment Scale of Harms (McHarm).[41] In particular, the process of harms ascertainment was noted and characterized as either an active process if structured questionnaires were used, a passive process if only spontaneous patient reports were collected, or intermediate if active surveillance for at least one adverse event was reported. Trials using only passive harms ascertainment were considered to have a high risk of bias—specifically, underreporting or inconsistent reporting of harms.

Two reviewers independently assessed the risk of bias of relevant systematic reviews and meta-analyses using the following criteria derived from the AMSTAR tool and AHRQ guidance:[42]

- Details of the literature search were provided.
- Study inclusion and exclusion criteria were stated.
- The quality assessment of included studies was described and documented.

Data Synthesis and Analysis

Evidence on the comparative effectiveness and harms for each class comparison was summarized in narrative text. Quantitative pooling of results (meta-analysis) was considered if three or more clinically and methodologically similar studies reported on a given outcome. Three was an arbitrary number used as an operational criterion for meta-analyses. Only studies that reported variance estimates for group-level treatment effects could be pooled. The pooling method involved inverse variance weighting and a random-effects model. We assessed statistical heterogeneity by using Cochran's Q statistic ($p = 0.10$) and the I^2 statistic. Meta-analysis was performed for adverse events that investigators reported as severe or that led to discontinuation of treatment. Three or more trials reporting the adverse event were required for pooling. Mean differences were calculated for continuous outcomes (effectiveness outcomes), and risk differences were calculated for dichotomous outcomes (harms). For studies that could not be quantitatively pooled, results were qualitatively combined when it was reasonable to do so (e.g., for similar studies reporting similar treatment effects).

In this review, we formed conclusions about treatment classes based on meta-analyses of studies that compared single treatments. Methodological approaches for this type of analysis have not been published. However, we proceeded with this analysis with support from the TEP. For class comparisons that were poorly represented (i.e., a small proportion of drugs in a class were assessed in included studies), we applied conclusions to the specific drugs studied; how well such conclusions generalize to other drugs in the same class is uncertain.

To assess the magnitude of treatment effects, we searched the published literature for minimal clinically important differences (MCIDs) derived from anchor-based or distribution-

based methods. Anchor-based MCIDs are considered more robust and have been published for quality-of-life measures,[43,44] asthma rescue medication use,[45] and forced expired volume in 1 second (FEV_1).[45,46] Anchor-based MCIDs have not been defined for rhinitis symptom scales. One group defined a distribution-based MCID for total nasal symptom score (TNSS) as 0.52 on a 0-12 point scale.[47,48] This represented one-fifth of the standard deviation of baseline TNSS scores in a trial of 27 patients. Bousquet and colleagues[49] examined the responsiveness, defined as the ability of an instrument to measure change, of visual analog scale (VAS) scores to changes in TNSS scores (on an interval scale). A 2.9 cm improvement on a 10 cm VAS correlated with a 3-point improvement on a 0-12 point TNSS, defined a priori as a meaningful change. Although responsiveness and MCID are overlapping concepts, they are not identical. In allergen-specific immunotherapy trials, a minimum 30-percent greater improvement than placebo in composite symptom/rescue medication use scores is considered clinically meaningful.[50] This threshold was based on an evaluation of 68 placebo-controlled double-blind trials.

In the absence of gold-standard MCIDs for symptom rating scales used in clinical rhinitis research, we sought input from our TEP, as recommended in the AHRQ Methods Guide.[39] For TNSS on a 0–12 point scale, two experts considered a 4-point change meaningful and one expert considered a 2-point change meaningful.

For TNSS, potential MCIDs obtained from the sources described above are summarized in Table A. As shown, two sources (row 2 and row 4) converged around an MCID of 30-percent change in maximum TNSS score. This is supported by three TEP members who proposed a similar threshold for individual nasal symptoms (1 point on a 0–3 point scale) and two TEP members who proposed a similar threshold for total ocular symptom score (TOSS) (3 points on a 0–9 point scale). The concordance of these values increased our confidence that 30 percent of maximum score is a useful threshold for purposes of our analysis and could be applied across symptom scales. We therefore examined the strength of evidence for symptom outcomes using this MCID calculated for each scale used.

Table A. Quantified minimal clinically important differences for total nasal symptom score

Source	MCID	Scale
1. Distribution-based approach in 27 patients[47,48]	0.52	0–12 interval
2. Responsiveness of visual analog scale to interval scale[49]	2.9	0–10 visual analog
3. Allergen-specific immunotherapy recommendation[50]	30%[a]	Any
4. Technical Expert Panel input	2-4	0–12 interval

[a]A 30% greater improvement compared with placebo in composite symptom/rescue medication use scores was proposed as minimally clinically meaningful.

MCID = minimal clinically important difference.

We initially assessed the evidence to determine whether one treatment was therapeutically superior to another and found that, for many comparisons, the evidence suggested equivalence of the treatments compared. We therefore decided post hoc to adopt an equivalence approach to evidence assessment, in accordance with the AHRQ Methods Guide,[39] and assessed the body of evidence to support one of the following conclusions:

- Superiority: One treatment demonstrated greater effectiveness than the other, either for symptom improvement or harm avoidance.
- Equivalence: Treatments demonstrated comparable effectiveness, either for symptom improvement or harm avoidance.

- Insufficient evidence: The evidence supported neither a conclusion of superiority nor a conclusion of equivalence.

The strength of the body of evidence for each outcome was determined in accordance with the AHRQ Methods Guide[39] and is based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.[51,52] Two reviewers independently evaluated the strength of evidence, and agreement was reached through discussion and consensus when necessary. Four main domains were assessed: risk of bias, consistency, directness, and precision. The body of evidence was evaluated separately for each treatment comparison and each outcome of interest to derive a single GRADE of high, moderate, low, or insufficient evidence.

- A high GRADE indicates high confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
- A moderate GRADE indicates moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
- A low GRADE indicates low confidence that the evidence reflects the true effect. Further research is likely to change the confidence in the estimate of effect and is likely to change the estimate.
- A GRADE of insufficient indicates that evidence either is unavailable or does not permit a conclusion.

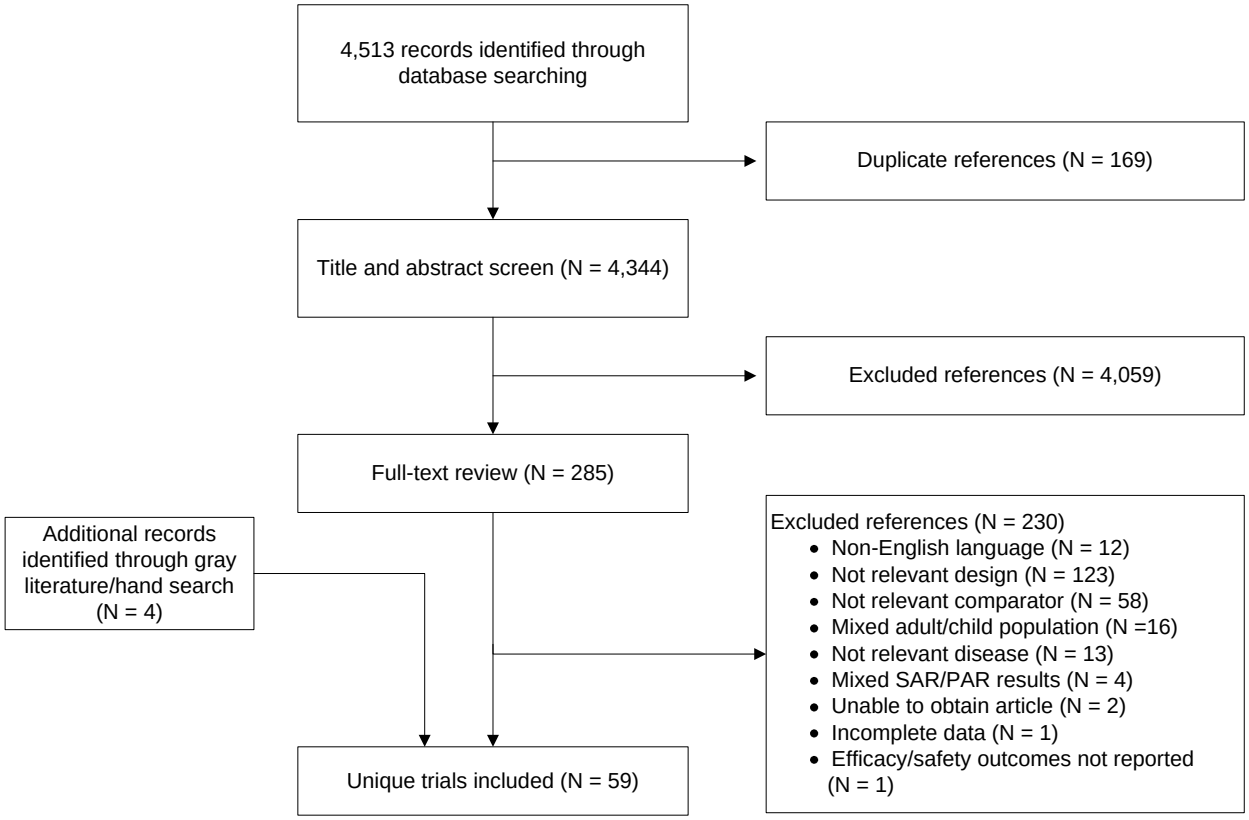
Decision rules used to assess each GRADE domain are provided in the full report.

Results

Overview

Of the 4,513 records identified through the literature search, 4,458 were excluded during screening. Four records were identified through gray literature and hand searching of bibliographies. One unpublished trial listed on ClinicalTrials.gov satisfied our inclusion criteria (NCT00960141). However, this trial was not included because quality assessment was not possible without the published report. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[53] diagram shown in Figure B depicts the flow of search screening and study selection. A total of 59 unique trials were included. For KQ 1 and KQ 2, 56 RCTs and 1 quasi-RCT that addressed 13 out of 22 comparisons of interest were found. For KQ 3, no studies that addressed any of 17 comparisons of interest were found. For KQ 4, two RCTs that addressed 1 of 21 comparisons of interest were found. No observational studies, systematic reviews, or meta-analyses that met our inclusion criteria were identified.

Figure B. PRISMA diagram for identified trials



PAR = perennial allergic rhinitis; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SAR = seasonal allergic rhinitis.

Key Question 1. Comparative Effectiveness of SAR Treatments in Adults and Adolescents 12 Years of Age or Older

Results for the 13 comparisons for which we found studies that satisfied our inclusion criteria are presented in Table B. For most outcomes, evidence was insufficient to form any comparative effectiveness conclusion. In five comparisons, we found evidence for comparable effectiveness (equivalence) of treatments for at least one outcome (rows 5, 6, 8, 11, and 12 in Table B). We found evidence for superior effectiveness of one treatment over another for one outcome in each of two comparisons (row 5 and row 9 in Table B). For seven comparisons, trials included only a small proportion of the drugs in each class (rows 1, 6, 8, 9, 10, 11, and 12 in Table B). Specific outcomes for the entries in Table B are detailed in the full report.

Table B. Summary of findings and strength of evidence for effectiveness in 13 treatment comparisons: Key Question 1—adults and adolescents

Comparison	Representation[a]	Nasal Symptoms	Eye Symptoms	Asthma Symptoms	Quality of Life
1. Oral S-AH vs. oral nS-AH	40% vs. 18%	Insufficient			Insufficient
2. Oral S-AH vs. nasal AH	60% vs. azelastine (50%)	Insufficient			Insufficient
3. Oral S-AH vs. INCS	60% vs. 62.5%	Insufficient	Insufficient		Insufficient
4. Oral S-AH vs. oral D	80% vs. pseudoephedrine (50%)	Insufficient	Insufficient		
5. Oral S-AH vs. LRA	60% vs. montelukast (100%)	Equivalent: moderate	Equivalent: moderate	LRA: moderate	Equivalent: moderate
6. INCS vs. nasal AH	25% vs. 100%	Equivalent: high	Equivalent: high		Insufficient
7. INCS vs. nasal C	62.5% vs. cromolyn (100%)	Insufficient			
8. INCS vs. LRA	25% vs. montelukast (100%)	Equivalent: high		Insufficient	
9. Oral S-AH + INCS vs. oral S-AH	40% oral S-AH, 25% INCS	Insufficient	Insufficient		Oral S-AH + INCS: low
10. Oral S-AH + INCS vs. INCS	60% oral S-AH, 25% INCS	Insufficient	Insufficient		Insufficient
11. INCS + nasal AH vs. INCS	FP (12.5%), azelastine (50%)	Equivalent: high	Equivalent: high		Insufficient
12. INCS + nasal AH vs. nasal AH	FP (12.5%), azelastine (50%)	Equivalent: high	Equivalent: high		Insufficient
13. Oral S-AH + oral D vs. oral S-AH	80% oral S-AH, pseudoephedrine (50%)	Insufficient	Insufficient		

Note: Entries indicate comparative efficacy conclusions supported by the evidence or insufficient evidence to form a conclusion. Empty cells indicate outcomes that were not assessed.

Conclusions are indicated by Conclusion: strength of evidence (SOE):

- "Equivalent" indicates sufficient evidence to support a conclusion of equivalence (comparable effectiveness) between compared treatments for the outcome indicated.
- "LRA" and "Oral S-AH + INCS" indicate sufficient evidence to support conclusions of superiority of these treatments over their respective comparators for the indicated outcomes.
- SOE is indicated by low, moderate, and high.

"Insufficient" indicates insufficient evidence to form a conclusion.

- For the comparison of oral S-AH vs. INCS (row 3), evidence was insufficient to form conclusions of superiority or equivalence for nasal and eye symptoms.
- For all other outcomes, "insufficient" indicates insufficient evidence for conclusions of superiority; equivalence was not assessed.

AH = antihistamine; C = cromolyn; D = sympathomimetic decongestant; FP = fluticasone propionate; INCS = intranasal corticosteroid; LRA = leukotriene receptor antagonist; nS-AH = nonselective antihistamine; S-AH = selective antihistamine.

Key Question 2. Comparative Adverse Effects of Treatments in Adults and Adolescents 12 Years of Age or Older

We identified two comparisons with sufficient evidence to support the use of one treatment over the other in order to avoid harm while treating SAR symptoms. These are shown in Table C. To avoid insomnia, moderate-strength evidence supported the use of oral selective antihistamine rather than either monotherapy with an oral decongestant or combination therapy with oral selective antihistamine plus oral decongestant. For all other comparisons, evidence to indicate superior harms avoidance with one treatment compared with another was insufficient or lacking. Because MCIDs for harms outcomes have not been defined, equivalence of treatments compared was not tested and cannot be assumed.

Key Question 3. Comparative Effectiveness and Adverse Effects of Treatments in Pregnant Women

For 17 comparisons of interest, no comparative trials, observational studies, meta-analyses, or systematic reviews met our inclusion criteria of directly comparing two drug classes used in pregnant women with SAR. We were unable to assess comparative effectiveness and harms of SAR treatments in pregnant women.

Key Question 4. Comparative Effectiveness and Harms of SAR Treatments in Children Younger Than 12 Years of Age

The TEP suggested 21 comparisons of interest. Two trials that compared oral selective antihistamine with oral nonselective antihistamine met our inclusion criteria. Evidence on nasal and eye symptoms and on harms was insufficient based on these trials, which had high risk of bias and reported imprecise results.

No observational studies, systematic reviews, or meta-analyses met the required inclusion criteria.

Table C. Summary of findings and strength of evidence for harms in 13 treatment comparisons: Key Question 2—adults and adolescents

Comparison	Headache	Sedation	Nosebleeds	Nasal Discomfort	Bitter Aftertaste	Burning	Anxiety	Insomnia	Palpitations	Dryness	Hypertension	Nasal Candidiasis	Nasal Atrophy	Odor Abnormality	Stinging
1. Oral S-AH vs. oral nS-AH	Insuff[a]	Insuff[a]													
2. Oral S-AH vs. nasal AH	Insuff[a]	Insuff	Insuff[a]		Insuff[a]										
3. Oral S-AH vs. INCS	Insuff[a]														
4. Oral S-AH vs. oral D	Insuff	Insuff					Insuff	Oral S-AH: moderate[b]							
5. Oral S-AH vs. LRA	Insuff[a]														
6. INCS vs. nasal AH	Insuff[a]	Insuff[a]	Insuff[a]	Insuff[a]	Insuff[a]										
7. INCS vs. nasal C	Insuff		Insuff[a]	Insuff		Insuff[a]				Insuff					
8. INCS vs. LRA	Insuff[a]		Insuff[a]												
9. Oral S-AH + INCS vs. oral S-AH	Insuff[a]	Insuff[a]	Insuff[a]			Insuff[a]									
10. Oral S-AH + INCS vs. INCS	Insuff[a]	Insuff[a]	Insuff[a]			Insuff[a]									
11. INCS + nasal AH vs. INCS	Insuff[a]	Insuff[a]	Insuff[a]	Insuff[a]	Insuff[a]										
12. INCS + nasal AH vs. nasal AH	Insuff[a]	Insuff[a]	Insuff[a]	Insuff[a]	Insuff[a]										

13. Oral S-AH + oral D vs. oral S-AH	**Insuff**	**Insuff**	**Insuff**	**Oral S-AH: moderate[b]**

[a]Based on trials that studied less than 50% of the drugs in at least 1 drug class compared.

[b]Moderate-strength evidence indicates fewer insomnia events at approximately 2 weeks with oral selective antihistamine.

Note: Entries indicate comparative efficacy conclusions supported by the evidence or insufficient evidence to form a conclusion. Empty cells indicate outcomes that were not assessed.

Conclusions are indicated by Conclusion: strength of evidence (SOE):

- "Oral S-AH" indicates sufficient evidence to support conclusions of superiority of oral selective antihistamine over its respective comparators to avoid the indicated harm.
- SOE is indicated by low, moderate, and high.

"Insuff" indicates insufficient evidence to form a conclusion.

AH = antihistamine; C = cromolyn; D = decongestant; INCS = intranasal corticosteroid; Insuff = insufficient; LRA = leukotriene receptor antagonist; nS-AH = nonselective antihistamine; S-AH = selective antihistamine.

Discussion

Key Questions 1 and 2. Comparative Effectiveness and Adverse Effects of Treatments in Adults and Adolescents 12 Years of Age or Older

We did not find evidence that any single treatment demonstrated both greater effectiveness and lower risk of harms. Table D shows the four comparisons for which there was evidence to support a conclusion of superiority, either for effectiveness or for harms avoidance. Moderate-strength evidence supported the use of oral selective antihistamine to avoid insomnia associated with sympathomimetic decongestant at approximately 2 weeks (row 1 and row 4), but evidence was insufficient to draw any conclusion about comparative effectiveness between treatments. (Equivalence was not assessed in either comparison due to the inability to conduct meta-analysis.) Similarly, of two treatments shown to be comparatively superior for effectiveness (row 2 and row 3), neither was preferred for harms avoidance.

Table D. Comparison of efficacy and harms findings for four treatment comparisons

Comparison	Representation[a]	Efficacy Outcome	Harms Outcome
1. Oral S-AH vs. oral D	80% vs. pseudoephedrine (50%)	Insufficient evidence[b]	Oral S-AH to avoid insomnia: moderate
2. Oral S-AH vs. oral LRA	60% vs. montelukast (100%)	Oral LRA for reduced asthma rescue medication use: moderate	Insufficient evidence[b]
3. Oral S-AH + INCS vs. oral S-AH	40% oral S-AH, 25% INCS	Oral S-AH + INCS for improved QoL: low	Insufficient evidence[b]
4. Oral S-AH + oral D vs. oral S-AH	80% oral S-AH, pseudoephedrine (50%)	Insufficient evidence[b]	Oral S-AH to avoid insomnia: moderate

[a]Representation indicates the proportion of drugs in each class that were studied.

[b]Insufficient evidence to support conclusions of superiority of one treatment over the other for efficacy or harms outcomes. Equivalence was not tested.**Note:** Outcome entries indicate conclusion: strength of evidence. "Moderate" indicates moderate-strength evidence to support the use of oral selective antihistamine over the indicated comparator to avoid insomnia.

AH = antihistamine; D = sympathomimetic decongestant; INCS = intranasal corticosteroid; LRA = leukotriene receptor antagonist; QoL = quality of life; S-AH = selective antihistamine.

Additional findings for comparative effectiveness in adults and adolescents were as follows.

- High-strength evidence for comparable effectiveness (equivalence) of:
    - Combination intranasal corticosteroid plus nasal antihistamine, intranasal corticosteroid monotherapy, and nasal antihistamine monotherapy for nasal and eye symptoms at 2 weeks
    - Intranasal corticosteroid and oral leukotriene receptor antagonist (montelukast) for nasal symptoms at 2 weeks
- Moderate strength evidence for comparable effectiveness of oral selective antihistamine and oral leukotriene receptor antagonist for nasal and eye symptoms and for improved quality of life at 2-4 weeks

Key Question 3. Comparative Effectiveness and Adverse Effects of Treatments in Pregnant Women

For this KQ, we considered only Pregnancy Category B drugs, for which teratogenic effects have not been identified in animal studies or replicated in human studies. Evidence for the assessment of this KQ was lacking. No RCTs, observational studies, systematic reviews, or meta-analyses met the inclusion criteria.

Drugs used for the treatment of SAR have wide therapeutic windows—that is, across the range of doses at which efficacy is seen, severe adverse events are not expected. Therefore, the choice of SAR treatment in pregnant women may be cautiously informed by comparative effectiveness evidence from the nonpregnant patient population. Because physiologic changes of pregnancy alter drug disposition, generalization of findings from nonpregnant populations to pregnant women requires knowledge of the magnitude and direction of these changes. However, for SAR treatments, this knowledge is currently limited.[54] The minimum effective dose is generally preferred during pregnancy.

Key Question 4. Comparative Effectiveness and Harms of SAR Treatments in Children Younger Than 12 Years of Age

Of 17 treatment comparisons of interest among children, studies that met our inclusion criteria were identified for 1, selective versus nonselective oral antihistamine. No observational studies, systematic reviews, or meta-analyses met the required inclusion criteria.

The evidence for effectiveness and for harms was insufficient to form any conclusion about oral selective and oral nonselective antihistamine for the treatment of nasal or eye symptoms in children younger than 12 years of age (mean age, 9 years; range, 4 to 12 years). This finding was based on studies of 20 percent of oral selective antihistamines and 9 percent of oral nonselective antihistamines used to treat children. As with harms outcomes, a finding of insufficient evidence to support a conclusion of superiority of one treatment over the other does not imply equivalence of the treatments. The evidence for benefit is truly insufficient; equivalence was not assessed.

Findings in Relationship to What Is Already Known

The three systematic reviews listed below provided current information about the pharmacologic treatment of allergic rhinitis, variably defined as SAR, perennial allergic rhinitis (PAR), and intermittent or persistent allergic rhinitis (IAR and PER). Each provided a description of the literature search, inclusion and exclusion criteria for identified trials, and quality assessments of included trials. Thus, the risk of bias was considered low for each.

- Guidelines from the international Allergic Rhinitis and its Impact on Asthma (ARIA) Working Group, updated in 2010[20]
- A 2009 systematic review of treatments for hay fever[55]
- A 2008 Practice Parameter from the Joint Task Force on Practice Parameters, representing the American Academy of Allergy, Asthma & Immunology (AAAAI), the American College of Allergy, Asthma and Immunology (ACAAI), and the Joint Council of Allergy, Asthma and Immunology (JCAAI)[5]

Of 13 comparisons for which we found studies, 3 were not addressed by the systematic reviews. In 2 of the remaining 10 comparisons, our conclusions agreed with at least 1 of the systematic reviews (ARIA guidelines[20] in both instances). For the remaining eight comparisons,

our results differed from those in the guidelines. In all cases, discordant conclusions could be attributed to differences in inclusion criteria for trials reviewed. For five of eight discordant conclusions, other systematic reviews formed conclusions about comparative effectiveness or harms and we found insufficient evidence to do so. The other three discordant conclusions involved intranasal corticosteroid alone (vs. nasal antihistamine and vs. oral leukotriene receptor antagonist) or in combination with nasal antihistamine (vs. nasal antihistamine). We concluded that there was comparable effectiveness (equivalence) of the treatments compared, and other systematic reviews concluded that there was comparative superiority of intranasal corticosteroid.

Limitations of Current Review and Evidence Base

To narrow the scope of this project to a manageable size, we made several decisions at the start that had downstream consequences. Examples follow.

- We restricted diagnosis to SAR. Given the current state of transition between classification schemes for allergic rhinitis, use of the original scheme may have excluded some trials. However, it is acknowledged that SAR and intermittent allergic rhinitis define different patient populations.[5] We decided to pick one disease to study and then find studies similar enough to compare results. Introducing studies of allergic rhinitis classified according to the newer scheme may have added to the variability of included studies.
- We did not examine every possible treatment comparison. Rather, guided by input from Key Informants and the TEP, we prioritized comparisons that reflect treatment decisions encountered in the clinical setting. It is hoped that we selected and found evidence to assess comparisons that are meaningful to users of this report.
- We excluded trials of one drug versus a placebo and focused on direct comparisons only. This decision was based on feasibility concerns, given the large scope of the project and time constraints. Harms assessment was limited by the absence of placebo groups, which can inform adverse event reporting particularly.
- We included FDA-approved drugs only. For the comparison of oral selective antihistamine with oral nonselective antihistamine, in particular, this significantly reduced the number of included trials. The majority of trials excluded for this reason used terfenadine or astemizole as the selective antihistamine comparator, neither of which is currently FDA approved. As a result, only three trials were included for this comparison.
- Our minimum 2-week duration excluded examination of other treatment features that may be important to patients—for example, onset of action and harms associated with shorter exposure. However, harms associated with the interventions as defined (i.e., minimum 2-week exposure) were included. Trials of less than 2 weeks' duration often did not replicate natural methods of exposure to airborne allergens (i.e., instead used environmental exposure chambers, direct application of allergen, or prolonged weekend visits to parks), and their results may be less applicable.
- As described below, reporting of efficacy outcomes in SAR research is currently nonstandard. To maximize our ability to compare outcomes across trials, we selected the most commonly used symptom measures, namely the four-symptom TNSS and the three-item TOSS. Symptoms potentially important to patients but seldom assessed (e.g., postnasal drip, and ear and palate itching) were not included in this review.
- The scope of this report is class comparisons of SAR treatments. As a consequence of this approach, individual drug comparisons were beyond the scope of this report. Also, when comparing trials that studied a small proportion of the drugs in a class, we were limited in our

ability to make conclusions about entire pharmacologic classes, particularly for larger classes such as intranasal corticosteroids and oral nonselective antihistamines. The impact of this limitation may be small for certain drug classes, such as oral nonselective antihistamines, which are less commonly used, and oral decongestants, of which the more commonly used drug (pseudoephedrine) was studied.

- Limitations in the quality of trial reporting directly impacted the conclusions that could be drawn and strength-of-evidence ratings, particularly for older trials. For example, insufficient group-level data reporting prevented equivalence assessments. It is hoped that continued implementation of guidelines for trial reporting will address such difficulties.

Limitations of the evidence base included nonstandard stratification and definitions of severity for symptoms and adverse events; underrepresentation of populations of interest, especially children and pregnant women; and nonstandard definitions and collection of nasal and eye symptoms. Additionally, the lack of well-defined MCIDs for symptom scales (which would preferably be anchor based but could be distribution based) is a prime research gap. Although our selection of clinically informed MCIDs permitted us to draw clinically relevant conclusions, validation of the values used (30% maximum score) using anchor-based approaches is desirable. Without such well-defined MCIDs, at least three analytic tools important for clinical research—power calculations, noninferiority margins, and responder analyses—are compromised.

Research Gaps

The greatest need in SAR research is increased methodological rigor. Widely used symptom rating scales require standardization and validation. Lack of anchor-based MCIDs is a major deficiency. Agreed-upon reporting standards for effectiveness and harms outcomes are needed. Agreed-upon classifications of patients by age and standardized definitions of symptom and harms severity also are needed. Study designs that can more efficiently assess the effects of additive therapies are lacking. Studies in which all patients are treated with one component of a combination (e.g., oral selective antihistamine) and only those who are resistant receive the second component (e.g., intranasal corticosteroid) may more efficiently isolate the additive effect of the second component. We identified one trial with this design.[56]

Lack of evidence on populations of interest is a research gap. Currently, the majority of trial participants are relatively homogeneous: white and middle-aged with moderate/severe SAR symptoms. Inclusion of different races, greater proportions of patients toward both ends of the age spectrum, and patients with mild symptoms may inform our understanding not only of the comparative effectiveness and harms of SAR treatments in different groups, but also of the expression of SAR in various ethnic groups, the natural history of the disease across the lifespan, and the effect (if any) of early treatment on later symptom expression. As noted above, however, ethical considerations may limit the inclusion of vulnerable populations (e.g., children) in well-designed studies of pharmacologic interventions.

For pregnant women, pregnancy registries and rigorous studies based on the data therein can fill the gap. This presumes the use of Pregnancy Category B drugs to avoid potential known or unknown teratogenic effects of other drugs. Additionally, greater understanding of how the physiologic changes of pregnancy affect the magnitude and direction of change in drug disposition may facilitate application of effectiveness and safety findings from the nonpregnant population to pregnant women.

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Introduction

Background

Seasonal allergic rhinitis (SAR), also known as hay fever, is an inflammatory condition of the upper airways that occurs in response to exposure to airborne allergens (typically tree, grass, and weed pollens and some molds) in sensitized individuals. Although there is geographic variability in the seasonal emergence of allergenic pollens across the United States (U.S.), tree pollens tend to emerge in the spring, grass pollens in the summer, and weed pollens in the fall. Outdoor molds generally are prevalent in the summer and fall. SAR is distinguished from perennial allergic rhinitis (PAR), which is triggered by continuous exposure to house dust mites, animal dander, and other allergens generally found in an individual's indoor environment. Patients may have either SAR or PAR or both (i.e., PAR with seasonal exacerbations). Regardless of the inciting allergen(s), the four defining symptoms of allergic rhinitis are nasal congestion, nasal discharge (rhinorrhea), sneezing, and/or nasal itch. Many patients also experience symptoms of allergic conjunctivitis, such as itchy and watery eyes.[1] Treatment effectiveness is assessed by improvement of these symptoms and improved quality of life. Additional signs of rhinitis include the allergic salute (rubbing the hand against the nose in response to itching and rhinorrhea), allergic shiner (bruised appearance of the skin under one or both eyes), and allergic crease (a wrinkle across the bridge of the nose caused by repeated allergic salute).[2-5]

Classification

Traditionally, allergic rhinitis syndromes were categorized as SAR, PAR, and PAR with seasonal exacerbation.[3] This is the classification scheme we used for our report. In 2001, the Allergic Rhinitis and its Impact on Asthma (ARIA) international working group proposed a new classification scheme consisting of four categories based on rhinitis severity and duration: 1) mild intermittent, 2) mild persistent, 3) moderate/severe intermittent, and 4) moderate/severe persistent.[6] This new scheme suggests a stepwise treatment approach according to the severity and duration of symptoms.[2] However, the new scheme is not interchangeable with the traditional one, as different patient populations are defined by each.[3, 7] In 2008, the American Academy of Allergy, Asthma and Immunology (AAAAI) and the American College of Allergy, Asthma and Immunology (ACAAI) updated a Joint Task Force Practice Parameter on the diagnosis and management of rhinitis. The update retained the terms seasonal and perennial because "[t]hese traditional descriptive terms are clinically useful and allow for accurate categorization of the vast majority of patients."[3] For our report, we searched for trials involving patients with seasonal allergic rhinitis only.

Burden of Disease

SAR afflicts approximately 10 percent of the U.S. population, or 30 million individuals.[8, 9] In 2009, 17.7 million U.S. adults (7.8 percent) were diagnosed with hay fever, and 7.2 million U.S. children (9.8 percent) reported having had hay fever in the previous 12 months.[10, 11] The 2007 Pediatric Allergies in America survey revealed that 313 (62 percent) of 500 children (younger than 18 years of age) diagnosed with allergic rhinitis had SAR. SAR has been demonstrated to

adversely affect quality of life,[12-14] sleep,[15, 16] cognition,[17] emotional life,[18] and work or school performance.[19-21]

Pathophysiology

Medications used to treat SAR target biochemical pathways that cause characteristic symptoms. SAR results from the binding of an inhaled aeroallergen to immunoglobulin E (IgE) on the surface of mast cells in the nasal mucosa. An early phase allergic response follows: Mast cell degranulation releases preformed inflammatory mediators, such as histamine, which produce immediate nasal itch and sneezing. Histamine stimulation of the histamine-1 (H_1) receptors on sensory nerves causes vascular dilation and increased plasma leakage. Mucus secretion from nasal glands is stimulated directly by leukotrienes and indirectly by activated parasympathetic (cholinergic) nerve fibers. Leukotrienes also increase vascular permeability. The result is nasal discharge and congestion, which is maximal after 15 to 30 minutes. Four to 12 hours after allergen exposure, a late-phase allergic response may occur. The late-phase response consists primarily of nasal congestion and is mediated by the influx and activation of inflammatory T-cells, basophils, and eosinophils.[2, 22, 23] Ongoing, prolonged allergen exposure and repeated late-phase responses lead to progressive inflammation of the nasal mucosa and increased allergen sensitivity. The amount of allergen capable of eliciting an allergic response lessens over time, an effect termed priming. The priming effect is thought to explain the development of mucosal hyper-responsiveness to nonallergen triggers, such as strong odors, cigarette smoke, and cold temperatures.[22, 24] It also provides the rationale for initiating effective rhinitis therapies prophylactically before the commencement of pollen season.[25]

Treatment

Treatments for allergic rhinitis comprise allergen avoidance, pharmacotherapy, and immunotherapy. Although allergen avoidance may be the preferred treatment, for SAR, total allergen avoidance may be an unrealistic approach, as it may require limiting time spent outdoors. Thus, pharmacotherapy is preferable to allergen avoidance for symptom relief of SAR. Allergen-specific immunotherapy is the subject of a separate review, also sponsored by the Agency for Healthcare Research and Quality (AHRQ) and posted on the Effective Health Care Web site (www.effectivehealthcare.ahrq.gov/reports/final/cfm). Six classes of drugs and nasal saline are used to treat SAR. Several drugs have more than one route of administration (e.g., intranasal and oral), as described below.

- *Antihistamines* used to treat allergic rhinitis target the H_1 receptor. Oral antihistamines are classified as selective and nonselective for peripheral H_1 receptors. Nonselective antihistamines (e.g., diphenhydramine) bind central H_1 receptors, which can cause sedation. They also bind cholinergic, α-adrenergic, and serotonergic receptors, which can potentially cause other adverse effects such as dry mouth, dry eyes, urinary retention, constipation, and tachycardia. Nonselective antihistamines are associated with impaired sleep, learning, and work performance and with motor vehicle, boating, and aviation accidents.[26] The selective antihistamines (e.g., loratadine), in contrast, are more specific for peripheral H_1 receptors and do not cross the blood-brain barrier to bind central H_1 receptors. Adverse effects, such as sedation, are therefore reduced.[27] The choice of which antihistamine to use may be influenced by cost, insurance coverage, adverse effect profile, patient preference, and drug interactions.[27] All nonselective and some selective

antihistamines are metabolized by hepatic cytochrome P450 enzymes. Plasma concentrations of these drugs are increased by cytochrome P450 inhibitors, such as macrolide antibiotics and imidazole antifungals.[2] Two nasal antihistamines—azelastine and olopatadine—are currently approved by the U.S. Food and Drug Administration (FDA) for the treatment of SAR. Adverse effects of nasal antihistamines may include a bitter aftertaste.

- *Corticosteroids* are potent anti-inflammatory molecules. Intranasal corticosteroids are recommended as first-line treatment for moderate/severe or persistent allergic rhinitis.[3, 28] However, whether they are superior to or equally effective as nasal antihistamines for the relief of nasal congestion is uncertain,[29, 30] particularly in patients with mild allergic rhinitis. Many preparations with differing pharmacokinetic and pharmacodynamic profiles exist. These can be used continuously (daily) during allergy season or as needed. It is unclear which approach is more effective in which patients or how benefits balance against potential adverse effects of each approach. Intranasal corticosteroids do not appear to cause adverse events associated with systemic absorption (e.g., adrenal suppression, bone fracture among the elderly, and reduced bone growth and height in children). Adverse local effects may include increased intraocular pressure and nasal stinging, burning, bleeding, and dryness. Aqueous formulations and proper technique may help to relieve these effects. Little is known about cumulative corticosteroid effects in patients who take concomitant oral or inhaled formulations for other diseases. For patients with persistent symptoms, it also is unclear whether adding oral or nasal antihistamine to intranasal corticosteroid provides any additional benefit. Oral corticosteroids are occasionally prescribed for short courses (5 to 7 days) as needed in patients with severe symptoms unresponsive to other treatments.[3] Because there is no alternative to this specific use of corticosteroids in SAR, oral corticosteroids are not reviewed in this report. Similarly, although FDA-approved for SAR, intramuscular corticosteroid injections are not recommended for the treatment of SAR[3, 28] and are not reviewed in this report.
- *Decongestants* are α-adrenergic agonists that produce vasoconstriction. In the nasal mucosa, this results in decreased vascular engorgement and edema with subsequent reduction of nasal obstruction. Intranasal decongestants (e.g., oxymetazoline) may be administered before intranasal corticosteroid or nasal antihistamine to increase delivery of these drugs in patients with very severe nasal airway obstruction. Rhinitis medicamentosa, a rebound of congestion with symptom worsening, may occur with several days of use, although the exact interval and the actual proportion of patients who develop this problem are unknown. Other local adverse effects may include nosebleeds, stinging, burning, and dryness. Oral decongestants (e.g., phenylephrine, pseudoephedrine) are used alone and often are found in combination products marketed for the relief of colds and sinus congestion. Because pseudoephedrine is a key ingredient used for illicit methamphetamine production, its sale in the U.S. is restricted, resulting in the substitution of phenylephrine for pseudoephedrine in many over-the-counter cold and cough remedies. Systemic adverse effects of decongestants may include hypertension, irritability, tachycardia, dizziness, insomnia, headaches, anxiety, sweating, and tremors.[2, 31] Decongestants are used with caution, if at all, in patients with diabetes mellitus, ischemic heart disease, unstable hypertension, prostatic hypertrophy, hyperthyroidism, and narrow-angle glaucoma. Oral decongestants are contraindicated with coadministered

monoamine oxidase inhibitors and in patients with uncontrolled hypertension or severe coronary artery disease.[32]

- *Ipratropium* is an anticholinergic agent that blocks parasympathetic nerve conduction and the production of glandular secretions within the nasal mucosa. Ipratropium nasal spray is approved by the FDA for treating rhinorrhea associated with SAR. Postmarketing experience suggests that there may be some systemic absorption; it is unclear whether this issue has been addressed in the peer-reviewed literature. Cautious use is advised for patients with narrow-angle glaucoma, prostatic hypertrophy, or bladder neck obstruction, particularly if another anticholinergic is coadministered by another route. Local adverse effects may include nosebleeds and nasal and oral dryness. Efficacy and safety beyond three weeks in patients with SAR have not been established.[33]
- Intranasal mast cell stabilizers inhibit the antigen-induced release of inflammatory mediators from mast cells. *Cromolyn* is the only mast cell stabilizer approved by the FDA for the treatment of SAR. It is commonly administered prophylactically, before an allergic reaction is triggered, during a loading period in which it is used four times daily for several weeks. As-needed use also has been described and may be of benefit. Systemic absorption is minimal. Local adverse effects may include nasal irritation, sneezing, and an unpleasant taste.[2, 31]
- Cysteinyl leukotrienes are biological inflammatory mediators. *Leukotriene receptor antagonists* are oral medications that reduce allergy symptoms by inhibiting inflammation.[34, 35] Montelukast is the only leukotriene receptor antagonist approved by the FDA for the treatment of SAR. Potential adverse effects include upper respiratory tract infection and headache.[31]

Nasal Saline

A 2007 Cochrane evidence review indicated that nasal saline is beneficial in treating nasal SAR symptoms.[36] Because it is associated with few adverse effects, nasal saline may be particularly well suited for treating SAR symptoms during pregnancy, in children, and in those whose treatment choices are restricted due to comorbidities, such as hypertension and urinary retention.

Pregnancy

The optimal treatment of SAR during pregnancy is unknown. Drugs that were effective before pregnancy may be effective during pregnancy, but their use may be restricted because of concerns about maternal and fetal safety. Because pregnancy is often an explicit exclusion criterion for clinical trials, data demonstrating efficacy and maternal and fetal safety are lacking for most drugs, including those used for SAR. Decisions about which treatments are best during pregnancy must weigh the potential treatment-related risks and benefits to both mother and fetus against the potential risks and benefits of enduring the symptoms of the disease. Drugs used to treat SAR are Pregnancy Category B (presumed safe based on animal studies but without adequate human data) or Category C (of uncertain safety, with no demonstrated adverse effects in animals or humans). The risk of congenital malformation is greatest during organogenesis in the first trimester. If medication cannot be avoided during this time, intranasal treatments with minimal systemic effects, such as nasal cromolyn (Pregnancy Category B) and nasal saline, are preferred.[3] Of the intranasal corticosteroids, only intranasal budesonide is Pregnancy Category B; the others are Category C. The intranasal anticholinergic, ipratropium, also is Pregnancy

Category B. The safety of intranasal decongestants during pregnancy has not been studied. Pregnancy Category B oral medications that may be considered for use after the first trimester include the selective antihistamines loratadine, cetirizine, and levocetirizine; several nonselective antihistamines (chlorpheniramine, clemastine, cyproheptadine, dexchlorpheniramine, and diphenhydramine); and the leukotriene receptor antagonist, montelukast. Oral decongestants are generally avoided during pregnancy, especially during the first trimester.

Children

Most pharmacologic treatments for SAR are approved for use in adults and adolescents older than 12 years of age. For children, toddlers, and infants, treatment choices are limited due to safety concerns. Thus, optimal treatments for these age groups have been difficult to identify. For children who are able and willing to use intranasal medication, nasal saline presents a treatment choice with few potential adverse events. Similarly, nasal cromolyn is approved for use in children older than 2 years of age. Intranasal corticosteroids (e.g., fluticasone, mometasone, and triamcinolone) are approved for use in children as young as 2 years of age. Potential adverse events resulting from systemic absorption, such as impaired bone growth, reduced height, suppression of the adrenal axis, hyperglycemia, and weight gain, have not been definitively demonstrated.

Children with occasional symptoms may be treated with antihistamines on days when symptoms are present or expected. Carbinoxamine is a nonselective antihistamine approved for use in infants. The selective antihistamines loratadine, desloratadine, and cetirizine are approved by the FDA for use in children older than 2 years of age. Nasal antihistamines are approved for children older than 5 (azelastine) or older than 12 (olopatadine) years of age. In children older than 6 years of age, oral decongestants generally have few adverse effects at age-appropriate doses. However, in infants and young children, the use of oral decongestants may be associated with agitated psychosis, ataxia, hallucinations, and death.[3] Extended-release formulations are not recommended for children younger than 12 years of age.

Scope of the Review

The scope of this review is the comparative effectiveness and harms of pharmacologic treatments for SAR in three patient populations: adults and adolescents 12 years of age and older; pregnant women; and children younger than 12 years of age. Drug classes of interest are: oral and nasal antihistamines and decongestants; intranasal corticosteroids, mast cell stabilizers (cromolyn), anticholinergics (ipratropium), and saline; and oral leukotriene receptor antagonists (montelukast). Included drugs were FDA-approved for SAR. For pregnant women, included drugs were limited to Pregnancy Category B. For children, drugs that are seldom used in patients younger than 12 years (oral and nasal decongestant and nasal anticholinergic [ipratropium]) were not included. Outcomes of interest were patient-reported improvements in symptoms and quality of life and common adverse effects of treatment. We limited this review to direct comparisons of the six drug classes listed above. However, not all class comparisons are clinically relevant: for example, comparison of intranasal anticholinergic (ipratropium), which treats rhinorrhea, to intranasal sympathomimetic decongestant, which treats nasal congestion. The Technical Expert Panel (TEP) provided input as to the relevant class comparisons. Ideally, for each relevant comparison, all drugs within each class would be compared. However, the evidence base is not complete in this respect, and the proportion of drugs represented for any class studied ranged

from five of five oral selective antihistamines to zero (intranasal sympathomimetic decongestants, anticholinergic [ipratropium], and nasal saline).

Although a comparison of short-term (weeks) and long-term (months) effectiveness and harms is desirable, we sought evidence from real-world treatment of symptomatic patients. Such studies are necessarily limited by natural pollen cycles, typically 8 to 10 weeks, and do not provide evidence on longer-term effectiveness and harms of SAR treatments. Studies of simulated exposure to aeroallergens are not reviewed here.

Although there are multiple guidelines for the treatment of allergic rhinitis,[3, 28, 37-40] the guidelines are not consistently based on systematic reviews of the literature and often do not address the treatment of SAR in children and pregnant women. Guidelines generally support the use of intranasal corticosteroids as first-line treatment of moderate/severe SAR. However, agreement is lacking about four other issues of importance to patients and clinicians:

1. First-line treatment for mild SAR.
2. The comparative effectiveness and safety of SAR treatments used in combination with each other for both mild and moderate/severe SAR.
3. The comparative effectiveness of as-needed use compared with daily dosing.
4. The comparative effectiveness and harms of SAR treatments for eye symptoms and asthma symptoms that often co-occur with SAR

This review addresses the four issues above. The scope of this review is comparisons across pharmacologic classes. With input from the TEP, we decided to focus on across-class comparisons, as this is the first question that patients, clinicians, and other decisionmakers face. Although there may be differences among drugs within the same class, previous comparative effectiveness reviews in allergic rhinitis[3, 28, 38, 41-47] have found insufficient evidence to support superior effectiveness of any single drug within a drug class. A direct consequence of the decision to conduct across-class comparisons is the inability to compare individual drugs across studies. Additionally, limited conclusions can be drawn about drug classes that are poorly represented by the drugs studied. To our knowledge, methodological approaches for meta-analysis of class comparisons based on studies of single treatment comparisons have not been published.

Key Questions

Key Question 1. What is the comparative effectiveness of pharmacologic treatments, alone or in combination with each other, for adults and adolescents (≥12 years of age) with mild or with moderate/severe SAR?

a. How does effectiveness vary with long-term (months) or short-term (weeks) use?
b. How does effectiveness vary with intermittent or continuous use?
c. For those with symptoms of allergic conjunctivitis, does pharmacologic treatment of SAR provide relief of eye symptoms (itching, tearing)?
d. For those codiagnosed with asthma, does pharmacologic treatment of SAR provide asthma symptom relief?

Key Question 2. What are the comparative adverse effects of pharmacologic treatments for SAR for adults and adolescents (≥12 years of age)?

a. How do adverse effects vary with long-term (months) and short-term (weeks) use?
b. How do adverse effects vary with intermittent or continuous use?

Key Question 3. For the subpopulation of pregnant women, what are the comparative effectiveness and comparative adverse effects of pharmacologic treatments, alone or in combination with each other, for mild and for moderate/severe SAR?

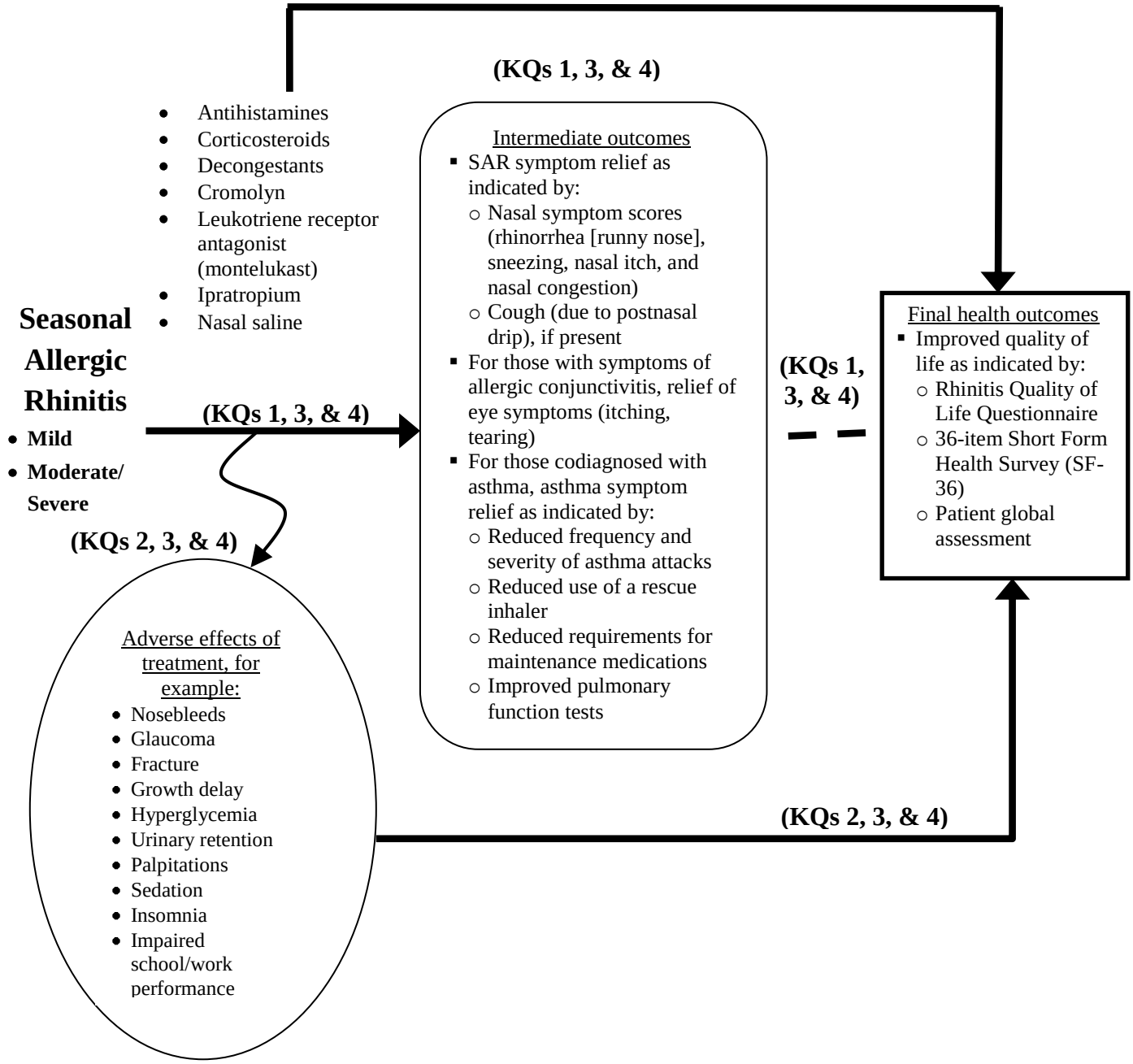
a. How do effectiveness and adverse effects vary with long-term (months) or short-term (weeks) use?
b. How do effectiveness and adverse effects vary with intermittent or continuous use?

Key Question 4. For the subpopulation of children (<12 years of age), what are the comparative effectiveness and comparative adverse effects of pharmacologic treatments, alone or in combination with each other, for mild and for moderate/severe SAR?

a. How do effectiveness and adverse effects vary with long-term (months) or short-term (weeks) use?
b. How do effectiveness and adverse effects vary with intermittent or continuous use?

The analytic framework for this report is presented in Figure 1. The figure depicts the Key Questions (KQs) in relation to SAR treatments, adverse effects, and outcomes. The six drug classes of SAR treatments and nasal saline may produce intermediate outcomes such as relief of rhinitis symptoms and, if present, eye and asthma symptoms. Treatments also may result in improved quality of life, the final health outcome. Adverse events may occur at any point after treatment is received and may impact quality of life directly.

Figure 1. Analytic framework



KQ = Key Question; SAR = seasonal allergic rhinitis.

Methods

Methods described below were suggested in the Agency for Healthcare Research and Quality (AHRQ) "Methods Guide for Effectiveness and Comparative Effectiveness Reviews."[48] The structure of this Methods chapter is aligned with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.[49] Unless otherwise specified all methods and analyses were determined a priori.

Topic Refinement and Review Protocol

Key Questions

For all Evidence-based Practice Center (EPC) reviews, Key Questions (KQs) were reviewed and refined as needed by the EPC with input from Key Informants and the Technical Expert Panel (TEP) to ensure that the questions are specific and explicit about what information is being reviewed. In addition, for the comparative effectiveness review, the KQs were posted for public comment and finalized by the EPC after review of the comments.

Key Informants

Key Informants are the end-users of research, including patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Within the EPC program, the Key Informant role is to provide input into identifying the KQs for research that will inform health care decisions. The EPC solicits input from Key Informants when developing questions for systematic review or when identifying high-priority research gaps and needed new research. Key Informants are not involved in analyzing the evidence or writing the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals are invited to serve as Key Informants and those who present with potential conflicts may be retained. The Task Order Officer (TOO) and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

Technical Experts

Technical Experts comprise a multidisciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes as well as identifying particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicting opinions are common and perceived as producing healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, study questions, design and/or methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and recommend approaches to specific issues as requested by the EPC. Technical Experts do not conduct analysis of any kind or contribute to the writing of the report; they do not review the report, except as given the opportunity to do so through the public review mechanism.

In addition to methodologists, the Technical Experts represented the diversity of practitioners whose care is sought for the treatment of seasonal allergies. They included allergists, family practitioners, pharmacists, and otolaryngologists.

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

Literature Search Strategy

Search Strategy

To identify relevant studies for the four KQs, literature search strategies were developed by an expert librarian in collaboration with the project team and were peer reviewed by a second librarian. The searches were developed on MEDLINE® (PubMed®) and adapted for the other databases. Methodological search filters were added to the disease and intervention terms to identify randomized controlled trials (RCTs), quasi-randomized trials, observational studies and systematic reviews. The databases searched for primary studies were MEDLINE® (PubMed® and Ovid®), Embase® (Ovid®), and the Cochrane Central Register of Controlled Trials (CENTRAL). For systematic reviews, the databases searched were the Cochrane Database of Systematic Reviews, Database of Abstracts and Reviews of Effects (DARE), and the Health Technology Assessment (HTA) databases of the Centre for Reviews and Dissemination (all through the Wiley InterScience platform). Articles were limited to those published in the English language. Technical Experts advised that the majority of the literature on this topic is published in English. Although the search was not limited by date, only systematic reviews published after 2010 were considered for potential incorporation of results into this review. Full details of the search strategies are given in Appendix A. All databases were searched on July 18, 2012, with no date restrictions.

Grey Literature

Grey literature was sought by searching the United States (U.S.) Food and Drug Administration (FDA) Web site; electronic conference abstracts of relevant professional organizations via Scopus; and the Web sites of two professional societies: The American Academy of Allergy, Asthma & Immunology (AAAAI) and the British Society for Allergy and Clinical Immunology (BSACI). In addition, the following Web sites were searched: the clinical trial registries of the U.S. National Institutes of Health (NIH) (ClinicalTrials.gov and NIH Reporter) and the World Health Organization (WHO); AHRQ Effective Health Care Program and AHRQ Home Page; and Current Controlled Trials. Scientific Information Packets provided by product manufacturers were evaluated to identify unpublished trials that met inclusion criteria. The grey literature searching was carried out between April 5 and September 26, 2012. Details of the Web sites and dates accessed are given in Appendix A.

Additional Searching

We scanned the bibliographies of relevant systematic reviews and meta-analyses and of the final list of included studies to identify any additional studies not retrieved by the electronic database or grey literature searches.

Inclusion and Exclusion Criteria

Key Question 1—Comparative Effectiveness of Treatments in Adults 12 Years of Age or Older

The focus of this KQ is the comparison of effectiveness of six pharmacologic classes of treatments for seasonal allergic rhinitis (SAR) and nasal saline. Drug classes, routes of administration, and specific drugs within each class are shown in Table 1. Only drugs approved by the FDA for the treatment of SAR were included. Antihistamines were classified into nonselective and selective subclasses based on their specificity for peripheral H_1 histamine receptors.

Within a pharmacologic class, previous CERs did not find sufficient evidence to support superior effectiveness of any single drug.[3, 28, 38, 41-47] Thus, the focus of the review was across-class treatment comparisons, except when multiple routes of administration were available for a single drug class (e.g., intranasal versus oral selective antihistamines, intranasal versus oral sympathomimetic decongestants).

We sought expert guidance to identify drug class comparisons most relevant for treatment decisionmaking. The checked boxes in Table 2 indicate the treatment comparisons identified. Reasons most often cited for not including a specific comparison were differential efficacy for specific SAR symptoms (e.g., intranasal anticholinergic [ipratropium] treats rhinorrhea versus intranasal sympathomimetic decongestant treats nasal congestion) and noncomparable indications (e.g., nasal antihistamine for long-term use versus intranasal sympathomimetic decongestant for short-term use).

We sought trials comprising the highest level of evidence for treatment effectiveness and applied the following inclusion and exclusion criteria:

- Head-to-head RCTs were preferred; the risk of bias in uncontrolled and noncomparative studies is magnified due to the subjective reporting of both efficacy outcomes and adverse events in SAR research.
- Trials of less than 2 weeks duration were excluded; this is the minimum treatment duration recommended in draft FDA guidance for industry.50
- Patients had to be symptomatic at the time of the intervention.
- Trials that involved exposure chambers or allergen challenge interventions were excluded.
- Only FDA-approved drugs administered at FDA-approved doses for SAR treatment were considered.
- To be most inclusive, a minimum number of trial participants was not required.

For comparisons that did not have data from RCTs, nonrandomized trials and observational study designs were considered. Inclusion criteria for these studies were:

- Any of the following designs:
    - Quasi-RCTs (crossover trials, before/after trials, open-label extensions, etc.)
    - Controlled (nonrandomized) clinical trials

    - Population-based comparative cohort studies
    - Case-control studies
- Each study must have compared two drug classes directly.
- Control of confounders, such as baseline comorbidities, baseline symptom severity, and pollen counts, was necessary.
- Detection bias was addressed through blinding of outcome assessors or clinicians to drug exposure.

Table 1. Pharmacologic treatments of seasonal allergic rhinitis

Drug Class	Oral	Included Drugs	Intranasal	Included Drugs
H1-antihistamine				
Nonselective	✓	Acrivastine (in combination with pseudoephedrine only), brompheniramine, carbinoxamine, chlorpheniramine, clemastine, cyproheptadine, dexbrompheniramine, dexchlorpheniramine, diphenhydramine, doxylamine, promethazine, triprolidine		
Selective	✓	Cetirizine, desloratadine, fexofenadine, levocetirizine, loratadine	✓	Azelastine, olopatadine
Corticosteroid	✓*		✓	Beclomethasone, budesonide, ciclesonide, flunisolide, fluticasone furoate, fluticasone propionate, mometasone, triamcinolone
Mast cell stabilizer			✓	Cromolyn
Leukotriene receptor antagonist	✓	Montelukast		
Sympathomimetic decongestants	✓	Phenylephrine, pseudoephedrine	✓	Levmetamfetamine, naphazoline, oxymetazoline, phenylephrine, propylhexedrine, tetrahydrozoline, xylometazoline
Anticholinergic			✓	Ipratropium bromide

*Oral corticosteroids are not reviewed in this report.

Table 2. Monotherapy and combination treatment comparisons reviewed for adults: Key Questions 1 and 2

	nS-AH, Oral	S-AH, Oral	S-AH, Nasal	INCS	D, Oral	D, Nasal	C, Nasal	LRA, Oral	AC, Nasal	NS
nS-AH, oral		✓								
S-AH, oral			✓	✓	✓		✓	✓	✓	✓
S-AH, nasal				✓	✓			✓	✓	✓
INCS							✓	✓	✓	✓
D, oral										
D, nasal										
C, nasal										
LRA, oral										
AC, nasal										
NS										
S-AH, oral + INCS		✓		✓						
S-AH, oral + D, oral		✓								
S-AH, nasal + INCS			✓	✓						

Note: The top portion of this table is a grid of monotherapy treatment comparisons included in this review (✓). The last three rows of the table indicate combination treatment comparisons included in this review (✓).

AC = anticholinergic; C = cromolyn; D = sympathomimetic decongestant; nS-AH = nonselective antihistamine; S-AH = selective antihistamine; INCS = intranasal corticosteroid; LRA = leukotriene receptor antagonist; NS = nasal saline.

For all studies, disease was limited to SAR. Studies that reported both SAR and perennial allergic rhinitis (PAR) were included if SAR outcomes were reported separately. Outcomes had to include patient-reported symptom scores and/or validated quality of life instruments; for comorbid asthma symptoms, pulmonary function tests also were required. Definitions of symptom severity were adapted from the Allergic Rhinitis in Asthma (ARIA) guidelines.[6] The ARIA definition of mild SAR excluded individuals with sleep disturbance, impairment of daily or leisure activities, impairment of school or work, or troublesome symptoms. Moderate/severe SAR is characterized by one or more of these disturbances. The following symptom rating scale is commonly used in SAR clinical trials.[50]

0 = Absent symptoms (no sign/symptom evident)
1 = Mild symptoms (sign/symptom clearly present, but minimal awareness; easily tolerated)
2 = Moderate symptoms (definite awareness of sign/symptom that is bothersome but tolerable)
3 = Severe symptoms (sign/symptom that is hard to tolerate; causes interference with activities of daily living and/or sleeping)

We examined results of existing systematic reviews and meta-analyses published after 2010 for potential incorporation into the report when they assessed relevant treatment comparisons, reported at least one outcome of interest, and were of high quality. Quality was assessed by two independent reviewers with criteria derived from the AHRQ "Methods Guide for Effectiveness and Comparative Effectiveness Reviews" and the Assessment of Multiple Systematic Reviews (AMSTAR) tool.[51] Narrative reviews were excluded, but their bibliographies were searched if they were thought to have relevant references. In addition, reference lists of RCTs, systematic reviews, and other reviews were hand searched to confirm that all relevant RCTs had been identified. These selection criteria are summarized in Table 3. References obtained through grey

literature searching were excluded if the study was not published in a peer-reviewed journal or if the full-text of the study could not be obtained.

Table 3. Key Question 1: Comparative effectiveness of treatments—study inclusion criteria

Category	Inclusion Criteria

Population	• Individuals with SAR
	  ○ Mild symptoms
	  ○ Moderate/severe symptoms
	• Age 12 or older
	• May also have comorbid eye symptoms or asthma

Interventions/Comparators	Comparisons of interest of pharmacologic treatments of SAR alone and in combination with each other (see Table 2) administered for at least 2 weeks

Outcomes	• Nasal symptom scores
	• Cough
	• Eye symptom scores
	• Asthma outcomes
	  ○ Frequency and severity of asthma attacks
	  ○ Use of rescue medication
	  ○ Maintenance medication dose
	  ○ Pulmonary function tests
	• Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ)
	• 36-item Short Form Health Survey (SF-36)
	• Patient global assessment (PGA)

Time Period	Minimum 2-week duration of treatment exposure
Setting	Outpatients during the pollen season

Study designs	• RCTs with active comparator
	  ○ Outcomes for patients with mild symptoms and with moderate/severe symptoms reported separately
	  ○ Combined outcome reporting allowed
	• For comparisons of interest with no RCT data, observational data were considered. Inclusion criteria for observational data were:
	  ○ Any of the following designs:
	  ▪ Quasi-RCTs (crossover trials, before/after trials, open-label extensions, etc.)
	  ▪ Controlled (nonrandomized) clinical trials
	  ▪ Population-based comparative cohort studies
	  ▪ Case-control studies
	  ○ Each study compared two drug classes directly.
	  ○ Confounders were controlled; for example, baseline asthma prevalence and severity are documented, pollen counts are documented in multicenter studies
	  ○ Detection bias was addressed through the use any of these: blinding of outcome assessors or blinding of patients or clinicians to treatment allocation
	• Systematic reviews and meta-analyses
	  ○ Assessed relevant treatment comparisons
	  ○ Reported at least one outcome of interest
	  ○ Were of high quality

Followup duration	Unrestricted
Sample size	Unrestricted

RCT = randomized controlled trial; SAR = seasonal allergic rhinitis.

Key Question 2—Comparative Adverse Effects of Treatments in Adults 12 Years of Age or Older

Comparative adverse effects reported in the RCTs, systematic reviews, meta-analyses, and observational studies identified for KQ1 were included. Additionally, systematic reviews and meta-analyses that specifically assessed adverse events associated with treatment comparisons of interest were sought. Table 4 lists systemic and local adverse effects of interest for making treatment decisions. Of particular interest were adverse effects associated with long-term

treatment exposures in locations where allergen seasons are of longer duration (e.g., certain parts of the U.S.). For these adverse effects, comparative clinical trials of at least 300 patients evaluated for 6 months or 100 patients evaluated for at least 1 year were sought, according to FDA draft guidance for industry.[50]

Table 4. Key Question 2: Systemic and local adverse effects of seasonal allergic rhinitis treatments

Treatment	Effect
Intranasal corticosteroids	• Systemic effects: adrenal suppression, hyperglycemia, bone demineralization/fracture, growth delay in children • Local effects: increased intraocular pressure, cataract formation, nasal septal atrophy, fungal infection, nosebleeds, stinging, burning, dryness, smell and taste abnormalities
Selective and nonselective antihistamines	• Systemic effects: sedation, impaired school/work performance, traffic accidents • Local effects: stinging, burning, dryness, bitter aftertaste
Sympathomimetic decongestants	• Systemic effects: hypertension, palpitations, insomnia, anxiety • Local effects: nosebleeds, stinging, burning, dryness, rhinitis medicamentosa
Leukotriene receptor antagonists	• Systemic effect: headache
Anticholinergic, cromolyn	• Local effects: nosebleeds, stinging, burning, dryness

Key Question 3—Comparative Effectiveness and Adverse Effects of Treatments in Pregnant Women

Treatment comparisons of interest included Pregnancy Category B oral and topical (intranasal) preparations and nasal saline, which is considered safe for use in pregnancy. These are presented in Table 5. Adverse effects of interest were the same as those listed for KQ2. Adverse fetal effects associated with SAR treatments in pregnant women were not specifically identified as a target adverse event because we restricted the drugs of interest to Pregnancy Category B only. Thus, we expected reporting of common treatment-related adverse events and adverse events associated with the physiologic changes of pregnancy, rather than teratogenic effects.

Oral sympathomimetic decongestants are Pregnancy Category C and were not included in this KQ.

Because pregnancy is commonly an exclusion criterion for participation in pharmaceutical RCTs, additional study designs in pregnant women with SAR (i.e., observational data, systematic reviews, and meta-analyses) were considered for KQ3. The inclusion criteria for these study designs were the same as for KQ1.

Table 5. Monotherapy and combination treatment comparisons reviewed for pregnant women: Key Question 3

	nS-AH, Oral[a]	S-AH, Oral[b]	INCS[c]	D, Nasal	C, Nasal[d]	LRA, Oral[e]	AC, Nasal[f]	NS
nS-AH, oral[a]		✓	✓					
S-AH, oral[b]			✓		✓	✓		✓
INCS[c]					✓	✓		✓
D, nasal						✓		
C, nasal[d]						✓		✓
LRA oral[e]								
AC, nasal[f]								
NS								
nS-AH, oral[a] + NS	✓		✓					✓
S-AH, oral[b] + NS		✓						✓

The top portion of this table is a grid of monotherapy treatment comparisons included in this review (✓). The last three rows of the table indicate combination treatment comparisons included in this review (✓).

AC = anticholinergic; nS-AH = nonselective antihistamine; S-AH = selective antihistamine; C = cromolyn; INCS = intranasal corticosteroid; LRA = leukotriene receptor antagonist; NS = nasal saline; D = sympathomimetic decongestant.

[a] Chlorpheniramine, clemastine, cyproheptadine, dexchlorpheniramine, and diphenhydramine are Pregnancy Category B.

[b] Cetirizine, loratadine, and levocetirizine are Pregnancy Category B.

[c] Budesonide is Pregnancy Category B.

[d] Cromolyn is Pregnancy Category B.

[e] Montelukast is Pregnancy Category B.

[f] Ipratropium is Pregnancy Category B.

Key Question 4—Comparative Effectiveness and Adverse Effects of Treatments in Children Younger Than 12 Years of Age

The population of interest was children younger than 12 years of age who have SAR. Identified treatment comparisons of interest for KQ4 are presented in Table 6. Because of concerns about the use of sympathomimetic decongestants in children, comparisons of oral and nasal preparations as monotherapy were not included. Similarly, intranasal anticholinergic (ipratropium) was not included because Technical Experts indicated that this drug is rarely used in children younger than 12 years of age. Potential comparative harms of intranasal corticosteroids in this population (reduced bone growth and height) were of particular interest. Comparative effect on school performance in school-age children was an additional key outcome.

Selection criteria are the same as in KQ1, that is, RCTs were the preferred study type. For comparisons of interest that did not have RCT data, observational study designs were considered. Inclusion criteria for RCTs, observational studies, systematic reviews, and meta-analyses were those outlined in Table 3, with the exception that the study population was younger than 12 years old. For comparisons with sparse bodies of evidence, we considered inclusion of studies that mixed results for adults and children together.

Table 6. Monotherapy and combination treatment comparisons reviewed for children younger than 12 years of age: Key Question 4

	nS-AH, Oral	S-AH, Oral	S-AH, Nasal	INCS	C, Nasal	LRA, Oral	NS
nS-AH, oral		✓	✓	✓		✓	
S-AH, oral			✓	✓	✓	✓	
S-AH, nasal				✓	✓	✓	
INCS					✓	✓	✓
C, nasal						✓	✓
LRA, oral							
NS							
S-AH, oral + D, oral		✓		✓			
S-AH, oral + INCS		✓	✓	✓			

The top portion of this table (above the dark line) is a grid of monotherapy treatment comparisons included in this review (✓). The last three rows of the table indicate combination treatment comparisons included in this review (✓).

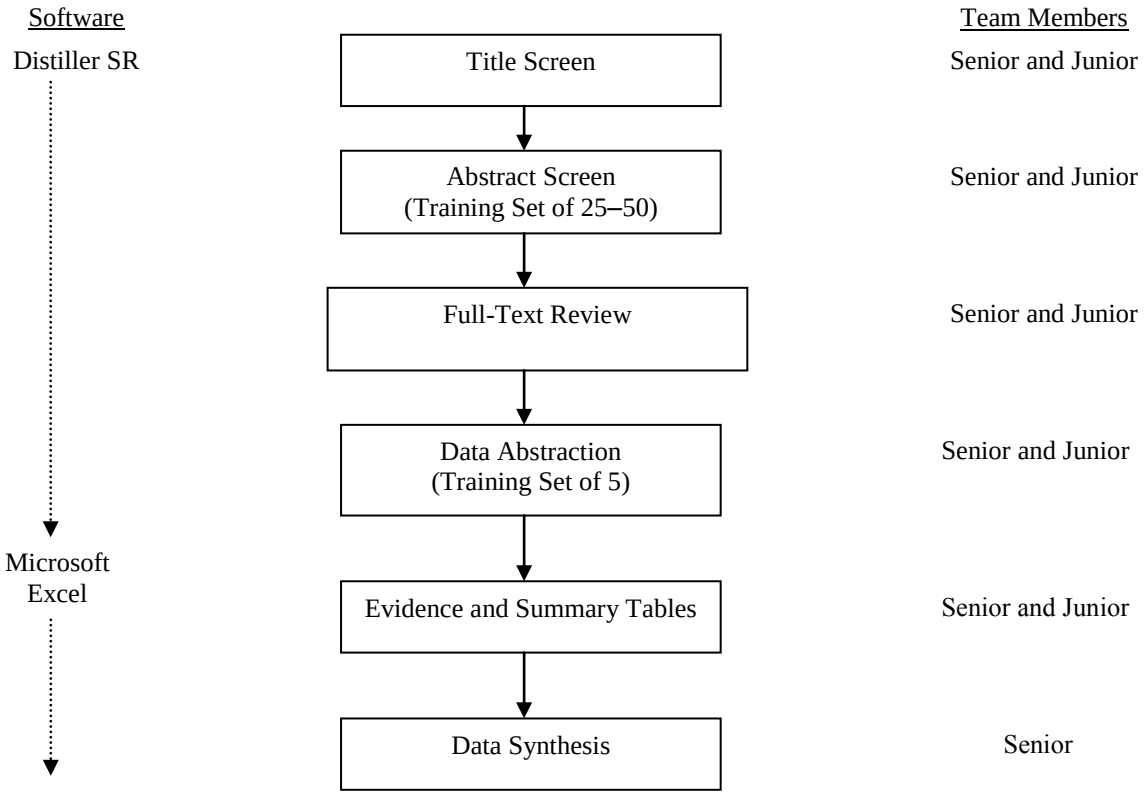
AC = anticholinergic; nS-AH = nonselective antihistamine; S-AH = selective antihistamine; C = cromolyn; INCS = intranasal corticosteroid; LRA = leukotriene receptor antagonist; NS = nasal saline; D = sympathomimetic decongestant.

Study Selection

Figure 2 shows the flow of data from article screening to data synthesis. Search results were transferred to EndNote®[52] and subsequently into DistillerSR[53] for selection. Using the study selection criteria for screening titles and abstracts, each citation was marked as: (1) eligible for review as full-text articles; (2) ineligible for full-text review; or (3) uncertain. A training set of 25 to 50 abstracts was initially examined by all team members to ensure uniform application of screening criteria. A first-level title screen was performed by one senior and one junior team member. Discrepancies were decided through discussion and consensus. A second-level abstract screen was conducted in duplicate manner by senior and junior team members according to defined criteria. When abstracts were not available, the full-text papers were obtained wherever possible and reviewed in the same way to determine whether selection criteria had been satisfied. For additional citations identified through subsequent literature searches, combined title and abstract screening was performed by senior and junior team members as described. Inclusion and exclusion were decided by consensus opinion.

Full-text articles were reviewed in the same fashion to determine their inclusion in the systematic review. Records of the reason for exclusion for each paper retrieved in full text, but excluded from the review, were kept in the DistillerSR database.

Figure 2. Schematic for data management and abstraction



The complete set of data to be extracted was developed during the abstraction phase and included some anticipated elements. The final set of abstracted data included the following: general study characteristics (e.g., author, study year, enrollment dates, center[s], and funding agency), eligibility criteria, blinding, numbers of patients enrolled, baseline characteristics of patients enrolled (e.g., age and disease severity and duration), intervention, outcome instrument(s), adverse events and method of ascertainment, and results.

A list of excluded studies is available in Appendix B.

Data Extraction

Data were abstracted directly into tables created in DistillerSR with elements defined in an accompanying data dictionary. A training set of five articles was abstracted by all team members who were abstracting data. From this process, an abstraction guide was created and used by all abstractors to ensure consistency. Two team members abstracted data from each article, and discrepancies were reconciled during daily team discussions. Abstracted data were transferred from DistillerSR to Microsoft Excel[54] for construction of the study-level evidence tables and summary tables included in this report.

Data abstraction form elements are located in Appendix D.

Quality (Risk of Bias) Assessment of Individual Studies

In accordance with the AHRQ Methods Guide,[48] individual RCTs were assessed using the United States Preventive Services Task Force (USPSTF) criteria,[55] shown in Appendix E. Two

independent reviewers assigned ratings of good, fair, or poor to each study, with discordant ratings resolved with input from a third reviewer. Trials that did not use an intention-to-treat (ITT) analysis were rated poor quality, as per USPSTF criteria. [55] Trials that did not specify the type of analysis done and did not provide sufficient patient flow data to determine that an ITT analysis was done, also were rated poor quality. Additionally, because all outcomes of interest were patient-reported, particular care was taken to ascertain whether patients were properly blinded to treatment. Open-label trials and trials in which patient blinding was deemed inadequate based on the description provided received a quality rating of poor.

The quality of harms reporting was assessed using the USPSTF rating, with specific attention to both patient and assessor blinding, and the McMaster Quality Assessment Scale of Harms (McHarm) for primary studies,[56] shown in Appendix F. In particular, the process of harms ascertainment was noted and characterized as either an active process, if structured questionnaires were used; a passive process, if only spontaneous patient reports were collected; or intermediate, if active surveillance for at least one adverse event was reported. Trials using only passive harms ascertainment were considered to have a high risk of bias, specifically, underreporting or inconsistent reporting of harms.

For populations, comparisons, and interventions that were not adequately represented in RCTs, we sought nonrandomized comparative studies (observational, case-control, and cohort studies). We planned to assess studies of these designs using a selection of items proposed by Deeks and colleagues.[57] However, we found no such studies. Therefore, quality rating was not applicable.

Two reviewers independently assessed the risk of bias of relevant systematic reviews and meta-analyses using the following criteria derived from the AMSTAR tool and AHRQ guidance:[51]

1. Details of the literature search were provided.
2. Study inclusion and exclusion criteria were stated.
3. The quality assessment of included studies was described and documented.

These were considered the minimum criteria for assessing potential bias of any summary results and conclusions. Criteria 1 and 2 address the potential for selection bias. Criterion 3 is necessary to assess potential bias of included studies.

Data Synthesis

Evidence for effectiveness and safety provided by each treatment comparison was summarized in narrative text. The decision to incorporate formal data synthesis into this review was made after completing data abstraction.

Overall Approaches and Meta-Analyses for Direct Comparisons

Pooling of treatment effects was considered for each treatment comparison according to AHRQ guidance.[58] Three or more clinically and methodologically similar studies (i.e., studies designed to ask similar questions about treatments in similar populations and to report similarly defined outcomes) were required for pooling. Three was an arbitrary number used as an operational criterion for meta-analyses. Only trials that reported variance estimates (standard error, standard deviation, or 95 percent confidence interval) for group-level treatment effects could be pooled. The measure of the pooled effect was the mean difference or the standardized mean difference, depending on how treatment effects were reported in pooled trials. Some trials reported mean changes from baseline, and others reported mean final symptom scores. When

these trials were pooled together, the measure of the pooled effect was the mean difference.[48] Trials also used different symptom rating scales (e.g., 4-point integer scales or 10 cm visual analog scales [VAS]). When these trials were pooled together, the standardized mean difference (SMD) was calculated. Otherwise, the mean difference was the preferred measure for pooled effects. Trials that used both different calculations for treatment effects and different symptom rating scales could not be pooled together.

We used RevMan[59] to conduct meta-analyses using inverse variance weighting and random-effects models. For any meta-analysis performed, we identified the presence of statistical heterogeneity by using Cochran's Q statistic (chi-squared test) and assessed the magnitude of heterogeneity using the I^2 statistic.[60] For Cochran's Q statistic, a p-value less than or equal to 0.10 was considered statistically significant. An approximate guide for the interpretation of I^2 was:[61]

- 0 percent to 40 percent: may not be important
- 30 percent to 60 percent: may represent moderate heterogeneity
- 50 percent to 90 percent: may represent substantial heterogeneity
- 75 percent to 100 percent: considerable heterogeneity

When present, we explored statistical heterogeneity as well as clinical diversity by performing subgroup analyses, sensitivity analyses, and meta-regression when possible.[48] Statistical heterogeneity and clinical diversity are related concepts: Statistical heterogeneity describes variability in observed treatment effects that is due to clinical and/or methodological diversity, biases, or chance. Clinical diversity describes variability across trial study populations, interventions, and outcome assessments. In exploratory analyses, study level variables included study quality (risk of bias assessment), specific drugs studied, and covariates, such as inclusion of asthma patients or use of rescue or ancillary medications. Meta-analysis was planned for adverse events that investigators reported as severe or that led to discontinuation of treatment. Three or more trials reporting the adverse event were required for pooling. Adverse events of unspecified severity were considered not comparable across trials.

In this review, we formed conclusions about treatment classes based on meta-analyses of studies that compared single treatments. Methodological approaches for this type of analysis have not been published. However, we proceeded with this analysis with support from the TEP. For class comparisons that were poorly represented (i.e., a small proportion of drugs in a class were assessed in included studies), we applied conclusions to the specific drugs studied; how well such conclusions generalize to other drugs in the same class is uncertain. Previous comparative effectiveness reviews in allergic rhinitis[3, 28, 38, 41-47] have found insufficient evidence to support superior effectiveness of any single drug within a drug class.

Outcome Measures

To assess the magnitude of treatment effects, we searched the published literature for minimal clinically important differences (MCIDs) derived from anchor-based or distribution-based methods. Anchor-based methods correlate observed changes on an investigational outcome assessment instrument with those on a known, validated instrument. Distribution-based MCIDs are obtained from the pooled variance in a clinical trial, for example, 20 percent or 50 percent of the pooled baseline standard deviation.[62, 63] Anchor-based MCIDs are considered more robust than distribution-based MCIDs. FDA Guidance for patient-reported outcomes in clinical research supports the use of anchor-based MCIDs.[50, 64]

Anchor-based MCIDs have been published for quality of life measures commonly used in clinical research on rhinitis.[65, 66] For the Rhinitis Quality of Life Questionnaire (RQLQ) and the mini-RQLQ, anchor-based MCIDs are 0.5 and 0.7, respectively, on a 0-6 point scale. Another validated quality of life questionnaire, the Nocturnal RQLQ, does not have a well-defined (i.e., anchor-based preferably or distribution-based) MCID.[67]

For asthma outcomes, anchor-based MCIDs have been defined for rescue medication use[68] (1 puff per day) and forced expired volume in 1 second (FEV_1; 100-200 ml).[68, 69] A Health Canada Advisory Committee[70] proposed definitions of the MCID for FEV_1 using percent change from baseline (10 percent in adults [greater than age 11 years] and 7 percent in children [age 6 to 11 years]). For asthma symptoms,[71] asthma exacerbations, and morning peak expired flow [PEF], MCIDs have not been well-defined. Definitions of "asthma exacerbation" vary; it has been proposed that any reduction in severe exacerbations (e.g., requiring treatment with systemic corticosteroids) is clinically significant.[70] For PEF, a change of 25 L/min from baseline values is commonly considered clinically significant.[69] It is unclear how this value was derived.

For nasal and eye symptom scales, anchor-based MCIDs have not been published. We identified three published attempts to assess clinically important changes in these scales.

- A distribution-based approach yielded a very small MCID: One trial[62, 72] (n=27) defined a distribution-based MCID of 0.52 points on a 0-12 point total nasal symptom score (TNSS) scale.[62,] This value was derived by calculating one fifth of the standard deviation of baseline TNSS scores.
- A study of responsiveness yielded a minimum clinically meaningful change of 30% maximum score: Bousquet and colleagues[73] conducted a trial (n=839) that included a sub-study (n=796) comparing the responsiveness of VAS scores to changes in TNSS and RQLQ. Responsiveness and MCID are overlapping but not identical concepts. Responsiveness, defined as the ability of an instrument to measure change in a clinical state, ideally includes the ability to measure a clinically meaningful change,[74] but may overestimate the *minimal* meaningful change. Bousquet and colleagues found that patients with a "clinically relevant improvement" in TNSS had a reduction of 2.9 cm on a 10 cm VAS. In this study, "clinically relevant improvement" was defined *a priori* as a decrease of at least 3 points on a 0-12 point TNSS scale. This threshold was based on placebo- and active-controlled trials of intranasal corticosteroids in patients with SAR and PAR, which showed improvements in TNSS of 40 to 50 percent from baseline in the active treatment groups. Because baseline TNSS in the Bousquet trial was approximately 7 on a 0-12 point scale, a 40 percent improvement correlated to a 3-point reduction in TNSS ($7 \times 0.40 = 2.8 \approx 3$).
- In allergen-specific immunotherapy (SIT) trials, a minimum 30 percent greater improvement in composite scores compared to placebo is considered clinically meaningful:[75] The WHO currently recommends use of a composite outcome measure (symptoms plus rescue medication use) in SIT trials.[76] Although "minimal clinically relevant efficacy" for this outcome is considered to be a 20 percent greater improvement compared to placebo, the cited reference for this threshold [77] does not support the recommendation: It is a systematic review of pharmacologic (not immunologic) treatments in which only symptom scores (not combination scores) were assessed, and a difference between two treatments of 10 percent was assumed to be clinically relevant. In contrast, an earlier paper by a member of the WHO writing group[75] asserted that a 30 percent reduction in symptom/medication scores compared to placebo is minimally

clinically relevant. This threshold was based on an evaluation of 68 placebo-controlled, double-blind trials.

In the absence of gold-standard MCIDs for symptom rating scales in SAR patients, we sought input from our TEP as recommended in the AHRQ Methods Guide.[48] Three of seven experts provided input.

- For individual symptoms rated on a 0-3 point scale, all three experts considered a 1-point change meaningful.
- For TNSS on a 0-12 point scale, two experts considered a 4-point change and one expert considered a 2-point change meaningful.
- For total ocular symptom score (TOSS) on a 0-9 point scale, two experts considered a 3-point change and one expert considered a 1-point change meaningful.

For TNSS, potential MCIDs obtained from the three sources listed above and from the TEP are summarized in Table 7. As shown, two sources (row 2 and row 4) converged around an MCID of 30 percent change of maximum TNSS score. This was supported by three TEP members who proposed a similar threshold for individual nasal symptoms (1 point on a 0-3 point scale) and two TEP members who proposed a similar threshold for TOSS (3 points on a 0-9 point scale). The concordance of these values increased our confidence that 30 percent of maximum score is a useful threshold for purposes of our analysis and could be applied across symptom scales. We therefore examined the strength of evidence for symptom outcomes using this MCID calculated for each scale used.

Table 7. Quantified minimal clinically important differences for total nasal symptom score

Source	MCID	Scale
1. Distribution-based approach in 27 patients[62, 72]	0.52	0-12 interval
2. Responsiveness of visual analog scale to interval scale[73]	2.9	0-10 visual analog
3. Allergen-specific immunotherapy recommendation[75]	30%[a]	any
4. Technical Expert Panel input	2-4	0-12 interval

MCID = minimal clinically important difference.

[a] A 30 percent greater improvement compared to placebo in composite symptom/rescue medication use scores was proposed as minimally clinically meaningful.

A summary of MCIDs used in this report is presented in Table 8. As shown, three outcomes – asthma symptoms, quality of life assessed using the Nocturnal RQLQ, and harms – did not have MCIDs.

Table 8. Minimum clinically important differences used to assess seasonal allergic rhinitis outcomes

Outcome	MCID
Individual nasal and eye symptoms	30% of maximum score
Total nasal and eye symptoms	30% of maximum score
Asthma outcomes	
Asthma symptoms	None defined
Asthma exacerbations	One severe exacerbation, however defined
FEV_1	100 mL or 10% change from baseline (adults); 7% change from baseline (children)
PEF	25 L per minute
Rescue medication use	1 puff per day
Quality of life outcomes	
RQLQ	0.5
Mini RQLQ	0.7
Nocturnal RQLQ	None defined
Harms	None defined

FEV_1 = forced expired volume in 1 second; PEF = morning peak expired flow; RQLQ = Rhinitis Quality of Life Questionnaire.

Two types of symptom scores were reported: reflective and instantaneous. Reflective scores represent a drug's effectiveness throughout the dosing interval. Instantaneous scores represent effectiveness at the end of the dosing interval. Instantaneous scores are recommended by the FDA for clinical development programs of SAR drugs.[50] The FDA considers these scores a pharmacokinetic/pharmacodynamic feature of drugs in development, important for assessing dosing interval, but not important to patients. Consequently, only reflective symptom scores were abstracted for this review.

Symptom scores were reported at various time points, from 2 to 8 weeks. For treatment comparisons that involved intranasal corticosteroids, 2-week results were segregated from results at all other time points based on the pharmacodynamic profile of this class of drugs (onset of action occurs during the first 2 weeks of treatment). Results after 2 weeks were qualitatively synthesized. For all other drug classes, results from all time points were pooled. For trials that reported more than one time point, only results for the identified primary time point were included in meta-analysis. If a primary outcome (time point) was not identified, the latest outcome was included.

For adverse events, the measure of the pooled effect was the risk difference. Trials that reported adverse events as the proportion of patients experiencing the event were considered for pooling (meta-analysis or qualitative synthesis). Trials that reported adverse events as a proportion of all adverse events reported or did not report events by treatment group were not considered for pooling.

Evidence Synthesis

We initially assessed the evidence to determine whether one treatment was therapeutically superior to another and found that, for many comparisons, the evidence suggested equivalence of the treatments compared. We therefore decided post hoc to adopt an equivalence approach to evidence assessment in accordance with the AHRQ Methods Guide.[48] Equivalence assessments increased our ability to form conclusions about the comparative effectiveness of treatments. In contrast to superiority assessments, equivalence assessments aim to determine whether two treatments are therapeutically similar within a predefined margin of equivalence[48] (discussed further below). Therefore, we assessed the body of evidence to support one of the following conclusions:

- Superiority: One treatment demonstrated greater effectiveness than the other, either for symptom improvement or harm avoidance.
- Equivalence: Treatments demonstrated comparable effectiveness, either for symptom improvement or harm avoidance.
- Insufficient evidence: The evidence supported neither a conclusion of superiority nor a conclusion of equivalence.

To form clinically relevant conclusions, we compared both individual and pooled treatment effects to the MCID for each outcome, if one existed. Conclusions that could be drawn depended on whether or not an MCID existed and whether or not we were able to conduct meta-analysis:

- If an MCID existed and meta-analysis was done, one of *three* conclusions could be made: superiority, equivalence, or insufficient evidence. This was based on examination of the 95 percent confidence interval of the pooled effect in relation to the MCID (described further below).
- If there was no MCID and meta-analysis was done, one of *two* conclusions could be made: superiority or insufficient evidence. This was based on examination of the 95 percent confidence interval of the pooled effect in relation to the "no effect" line (i.e., treatment difference of zero). In this instance, a margin of equivalence could not be identified.
- If meta-analysis was not done, one of *two* conclusions could be made regardless of whether an MCID existed: superiority or insufficient evidence. In this instance, we estimated qualitatively the magnitude of the overall treatment effect for the body of evidence by inspection of individual trial results. Because a 95 percent CI for the overall effect was not generated, equivalence could not be assessed.

Strength of the Body of Evidence

The strength of the body of evidence for each outcome was determined in accordance with the AHRQ Methods Guide[48] and is based on the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system.[58, 78] Two reviewers independently evaluated the strength of evidence; agreement was reached through discussion and consensus when necessary. Four main domains were assessed: risk of bias, consistency, directness, and precision. Additional domains (dose-response association, strength of association, and publication bias) were considered for assessment. The body of evidence was evaluated separately for each treatment comparison and each outcome of interest, to derive a single GRADE of high, moderate, low, or insufficient evidence.

The GRADE definitions are as follows:

- High: high confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
- Moderate: moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
- Low: low confidence that the evidence reflects the true effect. Further research is likely to change the confidence in the estimate of effect and is likely to change the estimate.
- Insufficient: evidence either is unavailable or does not permit a conclusion.

We assessed the four strength of evidence domains using the following decision rules.

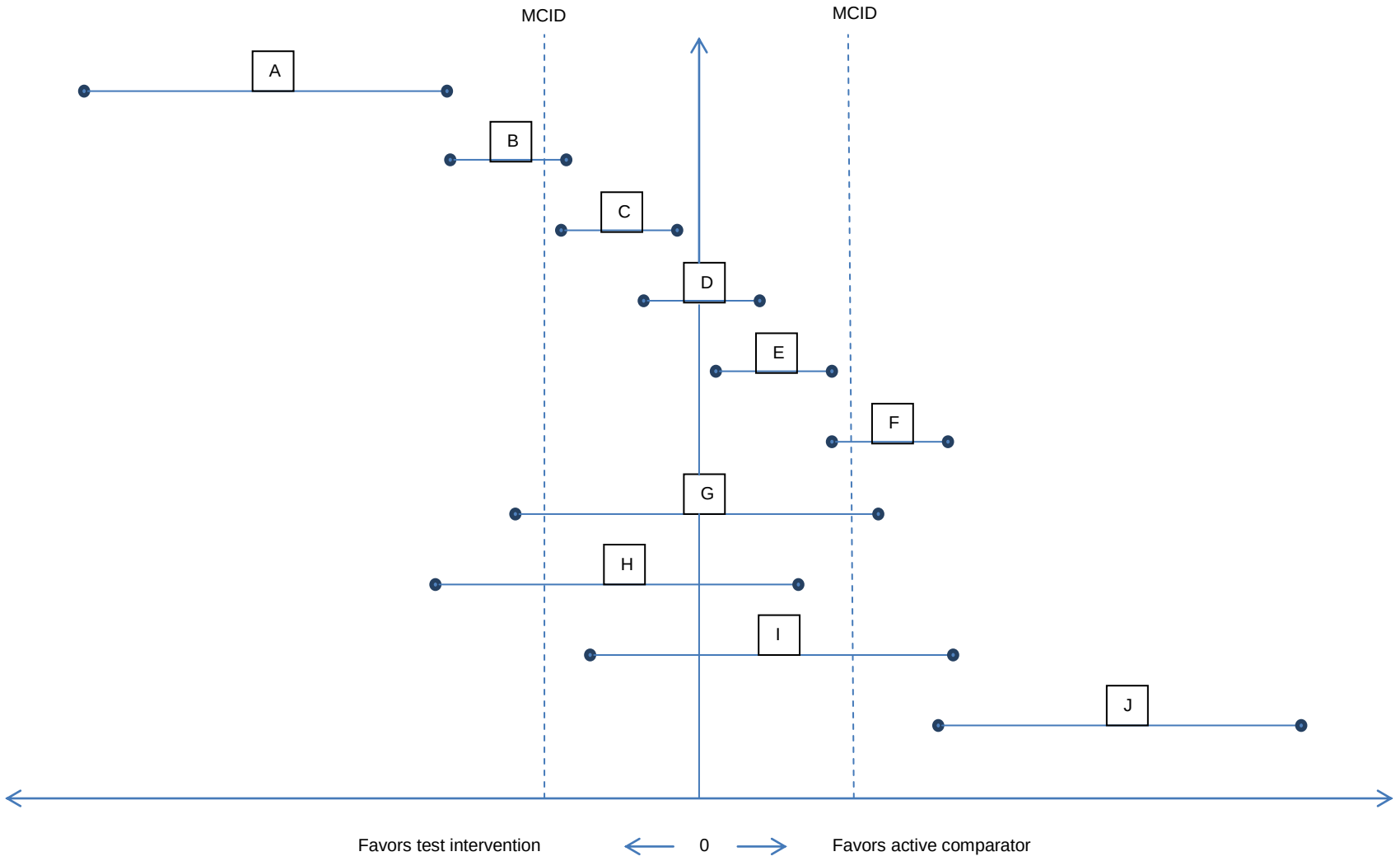
- Risk of bias: Ratings were based on USPSTF criteria applied to trials that reported on a given outcome, weighted by sample size using a semi-quantitative method. We used the following approximate cutoffs:
    - Low risk of bias: Most patients were in good quality trials, and fewer than one-third were in poor quality trials.
    - High risk of bias: Most patients were in poor quality trials, and fewer than two-fifths were in good quality trials.
    - Medium risk of bias: The body of evidence falls between low and high risk of bias.
    - For harms, active ascertainment of adverse events using structured questionnaires was considered to reduce the risk of bias, and passive ascertainment of adverse events by spontaneous patient report only, to increase the risk of bias.
- Consistency: We assessed consistency by comparing the direction of treatment effects. Because conclusions that could be drawn depended on whether or not an MCID existed and whether or not meta-analysis was done (as described above in "Evidence Synthesis"), the application of consistency assessments differed for outcomes with and without an MCID and for bodies of evidence without and without meta-analysis.
    - If an MCID existed and meta-analysis was done, we determined consistency by visual inspection of forest plots. As shown in Figure 3:
        - Point estimates and their 95 percent confidence intervals that fell completely above or below an interval bounded by the MCID (i.e., –MCID, +MCID) were considered consistent in support of a conclusion of superiority of the treatment favored. (See A and J in Figure 3.)
        - Point estimates and their 95 percent confidence intervals that fell completely within an interval bounded by the MCID (i.e., –MCID, +MCID) were considered consistent in support of a conclusion of equivalence of the two treatments. (See C, D, and E in Figure 3.)
        - Point estimates that fell on either side of the MCID (i.e., some greater than and some less than the MCID) or 95 percent confidence intervals that included the MCID were considered inconsistent. (See B, F, G, H, and I in Figure 3.)
    - If an MCID existed and meta-analysis was not done, treatment effects in the same direction (i.e., all greater than or all less than the MCID) were considered consistent. Effects in opposite directions were considered inconsistent.
    - If there was no MCID and meta-analysis was done, we also inspected forest plots.
        - Point estimates and their 95 percent confidence intervals that fell completely on one side of the line of "no effect" (i.e., treatment difference of zero) were considered consistent.
        - Point estimates that fell on either side of "no effect" (i.e., some treatment differences greater than zero and some less than zero) or 95 percent confidence intervals that included zero were considered inconsistent.
    - If there was no MCID and meta-analysis was not done, treatment effects in the same direction (i.e., all greater than or all less than a treatment difference of zero) were considered consistent. Effects in opposite directions were considered inconsistent.

    - A body of evidence that included both meta-analysis and additional trials reporting results that conflicted with the meta-analysis was considered consistent if 10 percent or less of patients reporting the outcome were in the additional trials.
    - For meta-analyses that used the mean difference as the measure of the pooled effect, we also examined statistical heterogeneity (Cochran's Q statistic and I2 statistic) to support the consistency assessments described above.
        - Low statistical heterogeneity supported consistency.
        - We examined moderate and greater statistical heterogeneity using additional analyses (as described above in "Overall Approaches and Meta-Analyses for Direct Comparisons") to determine an overall assessment of consistency.
- Directness: As displayed in the Analytic Framework (Figure 1), intermediate health outcomes and final health outcomes pertain directly to patients' experience of improvement in symptoms and quality of life. Therefore, all outcomes were considered direct.
- Precision: The assessment of precision depended on whether an MCID existed for the outcome and whether the body of evidence included meta-analysis.
    - If an MCID existed and meta-analysis was done, precision of the pooled effect estimate was determined by the 95 percent confidence interval of the estimate. As shown in Figure 3:
        - If both the point estimate and its 95 percent confidence interval fell completely above or below an interval bounded by the MCID (i.e., –MCID, +MCID), the body of evidence was considered precise in support of a conclusion of superiority of the favored treatment. (See A and J in Figure 3.)
        - If both the point estimate and its 95 percent confidence interval fell completely within an interval defined by the MCID (i.e., –MCID, +MCID), the body of evidence was considered precise in support of a conclusion of equivalence of the two treatments (See C, D, and E in Figure 3.)
        - If the 95 percent confidence interval included the MCID, the body of evidence was considered imprecise and insufficient to support a conclusion of either superiority or equivalence (See B, F, G, H, and I in Figure 3.)
    - If an MCID existed and meta-analysis was *not* done, effect estimates clearly exceeding the MCID (to accommodate unknown variance in the estimate) were considered precise in support of a conclusion of superiority of the favored treatment. Otherwise, effects were considered imprecise.
    - If there was no MCID and meta-analysis was done, pooled effects were considered precise if their 95 percent confidence intervals excluded conflicting conclusions (i.e., did not include treatment differences of zero).
    - If there was no MCID and meta-analysis was *not* done, statistically significant treatment effects were considered precise; statistically nonsignificant treatment effects were considered imprecise. Although conceptually different from precision, statistical significance of treatment effects is highly correlated with precision.
    - For bodies of evidence with additional trials not included in meta-analysis, we assessed the impact of the additional treatment effects on the pooled estimate semi-quantitatively. We considered both the direction and magnitude of the

additional treatment effects as well as trial size (i.e., the number of patients reporting the outcome):

- Effects that clearly would have little impact on the pooled estimate if included in the meta-analysis were noted (e.g., 5 percent of patients reporting the outcome in a trial with an effect estimate very close to the pooled estimate).
- Effects that would have uncertain impact on the pooled estimate were added to the meta-analysis with assumed standard deviations equal to half the mean change in outcome score in each treatment group. This assumption was based on the observation that reported group-level standard deviations were often approximately equal to group means (Appendix C). Because we used inverse variance weighting in our pooling method, larger standard deviations would have yielded smaller confidence intervals for treatment effects and increased the risk of a Type I error (i.e., a 95 percent confidence interval that erroneously excluded the MCID would lead to an incorrect conclusion of equivalence or superiority; if there was no MCID, a 95 percent confidence interval that erroneously excluded zero would lead to an incorrect conclusion of superiority). Using a smaller standard deviation was a more conservative approach.
- For trials that did not report treatment effect magnitudes, a body of evidence could be considered precise if the trials represented less than 10 percent of patients reporting the outcome.

Figure 3. Interpretation of pooled treatment effects–consistency and precision in support of conclusions of superiority, equivalence, or insufficient evidence



Note: A: comparison showing superiority; B, F, G, H and I: comparisons showing inconclusive evidence and equivalence cannot be claimed; C, D and E: comparisons showing equivalence; J: comparison showing inferiority; A, C, D, E and J would be rated as consistent and precise; B, F G, H and I would be rated as inconsistent and imprecise.

We assigned overall strength of evidence grades using a semi-quantitative approach. Because our body of evidence comprised RCTs, we began with an overall rating of high strength of evidence, which assumed low risk of bias and consistent and precise effects. (All outcomes were considered direct as noted above). We downgraded the strength of evidence one level for each domain rating that differed from this starting assumption. For example, if the risk of bias was medium and the evidence was inconsistent, the strength of evidence was downgraded two levels, from high to low. The one exception to this approach was precision: Any imprecise body of evidence was considered insufficient to support a conclusion about the comparative effectiveness or harms of the treatments compared.

Applicability

The objective of this review was to provide an evidence-based understanding of the comparative effectiveness of available treatments for SAR. Populations of interest were children, adolescents, and adults (including pregnant women) who experience mild or moderate/severe SAR symptoms. In this context, applicability is defined as the extent to which treatment effects observed in published studies reflect expected results when treatments are applied to these populations in the real world.[79, 80]

Potential factors that may affect the applicability of the evidence for the KQs include:

- Underrepresentation of populations of interest, especially pregnant women
- Selection of patients with predominantly severe symptoms
- Dosage of comparator interventions not reflective of current practice
- Effects of keeping a patient diary on treatment adherence

The applicability of the body of evidence for each KQ was assessed by two reviewers with agreement reached through discussion and consensus when necessary. Limitations to the applicability of individual studies are described in the Discussion chapter.

Peer Review and Public Commentary

Peer Reviewers

Peer Reviewers were invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. The EPC addressed Peer Review comments on the preliminary draft of the report when preparing the final draft of the report. Peer Reviewers did not participate in writing or editing the final report or other products. The synthesis of the scientific literature presented in the final report does not necessarily represent the views of individual reviewers. The dispositions of the Peer Review comments were documented and will be published three months after publication of the final report.

Potential reviewers disclosed any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers could not have any financial conflict of interest greater than $10,000. Peer reviewers who disclosed potential business or professional conflicts of interest could submit comments on draft reports through the public comment mechanism.

Public Commentary

The Research Protocol was posted for public comment on March 8, 2012. The Draft Report was available for public comment from August 2, 2012 to August 30, 2012. No public comments were received.

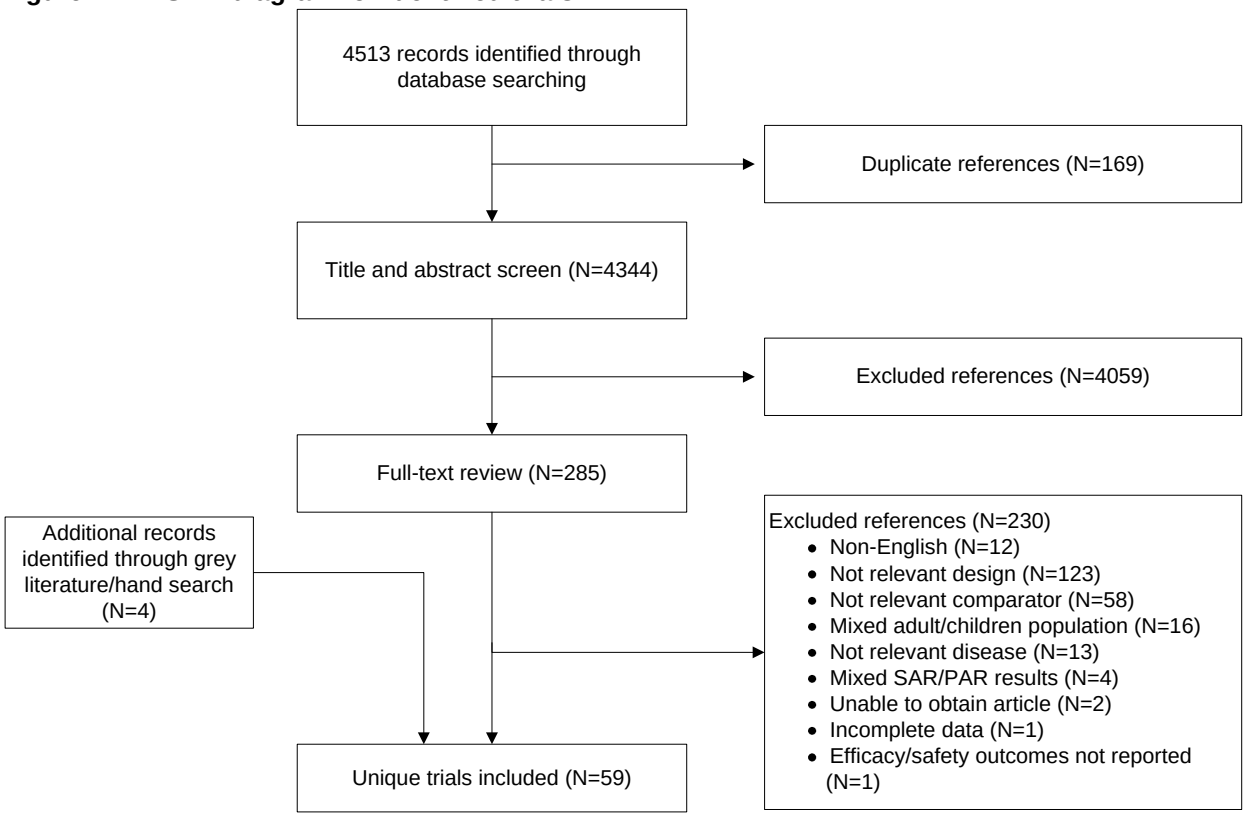
Results

Results of Literature Searches

Of the 4,513 records identified through the literature search, 4,458 were excluded during screening. Four records were identified through grey literature and hand searching of bibliographies. One unpublished trial listed on ClinicalTrials.gov satisfied our inclusion criteria (NCT00960141). However, this trial was not included because quality assessment was not possible without the published report. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[49] diagram shown in Figure 4 depicts the flow of screening and study selection. A total of 59 unique trials were included. Several of these were three arm trials that addressed more than one comparison. Occasionally, more than one trial was reported in a single publication. Although search strategies were designed with the appropriate methodological filters to identify randomized controlled trials (RCTs), observational studies, systematic reviews and meta-analyses, the results did not yield studies for all comparisons of interest. For Key Question (KQ) 1 and KQ2, 56 RCTs, and one quasi-RCT, that addressed 13 of 22 comparisons of interest were found. For KQ3, no studies that addressed any of 17 comparisons of interest were found, and for KQ4, two RCTs that addressed one of 21 comparisons of interest were found. No observational studies, systematic reviews, or meta-analyses that met our inclusion criteria.

The list of excluded studies with reasons for exclusion is presented in Appendix B.

Figure 4. PRISMA diagram for identified trials



Overview

Of 22 comparisons of interest for adults and adolescents (KQ1 and KQ2), we found studies that addressed 13 (Table 9). Of 21 comparisons of interest for children younger than 12 years of age (KQ4), we found studies that addressed one, oral selective antihistamine versus oral nonselective antihistamine. No studies were identified for pregnant women (KQ3). An overview of included studies is presented in Table 10. A summary of drugs studied in included trials is shown in Table 11.

The number of studies for each comparison ranged from two to 13. This variability was due in part to our inclusion requirement of Food and Drug Administration (FDA)-approved drugs only, which impacted particularly the comparison of oral selective antihistamine to oral nonselective antihistamine. The majority of these trials used terfenadine or astemizole as the selective antihistamine comparator, neither of which is currently FDA-approved due to postmarketing safety concerns. As a result, only three trials were included for this comparison.

Trial sizes ranged from 27 to 1343 patients (13 to 672 patients per treatment arm). Fourteen percent of trials had fewer than 25 patients per treatment arm, 10 percent had 25 to 50, and 32 percent had more than 100. The proportion of good and poor quality trials varied across comparisons, from 100 percent good quality trials for the comparisons of combination intranasal corticosteroid plus nasal antihistamine both to intranasal corticosteroid and to nasal antihistamine, to 100 percent poor quality trials for the comparison of intranasal corticosteroid to nasal cromolyn. Overall, approximately half of trials were rated poor quality using United States Preventive Services Task Force (USPSTF) criteria, and one quarter was rated good quality.

Table 9. Results of literature searches for Key Question 1 and Key Question 2 comparisons of interest

	nS-AH, Oral	S-AH, Oral	S-AH, Nasal	INCS	D, Oral	D, Nasal	C, Nasal	LRA, Oral	AC, Nasal	NS
nS-AH, oral		✓								
S-AH, oral			✓	✓	✓		✓	X	X	X
S-AH, nasal				✓	X			X	X	X
INCS							✓	✓	X	X
D, oral										
D, nasal										
C, nasal										
LRA, oral										
AC, nasal										
NS										
S-AH, oral + INCS		✓		✓						
S-AH, oral + D, oral		✓								
S-AH, nasal + INCS			✓	✓						

The top portion of this table is a grid of monotherapy treatment comparisons of interest for which studies were identified (✓) or not identified (X). The last three rows of the table indicate combination treatment comparisons for which studies were identified (✓).

AC = anticholinergic; C = cromolyn; D = sympathomimetic decongestant; nS-AH = nonselective antihistamine; S-AH = selective antihistamine; INCS = intranasal corticosteroid; LRA = leukotriene receptor antagonist; NS = nasal saline.

Table 10. Overview of included randomized controlled trials

Treatment Comparison Date	N/n	Outcomes	Drugs Studied	% Industry Funded	% Good Quality	% Fair Quality	% Poor Quality
Oral S vs. Oral nS 1987-1996	3[81-83]/515	Nasal, QoL, AE	Cetirizine, loratadine Clemastine, chlorpheniramine	33	0	33	67
Oral S vs. Nasal AH 1993-2006	5[84-88]/1052	Nasal, QoL, AE	Cetirizine, desloratadine, loratadine Azelastine	40	40	0	60
Oral S vs. INCS 1995-2009	13[89-100] /4403	Nasal, Eye, QoL, AE	Cetirizine, fexofenadine, loratadine Beclomethasone, fluticasone furoate, fluticasone propionate, mometasone, triamcinolone	92	15	23	62
Oral S vs. Oral D 1995-2009	7[101-107]/3595	Nasal, Eye, QoL, AE	Cetirizine, desloratadine, fexofenadine, loratadine Pseudoephedrine	71	43	14	43
Oral S vs. Oral LRA 2000-2009	9[97, 108-114]/ 4404	Nasal, Eye, Asthma, QoL, AE	Desloratadine, levocetirizine, loratadine Montelukast	78	33	22	45
INCS vs. Nasal AH 1995-2012	9[115-121]/3527	Nasal, Eye, QoL, AE	Beclomethasone, fluticasone propionate Azelastine, olopatadine	67	56	0	44
INCS vs. Nasal C 1985-2005	4[122-125]/436	Nasal, QoL, AE	Beclomethasone, budesonide, flunisolide, fluticasone propionate, mometasone, Cromolyn	75	0	0	100
INCS vs. Oral LRA 2002-2009	5[97, 126-129] /2444	Nasal, Asthma, QoL, AE	Beclomethasone, fluticasone propionate Montelukast	100	60	0	40
Oral S + INCS vs. Oral S 1998-2008	3[90, 98, 130]/677	Nasal, Eye, QoL, AE	Cetirizine, loratadine Mometasone, fluticasone propionate	33	0	67	33
Oral S + INCS vs. INCS 1994-2008	5[62, 90, 98, 131, 132] /1170	Nasal, Eye, QoL, AE	Cetirizine, levocetirizine, loratadine Fluticasone propionate, mometasone	40	20	20	60
INCS + Nasal AH vs. INCS 2008-2012	5[115, 117, 121] /3151	Nasal, Eye QoL, AE	Azelastine Fluticasone propionate	100	100	0	0
INCS + Nasal AH vs. Nasal AH 2008-2012	5[115, 117, 121] /3151	Nasal, Eye QoL, AE	Azelastine Fluticasone propionate	100	100	0	0

Treatment Comparison Date	N/n	Outcomes	Drugs Studied	% Industry Funded	% Good Quality	% Fair Quality	% Poor Quality
Oral S + Oral D vs. Oral S 1995-2009	7[101-107]/3575	Nasal, Eye QoL, AE	Cetirizine, desloratadine, fexofenadine, loratadine Pseudoephedrine	71	43	14	43
Pedi Oral S vs. Oral nS 1989-1996	2[133, 134] /166	Nasal, Eye QoL, AE	Cetirizine, loratadine Chlorpheniramine, dexchlorpheniramine	50	0	50	50

Note: N/n=number of trials/number of patients in treatment arms of interest. Date is the range of publication dates.

AC = anticholinergic; AE = adverse events; C = cromolyn; INCS = intranasal corticosteroid; LRA = leukotriene receptor antagonist; NS = nasal saline; nS = nonselective antihistamine; QoL= quality of life; RCT = randomized controlled trial; S = selective antihistamine; D = sympathomimetic decongestant.

Table 11. Drugs studied in included trials

Drug Class[a]	Studied	Not Studied	Representation[b]
Oral H1-antihistamine			
Nonselective	Chlorpheniramine, clemastine, dexchlorpheniramine	Acrivastine (in combination with pseudoephedrine only), brompheniramine, carbinoxamine, cyproheptadine, dexbrompheniramine, diphenhydramine, doxylamine, promethazine, triprolidine	3/12 (25%)
Selective	Cetirizine, desloratadine, fexofenadine, levocetirizine, loratadine		5/5 (100%)
Nasal H1 antihistamine			
Selective	Azelastine, olopatadine		2/2 (100%)
Intranasal corticosteroid	Beclomethasone, budesonide, flunisolide, fluticasone furoate, fluticasone propionate, mometasone, triamcinolone	Ciclesonide	7/8 (87.5%)
Mast cell stabilizer	Disodium cromoglycate (cromolyn)		1/1 (100%)
Leukotriene receptor antagonist	Montelukast		1/1 (100%)
Oral sympathomimetic decongestants	Pseudoephedrine	Phenylephrine	1/2 (50%)
Nasal sympathomimetic decongestants		Levmetamfetamine, naphazoline, oxymetazoline, phenylephrine, propylhexedrine, tetrahydrozoline, xylometazoline	0/7 (0%)
Anticholinergic		Ipratropium bromide	0/1 (0%)

[a] Classes containing drugs administered by oral and nasal routes are divided into subclasses here.

[b] Representation indicates the proportion of drugs in each class that were studied.

Detailed descriptions of trials and patient characteristics are shown in abstraction tables located in Appendix C. Eighty-one percent of trials were double-blinded. Seventy-one percent included a run-in period, a period before the start of a clinical trial used to establish baseline characteristics and to assess compliance and stability of enrolled patients; either no treatment or placebo treatment (favored by the FDA[50]) was given. Half of trials reported pollen counts. Most (88 percent) confirmed seasonal allergic rhinitis (SAR) diagnosis by either skin prick test or intradermal skin test. For inclusion, most trials required either a minimum duration of SAR symptoms (17 percent), or minimum severity (14 percent), or both (63 percent). Exclusions included infection (15 percent), anatomical deformity including nasal polyps (15 percent), or both (50 percent). Forty-eight trials (81 percent) restricted the use of SAR medications before trial entry. Of these, approximately half reported using FDA-recommended washout periods. Five trials excluded patients with a past or recent history of immunotherapy. Others admitted patients receiving immunotherapy provided treatments were stable before and during the trial. Seventy-one percent of trials explicitly excluded pregnant women.

For pharmacologic classes that have more than one drug, no comparison had 100 percent representation (that is, included all drugs in class). As shown in Table 11, representation of drug classes varied across comparisons. Collectively across all comparisons, oral and nasal antihistamine and intranasal corticosteroid were well represented. However, the level of representation varied across individual comparisons. Three of five oral selective antihistamines (60 percent) and five of eight intranasal corticosteroids (62.5 percent) were included in direct comparison with each other. Oral selective antihistamine also was well represented (by at least three of five drugs [60 percent]) in comparisons to nasal antihistamine, oral decongestant (alone and in combination), and oral leukotriene receptor antagonist (montelukast). In contrast, for the comparisons of combination intranasal corticosteroid and nasal antihistamine to each component, only one of eight intranasal corticosteroids (fluticasone propionate; 12.5 percent) was studied. Fluticasone propionate was the most studied intranasal corticosteroid and appeared in every comparison involving intranasal corticosteroids. The intranasal corticosteroid ciclesonide was not studied in any identified trial. No trials of nasal anticholinergic (ipratropium) or nasal decongestant were identified. One of two oral decongestants (pseudoephedrine) was studied. Only three of eleven oral nonselective antihistamines (27 percent) were represented in two comparisons, one in adolescents and adults (KQ1), and one in children (KQ4). Conclusions based on comparisons of pharmacologic classes that were poorly represented are limited to the specific drugs studied. How well such conclusions generalize to other drugs in the same class is uncertain.

Half of trials reported eye outcomes. Only two[108, 127] reported asthma outcomes. Only one trial[96] assessed as-needed (prn) dosing. All others used continuous daily dosing. We were therefore unable to compare intermittent to continuous treatment, a subquestion to each of our KQs. Most trials (86 percent) were 2 or 4 weeks in duration. Six trials[88, 120, 123, 128, 131, 132] were 6 to 8 weeks in duration. These trials reported on five different treatment comparisons. For the remaining eight comparisons, we were unable to compare short-term to longer-term use.

The reporting of efficacy outcomes varied across trials. Most trials that assessed nasal symptoms assessed four individual symptoms (congestion, rhinorrhea, sneezing, and nasal itch) and/or a total nasal symptom score (TNSS) comprising the sum or average of scores for the individual symptoms. However, some trials reported only a total symptom score (TSS) comprising four nasal symptoms plus up to five additional symptoms (eye itching, tearing, and redness; itching of the ears and palate). Trials comparing oral antihistamine and oral

decongestant assessed "TNSS minus congestion" (defined a priori) because of the known differential efficacy of the drugs for treatment of congestion. Similarly, for eye outcomes, three symptoms were most commonly assessed (itching, tearing, and redness) and summed or averaged to produce a total ocular symptom score (TOSS). However, some trials incorporated ocular swelling into the TOSS or did not define which eye symptoms were assessed by the TOSS. To facilitate comparisons of results across trials, individual symptom scores, the four-symptom TNSS, and three-symptom TOSS were abstracted.

For assessing nasal and eye symptom severity, most trials used a 4-point interval rating scale, from 0 for no symptoms to 3 for severe symptoms that interfere with one's daily activity. However, some used 6-point (0 to 5) or 3-point (0 to 2) scales. Five trials[98, 100, 126, 127, 129] reported on the outcome of TNSS using a 0-10 or 0-100 visual analog scale (VAS). When pooling results for meta-analyses, differences in scales were accommodated by use of standardized rather than non-standardized mean differences. This was necessary in three of 28 meta-analyses conducted. Most trials could not be pooled due to a lack of reported variance for group-level treatment effects.

Most trials that assessed quality of life used the Rhinitis Quality of Life Questionnaire (RQLQ). The RQLQ is a 27-item questionnaire validated in patients with rhinoconjunctivitis. Scores range from 0 (no impairment) to 6 (severe impairment). The anchor-based minimum clinically important difference (MCID) is 0.5 points.[65] Two trials in a single publication[89] used the Nocturnal RQLQ to assess sleep disturbance due to nasal symptoms at 2 weeks. The Nocturnal RQLQ is a 16-item questionnaire validated in patients with nocturnal rhinoconjunctivitis. Nocturnal symptoms are scored on a 7-point Likert scale from 0 (not troubled) to 6 (extremely troubled). An MCID has not been identified.[67] One trial used the mini-RQLQ to assess nasal symptoms.[62] The mini-RQLQ is a 14-item questionnaire validated in patients with rhinoconjunctivitis. Each question is scored on a scale from 0 (not troubled) to 6 (extremely troubled). The global mini-RQLQ score is the mean of all question scores. The anchor-based MCID is 0.7 points.[66]

Some trials used a patient global assessment (PGA) scale to assess patient satisfaction with treatment. Integer rating scales were commonly used, but these varied in design (e.g., 7 or 11-point Likert scales of treatment response ranging from very much improved to very much worse, or 4-point scales of satisfaction with treatment ranging from extremely satisfied to not at all satisfied). Results were reported either categorically (proportion of patients with good or very good response to treatment) or continuously (mean PGA scores). Because of this variability, comparison across trials was not possible. Further, although the interpretation of PGA results is clearer when outcomes are aligned with other reported results, statistically significant improvements in PGA in a trial reporting nonstatistically significant improvements in SAR symptoms were difficult to interpret. Most PGA assessments were made at the end of treatment only, without comparison to baseline values, further limiting their utility. For the purposes of this report, PGA results aligned with other treatment effects were considered supportive findings that enhanced the robustness of the trial. Discrepant PGA results were noted. In either case, PGA was not incorporated into the formal strength of evidence assessment for any outcome.

Finally, treatment effects were calculated in a variety of ways. Most trials calculated mean change from baseline symptom scores by subtracting mean baseline scores from symptom scores averaged across the entire treatment duration. However, some used endpoint values rather than mean values for this calculation, and others performed no calculation, comparing endpoint values rather than change from baseline values. A third approach was to calculate change from baseline

using mean scores during an interval of the treatment duration, for example, the mean of scores during the third and fourth week of treatment compared with baseline. Finally, some reported only relative results, for example, the percent reduction from baseline scores. When pooling results for meta-analysis, differences in efficacy calculations were accommodated by reporting mean differences rather than standardized mean differences.[48] When meta-analysis was not possible, comparisons of treatment effects were approximated. The degree to which different methods of results reporting impacted the magnitude or statistical significance of observed treatment effects is uncertain. As above, when the result of statistical testing was reported, it became the main parameter for comparison of efficacy across trials.

For KQ2, 33 trials reported directly comparable, group level adverse event information. Of these, 17 were rated good quality and 16 were rated poor quality. Additionally, 14, 6, and 11 trials used active, intermediate, and passive surveillance, respectively. Headache, sedation and nosebleeds were the most commonly reported events across the treatment comparisons. There were no reports in any trials for nine of 24 adverse event categories (37.5 percent), including all systemic effects of corticosteroids. No adverse events met our criteria for performing meta-analysis.

Reporting of adverse events fell into one of three categories: (1) general statements such as, "All groups were similar in the percentage of patients with clinical and laboratory adverse experiences;"[97] (2) accounts only of adverse events that occurred with a frequency greater than zero; and (3) accounts of adverse events in each treatment group. Adverse event data from trials in the second category were uninformative because we could not distinguish between missing adverse event reports and adverse events that occurred with a frequency of zero in other treatment groups. In the third category, trials that reported events as a proportion of reports rather than a proportion of patients were not useful for comparative purposes; these data were abstracted to assess consistency of the body of evidence. Trials that reported efficacy results at multiple time points did not report adverse events by occurrence in time. For this reason, it was not possible to compare the emergence of adverse events across varying treatment exposures.

As described in the Methods section, we assessed the strength of the body of evidence for each outcome using a system based on Grading of Recommendations Assessment, Development, and Evaluation (GRADE). In addition to the four main domains assessed (risk of bias, consistency, directness, and precision), the following additional domains were considered and deemed not relevant for the reasons listed:

- Dose-response association – Levels of exposure tended to be standard for each intervention.
- Strength of association – Effect sizes generally were small.
- Publication bias – We found no indication that relevant empirical findings were unpublished.

How This Section Is Organized

Results are organized by KQ and then by the treatment comparisons of interest for each KQ. A Description of Included Studies, Key Points, and Synthesis and Strength of Evidence are presented for each treatment comparison.

- Description of Included Studies
    - For additional information, detailed abstraction tables are located in Appendix C. These include trial description, patient characteristics, USPSTF quality rating, outcomes, and harms tables.

- Key Points
    - Key Points are organized by outcome. The strength of evidence was summarized in bullet points and in tabular form.
    - In some cases, separate outcomes with similar strength of evidence ratings are bundled together for reporting in the bullet points.
- Synthesis and Strength of Evidence
    - This section is organized by type of outcome (nasal symptoms, eye symptoms, asthma symptoms, and quality of life). For each type of outcome, individual outcomes are presented usually in two paragraphs: The first summarizes the findings for that outcome. The second describes the overall rating of the strength of evidence for that outcome.
    - For outcomes that are straightforward, findings and strength of evidence assessment may be presented in a single paragraph. For outcomes or comparisons that are more complex, more than two paragraphs may be required.
    - Tables of treatment effects for each type of outcome discussed follow the discussion.
    - For each type of outcome, meta-analyses follow the tables. For example, a treatment effect table may summarize four nasal symptom outcomes. If meta-analyses were conducted for three of the outcomes, these would follow the treatment effect summary table for nasal outcomes.

Key Question 1. Comparative Effectiveness of SAR Treatments in Adults and Adolescents 12 Years of Age or Older

Oral Selective Antihistamine Versus Oral Nonselective Antihistamine

Description of Included Studies

Three RCTs[81-83] published between 1987 and 1996 were identified (N=515). All three were 2-week, multicenter trials conducted in North America. Trial size ranged from 86 to 220 patients randomized to treatment groups of interest. Oral selective antihistamines studied were loratadine (two trials[81, 83]) and cetirizine (one trial[82]); oral nonselective antihistamines were clemastine (two trials[81, 83]) and chlorpheniramine (one trial[82]). Two trials[81, 83] were double-blinded, and one[82] was assessor-blinded only. One trial[82] was industry-funded, and the other two did not report funding source.

Average patient ages were in the early 30s. Approximately 40 percent of patients were women. When reported, the majority of patients were white (74-93 percent). All three trials required a minimum severity of SAR symptoms and, in the one trial that reported values, baseline symptoms were in the moderate range. Although none of the trials required a minimum duration of SAR history, most patients had SAR symptoms for more than 16 years.

Information from one trial each was available for nasal symptoms,[83] adverse events,[81] and quality of life.[82] No trial assessed eye or asthma symptoms. Nasal symptom outcomes were assessed using a 4-point (0=no symptoms, 3=severe symptoms) scale; the scores for congestion, rhinorrhea, sneezing and itching were summed for a TNSS ranging from 0 to 12.[83] One trial[82]

used the RQLQ to measure quality of life (0=no impairment, 6=severely impaired), with 28 questions in 7 domains summed for a total score ranging from 0 to 168. The usual use of the RQLQ is to average the scores of each domain and the MCID is 0.5.[65] By extrapolation, the MCID is 14 for this trial.

Two trials[81, 82] were rated poor quality and one[83] was rated fair.

Key Points

These results are summarized in Table 12.

- TNSS at 2 weeks: Evidence was insufficient to support the use of one treatment over the other based on one trial 83 with medium risk of bias and imprecise results.
- Quality of life at 2 weeks: Evidence was insufficient to support the use of one treatment over the other based on one trial 82 with high risk of bias. Although a statistically significant treatment effect was reported, the magnitude of the treatment effect was less than the MCID.
- These results are based on trials of two of five oral selective antihistamines (40 percent) and two of eleven oral nonselective antihistamines (18 percent).

Table 12. Strength of evidence: oral selective antihistamine versus oral nonselective antihistamine

Outcome	RCTs (Patients)	Risk of Bias	Consistency	Directness	Precision	Overall GRADE
2-week TNSS	1[83] (209)	Medium	Unknown (single study)	Direct	Imprecise	Insufficient
2-week QoL	1[82] (86)	High	Unknown (single study)	Direct	Imprecise	Insufficient

GRADE = Grading of Recommendations Assessment, Development and Evaluation; QoL = quality of life; RCTs (Patients) = number of randomized controlled trials (number of patients randomized to treatment groups of interest); TNSS = total nasal symptom score.

Synthesis and Strength of Evidence

Nasal symptom results discussed below are summarized in Table 13. Quality of life results are summarized in Table 14. Meta-analysis was not possible due to the small number of trials.

Nasal Symptoms

Of three identified trials, one[83] (N=209) reported nasal symptom outcomes (TNSS). This trial was rated fair quality, and reported a non-statistically significant treatment effect of 0.3 on a 0-12 point scale (3 percent of maximum score) favoring oral selective antihistamine. Risk of bias was considered moderate based on trial quality. Because consistency of the observed effect cannot be assessed with a single trial and because the effect was imprecise, the evidence was insufficient to support the use of one treatment over the other.

Quality of Life

Of three identified trials, one[82] (N=86) reported quality of life outcomes. This trial was rated poor quality due to noncomparable groups at baseline and inappropriate analysis of results (unadjusted for baseline group differences). The treatment effect was 12.9 on a 0-168 point scale favoring oral selective antihistamine and was statistically significant. Extrapolating the anchor-based MCID (0.5) for the RQLQ 0-6 point scale yields an MCID of 14 points. Risk of bias for this outcome was considered high based on both trial quality and the use of quality of life measures in an unblinded trial population. Consistency is unknown with a single trial, and the

treatment effect was imprecise. The evidence was therefore insufficient to support the use of one treatment over the other for this outcome.

Table 13. Treatment effects: nasal symptoms–oral selective antihistamine versus oral nonselective antihistamine

Outcome	Variance	SS Favors Oral S-AH MD	NSS Favors/NR Oral S-AH MD	Favors Neither MD=0	NSS Favors/NR Oral nS-AH MD	SS Favors Oral nS-AH MD
2-Week Outcomes						
TNSS						
Kemp, 1987[83] (scale 0-12)			0.3 (NSS)			

MD = mean difference between group mean changes from baseline; NR = p-value not reported; nS-AH = nonselective antihistamine; NSS = not statistically significant; S-AH = selective antihistamine; SS = statistically significant; TNSS = total nasal symptom score.

Table 14. Treatment effects: quality of life–oral selective antihistamine versus oral nonselective antihistamine

Outcome	Variance	SS Favors Oral S-AH MD	NSS Favors/NR Oral S-AH MD	Favors Neither MD=0	NSS Favors/NR Oral nS-AH MD	SS Favors Oral nS-AH MD
2-Week Outcomes						
RQLQ						
Harvey, 1996[82] (scale 0-168)		12.9[a]				

MD = mean difference between group mean changes from baseline; NR = p-value not reported; nS-AH = nonselective antihistamine; NSS = not statistically significant; RQLQ = Rhinoconjunctivitis Quality of Life Questionnaire; S-AH = selective antihistamine; SS = statistically significant.

[a] Validated minimum clinically important difference (MCID) of 0.5 on a 0-6 scale corresponds to MCID of 14 on a 0-168 scale.

Oral Selective Antihistamine Versus Nasal Antihistamine

Description of Included Studies

Five double-blind, RCTs[84-88] published between 1993 and 2006 were identified (N=1,052). Four[84-87] were multicenter trials. Three trials[84, 85, 87] were conducted in North America and two[86, 88] in Europe. All trials were 2 weeks in duration. Trial size ranged from 30 to 360 patients randomized to treatment groups of interest. Oral selective antihistamines studied were cetirizine (three trials[85-87]), loratadine (one trial[88]), and desloratadine (one trial[84]); nasal antihistamine was azelastine in all five trials. Two older trials[86, 88] used the lower of two FDA-approved doses of azelastine, equivalent to half the dose used in more recent trials. Two trials[86, 87] were industry-funded. Three trials[84, 85] did not report funding source.

Average patient ages ranged from 30 to 36 years. In most trials, the majority of patients were women (56-67 percent). In three trials that reported information on race, the majority was white (69-81 percent). Four trials required a minimum severity of SAR symptoms. Average TNSS at baseline were most commonly in the severe range. Patients with chronic asthma were excluded from four trials. One trial[88] did not specify whether patients with chronic asthma were included. All five trials required a minimum duration of SAR history. Most patients had SAR symptoms for more than 18 years. Two trials[84, 88] did not report disease duration.

Of four trials[84-87] that assessed nasal symptoms, all reported 2-week outcomes. Three trials[84, 85, 87] used a 4-point (0=no symptoms, 3=severe symptoms) rating scale for the assessment of four nasal symptoms (congestion, rhinorrhea, sneezing, and itch). In three trials[84, 85, 87] patients

assessed symptoms in both the morning and evening, yielding 6-point maximums for individual symptoms and a 24-point maximum for TNSS. One trial[86] collected nasal symptom scores once daily using a 0 (no symptoms) to 100 (severe symptoms) VAS. Three trials[85-87] assessed quality of life using the RQLQ. Of several outcomes reported by Gambardella (1993)[88], sufficient information was provided to abstract adverse events only. No trials assessed eye or asthma symptoms.

Three trials[84, 85, 87] were rated good quality and two[86, 88] were rated poor.

Key Points

These results are summarized in Table 15.

- Individual nasal symptoms and TNSS at 2 weeks: Evidence was insufficient to support the use of one treatment over the other based on three trials (for rhinorrhea,[84, 86, 87] nasal itch,[84, 86, 87] and TNSS[84, 85, 87]) or four trials[84-87] (for congestion and sneezing) with low risk of bias and consistent but imprecise results.
- Quality of life at 2 weeks: Evidence was insufficient to support the use of one treatment over the other based on two trials[85, 87] with low risk of bias and consistent but imprecise results. Although statistically significant treatment effects were reported, the magnitude of effects was less than the MCID.
- These results are based on trials of three of five oral selective antihistamines (60 percent) and one of two nasal antihistamines (50 percent).

Table 15. Strength of evidence: oral selective antihistamine versus nasal antihistamine

Outcome	RCTs (Patients)	Risk of Bias	Consistency	Directness	Precision	Overall GRADE
2-week congestion, sneezing	4[84-87] (1022)	Low	Consistent	Direct	Imprecise	Insufficient
2-week rhinorrhea, nasal itch	3[84, 86, 87] (662)	Low	Consistent	Direct	Imprecise	Insufficient
2-week TNSS	3[84, 85, 87] (886)	Low	Consistent	Direct	Imprecise	Insufficient
2-week RQLQ	2[85, 87] (667)	Low	Consistent	Direct	Imprecise	Insufficient

GRADE = Grading of Recommendations Assessment, Development and Evaluation; RCTs (Patients) = number of randomized controlled trials (number of patients randomized to treatment groups of interest); RQLQ = Rhinoconjunctivitis Quality of Life Questionnaire; TNSS = total nasal symptom score.

Synthesis and Strength of Evidence

Nasal symptom results discussed below are summarized in Table 16. Quality of life results are summarized in Table 17. As shown in these tables, only two trials provided variance estimates for reported outcomes. Thus, meta-analysis was not possible.

Nasal Symptoms

Four trials[84-87] (N=1022) assessed congestion after 2 weeks of treatment and reported greater improvement with nasal antihistamine than with oral selective antihistamine. Of three trials that reported p-values, this result was statistically significant in two.[85, 86] One[85] was a good quality trial of 360 patients (35 percent of patients reporting this outcome) that did not report the magnitude of the treatment effect. The other trial[86] (n=136) was rated poor quality due to noncomparable groups at baseline and inappropriate analysis of results (unadjusted for baseline

group differences). The magnitude of the treatment effect was not reported. Treatment effects of 0.08 and 0.17 on a 0-6 point scale (both less than 3 percent of maximum score) were reported by two trials[84, 87] that were rated good quality (51 percent of patients reporting). Statistical significance of the former result was not assessed. The latter result was not statistically significant.

For the outcome of congestion at 2 weeks, the risk of bias was rated as low. Eighty-seven percent of patients assessed for this outcome were in good quality trials. All four trials were consistent in favoring nasal antihistamine, but treatment effects were imprecise. The evidence was therefore insufficient to support the use of one treatment over the other for this outcome.

Three trials[84, 86, 87] (N=662) assessed rhinorrhea after 2 weeks of treatment and reported greater improvement with nasal antihistamine than with oral selective antihistamine. Of two trials that reported p-values, this result was statistically significant in both.[86, 87] One[87] was a good quality trial of 307 patients (46 percent of patients reporting this outcome) that reported a treatment effect of 0.46 on a 0-6 point rating scale (8 percent of maximum score). The other[86] was the poor quality trial identified above. The magnitude of the treatment effect was not reported. A treatment effect of 0.22 on a 0-6 point scale (4 percent of maximum score) was reported by one trial[84] that was rated good quality (33 percent of patients reporting). Statistical significance was not assessed.

For the outcome of rhinorrhea at 2 weeks, the risk of bias was rated as low. Seventy-nine percent of patients assessed for this outcome were in good quality trials. All three trials were consistent in favoring nasal antihistamine, but treatment effects were imprecise. The evidence was therefore insufficient to support the use of one treatment over the other for this outcome.

Four trials[84-87] (N=1022) assessed sneezing after 2 weeks of treatment and reported greater improvement with nasal antihistamine than with oral selective antihistamine. Of three trials that reported p-values, this result was statistically significant in one.[85] This was a good quality trial of 360 patients (35 percent of patients reporting this outcome) that did not report the magnitude of the treatment effect. A statistically nonsignificant treatment effect of 0.29 on a 0-6 point scale (5 percent of maximum score) was reported by another good quality trial[87] of 307 patients (30 percent of patients reporting). The magnitude of the statistically nonsignificant treatment effect in the poor quality trial[86] identified above was not reported. A treatment effect of 0.23 on a 0-6 point scale (4 percent of maximum score) was reported by another good quality trial[84] of 219 patients (21 percent of patients reporting). Statistical significance was not assessed.

For the outcome of sneezing at 2 weeks, the risk of bias was rated as low. Eighty-seven percent of patients assessed for this outcome were in good quality trials. All four trials were consistent in favoring nasal antihistamine, but treatment effects were imprecise. The evidence was therefore insufficient to support the use of one treatment over the other for this outcome.

Three trials[84, 86, 87] (N=662) assessed nasal itch after 2 weeks of treatment and reported greater improvement with nasal antihistamine than with oral selective antihistamine. Of two trials[84, 87] that reported p-values, results were not statistically significant in either. One[87] was a good quality trial of 307 patients (46 percent of patients reporting this outcome) that reported a treatment effect of 0.30 on a 0-6 point scale (5 percent of maximum score). The other[86] was the poor quality trial previously identified. No treatment effect was reported. A treatment effect of 0.25 on a 0-6 point scale (4 percent of maximum score) was reported by another good quality trial[84] of 219 patients (33 percent of patients reporting). Statistical significance was not assessed.

For the outcome of nasal itch at 2 weeks, the risk of bias was rated as low. Seventy-nine percent of patients assessed for this outcome were in good quality trials. All three trials were

consistent in favoring nasal antihistamine, but treatment effects were imprecise. The evidence was therefore insufficient to support the use of one treatment over the other for this outcome.

Three trials[84, 85, 87] (N=886) assessed TNSS at 2 weeks and reported greater improvement with nasal antihistamine than with oral selective antihistamine. Of three trials[84, 85, 87] that reported p-values, this result was statistically significant in one trial.[87] This was a good quality trial of 307 patients (35 percent of patients reporting this outcome) that reported a treatment effect of 1.24 on a 0-24 point scale (5 percent of maximum score). Treatment effects of 0.78 and 0.70 on a 0-6 point scale (13 percent and 12 percent of maximum score, respectively) were reported by two trials[84, 85] that were rated good quality (65 percent of patients reporting). Statistical significance of the former result was not assessed. The latter result was not statistically significant.

For the outcome of TNSS at 2 weeks, the risk of bias was rated as low. All three trials reporting this outcome were rated as good quality. All three trials also were consistent in favoring nasal antihistamine, but treatment effects were imprecise. The evidence was therefore insufficient to support the use of one treatment over the other for this outcome.

Quality of Life

Two trials[85, 87] (N=667) assessed quality of life at 2 weeks using the RQLQ. Both were good quality trials that reported statistically significant reductions in RQLQ with nasal antihistamine compared to oral selective antihistamine. Treatment effects on a 0-6 scale were 0.4 points in one trial[85] and 0.3 points in the other.[87] One poor quality trial[86] of 136 patients reported a statistically nonsignificant difference in the proportion of patients who reported an excellent or good response to treatment rather than a fair or poor response, with a treatment difference of 0.6 percent favoring nasal antihistamine.

For the outcome of quality of life as measured by the RQLQ at 2 weeks, the risk of bias was rated as low. Both trials reporting this outcome were rated good quality. Trials were consistent in favoring nasal antihistamine over oral selective antihistamine, but neither treatment effect exceeded the MCID of 0.5 and was therefore imprecise. The evidence was therefore insufficient to support the use of one treatment over the other for this outcome.

Table 16. Treatment effects: nasal symptoms–oral selective antihistamine versus nasal antihistamine

Outcome	Variance	SS Favors Oral S-AH MD	NSS Favors/NR Oral S-AH MD	Favors Neither MD=0	NSS Favors/NR Nasal AH MD	SS Favors Nasal AH MD
2-Week Outcomes						
Congestion						
Berger, 2003[84] (scale 0-6)					0.08 (NR)	
Berger, 2006[85] (scale 0-6)						[a]
Charpin, 1995[86] (scale 0-100)						[a]
Corren, 2005[87] (scale 0-6)	SD				0.17 (NSS)	
Rhinorrhea						
Berger, 2003[84] (scale 0-6)					0.22 (NR)	
Charpin, 1995[86] (scale 0-100)						[a]
Corren, 2005[87] (scale 0-6)	SD					0.46
Sneezing						
Berger, 2003[84] (scale 0-6)					0.23 (NR)	
Berger, 2006[85] (scale 0-6)						[a]
Charpin, 1995[86] (scale 0-100)					[a] (NSS)	
Corren, 2005[87] (scale 0-6)	SD				0.29 (NSS)	
Nasal itch						
Berger, 2003[84] (scale 0-6)					0.25 (NR)	
Charpin, 1995[86] (scale 0-100)					[a] (NSS)	
Corren, 2005[87] (scale 0-6)	SD				0.30 (NSS)	
TNSS						
Berger, 2003[84] (scale 0-24)					0.78 (NR)	
Berger, 2006[85] (scale 0-24)	SD				0.70 (NSS)	
Corren, 2005[87] (scale 0-24)	SD					1.24

AH = antihistamine; MD = mean difference between group mean changes from baseline; NR = p-value not reported; NSS = not statistically significant; S-AH = selective antihistamine; SS = statistically significant; TNSS = total nasal symptom score.

Variance/confidence interval reported: CI=confidence interval; SD=standard deviation; SE=standard error.

[a] Only p-values reported.

Table 17. Treatment effects: quality of life–oral selective antihistamine versus nasal antihistamine

Outcome	Variance	SS Favors Oral S-AH MD	NSS Favors/NR Oral S-AH MD	Favors Neither MD=0	NSS Favors/NR Nasal AH MD	SS Favors Nasal AH MD
2-Week Outcomes						
RQLQ						
Berger, 2006[85]						0.40
Corren, 2005[87]	SD					0.30
PGA						
Charpin, 1995[86] (% reporting excellent or good response to treatment)					0.6[a] (NSS)	

AH = antihistamine; MD = mean difference between group mean changes from baseline; NR = p-value not reported; NSS = not statistically significant; PGA = patient global assessment; RQLQ = Rhinoconjunctivitis Quality of Life Questionnaire; S-AH = selective antihistamine; SS = statistically significant.

Variance/confidence interval reported: CI=confidence interval; SD=standard deviation; SE=standard error.

[a] 4-point scale: Excellent, Good, Fair and Poor response. Statistical testing is over all four categories.

Oral Selective Antihistamine Versus Intranasal Corticosteroid

Description of Included Studies

Thirteen RCTs[89-100] published between 1995 and 2009 were identified (N=4403). Twelve were double-blinded, multicenter trials,[89-95, 97-100] and one[96] was an unblinded, single center trial. Eleven[89-93, 95-99] were conducted in North America, and two[94, 100] in Europe. Trial sizes ranged from 88 to 623 patients randomized to treatment groups of interest. Oral selective antihistamines studied were loratadine (10 trials[90-99]), fexofenadine (two trials[89] in one publication), and cetirizine (one trial[100]); intranasal corticosteroids were fluticasone propionate (six trials[91, 94-98]), fluticasone furoate (two trials[89] in one publication), triamcinolone (three trials[92, 93, 99]), mometasone (one trial[90]), and beclomethasone (one trial[97]). One trial[96] assessed as-needed (prn) dosing of both the oral selective antihistamine (loratadine) and the intranasal corticosteroid (fluticasone propionate). All other trials evaluated continuous scheduled dosing of both drugs. Five trials[89, 90, 97, 98] were 2 weeks in duration, one[100] was 3 weeks, and seven[91-96, 99] were 4 weeks. Twelve trials were industry-funded, and one[90] did not report funding source.

Mean age ranged from 25 to 41 years. In most trials, the majority of patients were female (51-68 percent); no trial had less than 40 percent female patients. In nine trials[89, 91-93, 96-99] that reported information on race, most patients were white (57-92 percent). Eleven trials[89-94, 96-100] required a minimum severity of SAR symptoms. In nine trials[89-92, 97-100] that reported baseline values, nasal symptom scores were most commonly in the moderate range; two trials[89] in the same publication (N=1074) reported mean baseline scores in the severe range, and one trial[97] reported mean baseline scores in the mild range. In five trials[89, 91, 92, 99] that reported baseline eye symptoms, values were in the moderate/severe range in three trials[89, 91] and in the mild range in two trials.[92, 99] Ten trials[89-93, 96-99] required a minimum duration of SAR history. In eight trials[89, 90, 93, 94, 97, 99, 100] that reported SAR duration, most patients had SAR symptoms for more than 10 years. In one trial[94], most patients had SAR for 2 to 5 years, and in another[100], most patients had SAR for more than 8 years.

All 13 trials assessed at least one individual nasal symptom or TNSS. Most trials used a 4-point scale (0=no symptoms, 3=severe symptoms) to assess four individual nasal symptoms (congestion, rhinorrhea, sneezing, and itch), yielding a 12-point maximum for TNSS. Two trials[91, 98] used a visual analog scale to rate these nasal symptoms on a scale of zero to 100, for a maximum TNSS of 400. One trial[100] used the 4-point scale to assess five nasal symptoms (congestion when waking, daytime congestion, rhinorrhea, sneezing, and itch), for a 15-point maximum TNSS.

Of seven trials[89-93, 99] that assessed eye symptoms, most assessed ocular itching, tearing, and redness using the 4-point scale described above. The maximum TOSS was 9. One trial[91] used a VAS to rate ocular symptoms on a scale of zero to 100, for a maximum TOSS of 300. Two trials[93, 99] did not identify which ocular symptoms were assessed. One trial[90] assessed three ocular symptoms but reported results for tearing only.

Of eight trials[89, 91, 92, 94, 96, 98, 100] that assessed quality of life, five[91, 92, 94, 96, 98] used the RQLQ. Measures on a 0 (no impairment) to 6 (severe impairment) rating scale were recorded at 2 weeks in three trials[92, 96, 98] and at 4 weeks in four trials.[91, 92, 94, 96] Two trials[89] in the same publication used the Nocturnal RQLQ to assess sleep disturbance due to nasal symptoms at 2 weeks. Nocturnal symptoms were scored on a 7-point scale from 0 (not troubled) to 6 (extremely troubled).

Two trials[91, 95] were rated good quality, three were rated fair[89, 98] and eight[90, 92-94, 96, 97, 99, 100] were rated poor.

Key Points

These results are summarized in Table 18.

- Individual nasal symptoms (congestion, rhinorrhea, sneezing, and nasal itch) at 2 weeks: Evidence was insufficient to support the use of one treatment over the other based on one trial90 with high risk of bias and imprecise results.
- TNSS at 2 weeks: Evidence was insufficient to support the use of one treatment over the other based on six trials89, 90, 93, 97, 98 with medium risk of bias and consistent but imprecise results.
- Individual nasal symptoms at 4 weeks: Evidence was insufficient to support the use of one treatment over the other based on six trials91-93, 95, 96, 99 (for congestion), five trials92, 93, 95, 96, 99 (for sneezing), and four trials (for rhinorrhea92, 95, 96, 99 and nasal itch92, 93, 95, 99) with high risk of bias and consistent but imprecise results.
- TNSS at 3-4 weeks: Evidence was insufficient to support the use of one treatment over the other based on four trials92-94, 100 with high risk of bias and consistent but imprecise results.
- Eye symptoms (tearing, TOSS) at 2 weeks: Evidence was insufficient to support the use of one treatment over the other based on three trials89, 90, 93 with high risk of bias and consistent but imprecise results.
- TOSS at 4 weeks: Evidence was insufficient to support the use of one treatment over the other based on four trials91-93, 99 with high risk of bias and inconsistent, imprecise results.
- Quality of life assessed by RQLQ at 2 weeks: Evidence was insufficient to support the use of one treatment over the other based on three trials 92, 96, 98 with medium risk of bias and consistent but imprecise results.
- Quality of life assessed by RQLQ at 4 weeks: Evidence was insufficient to support the use of one treatment over the other based on four trials 91, 92, 94, 96 with high risk of bias and consistent but imprecise results.
- Quality of life assessed by Nocturnal RQLQ at 2 weeks: Evidence was insufficient to support the use of one treatment over the other based on two trials 89 with medium risk of bias and consistent but imprecise results.
- These results are based on trials of three of five oral selective antihistamines (60 percent) and five of eight intranasal corticosteroids (62.5 percent).

Table 18. Strength of evidence: oral selective antihistamine versus intranasal corticosteroid

Outcome	RCTs (Patients)	Risk of Bias	Consistency	Directness	Precision	Overall GRADE
2-week congestion, rhinorrhea, sneezing, nasal itch	1[90] (341)	High	Unknown (single study)	Direct	Imprecise	Insufficient
2-week TNSS	6[89, 90, 93, 97, 98] (2644)	Medium	Consistent	Direct	Imprecise	Insufficient
4-week congestion	6[91-93, 95, 96, 99] (1600)	High	Consistent	Direct	Imprecise	Insufficient
4-week rhinorrhea	4[92, 95, 96, 99] (979)	High	Consistent	Direct	Imprecise	Insufficient
4-week sneezing	5[92, 93, 95, 96, 99] (1284)	High	Consistent	Direct	Imprecise	Insufficient
4-week nasal itch	4[92, 93, 95, 99] (1196)	High	Consistent	Direct	Imprecise	Insufficient
3-4 week TNSS	4[92-94, 100] (1008)	High	Consistent	Direct	Imprecise	Insufficient
2-week eye symptoms[a] (tearing, TOSS)	3[89, 90, 93] (1905)	High	Consistent	Direct	Imprecise	Insufficient
4-week TOSS	4 [91-93, 99] (1270)	High	Inconsistent	Direct	Imprecise	Insufficient
2-week RQLQ	3[92, 96, 98] (889)	Medium	Consistent	Direct	Imprecise	Insufficient
4-week RQLQ	4[91, 92, 94, 96] (869)	High	Consistent	Direct	Imprecise	Insufficient
2-week NRQLQ	2[89] (1074)	Medium	Consistent	Direct	Imprecise	Insufficient

GRADE = Grading of Recommendations Assessment, Development and Evaluation; NRQLQ = Nocturnal Rhinoconjunctivitis Quality of Life Questionnaire; RCTs (Patients) = number of randomized controlled trials (number of patients randomized to treatment groups of interest); RQLQ = Rhinoconjunctivitis Quality of Life Questionnaire; TNSS = total nasal symptom score, TOSS = total ocular symptom score.

[a] One trial[93] did not specify which eye symptoms were assessed.

Synthesis and Strength of Evidence

Nasal symptom results discussed below are summarized in Table 19, eye symptom results in Table 20, and quality of life results in Table 21. As shown in Table 19 and Table 20, three trials[91, 92, 99] provided variance estimates for a nasal outcome (congestion at 4 weeks) and an eye outcome (TOSS at 4 weeks). Thus, meta-analyses of these results were conducted.

Nasal Symptoms

The one trial[90] that reported on nasal congestion at 2 weeks (N=341) reported a treatment effect of 0.3 on a 0-6 point scale (5 percent of maximum score) favoring intranasal corticosteroid. This trial was rated poor quality, and the result was not statistically significant. Evidence for the outcome of congestion at 2 weeks is therefore insufficient to support the use of one treatment over the other. One poor quality trial[90] with high risk of bias reported an imprecise treatment effect.

Six trials[91-93, 95, 96, 99] assessed congestion at 4 weeks (N=1600). All six showed statistically significant improvements in congestion with intranasal corticosteroid. Two[91, 95] were good quality trials of 558 patients total (35 percent of patients reporting this outcome). One[95] reported results using a 0-3 point scale but did not report the magnitude of the treatment effect. The other[91] reported a treatment effect of 10.3 on a 0-100 VAS (10 percent of maximum score). Four trials[92, 93, 96, 99] were rated poor quality due to noncomparable groups at baseline[92, 93, 96] and inappropriate analysis of results (unadjusted for baseline group differences[93, 96] and not intention to treat[99]). Two[92, 99] of these trials reported treatment effects of 0.3 and 0.46 on a 0-3 point scale (10 percent and 15 percent of maximum score, respectively).

Three trials[91, 92, 99] (N=938; 59 percent of patients reporting this outcome) were pooled in a meta-analysis (Figure 5). Because trials used different symptom rating scales (0-3 and 0-100), the standardized mean difference was calculated. The pooled effect estimate was 0.45 (95 percent confidence interval (CI): 0.28 to 0.61), a statistically significant result that favored intranasal corticosteroid and was consistent with the direction of effect reported by individual trials. Effect estimates in the pooled trials were in the same direction, and their 95 percent CIs did not touch the "no effect" line. The magnitude of the pooled effect estimate could not be compared with estimates from individual trials not included in the meta-analysis because the latter were not reported.

For the outcome of congestion at 4 weeks, the risk of bias was rated as high. Sixty-five percent of patients were in poor quality trials, and 35 percent were in good quality trials. All six trials[91-93, 95, 96, 99] were consistent in finding statistically significant treatment effects favoring intranasal corticosteroid, and this finding was confirmed in a meta-analysis of three of these trials.[91, 92, 99] Because reported treatment effects were less than an MCID of 30 percent maximum score, and because the magnitude of effects in three trials[93, 95, 96] representing 40 percent of patients reporting this outcome were not reported, the body of evidence was considered imprecise. The evidence was therefore insufficient to form a conclusion about the comparative effectiveness of oral selective antihistamine and intranasal corticosteroid for this outcome.

The one trial[90] that assessed rhinorrhea at 2 weeks (N=341) reported a treatment effect of 0.3 on a 0-3 point scale (10 percent of maximum score) favoring intranasal corticosteroid. This trial was rated poor quality, and the result was not statistically significant. Five trials[92, 93, 95, 96, 99] assessed rhinorrhea at 4 weeks. One poor quality trial[93] reported neither the magnitude nor the direction of the treatment effect. This trial was excluded from analysis of this outcome, reducing the total number of patients assessed from 1284 to 979. The remaining four trials all favored

intranasal corticosteroid over oral selective antihistamine. One trial[95] was a good quality trial of 242 patients (25 percent of patients reporting this outcome) that demonstrated a statistically significant improvement in rhinorrhea with intranasal corticosteroid. The magnitude of the treatment effect was not reported. The remaining three trials[92, 96, 99] were rated poor quality due to noncomparable groups at baseline and inappropriate analysis of results, as described above. Two[96, 99] of these reported statistically significant treatment effects favoring intranasal corticosteroid. One[99] reported a treatment effect of 0.55 on a 0-3 point scale (18 percent of maximum score). The other[96] did not report the magnitude of the treatment effect. The third poor quality trial[92] reported a statistically nonsignificant treatment effect of 0.2 on a 0-3 scale (7 percent of maximum score).

Evidence for the outcome of rhinorrhea at 2 weeks was insufficient to support the use of one treatment over the other. One poor quality trial[90] with high risk of bias reported an imprecise treatment effect. For the outcome of rhinorrhea at 4 weeks, the risk of bias was rated as high. Seventy-five percent of patients were in poor quality trials. Effect estimates consistently favored intranasal corticosteroid. However, none exceeded an MCID of 30 percent maximum score, and the body of evidence was considered imprecise. Evidence was therefore insufficient to support the use of one treatment over the other for this outcome.

The one trial[90] that assessed sneezing at 2 weeks (N=341) reported a treatment effect of 0.1 on a 0-3 point scale (3 percent of maximum score) favoring intranasal corticosteroid. This trial was rated poor quality, and the result was not statistically significant. Five trials[92, 93, 95, 96, 99] assessed sneezing at 4 weeks (N=1284). All five showed statistically significant improvements in sneezing with intranasal corticosteroid. One of these was a good quality trial[95] of 242 patients (19 percent of patients reporting this outcome) that did not report the magnitude of the treatment effect. The remaining four trials[92, 93, 96, 99] were rated poor quality for noncomparable groups at baseline and inappropriate analysis of results, as described above. Two of these trials[92, 99] reported treatment effects of 0.3 and 0.45 on a 0-3 point scale (10 percent and 15 percent of maximum score, respectively). The other two[93, 96] did not report the magnitude of the treatment effects.

Evidence for the outcome of sneezing at 2 weeks was insufficient to support the use of one treatment over the other. One poor quality trial[90] with high risk of bias reported an imprecise treatment effect. For the outcome of sneezing at 4 weeks, the risk of bias was rated as high. Eighty-one percent of patients were in poor quality trials. All five trials[92, 93, 95, 96, 99] were consistent in finding statistically significant treatment differences favoring intranasal corticosteroid. However, reported treatment effects were imprecise. The evidence was therefore insufficient to support the use of one treatment over the other for this outcome.

The one trial[90] that assessed nasal itch at 2 weeks (N=341) reported no difference in effect between oral selective antihistamine and intranasal corticosteroid. This trial was rated poor quality. Four trials[92, 93, 95, 99] assessed nasal itch at 4 weeks (N=1196). All four reported statistically significant improvement with intranasal corticosteroid compared with oral selective antihistamine. One of these was a good quality trial[95] of 242 patients (20 percent of patients reporting this outcome). Treatment effect was not reported. The remaining three trials[92, 93, 99] were rated poor quality for noncomparable groups at baseline[92, 93] and inappropriate analysis of results (unadjusted for baseline group differences[93] and not intention to treat[99]). Two of these trials[92, 99] reported treatment effects of 0.2 and 0.29 points on a 0-3 scale (7 percent and 10 percent of maximum score, respectively). The third[93] did not report the magnitude of the treatment effect.

Evidence for the outcome of nasal itch at 2 weeks is insufficient to support the use of one treatment over the other. One poor quality trial[90] with high risk of bias reported no difference between treatments. For the outcome of nasal itch at 4 weeks, the risk of bias was rated as high. Eighty percent of patients were in poor quality trials. All four trials[92, 93, 95, 99] were consistent in finding statistically significant treatment effects favoring intranasal corticosteroid. However, the effects were imprecise. The evidence was insufficient to support the use of one treatment over the other for this outcome.

Six trials[89, 90, 93, 97, 98] assessed TNSS at 2 weeks (N=2756). Three[89, 98] of these showed statistically significant improvements with intranasal corticosteroid compared with oral selective antihistamine. All three were rated fair quality. Two of these trials[89] reported treatment effects of 1.0 and 1.3 using a 0-12 point scale (8 percent and 11 percent of maximum score, respectively). The other three trials[90, 93, 97] were rated poor quality due to noncomparable groups at baseline[93] and inappropriate analysis of results (unadjusted for baseline group differences[93] and not intention to treat[90, 97]). Two of these trials[90, 93] reported statistically nonsignificant treatment effects of 0.8 and 1.0 using a 0-12 point scale (7 percent and 8 percent of maximum score, respectively). The third[97] reported a treatment effect of 0.17 (1 percent of maximum score) but did not assess statistical significance.

Five trials[92-94, 99, 100] assessed TNSS after 2 weeks, that is, at 3 or 4 weeks. One poor quality trial[99] reported neither the magnitude nor the direction of the treatment effect at 4 weeks. This trial was excluded from analysis of this outcome, reducing the total number of patients assessed from 1306 to 1008. The four remaining trials[92-94, 100] reported improvement in TNSS with intranasal corticosteroid at 3 weeks[93, 100] and at 4 weeks.[92-94] All four trials were rated poor quality due to noncomparable groups at baseline[92-94] and inappropriate analysis of results (unadjusted for baseline group differences[93] and not intention to treat[100]). Treatment effects at 3 weeks were 1.2 on a 0-12 point scale[93] (10 percent of maximum score) and 2.17 on a 0-15 point scale[100] (14 percent of maximum score). At 4 weeks, treatment effects of 0.8 on a 0-12 point scale (7 percent of maximum score) were reported by two trials.[92, 93]

For the outcome of TNSS at 2 weeks, the risk of bias was rated as medium. Forty-five percent of patients reporting this outcome were in poor quality trials, and 55 percent were in fair quality trials. Treatment effects consistently favored intranasal corticosteroid, although effects were imprecise. The evidence was therefore insufficient to support the use of one treatment over the other for this outcome.

For TNSS at 3 to 4 weeks, the risk of bias was rated as high. All four trials[92-94, 100] reporting this outcome were rated poor quality. Treatment effects consistently favored intranasal corticosteroid but were imprecise. The evidence was therefore insufficient to support the use of one treatment over the other for this outcome.

Eye Symptoms

Eye symptoms were reported using a variety of measurement scales and varied definitions. Most treatment effects favored intranasal corticosteroid over oral selective antihistamine.

Four trials[89, 90, 93] that assessed eye symptoms at 2 weeks reported greater improvement with intranasal corticosteroid than with oral selective antihistamine (N=1905). For TOSS, statistically significant treatment effects of 0.3 and 0.6 on a 0-9 point scale (3 percent and 7 percent of maximum score, respectively) were reported in two fair quality trials[89] (N=1074). The other two trials[90, 93] were rated poor quality. One[90] reported a statistically significant treatment effect of

unknown magnitude for the single symptom of tearing. The other[93] reported a statistically nonsignificant treatment effect of unknown magnitude for undefined symptoms.

For eye symptoms at 2 weeks, the risk of bias was rated as medium. Forty-four percent of patients were in poor quality trials, and 56 percent were in fair quality trials. All four trials[89, 90, 93] were consistent in favoring intranasal corticosteroid. Reported treatment effects did not exceed an MCID of 30 percent maximum score and were considered imprecise. The evidence was therefore insufficient to support the use of one treatment over the other for eye symptoms at 2 weeks.

Four trials[91-93, 99] assessed TOSS[91, 92] and unspecified eye symptoms[93, 99] at 4 weeks (N=1270). Three[91, 93, 99] of these reported treatment effects that favored intranasal corticosteroid. One[91] was a good quality trial of 316 patients (25 percent of patients reporting this outcome) that showed a statistically significant treatment effect of 16.2 on a 0-300 point scale (5 percent of maximum score). The other two trials[93, 99] were rated poor quality. One[93] reported a statistically significant treatment effect of unknown magnitude for undefined eye symptoms, and the other[99] reported a statistically nonsignificant treatment effect of 0.11 on a 0-9 point scale (1 percent of maximum score). The fourth trial[92] was rated poor quality and reported no difference in effect for TOSS. A meta-analysis of three of these trials[91, 92, 99] was conducted (N=938 [74% of patients reporting this outcome]; Figure 6). Because trials used different symptom rating scales (0-9 and 0-300), the standardized mean difference was calculated. The pooled effect estimate was 0.13 (95 percent CI: -0.02 to 0.27), a statistically nonsignificant result that favored intranasal corticosteroid. Treatment effects in two[91, 99] of the pooled trials favored intranasal corticosteroid, and in the third,[92] showed no treatment difference. The meta-analysis excluded one trial[93] that showed a statistically significant treatment effect of unknown magnitude favoring intranasal corticosteroid.

For eye symptoms at 4 weeks, the risk of bias was rated as high. Seventy-five percent of patients were in poor quality trials.[92, 93, 99] Treatment effects at 4 weeks were not consistent across individual trials, with three[91, 93, 99] of four trials reporting effects in favor of intranasal corticosteroid and the fourth[92] (28 percent of patients reporting this outcome) showing no treatment difference. Because all reported effects were less than an MCID of 30 percent maximum score, and because one trial[93] (24 percent of patients reporting this outcome) did not report the magnitude of effect, the body of evidence was considered imprecise. The evidence was therefore insufficient to form a conclusion about the comparative effectiveness of oral selective antihistamine and intranasal corticosteroid for this outcome.

Quality of Life

All three trials[92, 96, 98] that used the RQLQ to assess quality of life at 2 weeks (N=889) reported statistically significant treatment effects with intranasal corticosteroid compared to oral selective antihistamine. In two[96, 98] of these trials, treatment effects of 1.0 and 0.9 on a 0-6 point scale exceeded the MCID of 0.5. The larger of these[98] was a fair quality trial of 450 patients (51 percent of patients reporting this outcome), and the other[96] was rated poor due to lack of blinding (n=88). The treatment effect in the third trial[92] (n=351) was 0.25 on a 0-6 scale. This trial was rated poor due to noncomparable groups at baseline.

For quality of life outcomes measured using the RQLQ at 2 weeks, the risk of bias was rated as medium. Forty-nine percent of patients were in poor quality trials, and 51 percent were in the fair quality trial. All three trials[92, 96, 98] were consistent in finding statistically significant treatment differences favoring intranasal corticosteroid. Treatment effects were larger than the

MCID in two trials[96, 98] but smaller in one trial[92] that accounted for 39 percent of patients reporting. The body of evidence was therefore considered imprecise. Evidence was insufficient to support the use of one treatment over the other for this outcome.

All four trials[91, 92, 94, 96] that assessed quality of life using the RQLQ at 4 weeks (N=869) reported statistically significant treatment effects favoring intranasal corticosteroid. One[91] of these was a good quality trial of 316 patients (36 percent of patients reporting this outcome). The magnitude of effect was not reported. The remaining three trials were rated poor quality. Of two trials[92, 96] that reported the magnitude of treatment effects, the effect in one[96] (0.9) exceeded the MCID. This was a trial of 88 patients[96] that was rated poor quality due to lack of blinding. The other[92] reported a treatment effect of 0.25. The fourth trial[94] did not report the magnitude of the treatment effect.

For quality of life outcomes measured using the RQLQ at 4 weeks, the risk of bias was rated as high. Sixty-four percent of patients were in the poor quality trials. All four trials[91, 92, 94, 96] were consistent in finding statistically significant treatment differences favoring intranasal corticosteroid. However, reported treatment effects exceeded the MCID in only one trial[96] representing 10 percent of patients reporting this outcome. The body of evidence was therefore considered imprecise. Evidence was insufficient to support the use of one treatment over the other for this outcome.

Two fair quality trials[89] (N=1074) that used the Nocturnal RQLQ at 2 weeks reported statistically significant treatment effects of 0.5 and 0.7 on a 0-6 point scale (8 percent and 12 percent of maximum score, respectively). For quality of life outcomes measured using the Nocturnal RQLQ at 2 weeks, the risk of bias was rated as medium. Both trials[89] from the same published article were rated fair quality. Both also were consistent in finding statistically significant treatment differences favoring intranasal corticosteroid. However, effect estimates were imprecise. Evidence was therefore insufficient to support one treatment over the other for this outcome.

Four trials[91, 94, 98, 100] reported PGA scores at 2 weeks,[98] 3 weeks,[100] and 4 weeks.[91, 94] Results supported the quality of life findings described above (intranasal corticosteroid favored), but statistical significance of effect estimates was variable.

Table 19. Treatment effects: nasal symptoms–oral selective antihistamine versus intranasal corticosteroid

Outcome	Variance	SS Favors Oral S-AH MD	NSS Favors/NR Oral S-AH MD	Favors Neither MD=0	NSS Favors/NR INCS MD	SS Favors INCS MD
2-Week Outcomes						
Congestion						
Anolik, 2008[90] (scale 0-3)					0.3 (NSS)	
Rhinorrhea						
Anolik, 2008[90] (scale 0-3)					0.3 (NSS)	
Sneezing						
Anolik, 2008[90] (scale 0-3)					0.1 (NSS)	
Nasal itch						
Anolik, 2008[90] (scale 0-3)				0		
TNSS						
Andrews, 2009 (Trial 1)[89] (scale 0-12)						1.0 (SE: 0.18; 95% CI: 0.7,1.4)
Andrews, 2009 (Trial 2)[89] (scale 0-12)						1.3 (SE: 0.22; 95% CI: 0.9,1.7)
Anolik, 2008[90] (scale 0-12)	SD				0.8 (NSS)	
Gawchik, 1997[93] (scale 0-3)					1.0 (NR)	
Lu, 2009 (Trial 1)[97] (scale 0-3)	CI				0.17 (NR)	
Ratner, 1998[98] (scale 0-400)						60
3-Week Outcomes						
TNSS						
Gawchik, 1997[93] (scale 0-3)					1.2 (NR)	
Vervloet, 1997[100] (scale 0-15)						2.17
4-Week Outcomes						
Congestion						
Bernstein, 2004[91] (scale 0-100)	SE					10.3
Condemi, 2000[92] (scale 0-3)	SD					0.3
Gawchik, 1997[93] (scale 0-3)						[a]
Jordana, 1996[95] (scale 0-3)						[a]
Kaszuba, 2001 [96] (scale 0-3)[b]						[a]
Schoenwetter, 1995[99] (scale 0-3)	SD					0.46
Rhinorrhea						
Condemi, 2000[92] (scale 0-3)	SD				0.2 (NSS)	
Jordana, 1996[95] (scale 0-3)						[a]
Kaszuba, 2001[96] (scale 0-3)[b]						[a]

Outcome	Variance	SS Favors Oral S-AH MD	NSS Favors/NR Oral S-AH MD	Favors Neither MD=0	NSS Favors/NR INCS MD	SS Favors INCS MD
Schoenwetter, 1995[99] (scale 0-3)	SD					0.55
Sneezing						
Condemi, 2000[92] (scale 0-3)	SD					0.3
Gawchik, 1997[93] (scale 0-3)						[a]
Jordana, 1996[95] (scale 0-3)						[a]
Kaszuba, 2001[96] (scale 0-3)[b]						[a]
Schoenwetter, 1995[99] (scale 0-3)	SD					0.45
Nasal itch						
Condemi, 2000[92] (scale 0-3)	SD					0.2
Gawchik, 1997[93] (scale 0-3)						[a]
Jordana, 1996[95] (scale 0-3)						[a]
Schoenwetter, 1995[99] (scale 0-3)	SD					0.29
TNSS						
Condemi, 2000[92] (scale 0-12)	SD					0.8
Gawchik, 1997[93] (scale 0-12)						0.8
Gehanno, 1997[94] (scale 0-15)						[a]

INCS = intranasal corticosteroid; MD = mean difference between group mean changes from baseline; NR = p-value not reported; NSS = not statistically significant; S-AH = selective antihistamine; SS = statistically significant; TNSS = total nasal symptom score.

Variance/confidence interval reported: CI=confidence interval; SD=standard deviation; SE=standard error.

[a] Only p-values reported.

[b] As needed (prn) dosing.

Figure 5. Congestion at 4 weeks: meta-analysis of 3 trials–oral selective antihistamine versus intranasal corticosteroid

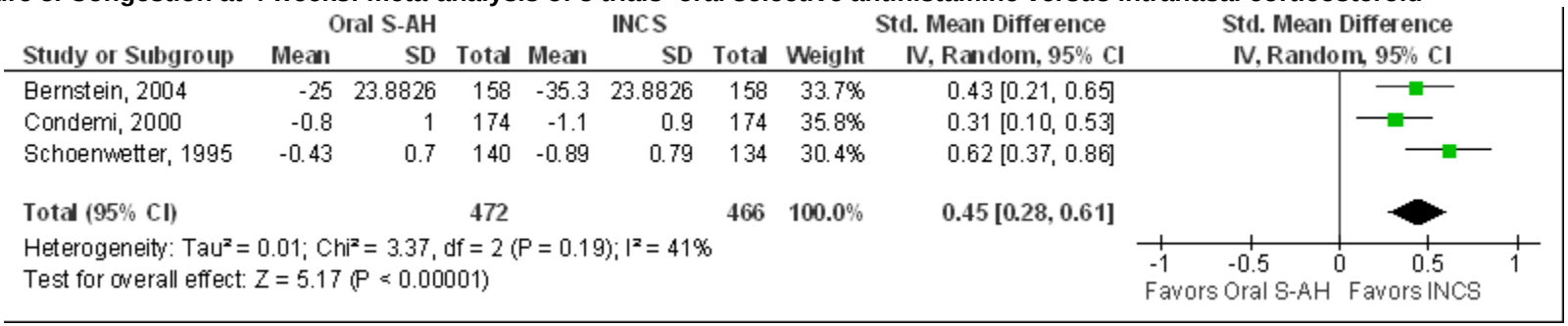


Table 20. Treatment effects: eye symptoms–oral selective antihistamine versus intranasal corticosteroid

Outcome[a]	Variance	SS Favors Oral S-AH MD	NSS Favors/NR Oral S-AH MD	Favors Neither MD=0	NSS Favors/NR INCS MD	SS Favors INCS MD
2-Week Outcomes						
TOSS						
Andrews, 2009 (Trial 1)[89] (scale 0-9)	SE/CI					0.3 (SE: 0.15; 95% CI: 0.0, 0.6)
Andrews, 2009 (Trial 2)[89] (scale 0-9)	SE/CI					0.6 (SE: 0.18; 95% CI: 0.2, 0.9)
Tearing						
Anolik, 2008[90] (scale 0-3)						[a]
Unspecified symptoms						
Gawchik, 1997[93]					[a] (NSS)	
4-Week Outcomes						
TOSS						
Bernstein, 2004[91] (scale 0-300)	SE					16.2
Condemi, 2000[92] (scale 0-9)	SD			0		
Unspecified symptoms						
Gawchik, 1997[93] (scale 0-9)						[a]
Schoenwetter, 1995[99] (scale unknown)	SD				0.11 (NSS)	

INCS = intranasal corticosteroid; MD = mean difference between group mean changes from baseline; NR = p-value not reported; NSS = not statistically significant; S-AH = selective antihistamine; SS = statistically significant; TOSS = total ocular symptom score.

Variance: CI=confidence interval; SD=standard deviation; SE=standard error.

[a] Only p-values reported.

Figure 6. Eye symptoms at 4 weeks: meta-analysis of 3 trials–oral selective antihistamine versus intranasal corticosteroid

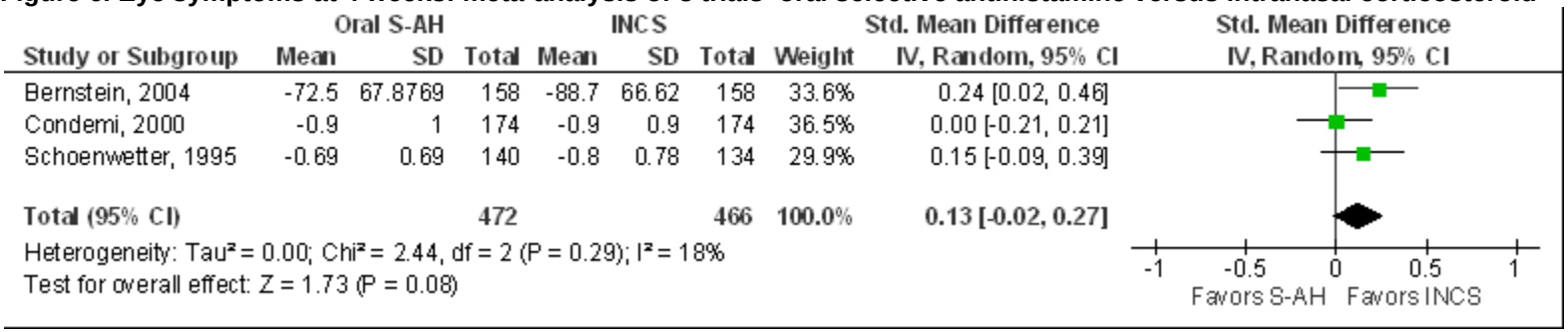


Table 21. Treatment effects: quality of life–oral selective antihistamine versus intranasal corticosteroid

Outcome	Variance	SS Favors Oral S-AH MD	NSS Favors/NR Oral S-AH MD	Favors Neither MD=0	NSS Favors/NR INCS MD	SS Favors INCS MD
2-Week Outcomes						
RQLQ						
Condemi, 2000[92]	SD					0.25
Kaszuba, 2001[96]						1.0[ab]
Ratner, 1998[98]	SD					0.9[b]
Nocturnal RQLQ						
Andrews, 2009 (Trial 1)[89]	SE/CI					0.5 (SE: 0.11; 95% CI: 0.3, 0.7)
Andrews, 2009 (Trial 2)[89]	SE/CI					0.7 (SE: 0.12; 95% CI: 0.4, 0.9)
PGA						
Ratner, 1998[98] (% signif, mod, or mild improve)[c]						24.8[de]
3-Week Outcomes						
PGA						
Vervloet, 1997[100] (scale 0-100)	SD					2.05
Vervloet, 1997[100] (% v. effective/effective)[f]						25.2
4-Week Outcomes						
RQLQ						
Bernstein, 2004[91]						[g]
Condemi, 2000[92]	SD					0.25
Gehanno, 1997[94]						[g]
Kaszuba, 2001[96]						0.9[ab]
PGA						
Bernstein, 2004[91] (% signif, mod, mild improve)[c]						18
Gehanno, 1997[94] (% v. effective/effective)[f]						10[e]

INCS = intranasal corticosteroid; MD = mean difference between group mean changes from baseline; NR = p-value not reported; NSS = not statistically significant; PGA = patient global assessment; RQLQ = Rhinoconjunctivitis Quality of Life Questionnaire; S-AH = selective antihistamine SS = statistically significant.

Variance/confidence interval reported: CI=confidence interval; SD=standard deviation; SE=standard error.

[a] Difference between group median changes from baseline.

[b] Exceeds minimum clinically important difference of 0.5 points.

[c] 7-point scale: significant, moderate, or mild improvement; no change; mild, moderate, or significant worsening

[d] Values from Engauge Digitizer.

[e] P-value calculated by report author using 2x2 chi-square at mild improvement cut point.

[f] 4-point scale: very effective, effective, slightly effective, ineffective

[g] Only p-values reported.

Oral Selective Antihistamine Versus Oral Decongestant

Description of Included Studies

Seven trials[101-107] published between 1995 and 2009 were identified (N=3592). All were multicenter, double-blinded, RCTs with a primary interest in comparing a combination antihistamine/decongestant product to its component parts and/or placebo (three to four treatment arms). Trial size ranged from 398 to 749 patients randomized to treatment groups of interest, and trial durations were approximately 2 weeks (2 to 2.6 weeks). Six trials[101, 102, 104-107] were conducted in North America, and one[103] in Europe. Oral selective antihistamines studied were desloratadine (four trials[102, 104-106]), fexofenadine (one trial[107]), cetirizine (one trial[103]), and loratadine (one trial[101]); the decongestant was pseudoephedrine in all seven trials. Five trials[101, 104-107] were industry funded, and two[102, 103] did not report funding source.

Average ages of patients in the trials ranged from 30 to 37 years. Approximately 60 percent of patients were female. In four trials[101, 104, 105, 107] reporting information on race, most patients were white (77-93 percent). Six[101-105, 107] of seven trials required a minimum severity of SAR symptoms, and at baseline, symptom scores for congestion were moderate. Six[101-106] of seven trials required a minimum duration of SAR history; the mean duration of SAR symptoms in the trial populations ranged from 8 to 19 years.

Nasal congestion was assessed in all seven trials. In six trials,[101-106] four-point rating scales (0=no symptoms, 3=severe symptoms) were used. In one trial,[107] a 5-point scale (0=no symptoms, 4=very severe symptoms) was used. TNSS was reported in 1 trial.[101] Two trials[103, 107] reported on individual nasal symptoms of rhinorrhea and sneezing, one of which also reported on nasal itch.[103] Two trials[103, 107] reported ocular outcomes. Grosclaude, (1997)[103] (n=454) assessed ocular itching using a 0 (absent) to 3 (severe) symptom scale. Sussman (1999)[107] (n=436) assessed total ocular symptoms (itching, tearing, and redness) using a 0 (absent) to 4 (very severe) symptom scale. No trial assessed asthma outcomes.

Three trials[101, 103, 107] were rated good, one[106] fair, and three[102, 104, 105] poor quality.

Key Points

These results are summarized in Table 22.

- Congestion at 2 weeks: Evidence was insufficient to support the use of one treatment over the other based on seven trials[101-107] with medium risk of bias and consistent but imprecise results.
- Rhinorrhea and sneezing at 2 weeks: Evidence was insufficient to support the use of one treatment over the other based on two trials[103, 107] with low risk of bias and consistent but imprecise results.
- Nasal itch and TNSS at 2 weeks: Evidence was insufficient to support the use of one treatment over the other based on one trial[103] that reported nasal itch and one trial[101] that reported TNSS. Both trials had low risk of bias and imprecise results.
- Eye symptoms at 2 weeks: Evidence was insufficient to support the use of one treatment over the other based on one trial[103] that reported ocular itch and one trial[107] that reported ocular itching, tearing, and redness. The overall risk of bias was low, and results were consistent but imprecise.
- These results are based on trials of four of five oral selective antihistamines (80 percent) and one of two oral decongestants (50 percent).

Table 22. Strength of evidence: oral selective antihistamine versus oral decongestant

Outcome	RCTs (Patients)	Risk of Bias	Consistency	Directness	Precision	Overall GRADE
2-week congestion	7[101-107] (3592)	Medium	Consistent	Direct	Imprecise	Insufficient
2-week rhinorrhea, sneezing	2[103, 107] (890)	Low	Consistent	Direct	Imprecise	Insufficient
2-week nasal itch	1[103] (454)	Low	Unknown (single study)	Direct	Imprecise	Insufficient
2-week TNSS	1[101] (437)	Low	Unknown (single study)	Direct	Imprecise	Insufficient
2-week eye symptoms[a]	2[103, 107] (890)	Low	Consistent	Direct	Imprecise	Insufficient

GRADE = Grading of Recommendations Assessment, Development and Evaluation; RCTs (Patients) = number of randomized controlled trials (number of patients randomized to treatment groups of interest); TNSS = total nasal symptom score, TOSS = total ocular symptom score.

[a] Includes one trial[103] that reported on ocular itching at 2 weeks and one trial[107] that reported on ocular itching, tearing, and redness at 2.6 weeks.

Synthesis and Strength of Evidence

Nasal symptom results discussed below are summarized in Table 23 and eye symptom outcomes in Table 24. As shown in these tables, variance estimates for reported outcomes were not provided. Thus, meta-analysis was not possible.

Nasal Symptoms

All seven trials[101-107] assessed nasal congestion at 2 weeks, and all reported greater improvement with oral decongestant than with oral selective antihistamine (N=3592). Treatment effects of 0.1 to 0.17 on a 0-3 point scale (3 percent and 6 percent of maximum score, respectively) were reported in three[101, 103, 107] good quality trials of 1327 total patients (37 percent of patients reporting this outcome). Statistical significance was not reported. Three trials[102, 104, 105] were rated poor quality due to inappropriate analysis of results (not intention to treat; N=1583). Treatment effects reported by these trials and by one trial[106] (n=682) rated fair quality ranged from 0.05 to 0.1 on a 0-3 point scale (all less than 3 percent of maximum score). In the two trials[105, 106] that reported p-values, results were not statistically significant.

For congestion at 2 weeks, the risk of bias was rated as medium. Forty-four percent of patients were in poor quality trials, and 37 percent were in good quality trials. All seven trials were consistent in finding treatment effects that favored oral decongestant. However, none of the effects exceeded an MCID of 30 percent maximum score, and all were considered imprecise. The evidence was therefore insufficient to support the use of one treatment over the other for the treatment of congestion.

Three[101, 103, 107] good quality trials assessed other nasal symptoms at 2 weeks (rhinorrhea, sneezing, nasal itch, TNSS). Grosclaude (1997)[103] and Sussman (1999)[107] reported treatment effects favoring oral selective antihistamine for rhinorrhea and sneezing (N=890). Grosclaude (1997)[103] reported treatment effects of 0.21 for rhinorrhea (7 percent of maximum score) and 0.32 for sneezing (11 percent of maximum score) using a 0-3 point scale. Sussman (1999)[107] reported treatment effects of 0.1 for rhinorrhea (3 percent of maximum score) and 0.2 for sneezing (5 percent of maximum score) using a 0-4 point scale. Grosclaude (1997; n=454) also assessed nasal itch at 2 weeks and reported a treatment effect of 0.13 on a 0-3 point scale (4

percent of maximum score). Bronsky (1995)[101] assessed TNSS at 2 weeks and reported a treatment effect of 0.1 on a 0-3 scale (3 percent of maximum score) favoring oral decongestant. Because the direct comparison of interest in these trials involved the combination treatment arm, p-values for comparative effects of the two components were not reported.

For other nasal symptoms at 2 weeks, the risk of bias is rated as low. Results come from good quality trials.[101, 103, 107] For rhinorrhea and sneezing, trials[103, 107] were consistent in showing treatment effects that favored oral selective antihistamine. For nasal itch and TNSS, results are from single trials,[101, 103] and consistency is unknown. All effects were imprecise, and evidence was insufficient to support the use of one treatment over the other for rhinorrhea, sneezing, nasal itch, or TNSS.

Eye Symptoms

Two[103, 107] of seven trials assessed ocular outcomes (N=890). Both were good quality trials. Oral selective antihistamine was favored for both ocular itching[103] and total ocular symptoms (itching, tearing, and redness).[107] Treatment effects were 0.08 on a 0-3 point scale[103] and 0.1 on a 0-4 point scale[107] (both 3 percent of maximum score). P-values were not reported.

For ocular outcomes at 2 weeks, the risk of bias was rated as low. Both trials[103, 107] reporting ocular outcomes were rated good quality. Trials were consistent in showing treatment effects that favored oral selective antihistamine. However, effects did not exceed an MCID of 30 percent maximum score and were considered imprecise. Evidence was therefore insufficient to support the use of one treatment over the other for ocular outcomes at 2 weeks.

Table 23. Treatment effects: nasal symptoms–oral selective antihistamine versus oral decongestant

Outcome	Variance	SS Favors Oral S-AH MD	NSS Favors/NR Oral S-AH MD	Favors Neither MD=0	NSS Favors/NR Oral Decongestant MD	SS Favors Oral Decongestant MD
2-Week Outcomes						
Congestion						
Bronsky, 1995[101] (scale 0-3)					0.1 (NR)	
Chervinsky, 2005[102] (scale 0-3)					0.1 (NR)	
Grosclaude, 1997[103] (scale 0-3)					0.17 (NR)	
Grubbe, 2009[104] (scale 0-3)					0.09 (NR)	
Pleskow, 2005[105] (scale 0-3)					0.08 (NSS)	
Schenkel, 2002[106] (scale 0-3)					0.05 (NSS)	
Sussman, 1999[107] (scale 0-4)[a]					0.1 (NR)	
Rhinorrhea						
Grosclaude, 1997[103] (scale 0-3)			0.21 (NR)			
Sussman, 1999[107] (scale 0-4)[a]			0.1 (NR)			
Sneezing						
Grosclaude, 1997[103] (scale 0-3)			0.32 (NR)			
Sussman, 1999[107] (scale 0-4)[a]			0.2 (NR)			
Itching						
Grosclaude, 1997[103] (scale 0-3)			0.13 (NR)			
TNSS						
Bronsky, 1995[101] (scale 0-3)					0.1 (NR)	

MD = mean difference between group mean changes from baseline; NR = p-value not reported; NSS = not statistically significant; S-AH = selective antihistamine; SS = statistically significant; TNSS = total nasal symptom score.

[a] Sussman, 1999 trial = 2.6 weeks.

Table 24. Treatment effects: eye symptoms–oral selective antihistamine versus oral decongestant

Outcome	Variance	SS Favors Oral S-AH MD	NSS Favors/NR Oral S-AH MD	Favors Neither MD=0	NSS Favors/NR Oral Decongestant MD	SS Favors Oral Decongestant MD
Average Change Rrom Baseline						
Grosclaude, 1997[103] itching eyes, 2 weeks[a]			0.08 (NR)			
Sussman, 1999[107] itching, watery, red eyes, 2.6 weeks[b]			0.1 (NR)			

MD = mean difference between group mean changes from baseline; NR = p-value not reported; NSS = not statistically significant; S-AH = selective antihistamine SS = statistically significant.

[a] 4-point scale: 0, absent; 1, mild; 2, moderate; 3, severe.

[b] 5-point scale: 0, absent; 1, mild; 2, moderate; 3, severe; 4, very severe.

Oral Selective Antihistamine Versus Oral Leukotriene Receptor Antagonist (Montelukast)

Description of Included Studies

Nine[97, 108-114] double-blinded, RCTs published between 2000 and 2009 were identified (N=4231). Eight[97, 108, 110-114] were multicenter trials conducted in North America. One[109] was a single center trial conducted in Europe. Trial size ranged from 187 to 950 patients randomized to treatment groups of interest. Oral selective antihistamines studied in comparison to montelukast were loratadine (seven trials[97, 110-114]), desloratadine (one trial[108]) and levocetirizine (one trial[109]). Six trials[97, 110-113] were 2 weeks in duration, and three trials[108, 109, 114] were 4 weeks. Seven trials[97, 110-114] were industry funded. Two trials[108, 109] did not report funding source.

Mean ages of patients ranged from 31 to 42 years. In most trials, the majority of patients were women (53-67 percent). In one trial,[109] men were the majority. Seven trials[108-114] reported information on race. In all of these, the majority was white (79-89 percent). Eight trials[97, 109-114] required a minimum severity of SAR symptoms. Nasal symptom scores at baseline were most commonly in the moderate range. All trials required a minimum duration of SAR history. All patients had SAR symptoms for more than 14 years. One trial[108] reported baseline asthma scores. Baseline asthma symptoms, as assessed by the Total Asthma Symptom Severity Score (TASS, described below) and forced expired volume in one second (FEV_1), were moderate in severity.

Eight trials[97, 109-114] assessed nasal symptoms, four[109, 110, 113, 114] assessed eye symptoms, one trial[108] assessed asthma symptoms, and six trials[109-114] assessed quality of life. All trials used a 4-point scale (0=no symptoms, 3=severe symptoms) to assess four nasal symptoms (congestion, rhinorrhea, sneezing, and itch) and averaged these scores to calculate a TNSS. Maximum TNSS was three points. All four trials that reported on eye symptoms assessed ocular tearing, itching, redness, and puffiness using the 4-point scale described above. Individual scores were averaged for a maximum TOSS of 3 points. In the one trial[108] that assessed asthma outcomes, the 4-point rating scale was used to assess three asthma symptoms, cough, wheezing, and difficulty breathing. Scores were summed to yield the 0-9 point TASS. An MCID was not reported. All six trials that assessed quality of life used the 27-item RQLQ. Scores ranged from 0 (no impairment) to 6 (severely impaired) with a validated MCID of 0.5 points. Measures were recorded at 2 weeks in five trials[110-114] and at 4 weeks in two trials.[109, 113]

Three trials[108, 110, 111] were rated good quality, two[113, 114] were rated fair, and four[97, 109, 112] were rated poor.

Key Points

These results are summarized in Table 25.

- Nasal congestion and rhinorrhea at 2 weeks: Evidence was insufficient to support the use of one treatment over the other based on three trials 110-112 with medium risk of bias and inconsistent, imprecise results.
- Sneezing and nasal itch at 2 weeks: Evidence was insufficient to support the use of one treatment over the other based on three trials 110-112 with medium risk of bias and consistent but imprecise results.
- TNSS and TOSS at 2-4 weeks: Moderate strength evidence for equivalence of oral selective antihistamine and oral leukotriene receptor antagonist based on eight trials97,

109-114 (for TNSS) and four trials 109, 110, 113, 114 (for TOSS) with medium risk of bias and consistent, precise results.

- Asthma rescue medication use at 2-4 weeks: Moderate strength evidence for superiority of oral leukotriene receptor antagonist over oral selective antihistamine based on one trial 108 with low risk of bias and precise results.
- Other asthma outcomes (individual asthma symptoms, TASS, and FEV1) at 2-4 weeks: Evidence was insufficient to support the use of one treatment over the other based on one trial108 with low risk of bias and imprecise results.
- Quality of life as assessed by the RQLQ at 2-4 weeks: Moderate strength evidence for equivalence of oral selective antihistamine and oral leukotriene receptor antagonist based on six trials109-114 with medium risk of bias and consistent, precise results.
- These results are based on trials of three of five oral selective antihistamines (60 percent) in comparison to montelukast (100 percent).

Table 25. Strength of evidence: oral selective antihistamine versus oral leukotriene receptor antagonist

Outcome	RCTs (Patients)	Risk of Bias	Consistency	Directness	Precision	Overall GRADE
2-week congestion, rhinorrhea	3[110-112] (1593)	Medium	Inconsistent	Direct	Imprecise	Insufficient
2-week sneezing, nasal itch	3[110-112] (1593)	Medium	Consistent	Direct	Imprecise	Insufficient
2-4 week TNSS	8[97, 109-114] (3609)	Medium	Consistent	Direct	Precise	Moderate[b]
2-4 week TOSS (eye tearing, itching, redness, puffiness)	4[109, 110, 113, 114] (1708)	Medium	Consistent	Direct	Precise	Moderate[b]
2-4 week asthma rescue medication use	1[108] (622)	Low	Unknown (single study)	Direct	Precise	Moderate[c]
2-4 week asthma symptom outcomes[a] and FEV_1	1[108] (622)	Low	Unknown (single study)	Direct	Imprecise	Insufficient
2-4 week RQLQ	6[109-114] (3114)	Medium	Consistent	Direct	Precise	Moderate[b]

FEV_1 = forced expired volume in 1 second; GRADE = Grading of Recommendations Assessment, Development and Evaluation; RCTs (Patients) = number of randomized controlled trials (number of patients randomized to treatment groups of interest); RQLQ = Rhinoconjunctivitis Quality of Life Questionnaire; TNSS = total nasal symptom score: TOSS = total ocular symptom score.

[a] Cough, wheeze, and shortness of breath.

[b] The body of evidence supports equivalence of oral selective antihistamine and oral leukotriene receptor antagonist for the outcomes identified.

[c] The body of evidence supports the superiority of oral leukotriene receptor antagonist over oral selective antihistamine for this outcome.

Synthesis and Strength of Evidence

Nasal symptom results discussed below are summarized in Table 26, eye symptoms in Table 27, asthma outcomes in Table 28, and quality of life outcomes in Table 29. As shown in these tables, variance estimates of observed effects are provided for TNSS, TOSS, and RQLQ. Thus, meta-analyses of these results were conducted.

Nasal Symptoms

Individual nasal symptom scores were assessed in three trials[110-112] at 2 weeks (N=1593). Two of these[110, 111] were good quality trials of 643 patients total (40 percent of all patients reporting this outcome). The third trial[112] (n=950) was rated poor quality due to the inappropriate analysis of results (not intention to treat). P-values were not reported for any outcome. For congestion and rhinorrhea, the good quality trials showed treatment effects ranging from 0.02 to 0.08 on a 0-3 point scale (both less than 3 percent of maximum score) favoring leukotriene receptor antagonist over oral selective antihistamine. For sneezing and itching, treatment effects in these trials favored oral selective antihistamine over leukotriene receptor antagonist and ranged from 0.02 to 0.12 (1 percent and 4 percent of maximum score, respectively). Treatment effects in the poor quality trial favored oral selective antihistamine for all four nasal symptoms and ranged from 0.10 to 0.18 (3 percent to 6 percent of maximum score).

For these outcomes at 2 weeks, the risk of bias was rated as medium. Sixty percent of patients reporting were in the poor quality trial,[112] and 40 percent were in good quality trials.[110, 111] Findings were not consistent across trials for congestion and rhinorrhea, but were consistent for sneezing and nasal itch. Treatment effects were imprecise. Evidence was therefore insufficient to support the use of one treatment over the other for these outcomes.

TNSS was assessed at 2 weeks in seven trials,[97, 110-114] one of which also reported 4-week outcomes.[114] An additional trial[109] reported 4-week results only (total N=3609). Two trials[110, 111] were good quality trials of 643 patients total (18 percent of patients reporting this outcome) and two[113, 114] were rated fair (1321 patients total; 37 percent of patients reporting). No trial reported p-values. All but two trials[110, 111] favored oral selective antihistamine over leukotriene receptor antagonist at 2 or 4 weeks, with treatment effects ranging from 0.01 to 0.17 on a 0-3 point scale (all less than 6 percent of maximum score). The two good quality trials[110, 111] favored leukotriene receptor antagonist at 2 weeks with treatment effects of 0.02 and 0.04 on a 0-3 point scale (both less than 2 percent of maximum score). A meta-analysis of seven[97, 109-111, 113, 114] of these eight trials was performed (total N=2648; 73 percent of patients reporting this outcome). The pooled treatment effect was 0.06 on a 0-3 point scale (95 percent CI: 0.00 to 0.12) favoring oral selective antihistamine (Figure 7). This was a statistically significant result. The larger bound of the 95 percent CI represented 4 percent of maximum score. Statistical heterogeneity was low to moderate but not statistically significant (I^2=39 percent, p=0.13) and likely due to variation in treatment effect direction and precision. An eighth trial[112] that was rated poor quality was not included in the meta-analysis due to lack of variance reporting (n=950). This trial reported a treatment effect of 0.1 on a 0-3 point scale (3 percent of maximum score) favoring oral selective antihistamine. A p-value was not provided. Finally, 4-week results from van Adelsberg (2003)[114] were not included in the meta-analysis because 2-week results were the identified primary outcome. The treatment effect at 4 weeks was 0.07 on a 0-3 point scale (2 percent of maximum score) favoring oral selective antihistamine. A p-value was not reported.

For TNSS at 2 to 4 weeks, the risk of bias was rated as medium. Eighteen percent of patients reporting this outcome were in good quality trials, and 45 percent were in poor quality trials. Although findings at 2 weeks were not consistent across individual trials, statistical heterogeneity of a meta-analysis that included trials with conflicting results was low to moderate. Further, the pooled treatment effect (0.06) favoring oral selective antihistamine was consistent with treatment effects reported by the one trial (Philip [2002]) not included in the meta-analysis[112] and by another trial[114] included in the meta-analysis that reported results at an additional time point (4 weeks). The 95 percent CI for the pooled estimate (0.00 to 0.12) fell

within an interval bounded by –MCID and +MCID (-0.9 and +0.9 on the 0-3 point scale used). The Philip (2002) trial[112] (26 percent of patients reporting this outcome) showed a treatment effect (0.1 on a 0-3 point scale) that was larger than the pooled effect (0.06) but smaller than the MCID (0.9). To determine the impact of this trial on the pooled estimate, we added it to the meta-analysis with an assumed standard deviation equal to half the mean change in score in each treatment group. Under this assumption, the pooled effect increased from 0.06 to 0.08 on a 0-3 point scale (95 percent CI: 0.03 to 0.12) favoring intranasal corticosteroid. The larger bound of the 95 percent CI represented 4 percent of maximum score. Based on this analysis, it is unlikely that the 95 percent confidence interval of a meta-analysis including the Philip (2002) trial[112] would contain the MCID. The body of evidence supporting a conclusion of equivalence of oral selective antihistamine and leukotriene receptor antagonist for this outcome is therefore precise. The overall strength of evidence for this conclusion is rated as moderate based on these considerations.

Eye Symptoms

Four trials[109, 110, 113, 114] assessed a four symptom TOSS comprising eye tearing, itching, redness, and puffiness (N=1708) at 2 or 4 weeks. One of these[110] was a good quality trial of 187 patients (11 percent of patients reporting this outcome) that showed a treatment effect of 0.03 on a 0-3 point scale (1 percent of maximum score) favoring leukotriene receptor antagonist. A p-value was not reported. All other assessments favored oral selective antihistamine, including two fair quality trials[113, 114] of 1321 patients (77 percent of patients reporting) and one trial[109] that was rated poor quality due to noncomparable groups at baseline and inappropriate analysis of results (unadjusted for baseline group differences). Treatment effects were 0.05 and 0.12 in the fair quality trials (2 percent and 4 percent of maximum score, respectively) and 0.16 in the poor quality trial (5 percent of maximum score). All four trials were included in a meta-analysis (Figure 8). The pooled treatment effect was 0.08 on a 0-3 point scale (95 percent CI: 0.02 to 0.14) favoring oral selective antihistamine over leukotriene receptor antagonist. The larger bound of the 95 percent CI represented 5 percent of maximum score. Statistical heterogeneity was low (I^2=14 percent, p=0.32). Four-week results from one trial[114] were not included in the meta-analysis because 2-week results were the identified primary outcome. At 4 weeks, the treatment effect was 0.02 on a 0-3 point scale (1 percent of maximum score) favoring oral selective antihistamine. A p-value was not reported.

For TOSS at 2 to 4 weeks, the risk of bias was rated as medium. Eleven percent of patients were in the good quality trial, and 12 percent were in the poor quality trial. Although results across individual trials were inconsistent at 2 weeks, statistical heterogeneity for the pooled treatment effect was low. The 95 percent CI for the pooled estimate fell within an interval bounded by –MCID and +MCID (-0.9 and +0.9 on the 0-3 point scale used). The body of evidence supporting a conclusion of equivalence of oral selective antihistamine and leukotriene receptor antagonist for this outcome is therefore precise. The strength of evidence for this conclusion is rated as moderate based on these considerations.

Asthma Symptoms

One good quality trial[108] (N=622) reported individual and TASS scores in addition to rescue medication use and FEV_1 at 2 and 4 weeks. Patients had moderate asthma symptoms at baseline. All outcomes had greater improvements with leukotriene receptor antagonist than with oral selective antihistamine, but no statistically significant differences between treatment groups were

observed for any outcome during the 4 weeks of the trial. For all outcomes, the risk of bias was rated as low, and consistency could not be assessed with a single trial.

Treatment effects at 2 and 4 weeks were:

- Total asthma symptoms on a 0-9 point scale: 0.09 at 2 weeks and 0.16 at 4 weeks (1 percent and 2 percent of maximum score, respectively).
- Rescue medication use: 2.4 puffs per day at 2 weeks and 3.8 puffs per day at 4 weeks (both greater than an MCID of 1 puff per day)

Treatment effects at 4 weeks were:

- Individual asthma symptoms on a 0-3 point scale: 0.02 for cough, 0.04 for wheeze, and 0.06 for difficulty breathing (1 percent, 1 percent and 2 percent of maximum score, respectively)
- FEV1: 0.03 percent predicted (less than an MCID of 10 percent)

For rescue medication use at 2 and 4 weeks, the treatment effect is precise, and there is moderate strength evidence to support the use of oral leukotriene receptor antagonist. For all other outcomes, evidence was insufficient to support the use of one treatment over the other.

Quality of Life

All six trials[109-114] that assessed quality of life at 2 and 4 weeks used the RQLQ (N=3114). Two of these were good quality trials[110, 111] of 643 patients (21 percent of patients reporting this outcome), two[113, 114] were fair quality trials of 1321 patients (42 percent of patients reporting), and two[109, 112] were poor quality trials of 1150 patients (37 percent of patients reporting). P-values were not reported in any trial. Treatment effects exceeded the MCID of 0.5 in three trials[109, 112, 113], two[112, 113] at 2 weeks (0.10 and 0.08 in a poor and fair quality trial, respectively) and one[109] at 4 weeks (0.13 in a poor quality trial). All three results favored oral selective antihistamine over leukotriene receptor antagonist. A meta-analysis of four trials[111-114] that reported 2-week RQLQ results was performed (N=2723; Figure 9). The pooled treatment effect favored oral selective antihistamine (mean difference 0.06; 95 percent CI: -0.03 to 0.15) but was not statistically significant. Statistical heterogeneity was low (I^2=0 percent, p=0.84). One[110] of two trials not included in the meta-analysis represented 6 percent of patients reporting this outcome and found no treatment difference between groups at 2 weeks. The other trial,[109] also representing 6 percent of patients reporting this outcome, showed a treatment effect of 0.13 favoring oral selective antihistamine at 4 weeks. One of the trials[114] included in the meta-analysis reported 4-week results, which were not included because 2-week results were the identified primary outcome. In contrast to the 2-week result, the treatment effect at 4 weeks favored leukotriene receptor antagonist. The effect was 0.04, which did not exceed the MCID.

For quality of life as assessed by the RQLQ, the risk of bias was rated as medium. Twenty-one percent of patients were in good quality trials, and 37 percent were in poor quality trials. Statistical heterogeneity for the pooled effect favoring oral selective antihistamine was low, and one trial[110] not included in the meta-analysis that showed a treatment difference of zero represented only 6 percent of patients reporting this outcome. The 95 percent CI for the pooled estimate (-0.03 to 0.15) fell within an interval bounded by –MCID and +MCID (-0.5 and +0.5). Of two trials not included in the meta-analysis,[109, 110] one[109] (6 percent of patients reporting this outcome) showed a treatment effect (0.13) favoring oral selective antihistamine that was smaller than the MCID but larger than the pooled effect (0.06). The other[110] (6 percent of patients reporting this outcome) showed a treatment difference of zero that was, therefore, smaller than both the MCID and the pooled effect. If these trials were included in the meta-analysis, the

pooled effect would change very little, and it is unlikely that the 95 percent confidence interval would contain the MCID. One trial,[114] a large trial representing 20 percent of patients reporting this outcome, was included in the meta-analysis of results at 2 weeks and reported an additional treatment effect of 0.04 at 4 weeks favoring leukotriene receptor antagonist. If this result were included in the meta-analysis, the effect estimate favoring oral selective antihistamine would decrease and possibly cross the "no effect" line to favor leukotriene receptor antagonist, but it is unlikely that the MCID would lie within the 95 percent confidence interval. Based on these considerations, the body of evidence supporting a conclusion of equivalence of oral selective antihistamine and leukotriene receptor antagonist for this outcome is therefore considered precise. The strength of evidence for this conclusion is rated as moderate.

Table 26. Treatment effects: nasal symptoms–oral selective antihistamine versus oral leukotriene receptor antagonist

Outcome	Variance	SS Favors Oral S-AH MD	NSS Favors/NR Oral S-AH MD	Favors Neither MD=0	NSS Favors/NR LRA MD	SS Favors LRA MD
2-Week Outcomes						
Congestion						
Meltzer, 2000[110] (scale 0-3)					0.08[a] (NR)	
Nayak, 2002[111] (scale 0-3)	95% CI				0.02 (NR)	
Philip, 2002[112] (scale 0-3)			0.11 (NR)			
Rhinorrhea						
Meltzer, 2000[110] (scale 0-3)					0.07[a] (NR)	
Nayak, 2002[111] (scale 0-3)	95% CI				0.03 (NR)	
Philip, 2002[112] (scale 0-3)			0.10 (NR)			
Sneezing						
Meltzer, 2000[110] (scale 0-3)			0.02[a] (NR)			
Nayak, 2002[111] (scale 0-3)	95% CI		0.12 (NR)			
Philip, 2002[112] (scale 0-3)			0.18 (NR)			
Itching						
Meltzer, 2000[110] (scale 0-3)			0.05[a] (NR)			
Nayak, 2002[111] (scale 0-3)	95% CI		0.07 (NR)			
Philip, 2002[112] (scale 0-3)			0.14 (NR)			
TNSS						
Lu, 2009 (Trial 1)[97] (scale 0-3)	95% CI		0.17 (NR)			
Lu, 2009 (Trial 2)[97] (scale 0-3)	95% CI		0.01 (NR)			
Meltzer, 2000[110] (scale 0-3)	95% CI				0.02 (NR)	
Nayak, 2002[111] (scale 0-3)	95% CI				0.04 (NR)	
Philip, 2002[112] (scale 0-3)			0.10 (NR)			
van Adelsberg, 2003[113] (scale 0-3)	95% CI		0.09 (NR)			
van Adelsberg, 2003[114] (scale 0-3)	95% CI		0.12 (NR)			

Outcome	Variance	SS Favors Oral S-AH MD	NSS Favors/NR Oral S-AH MD	Favors Neither MD=0	NSS Favors/NR LRA MD	SS Favors LRA MD
4-Week Outcomes						
TNSS						
Lombardo, 2006[109] (scale 0-3)	95% CI		0.09 (NR)			
van Adelsberg, 2003[114] (scale 0-3)	95% CI		0.07 (NR)			

LRA = leukotriene receptor antagonist; MD = mean difference between group mean changes from baseline; NR = p-value not reported; NSS = not statistically significant; S-AH = selective antihistamine; SS = statistically significant; TNSS = total nasal symptom score.

Variance/confidence interval reported: CI = confidence interval; SD = standard deviation; SE = standard error.

Figure 7. Total nasal symptom score at 2 to 4 weeks: meta-analysis of 7 trials–oral selective antihistamine versus leukotriene receptor antagonist

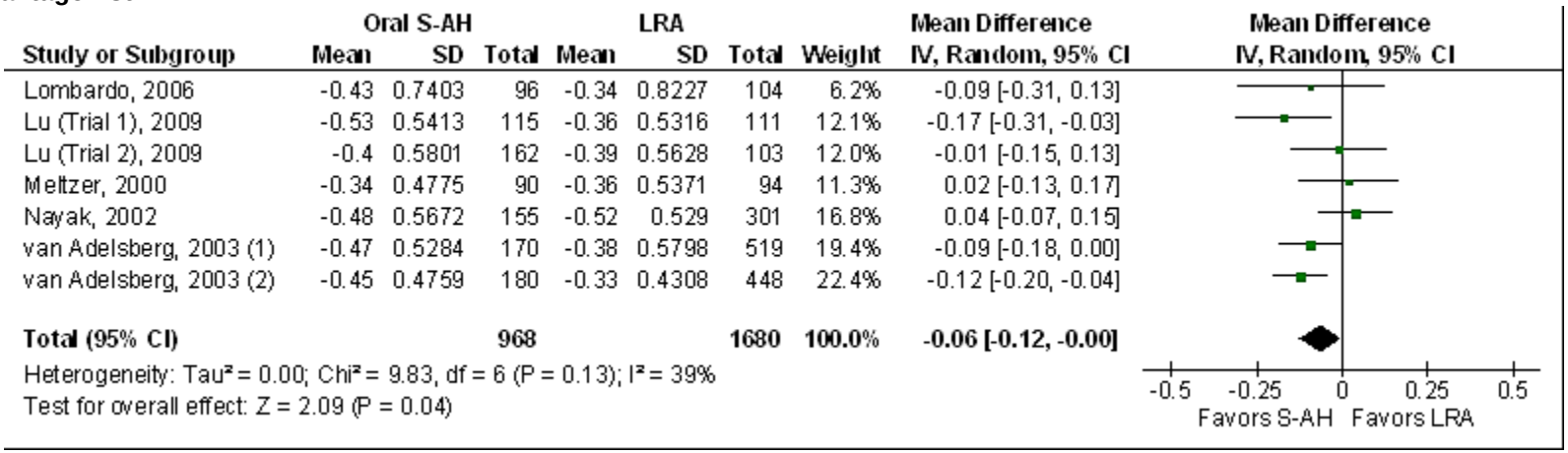


Table 27. Treatment effects: eye symptoms–oral selective antihistamine versus leukotriene receptor antagonist

Outcome	Variance	SS Favors Oral S-AH MD	NSS Favors/NR Oral S-AH MD	Favors Neither MD=0	NSS Favors/NR LRA MD	SS Favors LRA MD
2-Week Outcomes						
Total ocular symptom score						
Meltzer, 2000[110] (scale 0-3)	95% CI				0.03 (NR)	
van Adelsberg, 2003[113] (scale 0-3)	95% CI		0.12 (NR)			
van Adelsberg, 2003[114] (scale 0-3)	95% CI		0.05 (NR)			
4-Week Outcomes						
Total ocular symptom score						
Lombardo, 2006[109] (scale 0-3)	95% CI		0.16 (NR)			
van Adelsberg, 2003[114] (scale 0-3)	95% CI		0.02 (NR)			

LRA = Leukotriene receptor antagonist; MD = mean difference between group mean changes from baseline; NR = p-value not reported; NSS = not statistically significant; S-AH = selective antihistamine; SS = statistically significant.

Variance/confidence interval reported: CI = confidence interval; SD = standard deviation; SE = standard error.

Total ocular symptom score is the mean of scores for 4 ocular symptoms (itching, tearing, redness, and puffiness) using a 0 (no symptom) to 3 (severe symptom) rating scale.

Figure 8. Total ocular symptom score at 2 to 4 weeks: meta-analysis of 4 trials–oral selective antihistamine versus leukotriene receptor antagonist

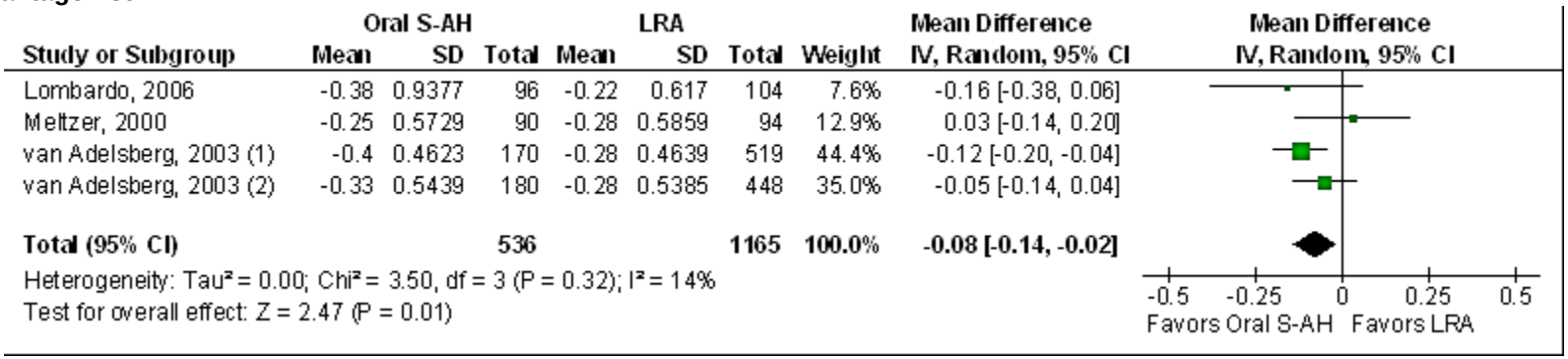


Table 28. Treatment effects: asthma outcomes–oral selective antihistamine versus leukotriene receptor antagonist

Outcome	Variance	SS Favors Oral S-AH MD	NSS Favors/NR Oral S-AH MD	Favors Neither MD=0	NSS Favors/NR LRA MD	SS Favors LRA MD
2-Week Outcomes						
TASS						
Baena-Cagnani, 2003[108]					0.09 (NSS)	
Rescue medication use[a]						
Baena-Cagnani, 2003[108]					2.4 (NSS)	
4-Week Outcomes						
Cough						
Baena-Cagnani, 2003[108]					0.02 (NSS)	
Wheeze						
Baena-Cagnani, 2003[108]					0.04 (NSS)	
Difficulty breathing						
Baena-Cagnani, 2003[108]					0.06 (NSS)	
TASS						
Baena-Cagnani, 2003[108]					0.16 (NSS)	
Rescue medication use[a]						
Baena-Cagnani, 2003[108]					3.8 (NSS)	
FEV_1, percent predicted						
Baena-Cagnani, 2003[108]					0.03 (NSS)	

FEV_1 = Forced expired volume in 1 second; LRA = leukotriene receptor antagonist; MD = mean difference between group mean changes from baseline; NR = p-value not reported; NSS = not statistically significant; S-AH = selective antihistamine; SS = statistically significant; TASS = total asthma symptom score.

Scale is 0 (no symptom) to 3 (severe symptom) for asthma symptoms. TASS is the sum of individual scores for coughing, wheezing, and difficulty breathing, and ranges from 0 to 9 points.

[a] Change in number of puffs of B-agonist use per day.

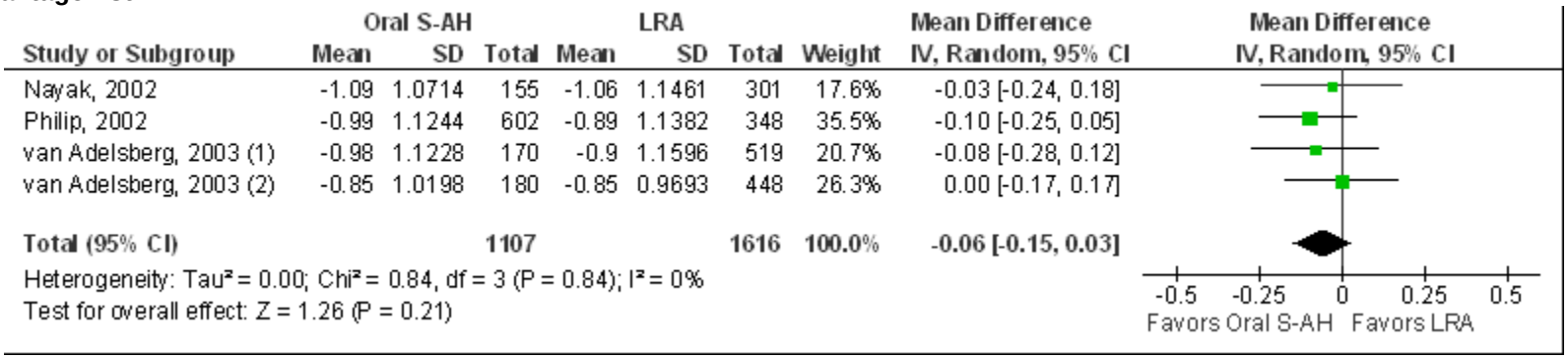
Table 29. Treatment effects: quality of life outcomes–oral selective antihistamine versus leukotriene receptor antagonist

Outcome	Variance	SS Favors Oral S-AH MD	NSS Favors/NR Oral S-AH MD	Favors Neither MD=0	NSS Favors/NR LRA MD	SS Favors LRA MD
2-Week Outcomes						
RQLQ						
Meltzer, 2000[110]				0		
Nayak, 2002[111]	95% CI		0.03 (NR)			
Philip, 2002[112]	95% CI		0.10 (NR)			
van Adelsberg, 2003[113]	95% CI		0.08 (NR)			
van Adelsberg, 2003[114]	95% CI			0		
4-Week Outcomes						
RQLQ						
Lombardo, 2006[109]			0.13 (NR)			
van Adelsberg, 2003[114]	95% CI				0.04 (NR)	

LRA = Leukotriene receptor antagonist; MD = mean difference between group mean changes from baseline; NR = p-value not reported; NSS = not statistically significant; RQLQ = Rhinoconjunctivitis Quality of Life Questionnaire; S-AH = selective antihistamine SS = statistically significant.

Variance/confidence interval reported: CI = confidence interval; SD = standard deviation; SE = standard error.

Figure 9. Rhinoconjunctivitis quality of life at 2 weeks: meta-analysis of 4 trials–oral selective antihistamine versus leukotriene receptor antagonist



Intranasal Corticosteroid Versus Nasal Antihistamine

Description of Included Studies

Nine[115-121] RCTs published between 1995 and 2012 were identified (N=2473). All but two[116, 120] were multicenter trials. Six[115, 117, 118, 121] trials were conducted in North America, two[119, 120] in Europe, one[116] in Asia. Six trials[115, 117, 120, 121] were double-blinded, one trial[116] was open-label, and two[118, 119] were considered to have inadequate patient blinding. Trials included 50 to 895 patients randomized to treatment groups of interest and used either fluticasone propionate (six trials[115, 117, 118, 121]) or beclomethasone (three trials[116, 119, 120]) as the intranasal corticosteroid, and azelastine (eight trials[115-117, 119-121]) or olopatadine (one trial[118]) as the nasal antihistamine. Seven trials[115, 117-119, 121] were 2 weeks in duration, one[116] was 4 weeks, and one[120] was six weeks. Six trials[115, 117, 118, 121] were industry funded, and three[116, 119, 120] did not report funding source.

The mean age of the trial populations was 36 years. Approximately 55 percent of patients were female, although men were the majority in two trials. [116, 120] In trials that reported on race, the majority of patients were white. Most patients had SAR symptoms for more than 15 years and had moderate to severe symptoms at baseline.

Trials reported outcomes after 2 to 5 weeks of treatment. Outcomes reported were nasal symptoms (nine trials[115-121]), eye symptoms (five trials[115, 117, 118]), and quality of life (two trials[117, 121]). All nine trials reported nasal symptom outcomes at 2 weeks, one[116] at 2, 3, and 4 weeks, and one[120] at 2, 3, 4 and 5 weeks. Most trials used a 4-point scale (0 = no symptoms, 3 = severe symptoms) for the assessment of nasal symptoms. Of these, the majority assessed symptoms twice daily and summed the scores for a daily TNSS ranging from 0 to 24; others assessed once daily for a TNSS of 0 to 12. Five trials[115, 117, 118] assessed ocular symptoms. All but one[118] assessed ocular itching, tearing, and redness using the 4-point scale (0 = no symptoms, 3 = severe symptoms) twice daily in the morning and evening (TOSS range 0 to 18); the other[118] assessed once daily (TOSS range 0 to 9). Finally, two trials[117, 121] assessed quality of life using the RQLQ, a validated quality of life instrument in this patient population with scores ranging from 0 (no impairment) to 6 (severely impaired); the MCID is 0.5 points.[65]

Five[115, 117, 121] of the nine identified trials were rated good quality and four[116, 118-120] were rated poor.

Key Points

These results are summarized in Table 30.

- Individual nasal symptoms, TNSS, and TOSS at 2 weeks: High strength evidence to support equivalence of intranasal corticosteroid and nasal antihistamine based on eight trials98, 115-119 (for congestion, rhinorrhea, and sneezing), seven trials (for nasal itch98, 115, 117-119 and TNSS98, 115, 117, 118, 120), and five trials115, 117, 118 (for TOSS) with low risk of bias and consistent, precise results.
- Quality of life at 2 weeks as assessed by the RQLQ: Evidence was insufficient to support the use of one treatment over the other based on two trials98, 117 with low risk of bias and consistent but imprecise results.
- Individual nasal symptoms (congestion, rhinorrhea, and sneezing) at 3-4 weeks: Evidence was insufficient to support the use of one treatment over the other based on one trial116 with high risk of bias and an imprecise result.

- TNSS at 3-5 weeks: Evidence was insufficient to support the use of one treatment over the other based on one trial120 with high risk of bias and an imprecise result.
- These results are based on trials of two of eight intranasal corticosteroids (25 percent) and both nasal antihistamines (100 percent).

Table 30. Strength of evidence: intranasal corticosteroid versus nasal antihistamine

Outcome	RCTs (Patients)	Risk of Bias	Consistency	Directness	Precision	Overall GRADE
2-week congestion	8[98, 115-119] (2443)	Low	Consistent	Direct	Precise	High[a]
2-week rhinorrhea	8[98, 115-119] (2443)	Low	Consistent	Direct	Precise	High[a]
2-week sneezing	8[98, 115-119] (2443)	Low	Consistent	Direct	Precise	High[a]
2-week nasal itch	7[98, 115, 117-119] (2393)	Low	Consistent	Direct	Precise	High[a]
2-week TNSS	7[98, 115, 117, 118, 120] (2257)	Low	Consistent	Direct	Precise	High[a]
2-week TOSS	5[115, 117, 118] (2128)	Low	Consistent	Direct	Precise	High[a]
2-week RQLQ	2[98, 117] (404)	Low	Consistent	Direct	Imprecise	Insufficient
3-4 week congestion, rhinorrhea, sneezing	1[116] (50)	High	Consistency unknown (single study)	Direct	Imprecise	Insufficient
3-5 week TNSS	1[120] (30)	High	Consistency unknown (single study)	Direct	Imprecise	Insufficient

GRADE = Grading of Recommendations Assessment, Development and Evaluation; RCTs (Patients) = number of randomized controlled trials (number of patients randomized to treatment groups of interest); RQLQ = Rhinoconjunctivitis Quality of Life Questionnaire; TNSS = total nasal symptom score; TOSS = total ocular symptom score.

[a] The body of evidence supports equivalence of intranasal corticosteroid and nasal antihistamine for the outcomes identified.

Synthesis and Strength of Evidence

Trial level comparative outcome data for nasal symptoms can be found in Table 31, for ocular symptoms in Table 32, and for quality of life in Table 33. As shown in Table 31 and Table 32, variance estimates of group-level effects were provided for individual nasal symptoms, TNSS, and TOSS. Meta-analyses for these outcomes were conducted.

Nasal Symptoms

Eight[115-119, 121] of nine trials assessed congestion after 2 weeks of treatment (N=2443 of 2473). Seven of these[115-119] reported treatment effects favoring intranasal corticosteroid, although none were reported to be statistically significant. In the eighth trial,[121] representing 4 percent of patients reporting this outcome, the treatment difference was zero. The USPSTF quality rating was good in five of these trials[115, 117, 121] (85 percent of patients reporting this outcome) and poor in three trials.[116, 118, 119] Poor USPSTF ratings were assigned for noncomparable groups at baseline,[116] inadequate blinding,[116, 118, 119] and inappropriate analysis of results (unadjusted for baseline group differences[116] and not intention to treat[119]). A meta-analysis of four good quality trials[115, 121] (N=1791; 73 percent of patients reporting this outcome) yielded a statistically significant pooled effect of 0.14 on a 0-6 point scale (95 percent CI: 0.02 to 0.26) favoring intranasal corticosteroid (Figure 10). The larger bound of the 95 percent CI represented 4 percent

of maximum score. Statistical heterogeneity was low (I^2=0 percent, p=0.54). Treatment effects for four trials[116-119] not included in the meta-analysis favored intranasal corticosteroid with a range of 0.11[117] on a 0-6 point scale (2 percent of maximum score) to 0.7[116] on a 0-3 point scale (23 percent of maximum score).

For nasal congestion at 2 weeks, the risk of bias was rated as low. Eighty-five percent of patients were in good quality trials. Treatment effects consistently favored intranasal corticosteroid in 96 percent of patients reporting on this outcome. This finding was consistent with results of a meta-analysis of four[115, 121] of these trials (73 percent of patients reporting this outcome), including the one trial[121] that reported a treatment effect of zero, and statistical heterogeneity was low. The 95 percent CI for the pooled effect (0.02 to 0.26) fell within an interval bounded by –MCID and +MCID (-1.8 and +1.8 on the 0-6 point scale used). Of four trials[116-119] not included in the meta-analysis, one[118] reported a treatment effect favoring intranasal corticosteroid but did not report the magnitude of the effect. Because this trial represented 5 percent of patients reporting this outcome, its impact on the pooled estimate if this trial were included in the meta-analysis likely would be minimal. One trial[117] (12 percent of patients reporting this outcome) showed a treatment effect (0.11 on a 0-6 point scale) that was smaller than both the pooled effect (0.14 on a 0-6 point scale) and the MCID (1.8). If this trial were included in the meta-analysis, the pooled effect estimate would decrease slightly, and it is unlikely that the 95 percent confidence interval would include the MCID. Two trials[116, 119] (9 percent of patients reporting this outcome) showed treatment effects of 0.5[119] and 0.7[116] on a 0-3 point scale (1.0 and 1.4 on a 0-6 point scale, respectively). These effects were substantially larger than the pooled effect (0.14 on a 0-6 point scale) but smaller than the MCID (1.8). To determine the impact of these two trials[116, 119] on the pooled estimate, we added both to the meta-analysis with assumed standard deviations equal to half the mean change in score in each treatment group. Under this assumption, the pooled effect increased from 0.14 to 0.45 on a 0-6 point scale (95 percent CI: 0.06 to 0.85) favoring intranasal corticosteroid. The larger bound of the 95 percent CI represented 14 percent of maximum score. Based on this analysis, it is unlikely that the 95 percent confidence interval of a meta-analysis including these two trials[116, 119] would contain the MCID. The body of evidence in support of a conclusion of equivalence of intranasal corticosteroid and nasal antihistamine for this outcome is therefore considered precise. The overall strength of evidence for this conclusion is rated as high.

Eight[115-119, 121] of nine trials assessed rhinorrhea after 2 weeks of treatment (N=2443 of 2473 patients). Seven[115, 117-119, 121] of eight reported treatment effects in favor of intranasal corticosteroid, although none were reported to be statistically significant. The eighth trial[116] (n=50; 2 percent of patients reporting this outcome) reported a treatment difference of zero. The USPSTF quality rating was good in five trials[115, 117, 121] (85 percent of patients reporting this outcome) and poor in three trials.[116, 118, 119] Poor USPSTF ratings were assigned for noncomparable groups at baseline,[116] inadequate blinding,[116, 118, 119] and inappropriate analysis of results (unadjusted for baseline group differences[116] and not intention to treat[119]). A meta-analysis of four trials[115, 121] (N=1791; 73 percent of patients reporting this outcome) yielded a statistically significant pooled effect estimate of 0.17 on a 0-6 point scale (95 percent CI: 0.04 to 0.30) favoring intranasal corticosteroid (Figure 11). The larger bound of the 95 percent CI represented 5 percent of maximum score. Statistical heterogeneity was low (I^2=0 percent, p=0.70). Of four trials[116-119] not included in the meta-analysis, three[117-119] reported treatment effects favoring intranasal corticosteroid. Reported effect sizes were 0.28[117] on a 0-6 point scale (5 percent of maximum score) and 0.4[119] on a 0-3 point scale (13 percent of maximum score,

respectively). One trial[118] did not report the magnitude of effect. The fourth trial[116] reported no treatment difference.

For rhinorrhea at 2 weeks, the risk of bias was rated as low. Eighty-five percent of patients were in good quality trials. Treatment effects consistently favored intranasal corticosteroid in 98 percent of patients reporting this outcome, and statistical heterogeneity in a meta-analysis of four trials[115, 121] (73 percent of patients reporting this outcome) was low. The 95 percent CI for the pooled effect (0.04 to 0.30) fell within an interval bounded by –MCID and +MCID (-1.8 and +1.8 on the 0-6 point scale used). Three[117-119] of four trials[116-119] not included in the meta-analysis reported treatment effects favoring intranasal corticosteroid. One[118] of these did not report the magnitude of effect, but this trial represented 5 percent of patients reporting this outcome. Two trials[117, 119] (19 percent of patients reporting this outcome) reported treatment effects of 0.28[117] on a 0-6 point scale and 0.4[119] on a 0-3 point scale (0.8 on a 0-6 point scale) that were larger than the pooled effect but smaller than the MCID. To determine the impact of these two trials[117, 119] on the pooled estimate, we added both to the meta-analysis with assumed standard deviations equal to half the mean change in score in each treatment group. Under this assumption, the pooled effect increased from 0.17 to 0.34 on a 0-6 point scale (95 percent CI: 0.10 to 0.57) favoring intranasal corticosteroid. The larger bound of the 95 percent CI represented 10 percent of maximum score. Based on this analysis, it is unlikely that the 95 percent confidence interval of a meta-analysis including these two trials[117, 119] would contain the MCID. The fourth trial[116] reported a treatment effect of zero (and therefore smaller than both the pooled estimate [0.17] and the MCID), but this trial represented 2 percent of patients reporting this outcome. The body of evidence in support of a conclusion of equivalence of intranasal corticosteroid and nasal antihistamine for this outcome is therefore considered precise. The overall strength of evidence for this conclusion is rated as high.

Eight[115-119, 121] of nine trials assessed sneezing after 2 weeks of treatment (N=2443 of 2473). Six[115-117, 119] of these reported treatment effects favoring intranasal corticosteroid, although none were reported to be statistically significant. One trial[121](4 percent of patients reporting this outcome) showed no treatment difference, and the eighth trial[118] (5 percent of patients reporting this outcome) reported a treatment effect favoring nasal antihistamine. This treatment effect was not statistically significant and its magnitude was not reported. The USPSTF quality rating was good in five trials [115, 117, 121] (85 percent of patients assessed for this outcome) and poor in three trials.[116, 118, 119] Poor USPSTF ratings were assigned for noncomparable groups at baseline,[116] inadequate blinding,[116, 118, 119] and inappropriate analysis of results (unadjusted for baseline group differences[116] and not intention to treat[119]). A meta-analysis of four good quality trials[115, 121] (N=1791; 73 percent of patients reporting this outcome) yielded a statistically nonsignificant pooled effect estimate of 0.12 on a 0-6 point scale (95 percent CI: -0.01 to 0.25) favoring intranasal corticosteroid (Figure 12). The larger bound of the 95 percent CI represented 4 percent of maximum score. Statistical heterogeneity was low (I^2=0 percent, p=0.89). Of four trials[116-119] not included in the meta-analysis, treatment effects favoring intranasal corticosteroid were reported by three.[116, 117, 119] Reported effect sizes were 0.1[116] and 0.4[119] on a 0-3 point scale (3 percent and 13 percent of maximum score, respectively), and 0.12[117] on a 0-6 point scale (2 percent of maximum score). One trial[118] reported a statistically nonsignificant treatment effect favoring nasal antihistamine but did not report the magnitude of effect.

For the outcome of sneezing at 2 weeks, the risk of bias was rated as low. Eighty-five percent of patients were in good quality trials. Statistical heterogeneity in a meta-analysis of four trials[115, 121] (73 percent of patients reporting this outcome) that favored intranasal corticosteroid was low.

This included one trial[121] (4 percent of patients reporting this outcome) that reported a treatment difference of zero. The pooled effect was consistent with three.[116, 117, 119]of four trials not included in the meta-analysis. The fourth trial[118] reported a treatment effect of unknown size favoring nasal antihistamine, but this trial represented 5 percent of patients reporting this outcome. The body of evidence was therefore considered consistent. The 95 percent CI for the pooled estimate (0.01 to 0.25) fell within an interval bounded by –MCID and +MCID (-1.8 and +1.8 on the 0-6 point scale used). Of four trials[116-119] not included in the meta-analysis, one[118] showed a treatment effect in the opposite direction (favoring nasal antihistamine) but did not report the magnitude of effect. Because this trial represented 5 percent of patients reporting this outcome, the reduction in the pooled estimate if this trial were included in the meta-analysis likely would be minimal, unless the treatment effect was unexpectedly large. One trial[117] (12 percent of patients reporting this outcome) showed a treatment effect (0.12 on a 0-6 point scale) equal to the pooled effect. Change in the pooled estimate likely would be minimal if this trial were included in the meta-analysis. Two trials[116, 119] reported treatment effects of 0.1[116]and 0.4[119] on a 0-3 point scale (0.2 and 0.8 on a 0-6 point scale, respectively). These effects were larger than the pooled effect (0.12 on a 0-6 point scale) but smaller than the MCID of 1.8. To determine the impact of these two trials[116, 119] on the pooled estimate, we added both to the meta-analysis with assumed standard deviations equal to half the mean change in score in each treatment group. Under this assumption, the pooled effect increased from 0.12 to 0.25 on a 0-6 point scale (95 percent CI: 0.03 to 0.54) favoring intranasal corticosteroid. The larger bound of the 95 percent CI represented 9 percent of maximum score. Based on this analysis, it is unlikely that the 95 percent confidence interval of a meta-analysis including these two trials[116, 119] would contain the MCID. The body of evidence in support of a conclusion of equivalence of intranasal corticosteroid and nasal antihistamine for this outcome is therefore considered precise. The overall strength of evidence for this conclusion is rated as high.

Seven[115, 117-119, 121] of nine trials assessed nasal itch after 2 weeks of treatment (N=2393 of 2473), all of which reported treatment effects favoring intranasal corticosteroid, although none were reported to be statistically significant. The USPSTF quality rating was good in five trials[115, 117, 121] (88 percent of patients reporting this outcome) and poor in two trials.[118, 119] Poor USPSTF ratings were assigned for inadequate blinding[118, 119] and inappropriate analysis of results (not intention to treat[119]). A meta-analysis of four good quality trials[115, 121] (N=1791; 75 percent of patients reporting this outcome) yielded a statistically significant pooled effect of 0.19 on a 0-6 point scale (95 percent CI: 0.03 to 0.34) favoring intranasal corticosteroid (Figure 13). The larger bound of the 95 percent CI represented 11 percent of maximum score. Statistical heterogeneity was low (I^2=27 percent, p=0.25). Of three trials[117-119] not included in the meta-analysis, two[117, 119] reported treatment effects of 0.09[117] on a 0-6 point scale (2 percent of maximum score) and 0.4[119] on a 0-3 point scale (13 percent of maximum score). The third trial[118] did not report the magnitude of the treatment effect.

For nasal itch at 2 weeks, the risk of bias was rated as low. Eighty-eight percent of patients reporting this outcome were in good quality trials. Treatment effects consistently favored intranasal corticosteroid in all trials, and statistical heterogeneity of a meta-analysis of four trials[115, 121] (75 percent of patients reporting this outcome) was low. The 95 percent CI for the pooled estimate (0.03 to 0.34) fell within an interval bounded by –MCID and +MCID (-1.8 and +1.8 on the 0-6 point scale used). Of three trials[117-119] not included in the meta-analysis, one[118] did not report the magnitude of the treatment effect, but this trial represented 5 percent of patients reporting this outcome. One trial[117] (13 percent of patients reporting this outcome)

showed a treatment effect (0.09) that was less than both the pooled effect (0.19) and the MCID. If this trial were included in the meta-analysis, the pooled effect would decrease, and it is unlikely that the 95 percent CI would include an MCID of 30 percent maximum score. The third trial[119] (7 percent of patients reporting this outcome) showed a treatment effect of 0.4 on a 0-3 point scale (0.8 on a 0-6 point scale). This effect was larger than the pooled effect but smaller than the MCID. To determine the impact of this trial[119] on the pooled estimate, we added it to the meta-analysis with an assumed standard deviation equal to half the mean change in score in each treatment group. Under this assumption, the pooled effect increased from 0.19 to 0.35 on a 0-6 point scale (95 percent CI: 0.02 to 0.68) favoring intranasal corticosteroid. The larger bound of the 95 percent CI represented 11 percent of maximum score. Based on this analysis, it is unlikely that the 95 percent confidence interval of a meta-analysis including this trial[119] would contain the MCID. The body of evidence in support of a conclusion of equivalence of intranasal corticosteroid and nasal antihistamine for this outcome is therefore considered precise. The overall strength of evidence for this conclusion is rated as high.

Seven[115, 117, 118, 120, 121] of nine trials assessed TNSS after 2 weeks of treatment (N=2257 of 2473). Five[115, 117, 121] reported treatment effects favoring intranasal corticosteroid, and two[118, 120] reported treatment effects favoring nasal antihistamine. None were reported to be statistically significant. The USPSTF quality rating was good in five trials[115, 117, 121] (93 percent of patients reporting this outcome) and poor in two trials.[118, 120] Poor USPSTF ratings were assigned for noncomparable groups at baseline,[120] inadequate blinding,[118] and inappropriate analysis of results (unadjusted for baseline group differences[120]). A meta-analysis of five good quality trials[115, 117, 121] (N=2097; 93 percent of patients reporting this outcome) yielded a statistically significant pooled effect estimate of 0.65 on a 0-24 point scale (95 percent CI: 0.25 to 1.05) favoring intranasal corticosteroid (Figure 14). The larger bound of the 95 percent CI represented 4 percent of maximum score. Statistical heterogeneity was low (I^2=0 percent, p=0.98). Two trials[118, 120] not included in the meta-analysis reported treatment effects favoring nasal antihistamine. Effect sizes were not reported.

For TNSS at 2 weeks, the risk of bias was rated as low. Ninety-three percent of patients were in good quality trials. Treatment effects consistently favored intranasal corticosteroid in 93 percent of patients reporting this outcome. The 95 percent CI for the pooled estimate (0.25 to 1.05) fell within an interval bounded by –MCID and +MCID (-7.2 and +7.2 on the 0-24 point scale used). The two trials[118, 120] not included in the meta-analysis did not report treatment effect magnitudes, but both favored nasal antihistamine. If these trials were included in the meta-analysis, the pooled effect would decrease. Because these trials represented only 7 percent of patients reporting this outcome, it is unlikely that the 95 percent confidence interval would include the MCID. The body of evidence in support of a conclusion of equivalence of intranasal corticosteroid and nasal antihistamine for this outcome is therefore considered precise. The overall strength of evidence for this conclusion is rated as high.

Individual nasal symptoms of congestion, rhinorrhea, and sneezing were assessed at 3 weeks and 4 weeks in one trial[116] (N=50). For congestion, a treatment effect of 0.5 on a 0-3 point scale (17 percent of maximum score) favored nasal antihistamine at both 3 weeks and 4 weeks. For rhinorrhea and sneezing, treatment differences were zero at both 3 weeks and 4 weeks. Statistical significance was not reported for any outcome. This trial was rated poor quality due to noncomparable groups at baseline, inadequate blinding, and inappropriate analysis of results (unadjusted for baseline group differences). Consistency could not be assessed in a single trial, and no observed result at any assessment period exceeded an MCID of 0.9, representing 30

percent of maximum score. The evidence was therefore insufficient to support the use of one treatment over the other for these outcomes.

At 3, 4 and 5 weeks, one trial[120] (N=30) reported improvement in TNSS with nasal antihistamine. Treatment effects ranged from 1.0 to 1.4 on a 0-12 point scale (from 8 percent to 12 percent of maximum score) and were statistically nonsignificant. This trial was rated poor quality due to noncomparable groups at baseline and inappropriate analysis of results (unadjusted for baseline group differences). Risk of bias is therefore high. Consistency could not be assessed in a single trial, and no observed result at any assessment period exceeded an MCID of 4, representing 30 percent of maximum score. The evidence was therefore insufficient to support the use of one treatment over the other for this outcome.

Eye Symptoms

Five[115, 117, 118] of nine trials (N=2128 of 2473 patients) assessed eye symptoms at 2 weeks. Four[115, 117] were rated good quality (94 percent of patients reporting this outcome). Treatment effects in these trials favored nasal antihistamine and ranged from 0.2 to 0.45 on a 0-18 point scale (from 1 percent to 3 percent of maximum score). A meta-analysis of three[115] of these trials (N=1697; 80 percent of patients reporting this outcome) yielded a statistically nonsignificant pooled effect estimate of 0.22 on a 0-18 point scale (95 percent CI: -0.12 to 0.57) favoring nasal antihistamine (Figure 15). The larger bound of the 95 percent CI represented 3 percent of maximum score. Statistical heterogeneity was low (I^2=0 percent, p=0.97). The fourth good quality trial[117] (n=305; 14 percent of patients reporting this outcome) showed a treatment effect of 0.45 on a 0-18 point scale (11 percent of maximum score). The fifth trial[118] (n=130; 7 percent of patients reporting this outcome) showed a statistically nonsignificant treatment effect of 0.6 on a 0-9 point scale (7 percent of maximum score) favoring intranasal corticosteroid. This trial was rated poor quality due to inadequate blinding.

For the outcome of eye symptoms, the risk of bias was rated as low. Ninety-four percent of patients were in good quality trials. Treatment effects consistently favored nasal antihistamine in 94 percent of patients reporting this outcome, and statistical heterogeneity of a meta-analysis of 80 percent of patients was low. The 95 percent CI for the pooled estimate (-0.12 to 0.57) fell within an interval bounded by –MCID and +MCID (-5.4 and +5.4 on the 0-18 point scale used). Of two trials[117, 118] not included in the meta-analysis, one[118] reported a treatment effect of 0.06 on a 0-9 point scale (0.12 on a 0-18 point scale) favoring intranasal corticosteroid. If this trial were included in the meta-analysis, the pooled effect estimate (0.22 favoring nasal antihistamine) would decrease. Because this trial represented 7 percent of patients reporting this outcome, it is unlikely that the 95 percent CI of the pooled effect would include the MCID of 5.4. The other trial[117] (14 percent of patients reporting this outcome) showed a treatment effect of 0.45 on a 0-18 point scale favoring nasal antihistamine. If this trial were included in the meta-analysis, the pooled effect estimate would increase, but it is unlikely that the 95 percent CI would include the MCID. The body of evidence to support a conclusion of equivalence of intranasal corticosteroid and nasal antihistamine for this outcome was therefore considered precise. The overall strength of evidence supporting this conclusion is rated as high.

Quality of Life

Two trials[117, 121] (N=404; 16 percent of the total patient sample for this comparison) assessed quality of life using the RQLQ instrument. Both were good quality trials, and both observed statistically nonsignificant treatment effects in favor of intranasal corticosteroid (0.26 for both).

For RQLQ at 2 weeks, the risk of bias is rated as low based in the good quality of the trials. Results consistently favored intranasal corticosteroid, but neither exceeded the MCID of 0.5 points. Evidence was therefore insufficient to support the use of one treatment over the other for this outcome.

A meta-analysis of 2-week RQLQ outcomes from three good quality trials[115] (N=1693) yielded a pooled effect estimate of 0.1 favoring intranasal corticosteroid. This result is consistent with the treatment effects reported in two trials[117, 121] described above. Because the published meta-analysis lacked details about the how the analysis was conducted, this result could not be replicated and was not included in the formal evidence assessment.

Table 31. Treatment effects: nasal symptoms–intranasal corticosteroid versus nasal antihistamine

Outcome[a]	Variance	SS Favors Nasal AH MD	NSS Favors/NR Nasal AH MD	Favors Neither MD=0	NSS Favors/NR INCS MD	SS Favors INCS MD
2-Week Outcomes						
Congestion						
Carr, 2012 (Trial 1)[115] (scale 0-6)	SD				0.3 (NR)	
Carr, 2012 (Trial 2)[115] (scale 0-6)	SD				0.1 (NR)	
Carr, 2012 (Trial 3)[115] (scale 0-6)	SD				0.1 (NR)	
Ghimire, 2007[116] (scale 0-3)					0.7 (NR)	
Hampel, 2010[117] (scale 0-6)					0.11 (NR)	
Kaliner, 2009[118] (scale 0-3)					[a] (NSS)	
Newson-Smith, 1997[119] (scale 0-3)					0.5 (NSS)	
Ratner, 2008[121] (scale 0-6)	SD			0		
Rhinorrhea						
Carr, 2012 (Trial 1)[115] (scale 0-6)	SD				0.2 (NR)	
Carr, 2012 (Trial 2)[115] (scale 0-6)	SD				0.3 (NR)	
Carr, 2012 (Trial 3)[115] (scale 0-6)	SD				0.1 (NR)	
Ghimire, 2007[116] (scale 0-3)				0		
Hampel, 2010[117] (scale 0-6)					0.28 (NR)	
Kaliner, 2009[118] (scale 0-3)					[a] (NSS)	
Newson-Smith, 1997[119] (scale 0-3)					0.4 (NSS)	
Ratner, 2008[121] (scale 0-6)	SD				0.2 (NR)	
Sneezing						
Carr, 2012 (Trial 1)[115] (scale 0-6)	SD				0.2 (NR)	
Carr, 2012 (Trial 2)[115] (scale 0-6)	SD				0.1 (NR)	
Carr, 2012 (Trial 3)[115] (scale 0-6)	SD				0.1 (NR)	
Ghimire, 2007[116] (scale 0-3)					0.1 (NR)	
Hampel, 2010[117] (scale 0-6)					0.12 (NR)	
Kaliner, 2009[118] (scale 0-3)			[a] (NSS)			
Newson-Smith, 1997[119] (scale 0-3)					0.4 (NSS)	
Ratner, 2008[121] (scale 0-6)	SD			0		
Nasal itch						
Carr, 2012 (Trial 1)[115] (scale 0-6)	SD				0.4 (NR)	
Carr, 2012 (Trial 2)[115] (scale 0-6)	SD				0.1 (NR)	
Carr, 2012 (Trial 3)[115] (scale 0-6)	SD				0.1 (NR)	
Hampel, 2010[117] (scale 0-6)					0.09 (NR)	
Kaliner, 2009[118] (scale 0-3)					[a] (NSS)	
Newson-Smith, 1997[119] (scale 0-3)					0.4 (NSS)	
Ratner, 2008[121] (scale 0-6)	SD				0.2 (NR)	

Outcome[a]	Variance	SS Favors Nasal AH MD	NSS Favors/NR Nasal AH MD	Favors Neither MD=0	NSS Favors/NR INCS MD	SS Favors INCS MD
TNSS						
Carr, 2012 (Trial 1)[115] (scale 0-24)	SD				0.9 (NR)	
Carr, 2012 (Trial 2)[115] (scale 0-24)	SD				0.6 (NR)	
Carr, 2012 (Trial 3)[115] (scale 0-24)	SD				0.6 (NR)	
Hampel, 2010[117] (scale 0-24)	SD				0.59 (NR)	
Kaliner, 2009[118] (scale 0-12)			[a] (NSS)			
Pelucchi, 1995[120] (scale 0-12)			[b] (NSS)			
Ratner, 2008[121] (scale 0-24)	SD				0.4 (NR)	
3-Week Outcomes						
Congestion						
Ghimire, 2007[116] (scale 0-3)			0.5 (NR)			
Rhinorrhea						
Ghimire, 2007[116] (scale 0-3)				0		
Sneezing						
Ghimire, 2007[116] (scale 0-3)				0		
TNSS						
Pelucchi, 1995[120] (scale 0-12)			1.1 (NSS)			
4-Week Outcomes						
Congestion						
Ghimire, 2007[116] (scale 0-3)			0.5 (NR)			
Rhinorrhea						
Ghimire, 2007[116] (scale 0-3)				0		
Sneezing						
Ghimire, 2007[116] (scale 0-3)				0		
TNSS						
Pelucchi, 1995[120] (scale 0-12)			1.0 (NSS)			
5-Week Outcomes						
TNSS						
Pelucchi, 1995[120] (scale 0-12)			1.4 (NSS)			

AH = antihistamine; INCS = intranasal corticosteroid; MD = mean difference between group mean changes from baseline; NR = p-value not reported; NSS = not statistically significant; SS = statistically significant; TNSS = total nasal symptom score.

Variance/confidence interval reported: CI=confidence interval; SD=standard deviation; SE=standard error.

[a] Mean difference could not be calculated from reference.

[b] Only p-values provided.

Figure 10. Congestion at 2 weeks: meta-analysis of 4 trials–intranasal corticosteroid versus nasal antihistamine

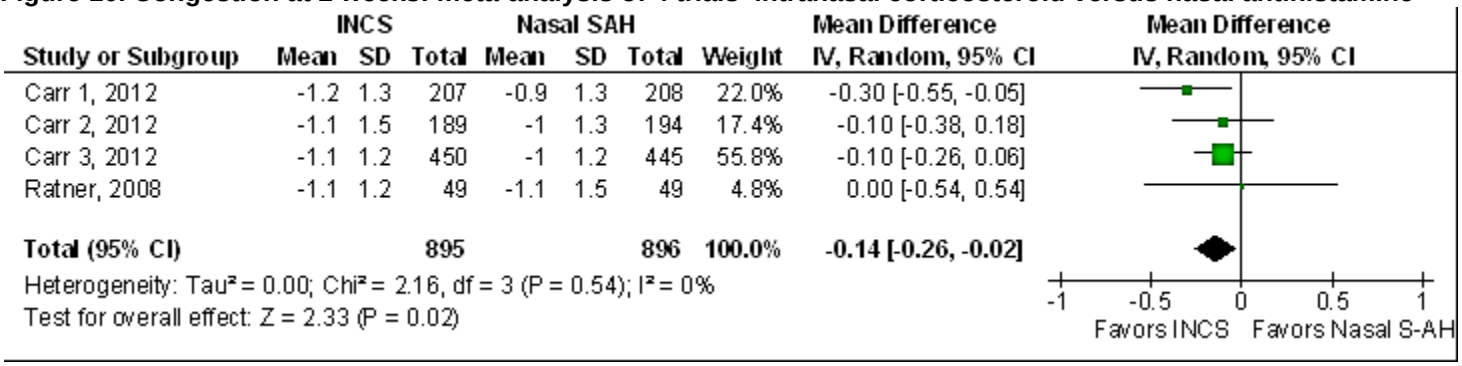


Figure 11. Rhinorrhea at 2 weeks: meta-analysis of 4 trials–intranasal corticosteroid versus nasal antihistamine

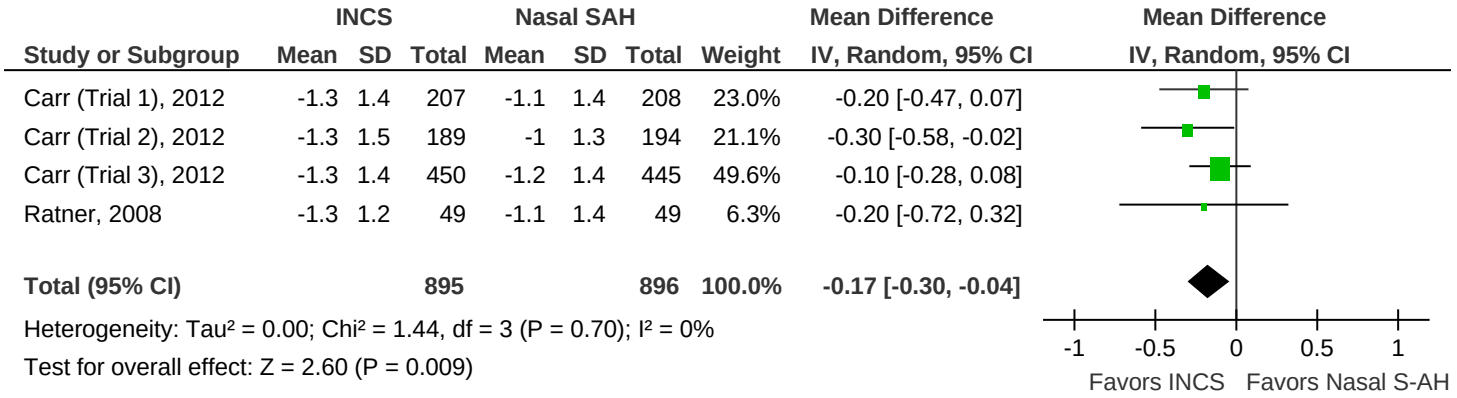


Figure 12. Sneezing at 2 weeks: meta-analysis of 4 trials–intranasal corticosteroid versus nasal antihistamine

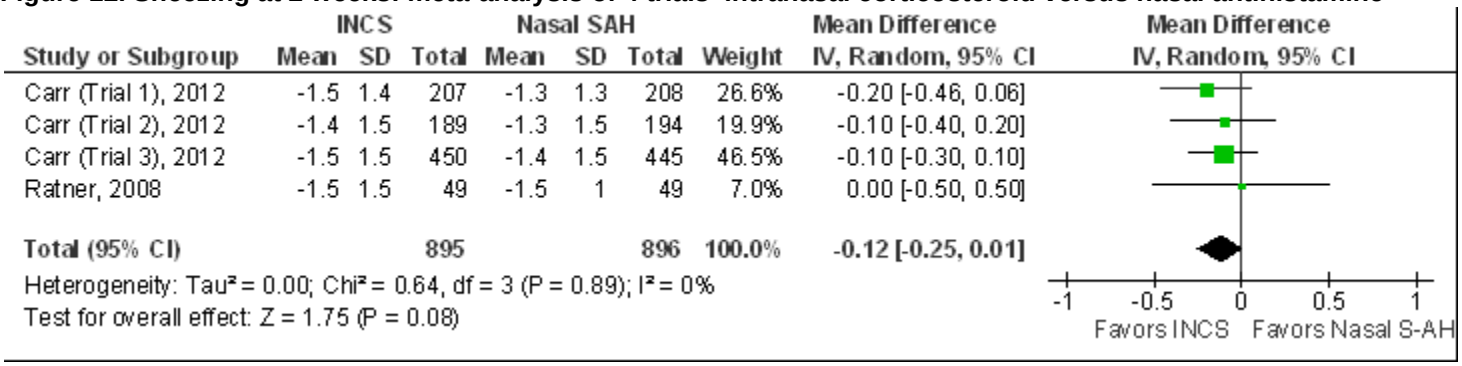


Figure 13. Nasal itch at 2 weeks: meta-analysis of 4 trials–intranasal corticosteroid versus nasal antihistamine

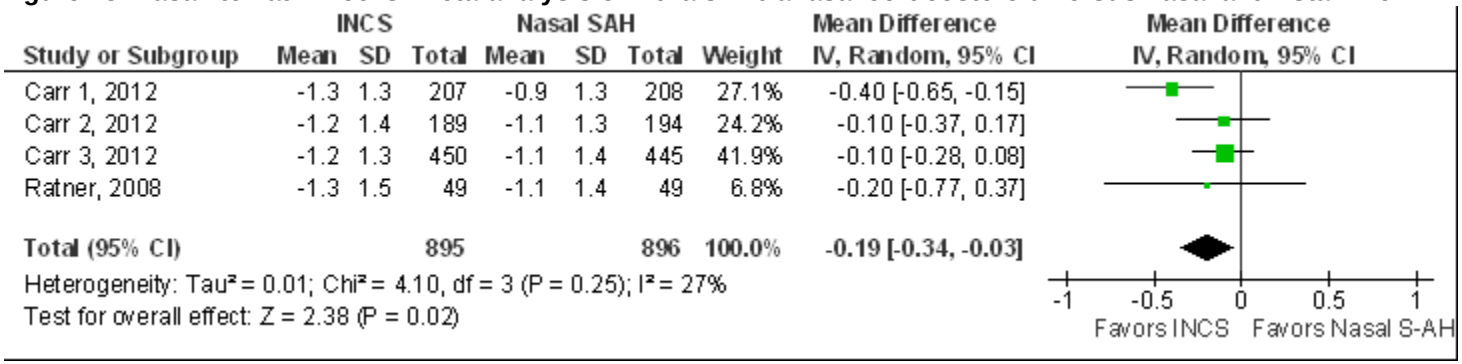


Figure 14. Total nasal symptom score at 2 weeks: meta-analysis of 5 trials–intranasal corticosteroid versus nasal antihistamine

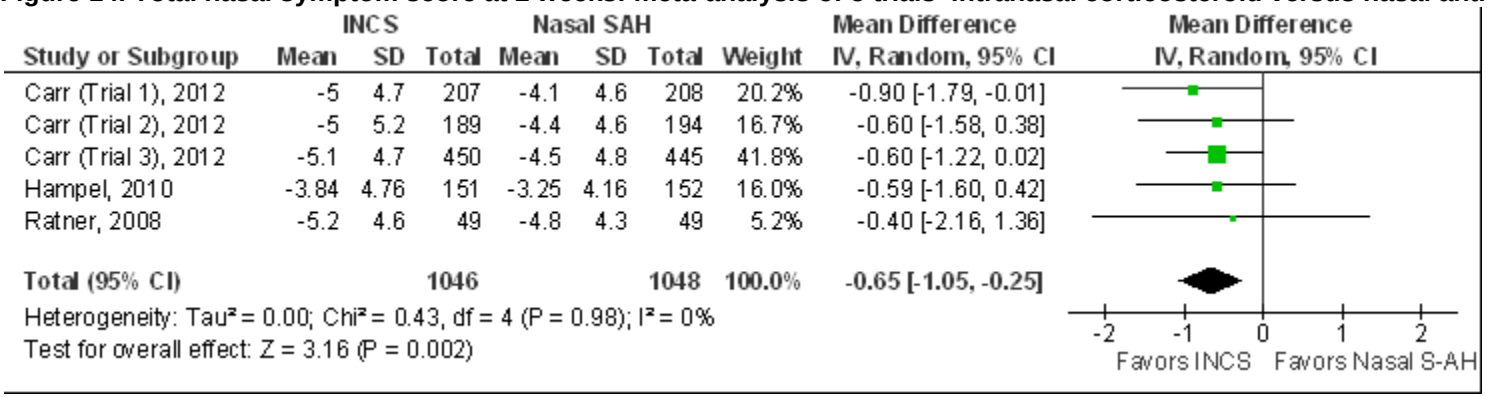


Table 32. Treatment effects: eye symptoms–intranasal corticosteroid versus nasal antihistamine

Outcome	Variance	SS Favors Nasal AH MD	NSS Favors/NR Nasal AH MD	Favors Neither MD=0	NSS Favors/NR INCS MD	SS Favors INCS MD
2-week TOSS						
Carr, 2012, (Trial 1)[115] (scale 0-18)	SD		0.2 (NR)			
Carr, 2012, (Trial 2)[115] (scale 0-18)	SD		0.3 (NR)			
Carr, 2012, (Trial 3)[115] (scale 0-18)	SD		0.2 (NR)			
Hampel, 2010[117] (scale 0-18)			0.45 (NR)			
Kaliner, 2009[118] (scale 0-9)					0.06 (NSS)	

AH = antihistamine; INCS = intranasal corticosteroid; MD = mean difference between group mean changes from baseline; NR = p-value not reported; NSS = not statistically significant; S-AH = selective antihistamine; SS = statistically significant; TOSS = total ocular symptom score.

Variance/confidence interval reported: CI = confidence interval; SD = standard deviation; SE = standard error. TOSS is the sum of scores for 3 ocular symptoms (itching, tearing, and redness).

Figure 15. Total ocular symptom score at 2 weeks: meta-analysis of 4 trials–intranasal corticosteroid versus nasal antihistamine

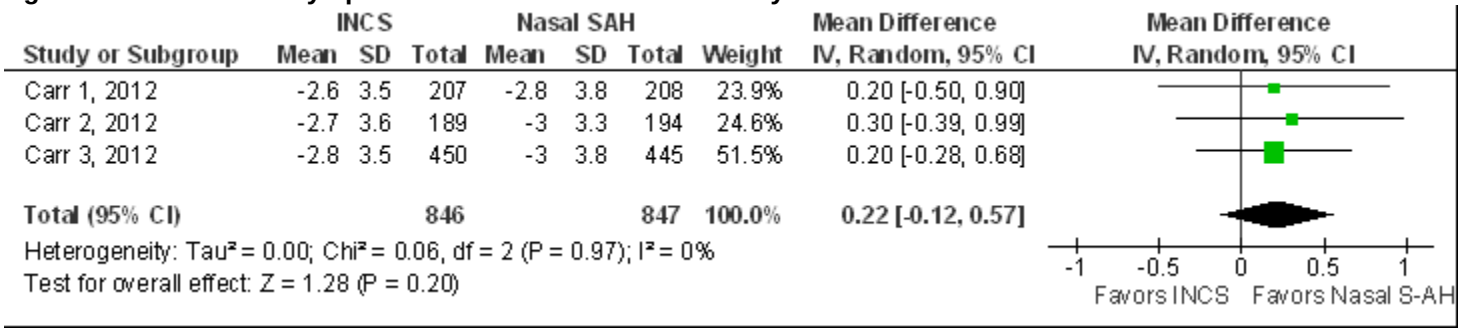


Table 33. Treatment effects: quality of life outcomes–intranasal corticosteroid versus nasal antihistamine

Outcome	Variance	SS Favors Nasal AH MD	NSS Favors/NR Nasal AH MD	Favors Neither MD=0	NSS Favors/NR INCS MD	SS Favors INCS MD
2-week RQLQ						
Hampel, 2010[117]					0.26 (NR)	
Ratner, 2008[121]	SD				0.26 (NR)	
Carr, 2012[115]					0.1[a] (NR)	

AH = antihistamine; INCS = intranasal corticosteroid; MD = mean difference between group mean changes from baseline; NR = p-value not reported; NSS = not statistically significant; RQLQ = Rhinoconjunctivitis Quality of Life Questionnaire; S-AH = selective antihistamine; SS = statistically significant.

Variance/confidence interval reported: CI = confidence interval; SD = standard deviation; SE = standard error.

[a] Meta-analysis estimate of Carr, 2012 trials 1, 2 and 3.

Intranasal Corticosteroid Versus Nasal Cromolyn

Description of Included Studies

Four[122-125] RCTs published between 1985 and 2005 were identified (N=434 patients randomized to treatment groups of interest). Two trials[122, 123] were double-blinded, one[124] was open-label, and one had inadequate patient blinding. [125] Three trials[122-124] were conducted in Europe. Two[122, 124] of these were single center trials, and one[123] was a multicenter trial. One trial[125] conducted in North America did not report if it was a single center or multicenter trial. Trials were 3, 4, 6 and 8 weeks in duration.[122-125] Cromolyn (disodium cromoglycate) was compared with budesonide,[122] mometasone,[124] and fluticasone propionate[123] in three separate trials, and to both flunisolide and beclomethasone in one trial.[125] Three trials[122, 124, 125] were industry funded and one did not identify its funding source.[123]

Trial participants tended to be young adults with mean ages ranging from 29 to 36 years. Most were men (approximately 55 percent). No trial reported on race. All trials required a minimum duration of SAR history, but none reported the mean duration of SAR symptoms. One trial[124] required a minimum baseline severity of SAR symptoms. In the one trial[122] that reported baseline TNSS, symptom severity was mild.

In three trials[122-124] that assessed nasal symptoms, 4-point rating scales (from 0=no symptom to 3=severe symptom) were used. For two trials,[122, 123] the identified outcome of interest was the mean change from baseline symptom scores. In Lange (2005),[124] the outcome of interest was the difference between post-treatment scores at 4 weeks. Lange (2005)[124] also reported mean post-treatment eye symptom scores but did not define which eye symptoms were assessed and reported only the statistical significance of treatment effects, not their magnitude. Eye symptom outcomes therefore are not reviewed here. Two trials[124, 125] reported quality of life outcomes at 4 weeks[124] and 8 weeks[125] using PGA of treatment efficacy. Results are noted in the text.

All four trials[122-125] were rated poor quality. Reasons included noncomparable groups at baseline,[122, 123] lack of blinding,[124, 125] and inappropriate analysis of results (unadjusted for baseline group differences[123]).

Key Points

These results are summarized in Table 34.

- Individual nasal symptoms and TNSS at 2 weeks: Evidence was insufficient to support the use of one treatment over the other based on one trial[122] with high risk of bias and imprecise results.
- Individual nasal symptoms (rhinorrhea, sneezing, and nasal itch) at 3-6 weeks: Evidence was insufficient to support the use of one treatment over the other based on three trials[122-124] with high risk of bias and consistent but imprecise results.
- TNSS at 3-4 weeks: Evidence was insufficient to support the use of one treatment over the other based on two trials[122, 124] with high risk of bias and consistent but imprecise results.
- These results are based on trials of five of eight intranasal corticosteroids (62.5 percent) in comparison with nasal cromolyn.

Table 34. Strength of evidence: intranasal corticosteroid versus nasal cromolyn

Outcome	RCTs (Patients)	Risk of Bias	Consistency	Directness	Precision	Overall GRADE
2-week nasal symptoms (congestion, rhinorrhea, sneezing, nasal itch, TNSS)	1[122] (43)	High	Consistency unknown (single study)	Direct	Imprecise	Insufficient
3-6 week congestion, rhinorrhea, sneezing, nasal itch	3[122-124] (344)	High	Consistent	Direct	Imprecise	Insufficient
3-4 week TNSS	2[122, 124] (128)	High	Consistent	Direct	Imprecise	Insufficient

GRADE = Grading of Recommendations Assessment, Development and Evaluation; RCTs (Patients) = number of randomized controlled trials (number of patients randomized to treatment groups of interest); TNSS = total nasal symptom score.

Synthesis and Strength of Evidence

Nasal symptom outcomes discussed below are summarized in Table 35. Meta-analysis was not considered for this treatment comparison due to lack of variance estimates for group-level treatment effects.

Nasal Symptoms

One[122] of three trials that assessed nasal symptoms reported outcomes (congestion, rhinorrhea, sneezing, nasal itch, and TNSS) at 2 weeks (N=43). The trial was rated poor quality due to noncomparable groups at baseline. Statistically significant treatment effects favoring intranasal corticosteroid were reported for four nasal symptoms and for TNSS. For individual symptoms, treatment effects ranged from 0.21 for nasal itch to 0.59 for rhinorrhea on a 0-3 point scale (from 7 percent to 20 percent of maximum score). For TNSS, the treatment effect was 1.53 on a 0-12 point scale (13 percent of maximum score).

For nasal symptoms at 2 weeks, the risk of bias was considered high because the trial[122] was small and of poor quality. Consistency cannot be assessed for a single trial. Effect estimates were imprecise because none exceeded an MCID of 30 percent maximum score. Evidence was insufficient to support the use of one treatment over the other for these outcomes.

Three trials (total N=344) assessed nasal symptoms beyond 2 weeks: Bjerrum (1985)[122] at 3 weeks, Lange (2005)[124] at 4 weeks, and Bousquet (1993)[123] at 6 weeks. Trial quality ratings were poor due to noncomparable groups at baseline,[122, 123] lack of blinding,[124] and inappropriate analysis of results (unadjusted for baseline group differences[123]).

At 3 weeks,[122] statistically significant treatment effects were shown for rhinorrhea, sneeze, nasal itch, and TNSS. All favored intranasal corticosteroid. Treatment effect magnitudes were comparable to those seen at 2 weeks[122] and ranged from 0.15 for nasal itch to 0.49 for rhinorrhea on a 0-3 point scale (from 5 percent to 16 percent of maximum score). The treatment effect for TNSS was 1.19 on a 12-point scale (10 percent of maximum score). Nasal congestion was the only symptom for which a statistically nonsignificant treatment effect was reported (0.28 on a 0-3 point scale [9 percent of maximum score]).

At 4 weeks[124] and 6 weeks[123], statistically significant treatment effects favoring intranasal corticosteroid were reported for four individual nasal symptoms. At 4 weeks,[124] there was a statistically significant treatment effect favoring intranasal corticosteroid for TNSS. TNSS was not assessed at 6 weeks. Magnitude of effects at 4 and 6 weeks were not reported.

For nasal symptoms at 3 to 6 weeks, the risk of bias was considered high. All three trials were rated poor quality. Treatment effects consistently favored intranasal corticosteroid. Most treatment effects were not reported. None of the reported treatment effects exceeded an MCID of 30 percent maximum score. The body of evidence was therefore imprecise, and evidence to support the use of one treatment over the other for these outcomes is insufficient.

Two trials reported PGA of treatment efficacy at 4 weeks[124] and 8 weeks[125] (N=173). Both trials were rated poor quality due to lack of blinding[124, 125] and lack of maintenance of comparable groups.[125] Both reported statistically significant results favoring intranasal corticosteroid.

Table 35. Treatment effects: nasal symptoms–intranasal corticosteroid versus nasal cromolyn

Outcome	Variance	SS Favors INCS MD	NSS Favors/NR INCS MD	Favors Neither MD=0	NSS Favors/NR Nasal C MD	SS Favors Nasal C MD
2-Week Outcomes						
Congestion						
Bjerrum, 1985[122] (scale 0-3)		0.35				
Rhinorrhea						
Bjerrum, 1985[122] (scale 0-3)		0.59				
Sneezing						
Bjerrum, 1985[122] (scale 0-3)		0.38				
Itching						
Bjerrum, 1985[122] (scale 0-3)		0.21				
TNSS						
Bjerrum, 1985[122] (scale 0-12)		1.53				
3- to 6-Week Outcomes						
Congestion						
Bjerrum, 1985[122] (scale 0-3)			0.28 (NSS)			
Bousquet, 1993[123]		[a]				
Lange, 2005[124]		[ab]				
Rhinorrhea						
Bjerrum, 1985[122] (scale 0-3)		0.49				
Bousquet, 1993[123]		[a]				
Lange, 2005[124]		[ab]				
Sneezing						
Bjerrum, 1985[122] (scale 0-3)		0.27				
Bousquet, 1993[123]		[a]				
Lange, 2005[124]		[ab]				
Itching						

Outcome	Variance	SS Favors INCS MD	NSS Favors/NR INCS MD	Favors Neither MD=0	NSS Favors/NR Nasal C MD	SS Favors Nasal C MD
Bjerrum, 1985[122] (scale 0-3)		0.15				
Bousquet, 1993[123]		[a]				
Lange, 2005[124]		[a,b]				
TNSS						
Bjerrum, 1985[122] (scale 0-12)		1.19				
Lange, 2005[124]		[a,b]				

C = cromolyn; INCS = intranasal corticosteroid; MD = mean difference between group mean changes from baseline; NR = p-value not reported; NSS = not statistically significant; SS = statistically significant; TNSS = total nasal symptom score.

[a] P-values only reported.

[b] Comparisons are between final outcome scores, not change in scores.

Intranasal Corticosteroid Versus Oral Leukotriene Receptor Antagonist (Montelukast)

Description of Included Studies

Five[97, 126-129] double-blinded, RCTs published between 2002 and 2009 were identified (N=2328 patients randomized to comparator groups of interest). All but one trial[128] was a multicenter trial conducted in North America. Trial durations were 2 to 8 weeks. One small trial[128] included 29 patients, and the others included 285 to 736 patients. The oral leukotriene receptor antagonist, montelukast, was compared to fluticasone propionate in four trials[126-129] and to beclomethasone in one trial[97]. All five trials were industry funded.

Mean ages of trial participants ranged from 28 to 40 years. Approximately 60 percent of patients were women. In one trial,[128] 40 percent were women. In two trials[97, 127] that reported on race, most patients were white (approximately 78 percent). In three trials, [97, 126, 129] patients reported SAR symptoms for an average of at least 15 years. Baseline symptom scores for the trials represented a range of severity, with patients reporting mild,[128] moderate,[97, 127] and severe[126, 129] baseline symptoms. All five trials included patients with asthma. One trial[127] included asthma outcomes and considered prior asthma treatment as a baseline characteristic in the analysis model.

All five trials assessed nasal symptoms. One trial[127] assessed asthma outcomes. No trial assessed eye symptoms. All five trials included 2-week symptom assessments. One trial[127] reported 4-week data, and one trial[128] reported 6 to 8-week data. Nasal symptoms were assessed using several scales. In three trials,[126, 127, 129] patients used a VAS to rate each nasal symptom (congestion, rhinorrhea, sneezing, and itch) on a scale of zero to 100. Scores were summed to yield a maximum TNSS of 400. In Pullerits (2002),[128] patients rated each nasal symptom on a 5-point (0 to 4) scale, and scores were summed to create the TNSS (16-points maximum). Individual symptom scores were not reported. In Lu (2009),[97] patients rated each nasal symptom on a 4-point (0 to 3) scale, and scores were averaged to create the TNSS (3-points maximum). Individual symptoms were not reported. To calculate the mean change from baseline, most trials subtracted baseline scores from scores averaged over the entire treatment duration. One trial[128] averaged data for intervals (weeks 1 and 2, weeks 3 to 5, weeks 6 to 8) and compared the mean change during each interval to baseline. For asthma outcomes, symptom-free days, morning and evening peak expiratory flow (PEF), and albuterol-free days were assessed. Symptoms were self-evaluated using a 0-5 point Likert scale. Morning and evening peak expiratory flow were self-measured (average of three readings) with flow meters provided to patients. Albuterol use and number of nighttime awakenings due to asthma were recorded in diaries.

Three trials[126, 127, 129] were rated good quality, and two[97, 128] were rated poor.

Key Points

The results below are summarized in Table 36.

- Individual nasal symptoms (congestion, rhinorrhea, sneezing, and nasal itch) at 2 weeks: High strength evidence for equivalence of intranasal corticosteroid and oral leukotriene receptor antagonist based on three trials 126, 127, 129 with low risk of bias and consistent, precise results.

- TNSS at 2 weeks: High strength evidence for equivalence of intranasal corticosteroid and oral leukotriene receptor antagonist based on five trials 97, 126-129 with low risk of bias and consistent, precise results.
- Individual nasal symptoms (congestion, rhinorrhea, sneezing, and nasal itch) and asthma outcomes (symptom-free days, albuterol-free days, morning and evening PEF, and asthma exacerbations) at 4 weeks: Evidence was insufficient to support one treatment over the other based on one trial 127 with low risk of bias and imprecise results.
- TNSS at 3 to 8 weeks: Evidence was insufficient to support one treatment over the other based on two trials 127, 128 with low risk of bias and consistent but imprecise results.
- These results are based on trials using two of eight intranasal corticosteroids (25 percent) in comparison with montelukast (100 percent).

Table 36. Strength of evidence: intranasal corticosteroid versus oral leukotriene receptor antagonist

Outcome	RCTs (Patients)	Risk of Bias	Consistency	Directness	Precision	Overall GRADE
2-week congestion, rhinorrhea, sneezing, nasal itch	3[126, 127, 129] (2014)	Low	Consistent	Direct	Precise	High[b]
2-week TNSS	5[97, 126-129] (2445)	Low	Consistent	Direct	Precise	High[b]
4-week congestion, rhinorrhea, sneezing, nasal itch	1[127](573)	Low	Consistency unknown (single study)	Direct	Imprecise	Insufficient
4-week asthma outcomes[a]	1[127](573)	Low	Consistency unknown (single study)	Direct	Imprecise	Insufficient
3-8 week TNSS	2[127, 128] (602)	Low	Consistent	Direct	Imprecise	Insufficient

GRADE = Grading of Recommendations Assessment, Development and Evaluation; RCTs (Patients) = number of randomized controlled trials (number of patients randomized to treatment groups of interest); TNSS = total nasal symptom score.

[a] Symptom-free days, albuterol-free days, morning and evening peak expiratory flow (PEF), and asthma exacerbations.

[b] The body of evidence supports equivalence of intranasal corticosteroid and oral leukotriene receptor antagonist for the outcomes identified.

Synthesis and Strength of Evidence

Nasal symptom outcomes discussed below are summarized in Table 37. Asthma outcomes are summarized in Table 38.

As shown in Table 37, variance estimates of treatment effects were provided for nasal outcomes at 2 weeks. For these outcomes, meta-analyses were conducted. For TNSS, the analysis required use of standardized mean differences (rather than mean differences) because different rating scales were used across trials. For individual nasal symptoms, all trials used the same rating scale. The meta-analyses therefore used mean differences.

Nasal Symptoms

Three[126, 127, 129] of five trials (2014 of 2328 patients, 87 percent) assessed individual nasal symptoms (congestion, rhinorrhea, sneezing, and nasal itch) at 2 weeks. All three trials were rated good quality. For each symptom, the treatment effect favored intranasal corticosteroid over oral leukotriene receptor antagonist and was statistically significant. Meta-analyses of the three trials for each symptom favored intranasal corticosteroid with statistically significant treatment effects ranging from 7.9 to 8.7 on a 100 VAS (Figure 16 through Figure 19). The larger bound of the 95 percent CIs ranged from 10.08 to 10.76 on a 100-point VAS (from 10 percent to 11 percent of maximum score, respectively). Statistical heterogeneity was low (I^2=0 percent for all four analyses, p=0.33 to 0.88).

For individual nasal symptoms at 2 weeks, the risk of bias was rated as low. All three trials were good quality. Treatment effects consistently favored intranasal corticosteroid in all three trials. The 95 percent CIs for the pooled estimates fell within an interval bounded by –MCID and +MCID (-30 and +30 on the 100-point VAS used). The body of evidence to support a conclusion of equivalence of intranasal corticosteroid and oral leukotriene receptor antagonist for each of these outcomes is therefore precise. The strength of evidence supporting these conclusions is high.

All five trials assessed TNSS at 2 weeks (N=2038). Three good quality trials[126, 127, 129] of 2014 patients represented 87 percent of patients reporting this outcome. Thirteen percent of patients were in two trials[97, 128] that were rated poor quality due to inappropriate analysis of results (not intention to treat). Treatment effects favored intranasal corticosteroid over oral leukotriene receptor antagonist and were statistically significant in all but one trial.[128] All three good quality trials[126, 127, 129] assessed TNSS using a 0-400 point VAS. Treatment effects were 33.6 (95 percent CI: 20.6 to 46.5);[126] 26.1 (95 percent CI: 9.7 to 42.5);[127] and 34.4 (95 percent CI: 23.4 to 49.3)[129] The larger bounds of the 95 percent CIs were 12 percent, 11 percent and 12 percent of maximum score, respectively. Of two poor quality trials reporting on this outcome using an interval rating scale, one[128] (n=29) reported a statistically nonsignificant effect of 0.8 on a 0-16 point scale (5 percent of maximum score), and the other (Trial 1 in Lu [2009];[97] n=285) reported a statistically significant effect of 0.34 on a 0-3 point scale (11 percent of maximum score).

A meta-analysis of four trials[97, 126, 127, 129] was performed. The fifth trial[128] was excluded due to lack of a variance estimate for the treatment effect. The meta-analysis yielded a statistically significant pooled effect (standardized mean difference) of 0.40 (95 percent CI: 0.27 to 0.52) favoring intranasal corticosteroid (Figure 20). Effect estimates in the pooled trials were in the same direction, and their 95 percent CIs did not touch the “no effect” line.

For TNSS at 2 weeks, the risk of bias was rated as low. Eighty-seven percent of patients were in good quality trials. Treatment effects consistently favored intranasal corticosteroid for all patients reporting this outcome. Ninety-five percent CIs of pooled treatment effects fell within an interval bounded by –MCID and +MCID (-120 and +120[126, 127, 129] or -1.8 and +1.8[97]). These effects were therefore considered precise. The one trial[128] excluded from the meta-analysis did not alter the precision assessment because this trial represented 1 percent of patients reporting this outcome. The body of evidence supporting a conclusion of equivalence of intranasal corticosteroid and leukotriene receptor antagonist for this outcome is therefore considered precise. The overall strength of evidence for this conclusion is rated as high.

One good quality trial[127] (N=573) assessed four individual nasal symptoms (congestion, rhinorrhea, sneezing, and nasal itch) at 4 weeks. All comparisons favored intranasal corticosteroid and were statistically significant. Using a 100-point VAS, treatment effects ranged from 6.0 for nasal itch to 8.3 for congestion (from 6 percent to 8 percent of maximum score).

The risk of bias for this outcome was rated as low based on the good quality of the trial reporting. Consistency cannot be addressed for a single trial. Results were imprecise because none exceeded an MCID of 30 percent maximum score. Evidence was therefore insufficient to support the use of one treatment over the other for this outcome.

Two trials[127, 128] assessed TNSS at time points beyond 2 weeks (N=602). One[127] was a good quality trial in 573 patients (95 percent of patients reporting this outcome) that reported 4-week outcomes. A statistically significant treatment effect of 28 points on a 0-400 scale (7 percent of maximum score) favored intranasal corticosteroid. The other was a poor quality trial[128] that reported outcomes (mean results during the previous 2 weeks) at 5 and 8 weeks. At 5 weeks, a statistically nonsignificant treatment effect of 1.4 on a 0-16 point scale (9 percent of maximum score) favored intranasal corticosteroid. At 8 weeks, a statistically significant treatment effect of 0.7 on a 0-16 point scale (4 percent of maximum score) favored intranasal corticosteroid.

The risk of bias for these outcomes was rated as low. Ninety-five percent of patients were in the good quality trial.[127] Treatment effects consistently favored intranasal corticosteroid, but none exceeded an MCID of 30 percent maximum score. The body of evidence for these outcomes was therefore imprecise. Evidence was insufficient to support the use of one treatment over the other for this outcome.

Asthma Symptoms

One good quality trial[127](N=573) assessed symptoms and objective measures of asthma over 4 weeks of treatment. There were no statistically significant differences between treatment groups in any outcome, nor were there differences when treatment groups were stratified by baseline asthma severity. For all outcomes, the risk of bias was rated as low, and consistency could not be assessed with a single trial.

Treatment effects favoring oral leukotriene receptor antagonist were:

- Proportion of symptom-free days: 1.3 percent difference between groups
- Proportion of albuterol-free days: 0.7 percent difference between groups

MCIDs for these outcomes have not been established. Because neither result was statistically significant, evidence was insufficient to support the use of one treatment over the other for these outcomes.

Treatment effects favoring intranasal corticosteroid were:

- Morning peak expiratory flow (PEF): 2.4 L/min
- Evening PEF: 1.8 L/min

- Proportion of patients experiencing an asthma exacerbation, defined as any asthma-related event that required treatment with asthma medications beyond study medications: less than 1 percent

For morning PEF, the treatment effect was less than an MCID of 25 L/min and therefore imprecise. For evening PEF, which has no well-defined MCID, the treatment effect was statistically nonsignificant and therefore imprecise. Evidence was insufficient to support the use of one treatment over the other for these outcomes.

For asthma exacerbations, any reduction in severe exacerbations may be considered clinically significant.[70, 135] Because the definition of "asthma exacerbation" used in this trial is broad, the severity of exacerbations observed is unclear. Further, the outcome measure reported patients rather than number of exacerbations; it is unclear whether exacerbations were in fact reduced. The effect is therefore considered imprecise and the evidence insufficient to support the use of one treatment over the other for this outcome.

Table 37. Treatment effects: nasal symptoms–intranasal corticosteroid versus oral leukotriene receptor antagonist

Outcome	Variance	SS Favors INCS MD	NSS Favors/NR INCS MD	Favors Neither MD=0	NSS Favors/NR LRA MD	SS Favors LRA MD
2 Weeks, Mean Change From Baseline						
Congestion						
Martin, 2006[126] (scale 0-100)	SE/CI	8.0 (4.7, 11.4)				
Nathan, 2005[127](scale 0-100)	SE	7.3				
Ratner, 2003[129] (scale 0-100)	SE/CI	8.6 (5.3, 11.9)				
Rhinorrhea						
Martin, 2006[126] (scale 0-100)	SE/CI	9.4 (6.0, 12.9)				
Nathan, 2005[127](scale 0-100)	SE	7.8				
Ratner, 2003[129] (scale 0-100)	SE/CI	8.2 (4.8, 11.7)				
Sneezing						
Martin, 2006[126] (scale 0-100)	SE/CI	8.7 (5.3, 12.0)				
Nathan, 2005[127](scale 0-100)	SE	6.3				
Ratner, 2003[129] (scale 0-100)	SE/CI	10.0 (6.6, 13.4)				
Itching						
Martin, 2006[126] (scale 0-100)	SE/CI	7.8 (4.3, 11.2)				
Nathan, 2005[127](scale 0-100)	SE	5.3				
Ratner, 2003[129] (scale 0-100)	SE/CI	9.5 (6.1, 12.8)				
TNSS						
Lu, 2009 (Trial 1)[97] (scale 0-3)	CI	0.34 (0.21, 0.47)				
Martin, 2006[126] (scale 0-400)	SE/CI	33.6 (20.6, 46.5)				
Nathan, 2005[127](scale 0-400)	SE	26.1 (9.7, 42.5)[a]				
Pullerits, 2002[128] (scale 0-16)			0.8 (NSS)			
Ratner, 2003[129] (scale 0-400)	SE/CI	34.4 (23.4, 49.3)				
4 Weeks, Mean Change From Baseline						
Congestion						

Outcome	Variance	SS Favors INCS MD	NSS Favors/NR INCS MD	Favors Neither MD=0	NSS Favors/NR LRA MD	SS Favors LRA MD
Nathan, 2005[127] (scale 0-100)	SE	8.3				
Rhinorrhea						
Nathan, 2005[127] (scale 0-100)	SE	8.0				
Sneezing						
Nathan, 2005[127] (scale 0-100)	SE	6.2				
Itching						
Nathan, 2005[127] (scale 0-100)	SE	6.0				
TNSS						
Nathan, 2005[127] (scale 0-400)	SE	27.9				
Average of Weeks 3-5, Change From Baseline						
TNSS						
Pullerits, 2002[128] (scale 0-16)	SE		1.4 (NSS)			
Average of Weeks 6-8, Change From Baseline						
TNSS						
Pullerits, 2002[128] (scale 0-16)	SE	0.7				

INCS = Intranasal corticosteroid; LRA = oral leukotriene receptor antagonist; MD = mean difference between group mean changes from baseline; NR = p-value not reported; NSS = not statistically significant; SS = statistically significant; TNSS = total nasal symptom score.

Variance/confidence interval reported: CI=confidence interval, SD=standard deviation, SE=standard error.

[a] 95% confidence interval calculated by report author using RevMan[59]

Figure 16. Congestion at 2 weeks: meta-analysis of 3 trials–intranasal corticosteroid versus oral leukotriene receptor antagonist

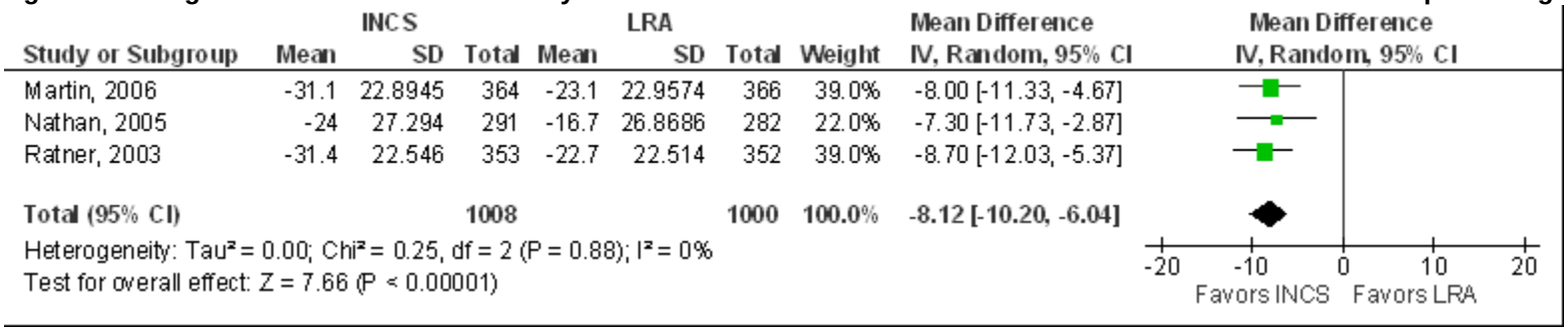


Figure 17. Rhinorrhea at 2 weeks: meta-analysis of 3 trials–intranasal corticosteroid versus oral leukotriene receptor antagonist

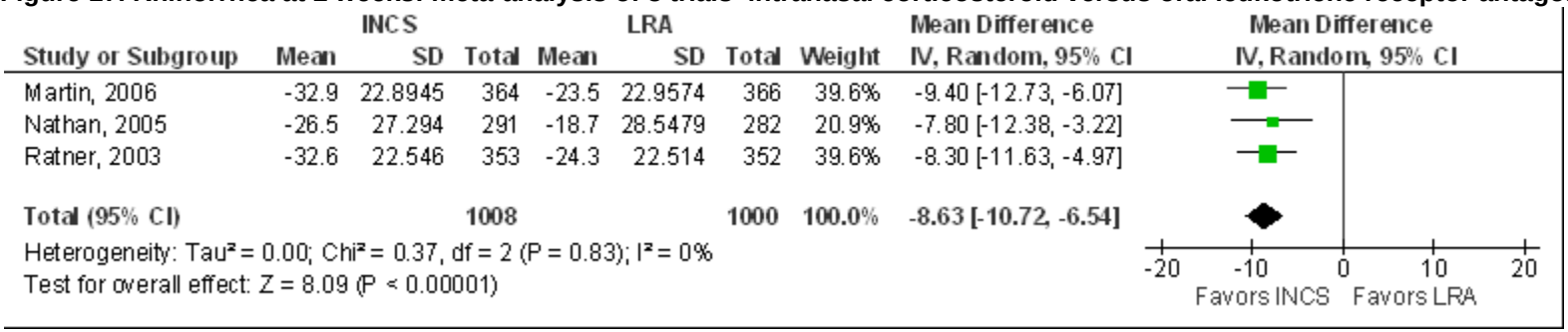


Figure 18. Sneezing at 2 weeks: meta-analysis of 3 trials–intranasal corticosteroid versus oral leukotriene receptor antagonist

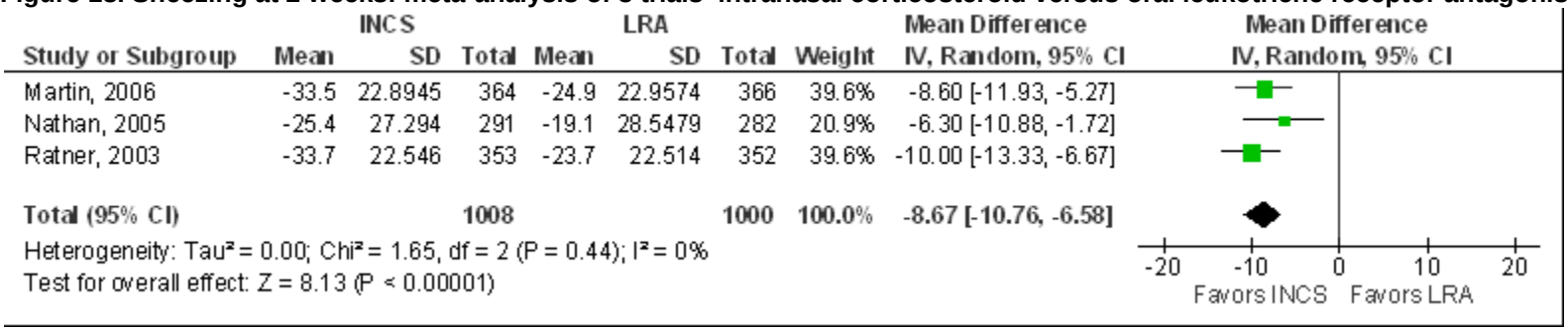


Figure 19. Nasal itch at 2 weeks: meta-analysis of 3 trials–intranasal corticosteroid versus oral leukotriene receptor antagonist

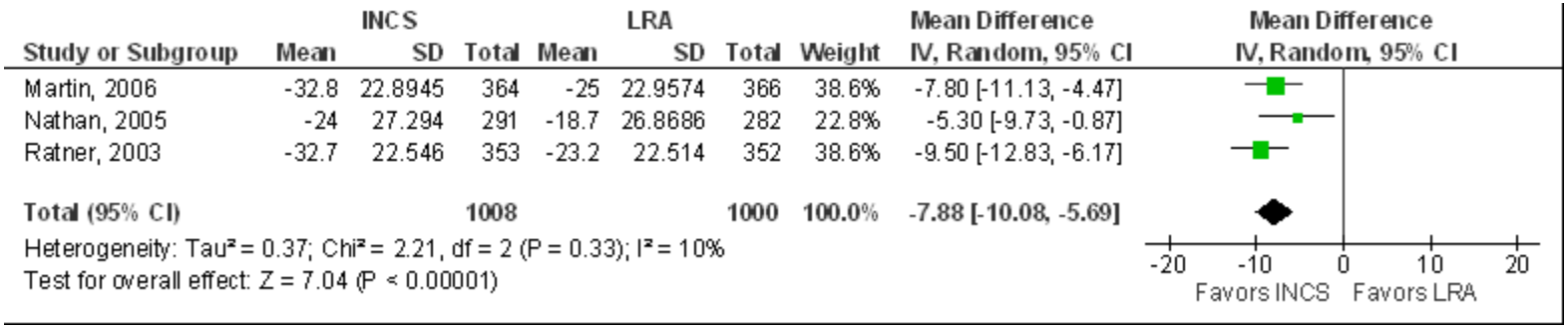


Figure 20. Total nasal symptom score at 2 weeks: meta-analysis of 4 trials–intranasal corticosteroid versus oral leukotriene receptor antagonist

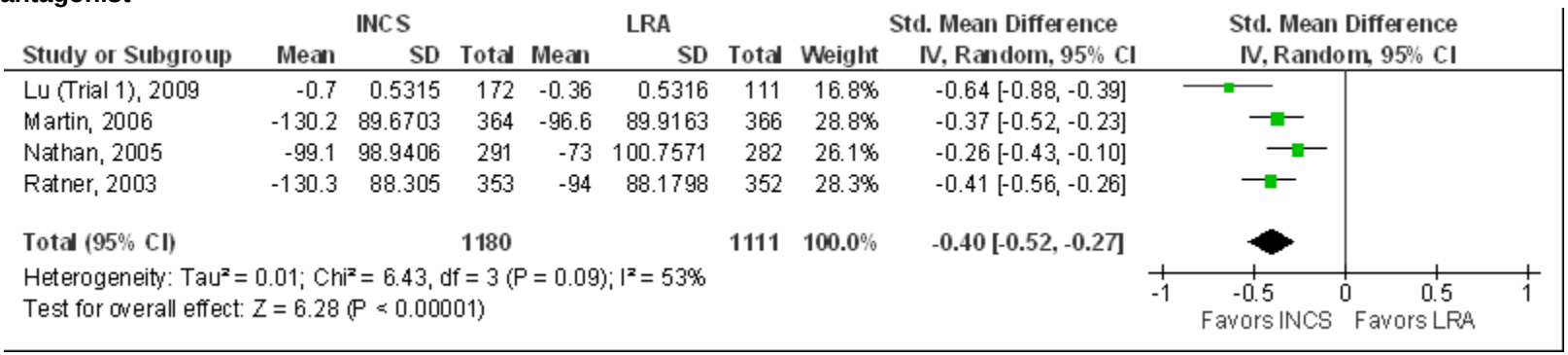


Table 38. Treatment effects: asthma outcomes–intranasal corticosteroid versus oral leukotriene receptor antagonist

Outcome	Variance	SS Favors INCS MD	NSS Favors/NR INCS MD	Favors Neither MD=0	NSS Favors/NR LRA MD	SS Favors LRA MD
4-Week Outcomes[a]						
Symptom-free days, %						
Nathan, 2005[127]	SE				1.3 (NSS)	
Albuterol-free days, %						
Nathan, 2005[127]	SE				0.7 (NSS)	
Morning PEF, L/min						
Nathan, 2005[127]	SE		2.4 (NSS)			
Evening PEF, L/min						
Nathan, 2005[127]	SE		1.8 (NSS)			
% of patients experiencing asthma exacerbations[b]						
Nathan, 2005[127]			<1 (NR)			

INCS = intranasal corticosteroid; LRA = oral leukotriene receptor antagonist; MD = mean difference between group mean changes from baseline; NR = p-value not reported; NSS = not statistically significant; PEF, L/min = peak expiratory flow, liters per minute; SS = statistically significant.

Variance/confidence interval reported: CI=confidence interval; SD=standard deviation; SE=standard error.

[a] With the exception of asthma exacerbations, outcomes are the average of 4th week of treatment compared with baseline run-in average.

[b] Defined by any asthma-related event that required treatment with asthma medications beyond study medications.

Combination Oral Selective Antihistamine Plus Intranasal Corticosteroid Versus Oral Selective Antihistamine

Description of Included Studies

Three[90, 98, 130] RCTs published between 1998 and 2009 were identified (N=677). Two trials[90, 98] were 2-week, double-blinded, multicenter trials in North America, and one[130] was a 4-week, patient-blinded, single center trial in Europe. Oral selective antihistamines studied were loratadine (two trials[90, 98]) and cetirizine (one trial[130]); intranasal corticosteroids were mometasone (two trials[90, 130]) and fluticasone propionate (one trial[98]). Two trials[90, 98] were industry funded, and one[130] was funded by a national health system.

The average age of patients in the trials ranged from 25 to 42 years. Women were the majority in all trials (range 50 percent to 77 percent). In the one trial[98] that reported on race, 77 percent were white, and 18 percent were Hispanic. Mean duration of SAR symptoms was 14 years in the one trial[90] that reported this measure. Baseline severity of nasal symptoms was mild to moderate,[130] moderate,[90] and moderate to severe.[98]

All three trials assessed TNSS. One[90] also assessed individual nasal symptoms (congestion, rhinorrhea, sneezing, and itching), two[90, 130] also assessed eye symptoms, and two[98, 130] also assessed quality of life. None of the trials assessed asthma outcomes. For the assessment of nasal symptoms, two trials[90, 130] used an interval scale. Patients rated symptoms daily[130] or twice daily[90] using a 0 (no symptoms) to 3 (severe symptoms) scale. Daily scores were summed, and twice daily scores were summed then averaged, to derive a 0-12 point TNSS. One trial[98] used a VAS to assess individual symptoms from 0 (no symptoms) to 100 (maximum symptoms). Scores were summed to derive a 0-400 point TNSS. For eye symptoms, patients rated each of three symptoms (itchiness, tearing, redness) on a 0 (no symptoms) to 3 (severe symptoms) scale. Scores were summed for a 0-9 point TOSS. The RQLQ was used to assess quality of life. Scores range from 0 (no impairment) to 6 (severe impairment). The minimum clinically important difference is 0.5 points.

Two trials[98, 130] were rated fair quality. One[90] was rated poor quality.

Key Points

The results discussed below are summarized in Table 39.

- Individual nasal symptoms (congestion, rhinorrhea, sneezing, and nasal itch) and eye symptoms (itching, tearing, and redness) at 2 weeks: Evidence was insufficient to support one treatment over the other based on one trial[90] with high risk of bias and imprecise results.
- TNSS at 2 weeks: Evidence was insufficient to support one treatment over the other based on three trials[90, 98, 130] with high risk of bias and consistent but imprecise results.
- TOSS at 2 weeks: Evidence was insufficient to support one treatment over the other based on one trial[130] with medium risk of bias and an imprecise result.
- Quality of life as assessed by the RQLQ at 2 weeks: There is low strength evidence for superiority of combination oral selective antihistamine plus intranasal corticosteroid over oral selective antihistamine monotherapy based on one trial[98] with medium risk of bias and a precise result.
- TNSS and TOSS at 4 weeks: Evidence was insufficient to support one treatment over the other based on one trial[130] with medium risk of bias and imprecise results.

- These results are based on trials of two of five oral selective antihistamines (40 percent) and two of eight intranasal corticosteroids (25 percent).

Table 39. Strength of evidence: combination oral selective antihistamine plus intranasal corticosteroid versus oral selective antihistamine

Outcome	RCTs (Patients)	Risk of Bias	Consistency	Directness	Precision	Overall GRADE
2-week nasal symptoms (congestion, rhinorrhea, sneezing, itching)	1[90] (350)	High	Unknown (single study)	Direct	Imprecise	Insufficient
2-week TNSS	3[90, 98, 130] (677)	High	Consistent	Direct	Imprecise	Insufficient
2-week eye symptoms (itching, tearing, redness)	1[90] (350)	High	Unknown (single study)	Direct	Imprecise	Insufficient
2-week TOSS	1[130] (27)	Medium	Unknown (single study)	Direct	Imprecise	Insufficient
2-week RQLQ	1[98] (300)	Medium	Unknown (single study)	Direct	Precise	Low[a]
4-week TNSS	1[130] (27)	High	Unknown (single study)	Direct	Imprecise	Insufficient
4-week TOSS	1[130] (27)	Medium	Unknown (single study)	Direct	Imprecise	Insufficient

GRADE = Grading of Recommendations Assessment, Development and Evaluation; RCTs (Patients) = number of randomized controlled trials (number of patients randomized to treatment groups of interest); RQLQ = Rhinoconjunctivitis Quality of Life Questionnaire; TNSS = total nasal symptom score, TOSS = total ocular symptom score.

[a] The body of evidence supports the superiority of combination oral selective antihistamine plus intranasal corticosteroid over oral selective antihistamine monotherapy for this outcome.

Synthesis and Strength of Evidence

Nasal symptom outcomes discussed below are summarized in Table 40, eye symptom outcomes in Table 41, and quality of life outcomes in Table 42. These tables show that there were few trials reporting each outcome. Several trials reported on TNSS at 2 weeks, but variance estimates for observed group effects were not provided. Thus, meta-analysis was not considered for this comparison.

Nasal Symptoms

One[90] of three trials[90, 98, 130] (350 of 677 patients) assessed individual nasal symptoms at 2 weeks. Statistically significant improvements in all four symptoms (congestion, rhinorrhea, sneezing, and itch) with combination therapy were shown. Treatment effects on a 0-3 point scale ranged from 0.1 for nasal itch to 0.3 for congestion (from 3 percent to 10 percent of maximum score). This trial was rated poor quality due to inappropriate analysis of results (not intention to treat).

For individual nasal symptoms at 2 weeks, the risk of bias was rated as high based on the poor quality rating of the trial.[90] Consistency cannot be assessed with a single trial. Estimates of treatment effects were imprecise. Evidence was insufficient to support the use of one treatment over the other for this outcome.

All three trials[90, 98, 130] assessed TNSS at 2 weeks (total N=677). All showed improvements in TNSS with combination therapy. In two trials, treatment effects reached statistical significance. One[98] of these was a fair quality trial of 300 patients (44 percent of total patients reporting this

outcome) that showed a treatment effect of 90 using a 0-400 VAS (22 percent of maximum score). The other[90] was a poor quality trial in 350 patients (52 percent of patients reporting) that reported a treatment effect of 1.1 on a 0-12 point scale (9 percent of maximum score). The third trial[130] assessed TNSS at both 2 weeks and 4 weeks. This was a fair quality trial of 27 patients. Treatment effects on a 0-12 point scale were 1.2 at 2 weeks and 0.9 at 4 weeks (10 percent and 8 percent of maximum score, respectively). Both favored combination therapy, but neither was statistically significant.

For the outcome of TNSS at both 2 weeks and 4 weeks, evidence was insufficient to support the use of one treatment over the other. At 2 weeks, the risk of bias was rated as high. Fifty-two percent of patients reporting this outcome were in the poor quality trial, and neither of the other two trials were rated good quality. Results were consistent across trials but also imprecise. At 4 weeks, the risk of bias was rated as high based on the small size and fair quality rating of the trial. Consistency of results could not be assessed in a single trial, and the effect estimate was imprecise.

Eye Symptoms

Two[90, 130] of three trials (377 of 677 patients) assessed eye symptoms. One trial[90] reported statistically significant improvements in individual symptoms of eye itching, tearing, and redness at 2 weeks with combination therapy. This was a trial of 350 patients that was rated poor quality due to inappropriate analysis of results (not intention to treat). Treatment effects were not reported. The other trial[130] assessed TOSS at 2 weeks and 4 weeks. The treatment effect at both time points was 0.2 on a 0-9 point scale (2 percent of maximum score). These were statistically nonsignificant effects that favored oral selective antihistamine monotherapy. This was a fair quality trial of 27 patients.

For individual eye symptoms at 2 weeks, the risk of bias was rated as high based on the poor quality rating of the trial.[90] Consistency of results could not be assessed in a single trial. Because the magnitude of the treatment effects is unknown, they are considered imprecise. Evidence was insufficient to support the use of one treatment over the other for this outcome.

For TOSS at 2 and 4 weeks, the evidence was insufficient to support the use of one treatment over the other. The risk of bias is medium based on the fair quality rating of the trial.[130] Consistency could not be assessed, and effect estimates at both time points were imprecise.

Quality of Life

One trial[98] assessed quality of life at 2 weeks using the RQLQ. This was a fair quality trial in 300 patients. A statistically significant treatment effect of 1.0 favoring combination therapy was shown. This exceeded the MCID of 0.5 points for the RQLQ. This trial[98] also reported a PGA of treatment response. A statistically significant treatment effect favoring combination therapy was reported (32-percentage point increase in the proportion of patients reporting moderate or significant improvement in the combination therapy arm using a 7-point Likert scale).

For quality of life at 2 weeks, the risk of bias was rated as medium based on the quality rating of the trial.[98] Although the effect estimate is precise, consistency cannot be assessed. The overall strength of evidence was low.

Table 40. Treatment effects: nasal symptoms–combination oral selective antihistamine plus intranasal corticosteroid versus oral selective antihistamine

Outcome	Variance	SS Favors Combo MD	NSS Favors/NR Combo MD	Favors Neither MD=0	NSS Favors/NR Antihistamine MD	SS Favors Antihistamine MD
2 Weeks, Average Change From Baseline						
Congestion						
Anolik, 2008[90] (scale 0-3)		0.3				
Rhinorrhea						
Anolik, 2008[90] (scale 0-3)		0.3				
Sneezing						
Anolik, 2008[90] (scale 0-3)		0.2				
Itching						
Anolik, 2008[90] (scale 0-3)		0.1				
TNSS						
Anolik, 2008[90] (scale 0-12)	SD	1.1				
Ratner, 1998[98] (scale 0-400)		90				
Wilson, 2000[130] (scale 0-12)			1.2 (NSS)			
4th Week of Treatment, Change From Baseline						
TNSS						
Wilson, 2000[130] (scale 0-12)			0.9 (NSS)			

MD = mean difference between group mean changes from baseline; NR = p-value not reported; NSS = not statistically significant; SS = statistically significant; TNSS = total nasal symptom score.

Variance/confidence interval reported: CI=confidence interval; SD=standard deviation; SE=standard error.

Table 41. Treatment effects: eye symptoms–combination oral selective antihistamine plus intranasal corticosteroid versus oral selective antihistamine

Outcome	Variance	SS Favors Combo MD	NSS Favors/NR Combo MD	Favors Neither MD=0	NSS Favors/NR Antihistamine MD	SS Favors Antihistamine MD
2 Weeks						
TOSS[a], average change from baseline						
Wilson, 2000[130] (scale 0-9)					0.2 (NSS)	
Itchy eyes						
Anolik, 2008[90] (scale 0 -3)		[b]				
Tearing						
Anolik, 2008[90] (scale 0 -3)		[b]				
Red Eyes						
Anolik, 2008[90] (scale 0 -3)		[b]				
4th Week, TOSS[a] Average Change From Baseline						
Wilson, 2000[130] (scale 0-9)					0.2 (NSS)	

MD = Mean difference calculated by authors with available data; NR = p-value not reported; NSS = not statistically significant; SS = statistically significant; TOSS = total ocular symptom score.

[a] Three symptoms (itchy eyes, watery eyes, red eyes) scored daily on a 0 (no symptoms) to 3 (severe symptoms) scale.

[b] No comparative values stated. All symptoms were significantly improved with combination versus monotherapy.

Table 42. Treatment effects: quality of life–combination oral selective antihistamine plus intranasal corticosteroid versus oral selective antihistamine

Outcome	Variance	SS Favors Combo MD	NSS Favors/NR Combo MD	Favors Neither MD=0	NSS Favors/NR Antihistamine MD	SS Favors Antihistamine MD
2 weeks						
RQLQ, change from baseline						
Ratner, 1998[98] (scale 0-6)		1.0				
% patients reporting moderate to significant improvement						
Ratner, 1998[98] (scale 0-100)		32				

MD = mean difference, calculated by authors from available data; NR = p-value not reported; NSS = not statistically significant; RQLQ = Rhinoconjunctivitis Quality of Life Questionnaire; SS = statistically significant.

Variance/confidence interval reported: CI = confidence interval; SD = standard deviation; SE = standard error.

Combination Oral Selective Antihistamine Plus Intranasal Corticosteroid Versus Intranasal Corticosteroid

Description of Included Studies

Five trials[62, 90, 98, 131, 132], published between 1998 and 2004 were identified (N=1201). Four[90, 98, 131, 132], (N=1136) were multicenter, double-blinded, RCTs based in Europe[131, 132] or North America.[90, 98] The fifth[62] was a single center European crossover trial in which the unit of randomization was the order in which treatments were received. Trials were 2 to 8 weeks in duration and included between 40 and 454 patients. Oral selective antihistamines studied were loratadine (two trials[90, 98]), cetirizine (two trials[131, 132]) and levocetirizine (one trial[62]); intranasal corticosteroids were fluticasone propionate (four trials[62, 98, 131, 132]) and mometasone (one trial[90]). Of four trials that reported funding, two[98, 131] were funded by industry, one[132] by a national health system, and one[62] by an academic institution.

The average age of patients in the trials ranged from 26 to 45 years. Approximately half of patients were female (range 50 percent to 57 percent). In the one trial that reported on race,[98] 77 percent of patients were white and 18 percent were Hispanic. Duration of SAR symptoms ranged from 2 to 4 years for the majority of patients in one trial[132] to an average of 14 years for patients in another trial.[90] Baseline severity of SAR symptoms ranged from mild-moderate to moderate-severe.

Three trials assessed individual nasal symptoms (congestion, rhinorrhea, sneezing, and itching), five assessed TNSS, two assessed eye symptoms, and two assessed quality of life. Three trials used an interval scale for nasal symptom severity. Patients rated symptoms daily[62, 132] or twice daily[90] using a 0 (no symptoms) to 3 (severe symptoms) scale. Daily scores were summed, and twice daily scores were summed then averaged, to derive a 0-12 point TNSS. One trial[98] used a VAS to assess individual symptoms from 0 (no symptoms) to 100 (maximum symptoms). Scores were summed to derive a 0-400 point TNSS. For eye symptoms, Anolik (2008)[90] used a 0 (no symptoms) to 3 (severe symptoms) scale to assess eye itching, tearing, and redness. Benincasa (1994)[131] used a 10-point scale (0= no symptoms, 1-3 = mild symptoms, 4-6 = moderate symptoms, and 7-9 = severe symptoms). Eye symptoms were not specifically defined. To assess quality of life, the RQLQ and the mini-RQLQ were used. For both the RQLQ and the mini-RQLQ, scores range from 0 (no impairment) to 6 (severely impaired). MCID for the RQLQ is 0.5 points and for the mini-RQLQ, 0.7 points.

The largest of the five trials[131] (n=454) was rated good quality. One trial[98] was rated fair, and three trials[62, 90, 132] were rated poor (total N=447).

Key Points

The results discussed below are summarized in Table 43.

- Individual nasal symptoms (congestion and rhinorrhea) at 2 weeks: Evidence was insufficient to support the use of one treatment over the other based on two trials[62, 90] with high risk of bias and inconsistent, imprecise results.
- Individual nasal symptoms (sneezing and itch) and TNSS at 2 weeks: Evidence was insufficient to support the use of one treatment over the other based on two trials[62, 90] (for sneezing and nasal itch) and three trials[62, 90, 98] (for TNSS) with high risk of bias and consistent but imprecise results.

- Individual eye symptoms (itching, tearing, and redness) at 2 weeks: Evidence was insufficient to support the use of one treatment over the other based on one trial[90] with high risk of bias and imprecise results.
- Quality of life as assessed by the RQLQ at 2 weeks: Evidence was insufficient to support the use of one treatment over the other based on two trials[62, 98] with medium risk of bias and inconsistent, imprecise results.
- Individual nasal symptoms (congestion, rhinorrhea, sneezing, and itch) at 6 weeks: Evidence was insufficient to support the use of one treatment over the other based on one trial[132] with high risk of bias and imprecise results.
- TNSS at 6 weeks and 8 weeks: Evidence was insufficient to support the use of one treatment over the other based on two trials[131, 132] with low risk of bias and inconsistent, imprecise results.
- TOSS at 8 weeks: Evidence was insufficient to support the use of one treatment over the other based on one trial[131] with low risk of bias and an imprecise result.
- These results are based on trials using three of five oral selective antihistamines (60 percent) and two of eight intranasal corticosteroids (25 percent).

Table 43. Strength of evidence: combination oral selective antihistamine plus intranasal corticosteroid versus intranasal corticosteroid

Outcome	RCTs (Patients)	Risk of Bias	Consistency	Directness	Precision	Overall GRADE
2-week congestion, rhinorrhea	2[62, 90] (407)	High	Inconsistent	Direct	Imprecise	Insufficient
2-week sneezing, nasal itch	2[62, 90] (407)	High	Consistent	Direct	Imprecise	Insufficient
2-week TNSS	3[62, 90, 98] (707)	High	Consistent	Direct	Imprecise	Insufficient
2-week eye symptoms (itching, tearing, redness)	1[90] (345)	High	Unknown (single study)	Direct	Imprecise	Insufficient
2-week QoL	2[62, 98] (362)	Medium	Inconsistent	Direct	Imprecise	Insufficient
6-week congestion, rhinorrhea, sneezing, nasal itch	1[132] (40)	High	Unknown (single study)	Direct	Imprecise	Insufficient
6 and 8-week TNSS	2[131, 132] (494)	Low	Inconsistent	Direct	Imprecise	Insufficient
8-week TOSS	1[131] (454)	Low	Unknown (single study)	Direct	Imprecise	Insufficient

GRADE = Grading of Recommendations Assessment, Development and Evaluation; QoL = quality of life; RCTs (Patients) = number of randomized controlled trials (number of patients randomized to treatment groups of interest); TOSS = total ocular symptom score; TNSS = total nasal symptom score.

Synthesis and Strength of Evidence

Nasal symptom results discussed below are summarized in Table 44, eye symptom results in Table 45, and quality of life results in Table 46. As shown in these tables, few trials reported on each outcome. Although three trials assessed TNSS at 2 weeks, variance estimates of symptom improvements were not provided consistently. Thus, meta-analysis was not possible for this comparison.

Nasal Symptoms

Evidence for the assessment of individual nasal symptoms comes from two[62, 90] of five trials (407 of 1201 patients) that assessed nasal symptoms at 2 weeks, and one trial[132] that assessed nasal symptoms at 6 weeks. All three trials were rated poor quality due to noncomparable groups at baseline[132] and inappropriate analysis of results (not intention to treat[62, 90]).

At 2 weeks, Anolik (2008)[90] showed no difference between treatments for congestion (treatment effect = 0), and Barnes (2006)[62] showed a statistically significant treatment effect of 0.11 on a 0-3 point scale (4 percent of maximum score) favoring intranasal corticosteroid monotherapy. At 6 weeks, Di Lorenzo (2004)[132] showed a statistically nonsignificant treatment effect of 0.04 on a 0-3 point scale (1 percent of maximum score).

Evidence for the outcome of congestion at 2 weeks was insufficient to support the use of one treatment over the other. Two poor quality trials[62, 90] with high risk of bias reported inconsistent and imprecise treatment effects. For the outcome of congestion at 6 weeks, evidence also is insufficient to support the use of one treatment over the other. One poor quality trial[132] with a high risk of bias reported an imprecise treatment effect.

At 2 weeks, Anolik (2008)[90] showed no difference between treatments for rhinorrhea (treatment effect = 0), and Barnes (2006)[62] showed a statistically nonsignificant treatment effect of 0.04 on a 0-3 point scale (1 percent of maximum score) favoring combination therapy. At 6 weeks, Di Lorenzo (2004)[132] also showed a statistically nonsignificant treatment effect of 0.04 on a 0-3 point scale (1 percent of maximum score), favoring intranasal corticosteroid monotherapy.

Evidence for the outcome of rhinorrhea at 2 weeks was insufficient to support the use of one treatment over the other. Two poor quality trials[62, 90] with high risk of bias reported inconsistent and imprecise treatment effects. For the outcome of rhinorrhea at 6 weeks, evidence also is insufficient to support the use of one treatment over the other. One poor quality trial[132] with a high risk of bias reported an imprecise treatment effect.

At 2 weeks, Anolik (2008)[90] and Barnes (2006)[62] both showed greater improvements in sneezing with combination therapy than with intranasal corticosteroid monotherapy. Treatment effects were 0.1 and 0.15 on a 0-3 point scale (3 percent and 5 percent of maximum score, respectively). Neither was statistically significant. At 6 weeks, Di Lorenzo (2004)[132] showed a statistically nonsignificant treatment effect of 0.08 on a 0-3 point scale (3 percent of maximum score) favoring combination therapy.

Evidence for the outcome of sneezing at 2 weeks was insufficient to support the use of one treatment over the other. Two poor quality trials[62, 90] with high risk of bias reported consistent but imprecise treatment effects. For the outcome of rhinorrhea at 6 weeks, evidence also is insufficient to support the use of one treatment over the other. One poor quality trial[132] with a high risk of bias reported an imprecise treatment effect.

At 2 weeks, Anolik (2008)[90] and Barnes (2006)[62] both showed greater improvements in nasal itch with combination therapy than with intranasal corticosteroid monotherapy. Treatment effects

were 0.1 and 0.03 on a 0-3 point scale (3 percent and 1 percent of maximum score, respectively). Neither was statistically significant. At 6 weeks, Di Lorenzo (2004)[132] reported a statistically significant treatment effect of 0.1 on a 0-3 point scale (3 percent of maximum score) favoring combination therapy.

Evidence for the outcome of nasal itch at 2 weeks was insufficient to support the use of one treatment over the other. Two poor quality trials[62, 90] with high risk of bias reported consistent but imprecise treatment effects. For the outcome of nasal itch at 6 weeks, evidence also is insufficient to support the use of one treatment over the other. One poor quality trial[132] with a high risk of bias reported an imprecise treatment effect.

Three[62, 90, 98] of five trials (707 of 1201 patients) assessed TNSS at 2 weeks. All three trials showed greater improvement in TNSS with combination therapy than with intranasal corticosteroid monotherapy. In two[62, 98] of these, this finding was statistically significant. One[98] of these was a fair quality trial of 300 patients (42 percent of patients reporting this outcome). The other [62] was rated poor quality due to inappropriate analysis of results (not intention to treat). This trial[62] reported results using a 0-12 point scale and showed a treatment effect of 0.11 (1 percent of maximum score). The fair quality trial[98] reported a treatment effect of 30 on a 0-400 VAS (8 percent of maximum score). The third trial[90] reported a statistically nonsignificant treatment effect of 0.3 on a 0-12 point scale (3 percent of maximum score). This was a poor quality trial of 345 patients (49 percent of patients reporting this outcome).

For the outcome of TNSS at 2 weeks, the risk of bias was rated as high. Fifty-eight percent of patients were in poor quality trials, and 42 percent were in a fair quality trial. Treatment effects consistently favored combination therapy in all three trials. However, treatment effects were imprecise. The evidence was therefore insufficient to support the use of one treatment over the other for this outcome.

Two trials[131, 132] assessed TNSS at time points beyond 2 weeks (N=494). The larger of these[131] (92 percent of patients reporting this outcome) was rated good quality, and the smaller[132] (n=40) was rated poor quality due to noncomparable groups at baseline. At 6 weeks, the latter trial[132] showed a statistically nonsignificant treatment effect of 0.2 on a 0-3 point scale (7 percent of maximum score) favoring combination therapy. At 8 weeks, the larger trial[131] reported a treatment difference of zero.

For the outcome of TNSS at 6 to 8 weeks, evidence also is insufficient to support the use of one treatment over the other. The risk of bias was considered low; 92 percent of patients reporting this outcome were in the good quality trial. However, reported treatment effects were inconsistent and imprecise.

Eye Symptoms

Two trials assessed eye symptoms, one[90] at 2 weeks (N=345) and one[131] at 8 weeks (N=454). At 2 weeks, Anolik (2008)[90] reported statistically nonsignificant treatment effects favoring combination therapy for itchy eyes, watery eyes, and red eyes. Effect sizes were not reported. This trial was rated poor quality due to inappropriate analysis of results (not intention to treat). At 8 weeks, Benincasa (1994)[131] reported a statistically nonsignificant treatment effect favoring combination therapy for unspecified eye symptoms. Effect size was not reported. This trial[131] was rated good quality.

Evidence for the outcome of eye symptoms at 2 weeks was insufficient to support the use of one treatment over the other. One trial[90] with a high risk of bias reported imprecise results. At 8

weeks, the evidence also is insufficient to support the use of one treatment over the other. One trial[131] with a low risk of bias reported imprecise results.

Quality of Life

Two trials[62, 98] assessed quality of life at 2 weeks using different measures. The larger trial[98] (83 percent of patients reporting this outcome) was rated fair quality and showed a treatment effect of 0.1 on the 0-6 point RQLQ scale favoring combination therapy. The smaller trial[62] was rated poor quality and showed a treatment effect of 0.1 on the 0-6 point mini-RQLQ scale favoring intranasal corticosteroid monotherapy. Neither result was statistically significant, and neither exceeded the MCID. The larger trial[98] also assessed PGA of treatment. More patients treated with combination therapy reported moderate to significant improvement using a 7-point Likert scale (significantly worse to significantly improved) than patients treated with intranasal corticosteroid monotherapy. This result was not statistically significant.

Evidence for quality of life outcomes at 2 weeks is insufficient to support one treatment over the other. Two trials[62, 98] with medium risk of bias reported inconsistent and imprecise results.

Table 44. Treatment effects: nasal symptoms–combination oral selective antihistamine plus intranasal corticosteroid versus intranasal corticosteroid

Outcome	Variance[a]	SS Favors Combo MD	NSS Favors/NR Combo MD	Favors Neither MD=0	NSS Favors/NR INCS MD	SS Favors INCS MD
2 Weeks, Average Change From Baseline						
Congestion						
Anolik, 2008[90] (scale 0-3)				0		
Barnes, 2006[62] (scale 0-3)	SE/CI[b]					0.11 (0.04,)[f]
Rhinorrhea						
Anolik, 2008[90] (scale 0-3)				0		
Barnes, 2006[62] (scale 0-3)	SE/CI[b]		0.04 (, 0.19)[f]			
Sneezing						
Anolik, 2008[90] (scale 0-3)			0.1 (NSS)			
Barnes, 2006[62] (scale 0-3)	SE/CI[b]		0.15 (, 0.31)[f]			
Itching						
Anolik, 2008[90] (scale 0-3)			0.1 (NSS)			
Barnes, 2006[62] (scale 0-3)	SE/CI[b]		0.03 (, 0.16)[f]			
TNSS						
Anolik, 2008[90] (scale 0-12)			0.3 (NSS)			
Barnes, 2006[62] (scale 0-12)	SE/CI[b]	0.11 (, 0.51)[f]				
Ratner, 1998[98] (scale 0-400)		30[c]				
6 Weeks, Average Change From Baseline						
Congestion						
Di Lorenzo, 2004[132] (scale 0-3)	CI		0.04 (-0.03, 0.1)			
Rhinorrhea						
Di Lorenzo, 2004[132] (scale 0-3)	CI				0.04 (-0.006, 0.88)	
Sneezing						
Di Lorenzo, 2004[132] (scale 0-3)	CI		0.08			

Outcome	Variance[a]	SS Favors Combo MD	NSS Favors/NR Combo MD	Favors Neither MD=0	NSS Favors/NR INCS MD	SS Favors INCS MD
			(-0.008, 0.1)			
Itching						
Di Lorenzo, 2004[132] (scale 0-3)	CI	0.1 (0.06, 0.2)				
TNSS						
Di Lorenzo, 2004[132] (scale 0-12)			0.2 (-0.08, 0.4)			
8 Weeks, Average Change From Baseline						
TNSS						
Benincasa, 1994[131] (scale 0-9)[d]	CI			(-0.3, 0.3)[e]		

INCS = Intranasal corticosteroid; MD = mean difference (calculated by authors with available data except where noted); NR = p-value not reported; NSS = not statistically significant; SS = statistically significant; TNSS = total nasal symptom score.

[a] Variance/confidence interval reported: CI=confidence interval, SD=standard deviation, SE=standard error.

[b] One sided confidence interval for non-superiority trial.

[c] Engauge Digitizer Software used to estimate treatment effects.

[d] Scale for symptoms: 0 (no symptoms), 1-3 (mild symptoms), 4-6 (moderate symptoms), 7-9 (severe symptoms).

[e] No point estimate provided.

[f] 95 percent confidence intervals as reported in Barnes, 2006[62]

Table 45. Treatment effects: eye symptoms–combination oral selective antihistamine plus intranasal corticosteroid versus intranasal corticosteroid

Outcome	Variance[a]	SS Favors Combo MD	NSS Favors/NR Combo MD	Favors Neither MD=0	NSS Favors/NR INCS MD	SS Favors INCS MD
2 Weeks						
Itchy eyes						
Anolik, 2008[90] (scale 0 -3)			[b] (NSS)			
Watery Eyes						
Anolik, 2008[90] (scale 0 -3)			[b] (NSS)			
Red Eyes						
Anolik, 2008[90] (scale 0 -3)			[b] (NSS)			
8 Weeks						
TOSS[c], average change from baseline						
Benincasa, 1994[131] (scale 0-9)	SD/CI		(-0.1, 0.4)[d]			

INCS = Intranasal corticosteroid; MD = mean difference calculated by authors from available data; NR = p-value not reported; NSS = not statistically significant; SS = statistically significant; TOSS = total ocular symptom score.

Adjusted mean differences reported by Carr, 2012, mean differences calculated by authors with available data (Hampel, 2010).

[a] Variance/confidence interval reported: CI=confidence interval; SD=standard deviation; SE=standard error.

[b] No comparative values stated.

[c] Eye symptoms not specified.

[d] No point estimate provided.

Table 46. Treatment effects: quality of life–combination oral selective antihistamine/intranasal corticosteroid versus intranasal corticosteroid

Outcome	Variance[a]	SS Favors Combo MD	NSS Favors/NR Combo MD	Favors Neither MD=0	NSS Favors/NR INCS MD	SS Favors INCS MD
2 Weeks						
RQLQ, change from baseline						
Ratner, 1998[98] (scale 0-6)			0.1 (NSS)			
Mini-RQLQ, change from baseline						
Barnes, 2006[62] (scale 0-6)					0.1 (NSS)	
% patients reporting moderate to significant improvement						
Ratner, 1998[98] (scale 0-100)			4 (NSS)			

INCS = Intranasal corticosteroid; MD = mean difference, calculated by authors from available data; NR = p-value not reported; NSS = not statistically significant; RQLQ = Rhinoconjunctivitis Quality of Life Questionnaire; SS = statistically significant.

[a] Variance/confidence interval reported: CI=confidence interval; SD=standard deviation; SE=standard error.

Combination Intranasal Corticosteroid Plus Nasal Antihistamine Versus Intranasal Corticosteroid

Description of Included Studies

Five[115, 117, 121] multicenter, RCTs published between 2008 and 2012 were identified (total N=2102). All were 2-week, double-blinded trials based in North America. Trial size ranged from 102 to 898 patients randomized to treatment groups of interest. In all five trials, the nasal antihistamine was azelastine, and the intranasal corticosteroid was fluticasone propionate. Three trials[115] from the same article used a newly approved combination product comprising both drugs, and two trials[117, 121] used a separate nasal inhaler for each drug in the combination. All five trials were industry funded.

The mean age of trial participants ranged from 34 to 40 years. Most participants were female (approximately 63 percent). The majority of patients were white (minimum 64 percent). Of two trials[117, 121] that reported the proportions of other races, one[121] included approximately 20 percent Hispanic patients. All trials required a minimum duration and severity of SAR symptoms. Mean SAR duration ranged from 16 to 22 years. Mean baseline nasal symptoms were in the severe range.

All five trials assessed both individual and total nasal symptoms. Four[115, 117] of five assessed eye symptoms, and two[117, 121] assessed quality of life. No trial assessed asthma outcomes. In all five trials, patients rated symptoms twice daily. Individual nasal symptoms (congestion, rhinorrhea, sneezing, and itching) and eye symptoms (itching, tearing, and redness) were rated on a scale from 0 (no symptoms) to 3 (severe symptoms). Morning and evening scores were summed to give a maximum score of 6 for each individual symptom. TNSS ranged from 0 to 24, and TOSS ranged from 0 to 18. The RQLQ was used to assess quality of life. Scores ranged from 0 (no impairment) to 6 (severe impairment). The MCID is 0.5 points.

All five trials were rated good quality.

Key Points

These results are summarized in Table 47.

- Individual nasal symptoms (congestion, rhinorrhea, sneezing, and itch), TNSS and TOSS at 2 weeks: High strength evidence for equivalence of combination intranasal corticosteroid plus nasal antihistamine and intranasal corticosteroid monotherapy based on five trials[115, 117, 121] (for individual nasal symptoms and TNSS) and four trials[115, 117] (for TOSS) with low risk of bias and consistent, precise results.
- Quality of life as assessed by the RQLQ at 2 weeks: Evidence was insufficient to support the use of one treatment over the other based on two trials[117, 121] with low risk of bias and consistent but imprecise results.
- These results are based on trials of one of eight intranasal corticosteroids (12.5 percent) and one of two nasal antihistamines (50 percent).

Table 47. Strength of evidence: combination intranasal corticosteroid plus nasal antihistamine versus intranasal corticosteroid

Outcome	RCTs (Patients)	Risk of Bias	Consistency	Directness	Precision	Overall GRADE
2-week congestion, rhinorrhea, sneezing, itch	5[115, 117, 121] (2102)	Low	Consistent	Direct	Precise	High[a]
2-week TNSS	5[115, 117, 121] (2102)	Low	Consistent	Direct	Precise	High[a]
2-week TOSS	4[115, 117] (2000)	Low	Consistent	Direct	Precise	High[a]
2-week RQLQ	2[117, 121] (408)	Low	Consistent	Direct	Imprecise	Insufficient

GRADE = Grading of Recommendations Assessment, Development and Evaluation; RCTs (Patients) = number of randomized controlled trials (number of patients randomized to treatment groups of interest); RQLQ = Rhinoconjunctivitis Quality of Life Questionnaire; TNSS = total nasal symptom score; TOSS = total ocular symptom score.

[a] The body of evidence supports equivalence of combination intranasal corticosteroid plus nasal antihistamine and intranasal corticosteroid monotherapy for the outcomes identified.

Synthesis and Strength of Evidence

Nasal symptom outcomes discussed below are summarized in Table 48, eye symptom outcomes in Table 49, and quality of life outcomes in Table 50. As shown in these tables and noted above, several trials reported on each outcome. Additionally, variance estimates of group-level treatment effects were provided. Thus, meta-analyses were performed for all nasal and eye outcomes.

Nasal Symptoms

All five trials[115, 117, 121] assessed four individual nasal symptoms and TNSS at 2 weeks (total N=2102). Four trials[115, 121] (85 percent of patients reporting this outcome) were included in meta-analyses for each nasal outcome. Variance estimates necessary for pooling were not reported by Hampel (2010),[117] preventing inclusion of this trial in the meta-analyses. All five trials were rated good quality. For each outcome, results were consistent across trials.

All five trials showed greater improvement in congestion with combination therapy than with intranasal corticosteroid monotherapy. In three trials, including Hampel (2010),[117] treatment effects were statistically significant and ranged from 0.3 to 0.6 on a 0-6 point scale (from 5 percent to 10 percent of maximum score). The pooled effect was 0.16 on a 0-6 point scale (95 percent CI: 0.02 to 0.30), a statistically significant result favoring combination therapy (Figure 21). The larger bound of the 95 percent CI represented 5 percent of maximum score. Statistical heterogeneity was low (I^2=17 percent, p=0.31).

For the outcome of congestion, the risk of bias was rated as low based on the quality of the trials. Statistical heterogeneity of a meta-analysis of four trials[115, 121] was low, and the pooled effect was consistent with the effect reported in the one trial[117] not included in the meta-analysis. The 95 percent CI for the pooled effect (0.02 to 0.30) fell within an interval bounded by –MCID and +MCID (-1.8 and +1.8 on the 0-6 point scale used). The Hampel (2010) trial[117] reported a treatment effect of 0.38 on a 0-6 point scale (6 percent of maximum score) favoring combination therapy. If this trial were included in the meta-analysis, the pooled effect (0.16; 3 percent of maximum score) would increase. Because the trial represented only 15 percent of patients reporting this outcome, it is unlikely that the 95 percent CI of the pooled effect would include an MCID of 30 percent maximum score. The body of evidence supporting a conclusion of equivalence of combination therapy and intranasal corticosteroid for this outcome was therefore considered precise. The overall strength of evidence for this conclusion is high.

All five trials showed greater improvement in rhinorrhea with combination therapy than with intranasal corticosteroid monotherapy. The treatment effect (0.25 on a 0-6 point scale; 4 percent of maximum score) was statistically significant in only one trial (Carr, Trial 1[115]). The pooled effect was 0.14 on a 0-6 point scale (95 percent CI: 0.01 to 0.28), a statistically significant result favoring combination therapy (Figure 22). The larger bound of the 95 percent CI represented 5 percent of maximum score. Statistical heterogeneity was low (I^2=0 percent, p=0.74).

For the outcome of rhinorrhea, the risk of bias was rated as low based on the quality of the trials. Statistical heterogeneity of a meta-analysis of four trials[115, 121] was low, and the pooled effect was consistent with the effect reported in the one trial[117] not included in the meta-analysis. The 95 percent CI for the pooled effect (0.01 to 0.28) fell within an interval bounded by –MCID and +MCID (-1.8 and +1.8 on the 0-6 point scale used). The Hampel (2010) trial[117] reported a treatment effect of 0.27 on a 0-6 point scale (5 percent of maximum score) favoring combination therapy. If this trial were included in the meta-analysis, the pooled effect (0.14; 2 percent of maximum score) would increase. Because the trial represented only 15 percent of patients

reporting this outcome, it is unlikely that the 95 percent CI of the pooled effect would include an MCID of 30 percent maximum score. The body of evidence supporting a conclusion of equivalence of combination therapy and intranasal corticosteroid for this outcome was therefore considered precise. The overall strength of evidence for this conclusion is high.

All five trials showed greater improvement in sneezing with combination therapy than with intranasal corticosteroid monotherapy. In four trials, including Hampel (2010),[117] treatment effects were statistically significant and ranged from 0.2 to 0.6 on a 0-6 point scale (from 3 percent to 10 percent of maximum score). The pooled effect was 0.22 on a 0-6 point scale (95 percent CI: 0.07 to 0.36), a statistically significant result favoring combination therapy (Figure 23). The larger bound of the 95 percent CI represented 6 percent of maximum score. Statistical heterogeneity was low (I^2=0 percent, p=0.50).

For the outcome of sneezing, the risk of bias was rated as low based on the quality of the trials. Statistical heterogeneity of a meta-analysis of four trials[115, 121] was low, and the pooled effect was consistent with the effect reported in the one trial[117] not included in the meta-analysis. The 95 percent CI for the pooled effect (0.07 to 0.36) fell within an interval bounded by –MCID and +MCID (-1.8 and +1.8 on the 0-6 point scale used). The Hampel (2010) trial[117] reported a treatment effect of 0.49 on a 0-6 point scale (8 percent of maximum score) favoring combination therapy. If this trial were included in the meta-analysis, the pooled effect (0.22; 4 percent of maximum score) would increase. Because the trial represented only 15 percent of patients reporting this outcome, it is unlikely that the 95 percent CI of the pooled effect would include an MCID of 30 percent maximum score. The body of evidence supporting a conclusion of equivalence of combination therapy and intranasal corticosteroid for this outcome was therefore considered precise. The overall strength of evidence for this conclusion is high.

All five trials showed greater improvement in nasal itch with combination therapy than with intranasal corticosteroid monotherapy. In two trials, one of which was Hampel (2010),[117] treatment effects of 0.31 and 0.6 on a 0-6 point scale (5 percent and 10 percent of maximum score, respectively) were statistically significant. The pooled effect was 0.10 on a 0-6 point scale (95 percent CI: -0.03 to 0.23), a statistically nonsignificant result favoring combination therapy (Figure 24). The larger bound of the 95 percent CI represented 4 percent of maximum score. Statistical heterogeneity was low (I^2=0 percent; p=0.39).

For the outcome of nasal itch, the risk of bias was rated as low based on the quality of the trials. Statistical heterogeneity of a meta-analysis of four trials[115, 121] was low, and the pooled effect was consistent with the effect reported in the one trial[117] not included in the meta-analysis. The 95 percent CI for the pooled effect (-0.03 to 0.23) fell within an interval bounded by –MCID and +MCID (-1.8 and +1.8 on the 0-6 point scale used). The Hampel (2010) trial[117] reported a treatment effect of 0.31 on a 0-6 point scale (5 percent of maximum score) favoring combination therapy. If this trial were included in the meta-analysis, the pooled effect (0.10; 2 percent of maximum score) would increase. Because the trial represented only 15 percent of patients reporting this outcome, it is unlikely that the 95 percent CI of the pooled effect would include an MCID of 30 percent maximum score. The body of evidence supporting a conclusion of equivalence of combination therapy and intranasal corticosteroid for this outcome was therefore considered precise. The overall strength of evidence for this conclusion is high.

All five trials showed statistically significant improvements in TNSS with combination therapy. Treatment effects ranged from 0.6 to 2.2 on a 0-24 point scale (from 3 percent to 9 percent of maximum score). The pooled effect was 0.61 on a 0-24 point scale (95 percent CI: 0.15 to 1.08), a statistically significant result favoring combination therapy (Figure 25). The

larger bound of the 95 percent CI represented 5 percent of maximum score. Statistical heterogeneity was low (I^2=0 percent, p=0.46).

For TNSS, the risk of bias was rated as low based on the quality of the trials. Effect estimates were precise. Statistical heterogeneity of a meta-analysis of four trials[115, 121] was low, and the pooled effect was consistent with the effect reported in the one trial[117] not included in the meta-analysis. The 95 percent CI for the pooled effect (0.15 to 1.08) fell within an interval bounded by –MCID and +MCID (-7.2 and +7.2 on the 0-24 point scale used). The Hampel (2010) trial[117] reported a treatment effect of 1.47 on a 0-24 point scale (6 percent of maximum score) favoring combination therapy. If this trial were included in the meta-analysis, the pooled effect (0.61; 3 percent of maximum score) would increase. Because the trial represented only 15 percent of patients reporting this outcome, it is unlikely that the 95 percent CI of the pooled effect would include an MCID of 30 percent maximum score. The body of evidence supporting a conclusion of equivalence of combination therapy and intranasal corticosteroid for this outcome was therefore considered precise. The overall strength of evidence for this conclusion is high.

Eye Symptoms

Four[115, 117] trials that assessed eye symptoms at 2 weeks (total N=2000) showed greater improvements in TOSS with combination therapy than with intranasal corticosteroid monotherapy. In two trials, one of which was Hampel (2010),[117] treatment effects of 0.45 and 0.88 on a 0-18 point scale (3 percent and 5 percent of maximum score, respectively) were statistically significant. The pooled effect from a meta-analysis of three trials[115] (85 percent of patients reporting this outcome; Hampel [2010][117] excluded) was 0.48 on a 0-18 point scale (95 percent CI: 0.07 to 0.90), a statistically significant result favoring combination therapy (Figure 26). The larger bound of the 95 percent CI represented 5 percent of maximum score. Statistical heterogeneity was low (I^2=21%, p=0.28).

For TOSS, the risk of bias was rated as low based on the quality of the trials. Statistical heterogeneity of a meta-analysis of three trials[115] was low, and the pooled effect was consistent with the effect reported in the one trial[117] not included in the meta-analysis. The 95 percent CI for the pooled effect (0.07 to 0.90) fell within an interval bounded by –MCID and +MCID (-5.4 and +5.4 on the 0-18 point scale used). The Hampel (2010) trial[117] reported a treatment effect of 0.45 on a 0-18 point scale (3 percent of maximum score) favoring combination therapy. If this trial were included in the meta-analysis, the pooled effect (0.48; 3 percent of maximum score) would decrease slightly. Because the trial represented only 15 percent of patients reporting this outcome, it is unlikely that the 95 percent CI of the pooled effect would include an MCID of 30 percent maximum score. The body of evidence supporting a conclusion of equivalence of combination therapy and intranasal corticosteroid for this outcome was therefore considered precise. The overall strength of evidence for this conclusion is high.

Table 48. Treatment effects: nasal symptoms–combination intranasal corticosteroid plus nasal antihistamine versus intranasal corticosteroid

Outcome	Variance[a]	SS Favors Combo MD	NSS Favors/NR Combo MD	Favors Neither MD=0	NSS Favors/NR INCS MD	SS Favors INCS MD
2 Weeks, Average Change From Baseline						
Congestion						
Carr, 2012 (Trial 1)[115] (scale 0-6)	SD/CI		0.2 (-0.06, 0.38)[b]			
Carr, 2012 (Trial 2)[115] (scale 0-6)	SD/CI	0.3 (0.04, 0.52)[b]				
Carr, 2012 (Trial 3)[115] (scale 0-6)	SD/CI		0.1 (-0.03, 0.28,)[b]			
Hampel, 2010[117] (scale 0-6)		0.38				
Ratner, 2008[121] (scale 0-6)	SD	0.6				
Rhinorrhea						
Carr, 2012 (Trial 1)[115] (scale 0-6)	SD/CI	0.25 (0.01, 0.50)				
Carr, 2012 (Trial 2)[115] (scale 0-6)	SD/CI		0.2 (-0.12, 0.41)[b]			
Carr, 2012 (Trial 3)[115] (scale 0-6)	SD/CI		0.1 (-0.05, 0.29)[b]			
Hampel, 2010[117] (scale 0-6)			0.27 (NR)			
Ratner, 2008[121] (scale 0-6)	SD		0.4 (NSS)			
Sneezing						
Carr, 2012 (Trial 1)[115] (scale 0-6)	SD/CI		0.19 (-0.06, 0.44)[b]			
Carr, 2012 (Trial 2)[115] (scale 0-6)	SD/CI	0.3 (0.01, 0.56)[b]				
Carr, 2012 (Trial 3)[115] (scale 0-6)	SD/CI	0.2 (0.04, 0.40)[b]				
Hampel, 2010[117] (scale 0-6)		0.49				
Ratner, 2008[121] (scale 0-6)	SD	0.6				
Itching						
Carr, 2012 (Trial 1)[115] (scale 0-6)	SD/CI		0.2 (-0.01, 0.47)[b]			
Carr, 2012 (Trial 2)[115] (scale 0-6)	SD/CI		0.2 (-0.02, 0.50)[b]			
Carr, 2012 (Trial 3)[115] (scale 0-6)	SD/CI		0.1 (-0.04, 0.27)[b]			
Hampel, 2010[117] (scale 0-6)		0.31				

Outcome	Variance[a]	SS Favors Combo MD	NSS Favors/NR Combo MD	Favors Neither MD=0	NSS Favors/NR INCS MD	SS Favors INCS MD
Ratner, 2008[121] (scale 0-6)	SD	0.6				
TNSS						
Carr, 2012 (Trial 1)[115] (scale 0-24)	SD/CI	0.9 (0.07, 1.74)[b]				
Carr, 2012 (Trial 2)[115] (scale 0-24)	SD/CI	1.0 (0.05, 1.91)[b]				
Carr, 2012 (Trial 3)[115] (scale 0-24)	SD/CI	0.6 (0.07, 1.22)[b]				
Hampel, 2010[117] (scale 0-24)	IQR	1.47				
Ratner, 2008[121] (scale 0-24)	SD	2.2				

INCS = Intranasal corticosteroid; MD = mean difference (calculated by authors with available data except where noted); NR = p-value not reported; NSS = not statistically significant; SS = statistically significant; TNSS = total nasal symptom score.

[a] Variance/confidence interval reported: CI=confidence interval; IQR = interquartile range; SD=standard deviation; SE=standard error.

[b] Differences between least squares means adjusted for center and baseline severity as reported by trial authors.

Figure 21. Congestion at 2 weeks meta-analysis: combination intranasal corticosteroid plus nasal antihistamine versus intranasal corticosteroid

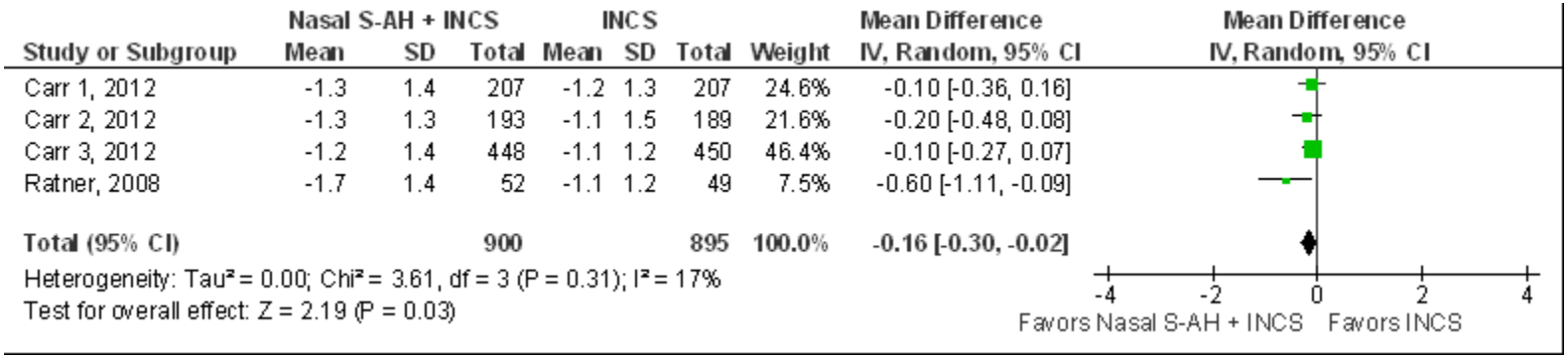


Figure 22. Rhinorrhea at 2 weeks meta-analysis: combination intranasal corticosteroid plus nasal antihistamine versus intranasal corticosteroid

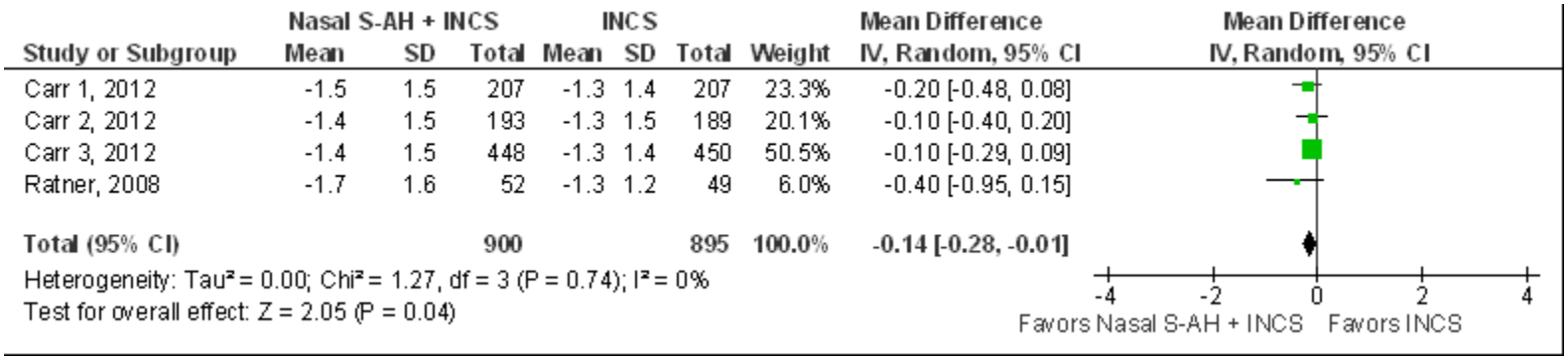


Figure 23. Sneezing at 2 weeks meta-analysis: combination intranasal corticosteroid plus nasal antihistamine versus intranasal corticosteroid

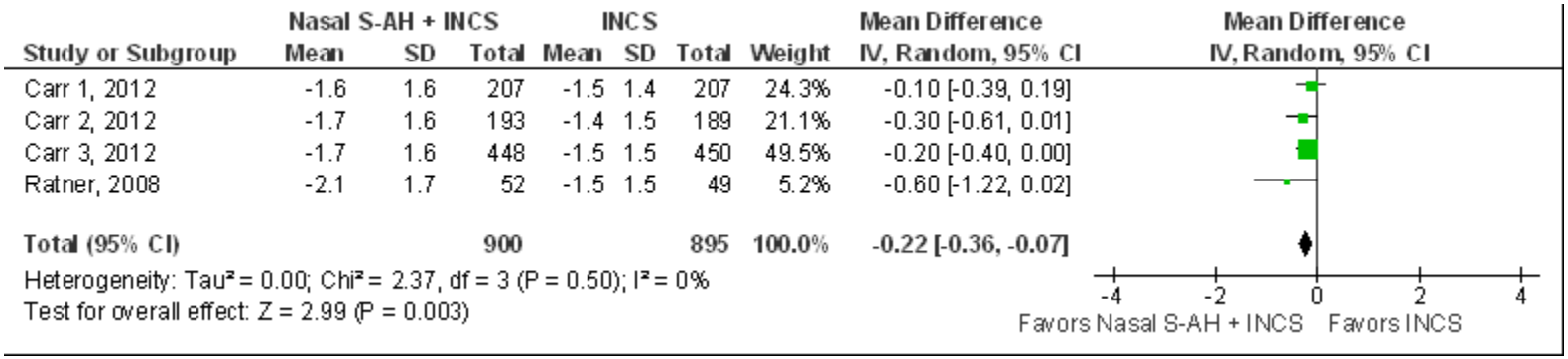


Figure 24. Nasal itch at 2 weeks meta-analysis: combination intranasal corticosteroid plus nasal antihistamine versus intranasal corticosteroid

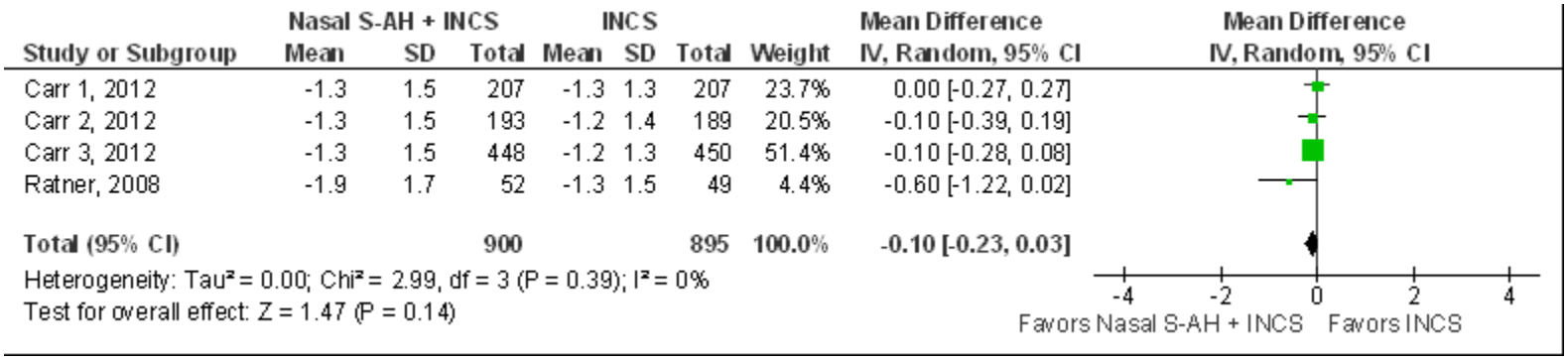


Figure 25. Total nasal symptom score at 2 weeks meta-analysis: combination intranasal corticosteroid plus nasal antihistamine versus intranasal corticosteroid

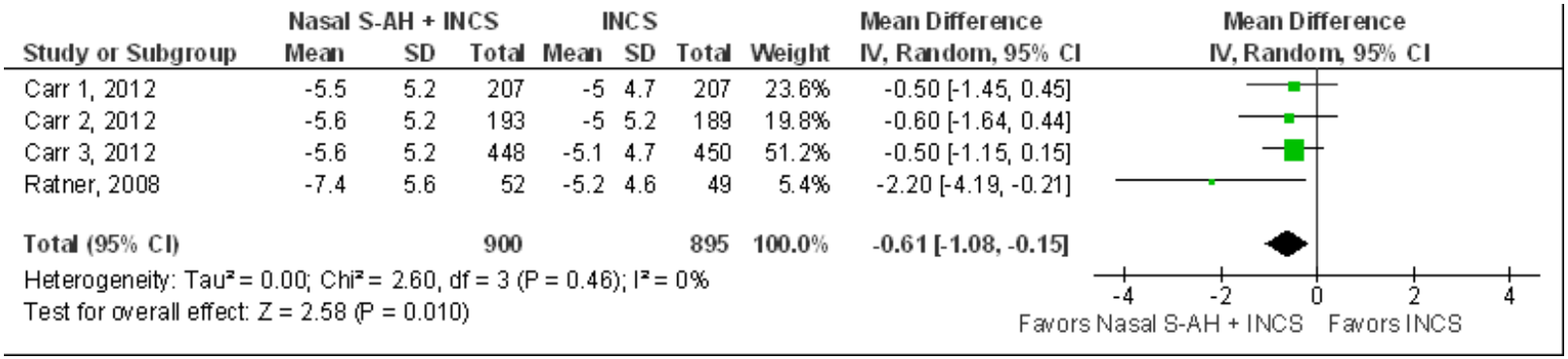


Table 49. Treatment effects: eye symptoms–combination intranasal corticosteroid plus nasal antihistamine versus intranasal corticosteroid

Outcome	Variance[a]	SS Favors Combo MD	NSS Favors/NR Combo MD	Favors Neither MD=0	NSS Favors/NR INCS MD	SS Favors INCS MD
TOSS[b], average change from baseline						
Carr, 2012 (Trial 1)[115]	SD/CI		0.52 (-0.10, 1.14)			
Carr, 2012 (Trial 2)[115]	SD/CI	0.88 (0.23, 1.54)				
Carr, 2012 (Trial 3)[115]	SD/CI		0.26 (-0.18, 0.69)			
Hampel, 2010[117]		0.45				

INCS = Intranasal corticosteroid; MD = mean difference calculated by authors with available data; NR = p-value not reported; NSS = not statistically significant; SS = statistically significant; TOSS = total ocular symptom score.

Adjusted mean differences reported by Carr, 2012, mean differences calculated by authors with available data (Hampel, 2010).

[a] Variance/confidence interval reported: CI=confidence interval; SD=standard deviation; SE=standard error.

[b] Three symptoms (itchy eyes, watery eyes, red eyes) each scored twice daily on a 0 (no symptoms) to 3 (severe symptoms) scale; maximum daily score = 18.

Figure 26. Total ocular symptom score at 2 weeks meta-analysis: combination intranasal corticosteroid plus nasal antihistamine versus intranasal corticosteroid

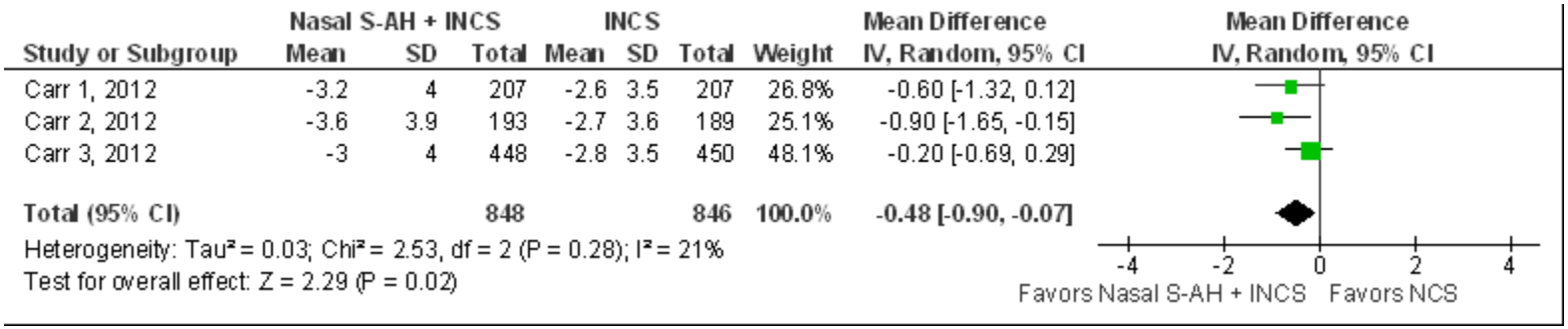


Table 50. Treatment effects: quality of life symptoms–combination intranasal corticosteroid plus nasal antihistamine versus intranasal corticosteroid

Outcome	Variance[a]	SS Favors Combo MD	NSS Favors/NR Combo MD	Favors Neither MD=0	NSS Favors/NR INCS MD	SS Favors INCS MD
RQLQ, change from baseline						
Hampel, 2010[117]			0.17 (NSS)			
Ratner, 2008[121]	SD		0.45 (NSS)			

INCS = intranasal corticosteroid; MD = mean difference calculated by authors from available data; NR = p-value not reported; NSS = not statistically significant; RQLQ = Rhinoconjunctivitis Quality of Life Questionnaire; SS = statistically significant.

[a] Variance/confidence interval reported: CI=confidence interval; SD=standard deviation; SE=standard error.

Quality of Life

Both trials[117, 121] that assessed quality of life (total N=408) showed greater improvement in RQLQ scores with combination therapy than with intranasal corticosteroid monotherapy. Treatment effects were 0.17 and 0.45, neither of which was statistically significant. Treatment effects did not exceed the MCID of 0.5 points.

For RQLQ, the risk of bias was rated low based on the quality of the trials. Results were consistent across trials, but effects were statistically and clinically nonsignificant, that is, imprecise. The evidence was insufficient to support the use of one treatment over the other for this outcome.

Combination Intranasal Corticosteroid Plus Nasal Antihistamine Versus Nasal Antihistamine

Description of Included Studies

Five[115, 117, 121] multicenter, RCTs published between 2008 and 2012 were identified (total N=2101). All were 2-week, double-blinded trials based in North America. Trial size ranged from 101 to 893 patients randomized to treatment groups of interest. In all five trials, the nasal antihistamine was azelastine, and the intranasal corticosteroid was fluticasone propionate. Three trials[115] from the same article used a newly approved combination product comprising both drugs, and two trials[117, 121] used a separate nasal inhaler for each drug in the combination. All five trials were industry funded.

The mean age of trial participants ranged from 36 to 40 years. Most participants were female (approximately 62 percent). The majority of patients were white (minimum 74 percent). Of two trials[117, 121] that reported the proportions of other races, one[121] included approximately 15 percent Hispanic patients. All trials required a minimum duration and severity of SAR symptoms. Mean SAR duration ranged from 16 to 22 years. Mean baseline nasal symptoms were in the severe range.

All five trials assessed both individual and total nasal symptoms. Four[115, 117] of five assessed eye symptoms, and two[117, 121] assessed quality of life. No trial assessed asthma outcomes. In all five trials, patients rated symptoms twice daily. Individual nasal symptoms (congestion, rhinorrhea, sneezing, and itching) and eye symptoms (itching, tearing, and redness) were rated on a scale from 0 (no symptoms) to 3 (severe symptoms). Morning and evening scores were summed to give a maximum score of 6 for each individual symptom. TNSS ranged from 0 to 24, and TOSS ranged from 0 to 18. The RQLQ was used to assess quality of life. Scores range from 0 (no impairment) to 6 (severe impairment). The MCID is 0.5 points.

All five trials were rated good quality.

Key Points

These results are summarized in Table 51.

- Individual nasal symptoms (congestion, rhinorrhea, sneezing, and itch), TNSS and TOSS at 2 weeks: High strength evidence for equivalence of combination intranasal corticosteroid plus nasal antihistamine and nasal antihistamine monotherapy based on five trials[115, 117, 121] (for individual nasal symptoms and TNSS) and four trials[115, 117] (for TOSS) with low risk of bias and consistent, precise results.

- Quality of life as assessed by the RQLQ at 2 weeks: Evidence was insufficient to support the use of one treatment over the other based on two trials[117, 121] with low risk of bias and consistent but imprecise results.
- These results are based on trials using one of eight intranasal corticosteroids (12.5 percent) and one of two nasal antihistamines (50 percent).

Table 51. Strength of evidence: combination intranasal corticosteroid plus nasal antihistamine versus nasal antihistamine

Outcome	RCTs (Patients)	Risk of Bias	Consistency	Directness	Precision	Overall GRADE
2-week congestion, rhinorrhea, sneezing, itch	5[115, 117, 121] (2097)	Low	Consistent	Direct	Precise	High[a]
2-week TNSS	5[115, 117, 121] (2097)	Low	Consistent	Direct	Precise	High[a]
2-week TOSS	4[115, 117] (1998)	Low	Consistent	Direct	Precise	High[a]
2-week RQLQ	2[117, 121] (404)	Low	Consistent	Direct	Imprecise	Insufficient

GRADE = Grading of Recommendations Assessment, Development and Evaluation; RCTs (Patients) = number of randomized controlled trials (number of patients randomized to treatment groups of interest); RQLQ = Rhinoconjunctivitis Quality of Life Questionnaire; TNSS = total nasal symptom score; TOSS = total ocular symptom score.

[a] The body of evidence supports equivalence of combination intranasal corticosteroid plus nasal antihistamine and nasal antihistamine monotherapy for the outcomes identified

Synthesis and Strength of Evidence

Nasal symptom outcomes discussed below are summarized in Table 52, eye symptom outcomes in Table 53, and quality of life outcomes in Table 54.

As shown in these tables and noted above, several trials reported on each outcome. Additionally, variance estimates of group-level treatment effects were provided. Thus, meta-analyses were performed for all nasal and eye symptom outcomes.

Nasal Symptoms

All five trials[115, 117, 121] assessed four individual nasal symptoms and TNSS at 2 weeks (total N=2101). Four trials[115, 121] (85 percent of patients reporting this outcome) were included in meta-analyses for each nasal outcome. Variance estimates necessary for pooling were not reported by Hampel (2010),[117] preventing inclusion of this trial in the meta-analyses. All five trials were rated good quality.

All five trials showed statistically significant improvements in congestion with combination therapy compared to nasal antihistamine monotherapy. Treatment effects ranged from 0.2 to 0.6 on a 0-6 point scale (from 3 percent to 10 percent of maximum score). The pooled effect was 0.28 on a 0-6 point scale (95 percent CI: 0.16 to 0.41), a statistically significant result favoring combination therapy (Figure 27). The larger bound of the 95 percent CI represented 7 percent of maximum score. Statistical heterogeneity was low (I^2=0 percent, p=0.41).

For the outcome of congestion, the risk of bias was rated as low based on the quality of the trials. Statistical heterogeneity of a meta-analysis of four trials[115, 121] was low, and the pooled effect was consistent with the effect reported in the one trial[117] not included in the meta-analysis. The 95 percent CI for the pooled effect (0.16 to 0.41) fell within an interval bounded by –MCID and +MCID (-1.8 and +1.8 on the 0-6 point scale used). The Hampel (2010) trial[117] reported a

treatment effect of 0.49 on a 0-6 point scale (8 percent of maximum score) favoring combination therapy. If this trial were included in the meta-analysis, the pooled effect (0.28; 5 percent of maximum score) would increase. Because the trial represented only 15 percent of patients reporting this outcome, it is unlikely that the 95 percent CI of the pooled effect would include an MCID of 30 percent maximum score. The body of evidence supporting a conclusion of equivalence of combination therapy and nasal antihistamine for this outcome was therefore considered precise. The overall strength of evidence for this conclusion is high.

All five trials showed greater improvement in rhinorrhea with combination therapy than with nasal antihistamine monotherapy. In four trials,[115, 117, 121] including Hampel (2010)[117] whose results were not pooled, treatment effects were statistically significant and ranged from 0.2 to 0.6 on a 0-6 point scale (3 percent to 10 percent of maximum score). The pooled effect was 0.31 on a 0-6 point scale (95 percent CI: 0.18 to 0.45), a statistically significant result favoring combination therapy (Figure 28). The larger bound of the 95 percent CI represented 8 percent of maximum score. Statistical heterogeneity was low (I^2=1 percent, p=0.39).

For the outcome of rhinorrhea, the risk of bias was rated as low based on the quality of the trials. Statistical heterogeneity of a meta-analysis of four trials[115, 121] was low, and the pooled effect was consistent with the effect reported in the one trial[117] not included in the meta-analysis. The 95 percent CI for the pooled effect (0.18 to 0.45) fell within an interval bounded by –MCID and +MCID (-1.8 and +1.8 on the 0-6 point scale used). The Hampel (2010) trial[117] reported a treatment effect of 0.55 on a 0-6 point scale (9 percent of maximum score) favoring combination therapy. If this trial were included in the meta-analysis, the pooled effect (0.31; 5 percent of maximum score) would increase. Because the trial represented only 15 percent of patients reporting this outcome, it is unlikely that the 95 percent CI of the pooled effect would include an MCID of 30 percent maximum score. The body of evidence supporting a conclusion of equivalence of combination therapy and nasal antihistamine for this outcome was therefore considered precise. The overall strength of evidence for this conclusion is high.

All five trials showed greater improvement in sneezing with combination therapy than with nasal antihistamine monotherapy. In four trials, including Hampel (2010),[117] treatment effects were statistically significant and ranged from 0.2 to 0.61 on a 0-6 point scale (from 3 percent to 10 percent of maximum score). The pooled effect was 0.34 on a 0-6 point scale (95 percent CI: 0.20 to 0.48), a statistically significant result favoring combination therapy (Figure 29). The larger bound of the 95 percent CI represented 6 percent of maximum score. Statistical heterogeneity was low (I^2=0 percent, p=0.74).

For the outcome of sneezing, the risk of bias was rated as low based on the quality of the trials. Statistical heterogeneity of a meta-analysis of four trials[115, 121] was low, and the pooled effect was consistent with the effect reported in the one trial[117] not included in the meta-analysis. The 95 percent CI for the pooled effect (0.20 to 0.48) fell within an interval bounded by –MCID and +MCID (-1.8 and +1.8 on the 0-6 point scale used). The Hampel (2010) trial[117] reported a treatment effect of 0.61 on a 0-6 point scale (10 percent of maximum score) favoring combination therapy. If this trial were included in the meta-analysis, the pooled effect (0.34; 6 percent of maximum score) would increase. Because the trial represented only 15 percent of patients reporting this outcome, it is unlikely that the 95 percent CI of the pooled effect would include an MCID of 30 percent maximum score. The body of evidence supporting a conclusion of equivalence of combination therapy and nasal antihistamine for this outcome was therefore considered precise. The overall strength of evidence for this conclusion is high.

All five trials showed greater improvement in nasal itch with combination therapy than with nasal antihistamine monotherapy. In three trials, including Hampel (2010),[117] treatment effects were statistically significant and ranged from 0.3 to 0.8 on a 0-6 point scale (from 5 percent to 13 percent of maximum score). The pooled effect was 0.30 on a 0-6 point scale (95 percent CI: 0.12 to 0.48), a statistically significant result favoring combination therapy (Figure 30). The larger bound of the 95 percent CI represented 8 percent of maximum score. Statistical heterogeneity was low to moderate (I^2=34%) but not statistically significant (p=0.21). The 95 percent CI of one of the trials (21 percent of the pooled sample) included zero (-0.48 to 0.08).

For the outcome of nasal itch, the risk of bias was rated as low based on the quality of the trials. Statistical heterogeneity of a meta-analysis of four trials[115, 121] was low to moderate, and the pooled effect was consistent with the effect reported in the one trial[117] not included in the meta-analysis. The 95 percent CI for the pooled effect (0.12 to 0.48) fell within an interval bounded by –MCID and +MCID (-1.8 and +1.8 on the 0-6 point scale used). The Hampel (2010) trial[117] reported a treatment effect of 0.40 on a 0-6 point scale (7 percent of maximum score) favoring combination therapy. If this trial were included in the meta-analysis, the pooled effect (0.30; 5 percent of maximum score) would increase. Because the trial represented only 15 percent of patients reporting this outcome, it is unlikely that the 95 percent CI of the pooled effect would include an MCID of 30 percent maximum score. The body of evidence supporting a conclusion of equivalence of combination therapy and nasal antihistamine for this outcome was therefore considered precise. The overall strength of evidence for this conclusion is high.

All five trials showed statistically significant improvements in TNSS with combination therapy. Treatment effects ranged from 0.7 to 2.6 on a 0-24 point scale (from 3 percent to 11 percent of maximum score). The pooled effect was 1.28 on a 0-24 point scale (95 percent CI: 0.82 to 1.74), a statistically significant result favoring combination therapy (Figure 31). The larger bound of the 95 percent CI represented 7 percent of maximum score. Statistical heterogeneity was low (I^2=0 percent, p=0.54).

For TNSS, the risk of bias was rated as low based on the quality of the trials. Statistical heterogeneity of a meta-analysis of four trials[115, 121] was low, and the pooled effect was consistent with the effect reported in the one trial[117] not included in the meta-analysis. The 95 percent CI for the pooled effect (0.82 to 1.74) fell within an interval bounded by –MCID and +MCID (-7.2 and +7.2 on the 0-24 point scale used). The Hampel (2010) trial[117] reported a treatment effect of 2.06 on a 0-24 point scale (9 percent of maximum score) favoring combination therapy. If this trial were included in the meta-analysis, the pooled effect (1.28; 5 percent of maximum score) would increase. Because the trial represented only 15 percent of patients reporting this outcome, it is unlikely that the 95 percent CI of the pooled effect would include an MCID of 30 percent maximum score. The body of evidence supporting a conclusion of equivalence of combination therapy and nasal antihistamine for this outcome was therefore considered precise. The overall strength of evidence for this conclusion is high.

Eye Symptoms

Four[115, 117] trials that assessed eye symptoms at 2 weeks (total N=2000) showed greater improvements in TOSS with combination therapy than with nasal antihistamine monotherapy. Treatment effects ranged from 0.03 to 0.71 on a 0-18 point scale (from less than 1 percent to 4 percent of maximum score), but effects were either statistically nonsignificant or statistical significance was not reported. The pooled effect from a meta-analysis of three trials (85 percent of patients reporting this outcome; Hampel [2010][117] excluded) was 0.25 on a 0-18 point scale

(95 percent CI: -0.12 to 0.61), a statistically nonsignificant result favoring combination therapy (Figure 32). The larger bound of the 95 percent CI represented 3 percent of maximum score. Statistical heterogeneity was low (I^2=0 percent, p=0.37).

For TOSS, the risk of bias was rated as low based on the quality of the trials. Statistical heterogeneity of a meta-analysis of three trials[115] was low, and the pooled effect was consistent with the effect reported in the one trial[117] not included in the meta-analysis. The 95 percent CI for the pooled effect (-0.12 to 0.61) fell within an interval bounded by –MCID and +MCID (-5.4 and +5.4 on the 0-18 point scale used). The Hampel (2010) trial[117] reported a treatment effect of 0.71 on a 0-18 point scale (4 percent of maximum score) favoring combination therapy. If this trial were included in the meta-analysis, the pooled effect (0.25; 1 percent of maximum score) would increase. Because the trial represented only 15 percent of patients reporting this outcome, it is unlikely that the 95 percent CI of the pooled effect would include an MCID of 30 percent maximum score. The body of evidence supporting a conclusion of equivalence of combination therapy and nasal antihistamine for this outcome was therefore considered precise. The overall strength of evidence for this conclusion is high.

Table 52. Treatment effects: nasal symptoms–combination intranasal corticosteroid plus nasal antihistamine versus nasal antihistamine

Outcome	Variance[a]	SS Favors Combo MD	NSS Favors/NR Combo MD	Favors Neither MD=0	NSS Favors/NR Antihistamine MD	SS Favors Antihistamine MD
2 Weeks, Average Change From Baseline						
Congestion						
Carr, 2012 (Trial 1)[115] (scale 0-6)	SD/CI	0.3 (0.12, 0.56)[b]				
Carr, 2012 (Trial 2)[115] (scale 0-6)	SD/CI	0.4 (0.14, 0.60) [b]				
Carr, 2012 (Trial 3)[115] (scale 0-6)	SD/CI	0.2 (0.07, 0.38)[b]				
Hampel, 2010[117] (scale 0-6)		0.49				
Ratner, 2008[121] (scale 0-6)	SD	0.6				
Rhinorrhea						
Carr, 2012 (Trial 1)[115] (scale 0-6)	SD/CI	0.41 (0.17, 0.66)[b]				
Carr, 2012 (Trial 2)[115] (scale 0-6)	SD/CI		0.3 (-0.01, 0.51,)[b]			
Carr, 2012 (Trial 3)[115] (scale 0-6)	SD/CI	0.2 (0.07, 0.41)[b]				
Hampel, 2010[117] (scale 0-6)		0.55				
Ratner, 2008[121] (scale 0-6)	SD	0.6				
Sneezing						
Carr, 2012 (Trial 1)[115] (scale 0-6)	SD/CI	0.33 (0.08, 0.59)[b]				
Carr, 2012 (Trial 2)[115] (scale 0-6)	SD/CI		0.30 (-0.02, 0.53,)[b]			
Carr, 2012 (Trial 3)[115] (scale 0-6)	SD/CI	0.2 (0.05, 0.40)[b]				
Hampel, 2010[117] (scale 0-6)		0.61				
Ratner, 2008[121] (scale 0-6)	SD	0.6				
Itching						
Carr, 2012 (Trial 1)[115] (scale 0-6)	SD/CI	0.3 (0.06, 0.54)[b]				
Carr, 2012 (Trial 2)[115] (scale 0-6)	SD/CI		0.2 (-0.04, 0.47,)[b]			
Carr, 2012 (Trial 3)[115] (scale 0-6)	SD/CI		0.29 (-0.01, 0.32,)[b]			
Hampel, 2010[117] (scale 0-6)		0.40				
Ratner, 2008[121] (scale 0-6)	SD	0.8				

Outcome	Variance[a]	SS Favors Combo MD	NSS Favors/NR Combo MD	Favors Neither MD=0	NSS Favors/NR Antihistamine MD	SS Favors Antihistamine MD
TNSS						
Carr, 2012 (Trial 1)[115] (scale 0-24)	SD/CI	1.4 (0.54, 2.22,)[b]				
Carr, 2012 (Trial 2)[115] (scale 0-24)	SD/CI	1.0 (0.09, 1.90)[b]				
Carr, 2012 (Trial 3)[115] (scale 0-24)	SD/CI	0.7 (0.13, 1.30)[b]				
Hampel, 2010[117] (scale 0-24)	IQR	2.06				
Ratner, 2008[121] (scale 0-24)	SD	2.6				

MD = Mean difference (calculated by authors with available data except where noted); NR = p-value not reported; NSS = not statistically significant; SS = statistically significant; TNSS = total nasal symptom score.

[a] Variance/confidence interval reported: CI=confidence interval; IQR = interquartile range; SD=standard deviation; SE=standard error.

[b] Adjusted mean differences reported by trial authors.

Figure 27. Congestion at 2 weeks: meta-analysis of 4 trials–combination intranasal corticosteroid plus nasal antihistamine versus nasal antihistamine

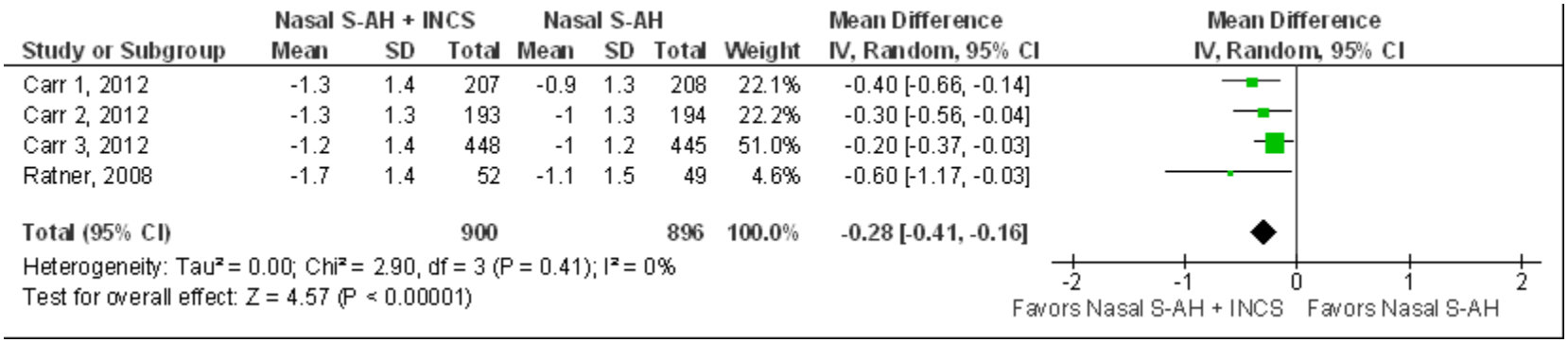


Figure 28. Rhinorrhea at 2 weeks: meta-analysis of 4 trials–combination intranasal corticosteroid plus nasal antihistamine versus nasal antihistamine

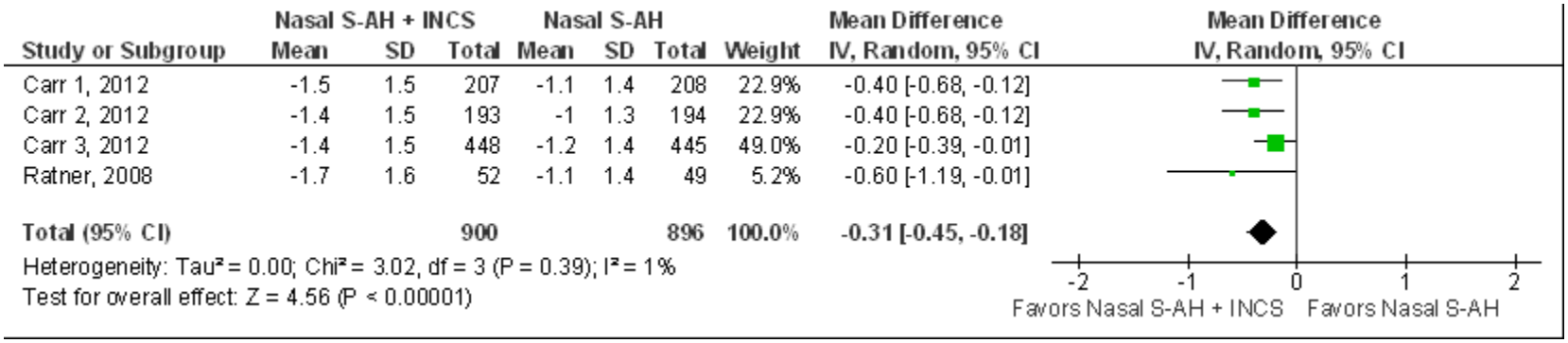


Figure 29. Sneezing at 2 weeks: meta-analysis of 4 trials–combination intranasal corticosteroid plus nasal antihistamine versus nasal antihistamine

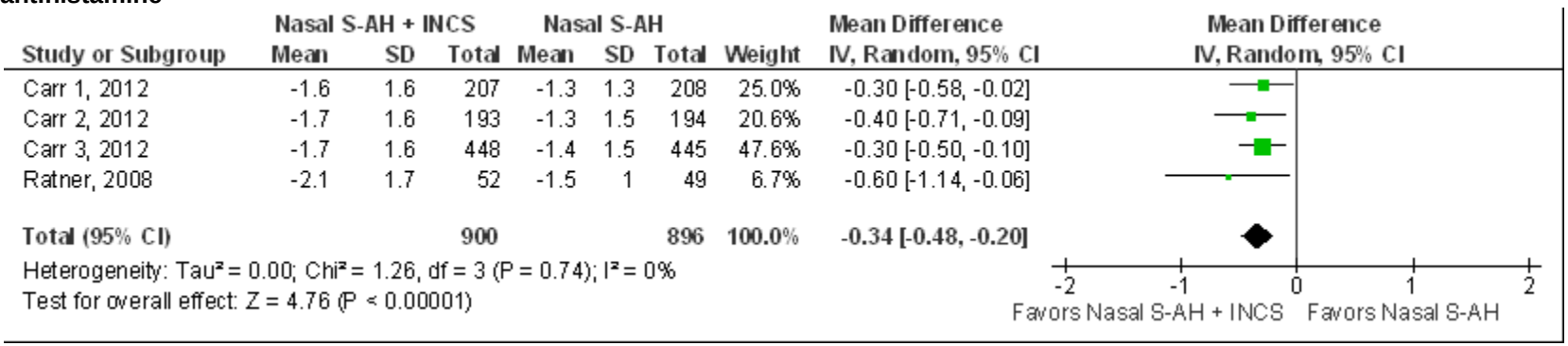


Figure 30. Nasal itch at 2 weeks: meta-analysis of 4 trials–combination intranasal corticosteroid plus nasal antihistamine versus nasal antihistamine

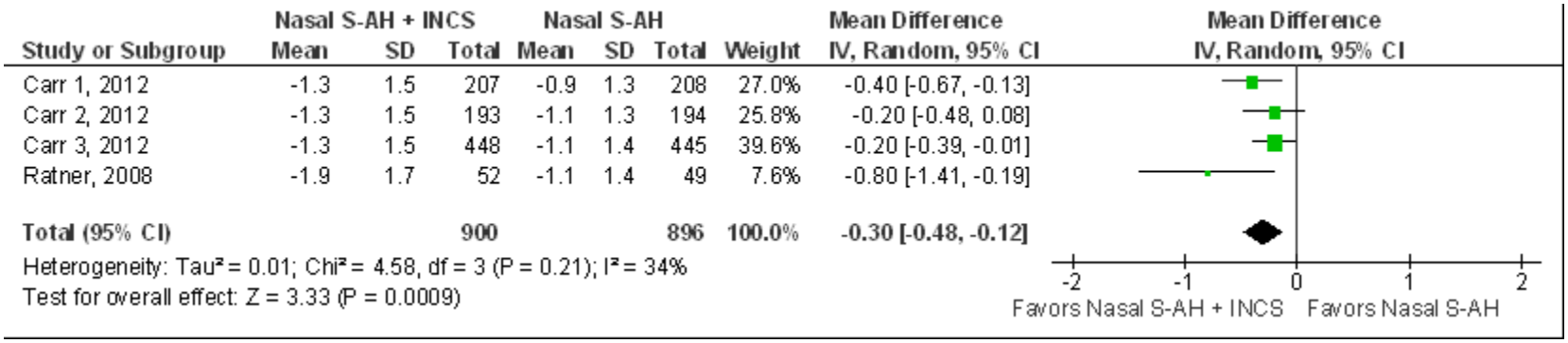


Figure 31. Total nasal symptom score at 2 weeks: meta-analysis of 4 trials–combination intranasal corticosteroid plus nasal antihistamine versus nasal antihistamine

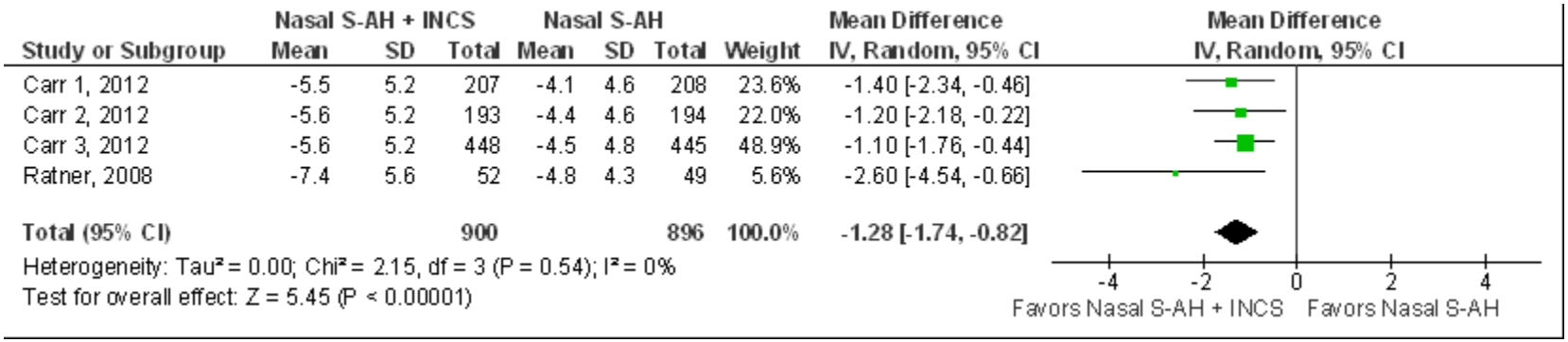


Table 53. Treatment effects: eye symptoms–combination intranasal corticosteroid plus nasal antihistamine versus nasal antihistamine

Outcome	Variance[a]	SS Favors Combo MD	NSS Favors/NR Combo MD	Favors Neither MD=0	NSS Favors/NR Antihistamine MD	SS Favors Antihistamine MD
TOSS[b], average change from baseline						
Carr, 2012 (Trial 1)[115]	SD/CI		0.25 (-0.41, 0.9)			
Carr, 2012 (Trial 2)[115]	SD/CI		0.6 (-0.05, 1.25)			
Carr, 2012 (Trial 3)[115]	SD/CI		0.03 (-0.42, 0.47)			
Hampel, 2010[117]			0.71 (NR)			

MD = Mean difference calculated by authors with available data; NR = p-value not reported; NSS = not statistically significant; SS = statistically significant; TOSS = total ocular symptom score.

Adjusted mean differences reported by Carr, 2012, mean differences calculated by authors with available data (Hampel, 2010)

[a] Variance/confidence interval reported: CI=confidence interval; SD=standard deviation; SE=standard error.

[b] Three symptoms (itchy eyes, watery eyes, red eyes) each scored twice daily on a 0 (no symptoms) to 3 (severe symptoms) scale; maximum daily score = 18.

Figure 32. Total ocular symptom score at 2 weeks: meta-analysis of 4 trials–combination intranasal corticosteroid plus nasal antihistamine versus nasal antihistamine

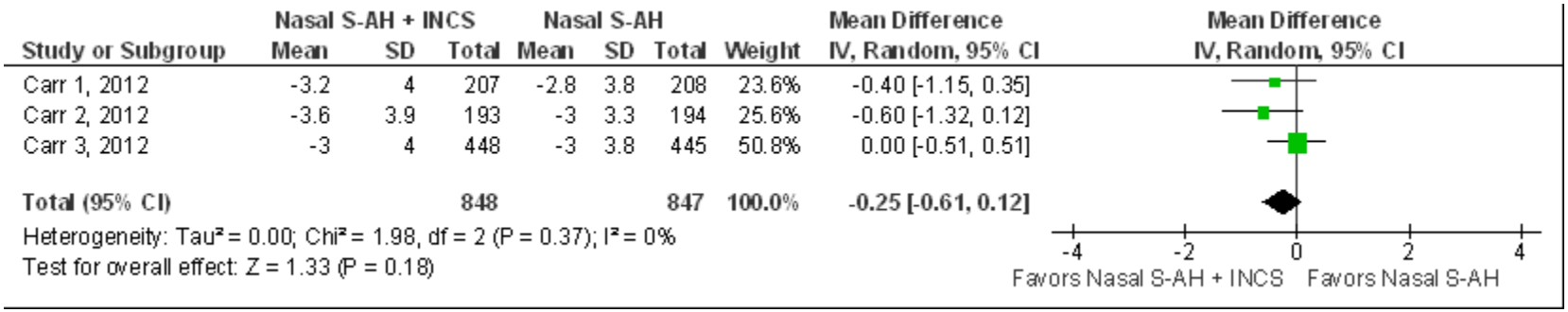


Table 54. Treatment effects: quality of life outcomes–combination intranasal corticosteroid plus nasal antihistamine versus nasal antihistamine

Outcome	Variance[a]	SS Favors Combo MD	NSS Favors/NR Combo MD	Favors Neither MD=0	NSS Favors/NR Antihistamine MD	SS Favors Antihistamine MD
RQLQ, change from baseline						
Hampel, 2010[117]		0.43				
Ratner, 2008[121]	SD	0.71				

MD = Mean difference, calculated by authors from available data; NR = p-value not reported; NSS = not statistically significant; RQLQ = Rhinoconjunctivitis Quality of Life Questionnaire; SS = statistically significant.

[a] Variance/confidence interval reported: CI=confidence interval; SD=standard deviation; SE=standard error.

Quality of Life

Both trials[117, 121] that assessed quality of life showed statistically significant improvement in RQLQ scores with combination therapy. The larger trial[117] (n=459; 75 percent of patients reporting this outcome) showed a treatment effect of 0.43. The smaller trial[121] showed a treatment effect of 0.71. The latter result exceeds the MCID for the RQLQ of 0.5 points.

For the outcome of quality of life, the risk of bias was rated as low based on the quality of the trials. Effect estimates were consistent across trials but not precise. Evidence to support the use of one treatment over the other for this outcome is insufficient.

Combination Oral Selective Antihistamine Plus Oral Decongestant Versus Oral Selective Antihistamine

Description of Included Studies

Seven[101-107] multicenter, RCTs published between 1995 and 2009 were identified (N=3575). All were double-blinded, 2-week trials. Six[101, 102, 104-107] were conducted in North America, and one[103] in Europe. Trial size ranged from 398 to 744 patients randomized to treatment groups of interest. Oral selective antihistamines studied were desloratadine in four trials[102, 104-106] and fexofenadine,[107] cetirizine,[103] and loratadine[101] in one trial each. Pseudoephedrine was the decongestant in all seven trials. Five trials[101, 104-107] were industry funded, and two[102, 103] did not report funding.

Mean ages of patients ranged from 30 to 37 years. Most patients were female (50 percent to 70 percent), and most were white (80 percent to 87 percent). The mean duration of SAR symptoms ranged from 9 to 19 years. All trials required a minimum duration and severity of SAR symptoms. Mean baseline nasal congestion scores were in the moderate to severe range.

All seven trials assessed nasal congestion. Two trials[103, 107] also assessed rhinorrhea, sneezing, and eye symptoms, and one[103] assessed nasal itch. In six trials,[101-106] patients rated symptom severity on 0 (no symptoms) to 3 (severe symptoms) scale. In the one trial[101] that reported on TNSS, individual nasal symptom scores were summed for a 0-12 point TNSS scale. One trial[107] used a 5-point (0 = no symptoms, 4 = very severe symptoms) scale. Of the two trials reporting on eye symptoms, one[103] assessed only ocular itching using a 4-point (0-3) symptom rating scale. The other trial[107] assessed ocular itching, tearing, and redness using the 5-point (0-4) scale.

Three trials[101, 103, 107] were rated good quality (37 percent of all patients), one[106] was fair (19 percent), and three[102, 104, 105] were poor (44 percent).

Key Points

Results discussed below are summarized in Table 55.

- Nasal congestion at 2 weeks: Evidence was insufficient to support one treatment over the other based on seven trials[101-107] with medium risk of bias and consistent but imprecise results.
- Rhinorrhea and sneezing at 2 weeks: Evidence was insufficient to support one treatment over the other based on two trials[103, 107] with low risk of bias and consistent but imprecise results.

- Nasal itch and TNSS at 2 weeks: Evidence was insufficient to support the use of one treatment over the other based on one trial[103] for nasal itch and one trial[101] for TNSS. Each trial had low risk of bias and an imprecise effect estimate.
- Eye symptoms (itching and TOSS) at 2 weeks: Evidence was insufficient to support the use of one treatment over the other based on two trials[103, 107] with low risk of bias and inconsistent, imprecise results.
- These results are based on trials using four of five oral selective antihistamines (80 percent) and one of two oral decongestants (50 percent).

Table 55. Strength of evidence: combination oral selective antihistamine plus oral decongestant versus oral selective antihistamine

Outcome	RCTs (Patients)	Risk of Bias	Consistency	Directness	Precision	Overall GRADE
2-week congestion	7[101-107] (3575)	Medium	Consistent	Direct	Imprecise	Insufficient
2-week rhinorrhea	2[103, 107] (891)	Low	Consistent	Direct	Imprecise	Insufficient
2-week sneezing	2[103, 107] (891)	Low	Consistent	Direct	Imprecise	Insufficient
2-week nasal itch	1[103] (458)	Low	Consistency unknown (single study)	Direct	Imprecise	Insufficient
2-week TNSS	1[101] (438)	Low	Consistency unknown (single study)	Direct	Imprecise	Insufficient
2-week eye symptoms (itching, TOSS)	2[103, 107] (891)	Low	Inconsistent	Direct	Imprecise	Insufficient

GRADE = Grading of Recommendations Assessment, Development and Evaluation; RCTs (Patients) = number of randomized controlled trials (number of patients randomized to treatment groups of interest); TNSS = total nasal symptom score; TOSS = total ocular symptom score.

Synthesis and Strength of Evidence

Nasal symptom outcomes discussed below are summarized in Table 56 and eye symptom outcomes in Table 57. Although several authors reported on the outcome of nasal congestion, none provided variance estimates of group-level treatment effects. Thus, meta-analysis was not possible.

Nasal Symptoms

All seven trials[101-107] assessed congestion at 2 weeks (total N=3575). All seven showed statistically significant improvements in nasal congestion with combination therapy. Three[101, 103, 107] were good quality trials of 1329 patients total (37 percent of patients reporting this outcome). Two[101, 103] showed treatment effects of 0.2 and 0.25 on a 0-3 point scale (7 percent and 8 percent of maximum score, respectively). One fair quality trial[106] (n=676, 19 percent of patients reporting) showed a treatment effect of 0.2 on a 0-3 point scale (7 percent of maximum score). Three trials[102, 104, 105] were rated poor quality due to inappropriate analysis of results (not intention to treat). Treatment effects reported by these trials ranged from 0.16 to 0.27 on a 0-3 point scale (from 5 percent to 9 percent of maximum score).

For the outcome of nasal congestion at 2 weeks, the risk of bias was assessed as medium. Forty-four percent of patients were in poor quality trials, and 37 percent were in good quality trials. Treatment effects consistently favored combination therapy in all trials. Although statistically significant, no treatment effect exceeded an MCID of 30 percent maximum score.

The body of evidence was therefore considered imprecise. Evidence was insufficient to support the use of one treatment over the other for the treatment of congestion.

Two[103, 107] of seven trials assessed rhinorrhea at 2 weeks (total N=891). Both trials were large (approximately 450 patients in each), and both were rated good quality. Both favored combination therapy over oral selective antihistamine monotherapy for this outcome. Treatment effects were 0.1 and 0.13 on a 0-3 point scale (3 percent and 4 percent of maximum score, respectively); the latter was statistically significant.

For the outcome of rhinorrhea at 2 weeks, the risk of bias was assessed as low based on the quality of the trials. Treatment effects were consistent but imprecise. The evidence was insufficient to support the use of one treatment over the other for this outcome.

Two[103, 107] of seven trials assessed sneezing at 2 weeks (total N=891). Both trials were large (approximately 450 patients in each), and both were rated good quality. Both favored combination therapy over oral selective antihistamine monotherapy. Treatment effects were 0.08 and 0.1 on a 0-3 point scale (both 3 percent of maximum score); the former was statistically significant.

For the outcome of sneezing at 2 weeks, the risk of bias was assessed as low based on the quality of the trials. Treatment effects were consistent but imprecise. The evidence was insufficient to support the use of one treatment over the other for this outcome.

One good quality trial[103] assessed nasal itch at 2 weeks (N=458). The treatment effect (0.1 on a 0-3 point scale; 3 percent of maximum score) favored combination therapy and was statistically significant.

For the outcome of nasal itch at 2 weeks, the risk of bias was rated as low based on the quality of the trial. Consistency of results could not be assessed in a single trial, and the effect estimate was imprecise. The evidence was insufficient to support the use of one treatment over the other for this outcome.

One good quality trial[101] assessed TNSS at 2 weeks (N=438). The treatment effect (0.6 on a 0-3 point scale; 20 percent of maximum score) favored combination therapy and was statistically nonsignificant.

For TNSS at two weeks, the risk of bias was rated as low based on the quality of the trial. Consistency could not be assessed in a single trial, and the effect estimate was imprecise. Evidence was insufficient to support the use of one treatment over the other for this outcome.

Eye Symptoms

Two good quality trials[103, 107] assessed eye symptoms at 2 weeks (total N=891). One trial[103] assessed ocular itching, and the other[107] assessed TOSS comprising ocular itching, tearing, and redness. The treatment effect for ocular itch[103] was 0.01 on a 0-3 point scale (less than 1 percent of maximum score), a statistically nonsignificant result that favored oral selective antihistamine monotherapy. The treatment effect for TOSS[107] was 0.1 on a 0-4 point scale (3 percent of maximum score), favoring combination therapy. Statistical significance was not reported.

For eye symptoms at 2 weeks, the risk of bias was low based on the quality of the trials. Treatment effect estimates were inconsistent and imprecise. Evidence was insufficient to support the use of one treatment over the other for this outcome.

Table 56. Treatment effects: nasal symptoms–combination oral selective antihistamine plus oral decongestant versus oral selective antihistamine

Outcome	Variance	SS Favors Combo MD	NSS Favors/NR Combo MD	Favors Neither MD=0	NSS Favors/NR Antihistamine MD	SS Favors Antihistamine MD
2 Weeks, Average Change From Baseline						
Congestion						
Bronsky, 1995[101] (scale 0-3)		0.2				
Chervinsky, 2005[102] (scale 0-3)		0.19				
Grosclaude, 1997[103] (scale 0-3)		0.25				
Grubbe, 2009[104] (scale 0-3)		0.27				
Pleskow, 2005[105] (scale 0-3)		0.16				
Schenkel, 2002[106] (scale 0-3)		0.20				
Sussman, 1999[107] (scale 0-4)[a]		0.2				
Rhinorrhea						
Grosclaude, 1997[103] (scale 0-3)		0.13				
Sussman, 1999[107] (scale 0-4)[a]			0.1 (NR)			
Sneezing						
Grosclaude, 1997[103] (scale 0-3)		0.08				
Sussman, 1999[107] (scale 0-4)[a]			0.1 (NR)			
Itching						
Grosclaude, 1997[103] (scale 0-3)		0.10				
TNSS						
Bronsky, 1995[101] (scale 0-3)			0.6 (NR)			

MD = Mean difference between group mean changes from baseline; NR = p-value not reported; NSS = not statistically significant; SS = statistically significant; TNSS = total nasal symptom score.

[a]Sussman, 1999 trial = 2.6 weeks.

Table 57. Treatment effects: eye symptoms–combination oral selective antihistamine plus oral decongestant versus oral selective antihistamine

Outcome	Variance	SS Favors Combo MD	NSS Favors/NR Combo MD	Favors Neither MD=0	NSS Favors/NR Antihistamine MD	SS Favors Antihistamine MD
Average Change From Baseline						
Grosclaude, 1997[103], itching eyes, 2 weeks[a]					0.01 (NSS)	
Sussman, 1999[107], itching, watery, red eyes, 2.6 weeks[b]			0.1 (NR)			

MD = Mean difference between group mean changes from baseline; NR = p-value not reported; NSS = not statistically significant; SS = statistically significant.

[a] 4-point scale: 0, absent; 1, mild; 2, moderate; 3, severe.

[b] 5-point scale: 0, absent; 1, mild; 2, moderate; 3, severe; 4, very severe.

Key Question 2. Comparative Adverse Effects of Treatments in Adults and Adolescents 12 Years of Age or Older

Oral Selective Antihistamine Versus Oral Nonselective Antihistamine

Key Points

- All three trials[81-83] that reported harms were 2-week trials.
- Evidence from three poor quality trials was insufficient to support the use of either oral selective or nonselective antihistamine to avoid sedation or headache.

Synthesis and Evidence Assessment

All three trials[81-83] (N=515) that reported efficacy outcomes also reported adverse events. Table 58 displays the risk differences and elements for the synthesis of evidence for this comparison.

All three trials reported sedation. In two[81, 82] of these, risk differences favored selective antihistamine to avoid moderate sedation (13 percent[81]) and unspecified severity sedation (28.9 percent[82]). Both results were statistically significant. Statistically nonsignificant differences also favored selective antihistamine to avoid severe sedation[81] and unspecified severity sedation.[83] Risk of bias was considered high in all three trials[81-83] due to poor USPSTF rating,[81-83] insufficient surveillance for adverse events,[83] and lack of patient blinding.[82] It is unclear whether effects were reported consistently based on differences in classification schemes across trials. Risk differences were otherwise consistent but imprecise. Forty-one percent of patients were in a trial[83] that reported a statistically nonsignificant result. Evidence was insufficient to conclude that either comparator is favored to avoid sedation.

In the two trials[81, 83] reporting headache, risk differences favored nonselective antihistamine to avoid headache (1.6 percent and 4.5 percent). Neither result was statistically significant. The risk of bias was considered high based on poor trial quality[81] and insufficient adverse event surveillance.[83] Risk differences were consistent but imprecise. Evidence was insufficient to conclude that either comparator is favored to avoid headache.

Table 58. Strength of evidence: comparative adverse events for oral selective antihistamine versus oral nonselective antihistamine

Outcome	Severity	Citation	Favors[a] Oral S-AH RD	Favors[a] Neither RD=0	Favors[a] Oral nS-AH RD	USPSTF	Active?[b]	Pt Blind?	Assessor Blind?	Risk of Bias	Cons	Dir	Prec	SOE
Sedation	Severe	Dockhorn 1987[81]	2.8			P	Int	Y	Y					
	Moderate	Dockhorn 1987[81]	13*			P	Int	Y	Y					
	Unspecified	Harvey 1996[82]	28.9*			P	Y	N	Y					
		Kemp 1987[83]	8			P	N	Y	Y					
										High	Cons	Dir	Imprec	Insuf
Headache	Moderate	Dockhorn 1987[81]			1.6	P	Int	Y	Y					
	Unspecified	Kemp 1987[83]			4.5	P	N	Y	Y					
										High	Cons	Dir	Imprec	Insuf

Cons = Consistent; Dir = direct; F = fair; Imprec = imprecision; Insuf = insufficient; Int = intermediate; N = no; nS-AH = nonselective antihistamine; P = poor; Pt = patient; RD = risk difference; S-AH = selective antihistamine; SOE = strength of evidence; USPSTF = U.S. Preventive Services Task Force; Y = yes.

[a] Values are not statistically significant unless otherwise indicated. "Favors" indicates avoidance of harm.

[b] The process of harms ascertainment was characterized as active, passive, or intermediate as defined in the Methods section.

* $p<0.05$, calculated by CER authors.

Oral Selective Antihistamine Versus Nasal Antihistamine

Key Points

- Four trials[84-87] that reported harms were 2-week trials. A fifth trial[88] reported harms at 6 weeks using passive surveillance only.
- Evidence was insufficient to support using either oral or nasal antihistamine to prevent common adverse events of sedation, headache, bitter aftertaste, and nosebleed.
- For bitter aftertaste, it is unclear whether future comparative trials would observe similar effects because all of the included trials used an older formulation of the currently available product. Newer formulations were designed to mitigate this adverse effect.

Synthesis and Evidence Assessment

All four trials[84-87] that reported efficacy outcomes also reported adverse events (N=886). Adverse event data also was abstracted from a fifth trial[88] (n=30) for this comparison. Table 59 displays the risk differences and elements for the synthesis of evidence for this comparison.

Only one trial reported nasal discomfort[87] (risk difference 0.3 percent, favoring oral antihistamine), insomnia[87] (reported in nasal antihistamine arm only [0.7 percent]), and hypertension leading to discontinuation[85] (risk difference 0.6 percent, favoring oral antihistamine). Synthesis of evidence was not conducted for these outcomes.

Sedation, described as severe or leading to discontinuation, was reported in two trials.[85, 88] Risk differences were not statistically significant, but favored oral antihistamine to avoid sedation in both (0.6 percent and 6.7 percent). Unspecified sedation was reported by four trials[84-87] with risk differences ranging from 1 percent in favor of oral antihistamine to 5 percent in favor of nasal antihistamine; none were statistically significant. The risk of bias was considered medium. Thirty-seven percent of the patient sample for this adverse event was in three[84, 86, 88] trials with poor USPSTF rating[86, 88] or inadequate surveillance for adverse events.[84, 88] Risk differences were inconsistent and imprecise. Evidence was insufficient to conclude that either comparator is favored to avoid sedation.

Headache was reported by four trials[84-87] with risk differences ranging from 1.6 percent in favor of oral antihistamine to 3 percent in favor of nasal antihistamine; none were statistically significant. The risk of bias was considered medium. Thirty-five percent of the patient sample for this adverse event was in two[84, 86] trials with poor USPSTF rating[86] or inadequate surveillance for adverse events.[84] Risk differences were small, inconsistent and imprecise. Evidence was insufficient to conclude that either comparator is favored to avoid headache.

Bitter aftertaste was reported by three trials[84, 85, 87] with risk differences ranging from 2.3 percent to 11 percent favoring oral antihistamine to avoid a bitter aftertaste. Risk differences were statistically significant in two of these trials.[84, 85] The risk of bias was considered medium. Fifty-six percent of the patient sample for this adverse event was in good quality trials[85, 87] that performed active surveillance for adverse events, and 44 percent were in a good quality trial[84] that did not perform active surveillance. Risk differences were consistent but not precise. Thirty-five percent of patients were in a trial[87] that reported a statistically nonsignificant difference. Evidence was insufficient to conclude that either comparator is favored to avoid a bitter aftertaste. It is important to note that all trials reporting on this outcome used an older

Table 59. Strength of evidence: comparative adverse events for oral selective antihistamine versus nasal antihistamine

Outcome	Severity		Favors[a] Oral S-AH RD	Favors[a] Neither RD = 0	Favors[a] Nasal S-AH RD	USPSTF	Active?[b]	Pt Blind?	Assessor Blind?	Risk of Bias	Cons	Dir	Prec	SOE
Sedation	Severe	Berger, 2006[85]	0.6			G	Y	Y	Y					
		Gambardella, 1993[88]	6.7			P	N	Y	Y					
	Unspecified	Berger, 2003[84]	1			G	N	Y	Y					
		Berger, 2006[85]		0		G	Y	Y	Y					
		Charpin, 1995[86]			5	P	Y	Y	Y					
		Corren, 2005[87]			0.6	G	Y	Y	Y					
										Med	Incons	Dir	Imprec	Insuf
Headache	Severe	Berger, 2006[85]	0.6			G	Y	Y	Y					
	Unspecified	Berger, 2003[84]			3	G	N	Y	Y					
		Berger, 2006[85]		0		G	Y	Y	Y					
		Charpin, 1995[86]		0		P	Y	Y	Y					
		Corren, 2005[87]	1.6			G	Y	Y	Y					
										Med	Incons	Dir	Inprec	Insuf
Bitter Aftertaste	Unspecified	Berger, 2003[84]	11*			G	N	Y	Y					
		Berger, 2006[85]	7.7*			G	Y	Y	Y					
		Corren, 2005[87]	2.3			G	Y	Y	Y					
										Med	Cons	Dir	Imprec	Insuf
Nosebleeds	Unspecified	Berger, 2006[85]		0		G	Y	Y	Y					
		Corren, 2005[87]	1			G	Y	Y	Y					
										Low	Incons	Dir	Imprec	Insuf

AE = adverse event; S-AH = selective antihistamine; Cons = consistent; Dir = direct; F = fair; G = good; Incons =inconsistent; Imprec = imprecision; Insuf = insufficient; Med = medium; N = no; P = poor; Pt = patient; RD = risk difference; SOE = strength of evidence; USPSTF = U.S. Preventive Services Task Force; Y = yes.

[a] Values are not statistically significant unless otherwise indicated. "Favors" indicates avoidance of harm.

[b] The process of harms ascertainment was characterized as active, passive, or intermediate as defined in the Methods section.

* $p<0.05$, calculated by CER authors.

formulation of azelastine nasal spray, which was reformulated to address this adverse effect. It is unclear whether future comparative trials would observe similar effects.

Nosebleeds were reported by two trials.[85, 87] Risk differences were 0 percent in one[85] and 1 percent (not statistically significant) favoring oral antihistamine in the other.[87] The risk of bias was considered low. Risk differences were inconsistent and imprecise. Evidence was insufficient to conclude that either comparator is favored to avoid nosebleeds.

Oral Selective Antihistamine Versus Intranasal Corticosteroid

Key Points

- Of six trials that reported harms, one[95] was 15 days in duration and five[90-93, 99] were 4 weeks in duration.
- Evidence from these trials was insufficient to support the use of either oral selective antihistamine or intranasal corticosteroid to avoid headache or nosebleed.

Synthesis and Evidence Assessment

Six[90-93, 95, 99] of 13 trials reporting efficacy outcomes also reported adverse events of interest (N=2038). Table 60 displays the risk differences and elements for the synthesis of evidence for this comparison.

One trial (Jordana [1996][95]) presented adverse events as percentages of total reports, rather than as percentages of patients. This trial was included in the synthesis of evidence only to assess consistency of effect. This trial was the only one to perform active surveillance for local corticosteroid effects (rhinoscopy). Nasal septal atrophy and nasal candidiasis were not reported. Only one trial[90] reported sedation (risk difference, 1 percent, favoring intranasal corticosteroid), nasal burning (0 percent in each group), and nosebleed (1 percent in each group). Synthesis of evidence was not conducted for these outcomes.

Five trials[90-93, 99] (N=1796) reported headache. In three trials[90-92] the risk difference favored intranasal corticosteroid (1-2 percent, none statistically significant) to avoid headache, and in two[93, 99] the risk difference favored oral selective antihistamine (4 percent and 8 percent, neither statistically significant). All but one[90] of the five trials was 4 weeks in duration. The risk difference in this 15-day trial[90] was 2 percent favoring intranasal corticosteroid to avoid headache. Risk of bias was considered high because of poor USPSTF quality rating in four trials[90, 92, 93, 99] and insufficient surveillance for adverse events in the fifth.[91] The observed effect was not consistent across trials, even when considering only 4-week trials, and imprecise. Evidence was insufficient to conclude that either comparator is favored to avoid headache.

Table 60. Strength of evidence: comparative adverse events for oral selective antihistamine versus intranasal corticosteroids

Outcome	Severity		Favors[a] Oral S-AH RD	Favors[a] Neither RD=0	Favors[a] INCS RD	USPSTF	Active?[b]	Pt Blind?	Assessor Blind?	Risk of Bias	Cons	Dir	Prec	SOE
Headache	Moderate	Anolik, 2008[90]			2.0	P	Int	Y	Y					
	Unspecified	Bernstein, 2004[91]			1.0	G	N	Y	Y					
		Condemi, 2000[92]			1.0	P	Y	Y	Y					
		Gawchik, 1997[93]	4.0			P	Y	Y	Y					
		Jordana, 1996[95c]	17.0			G	Int	Y	Y					
		Schoenwetter, 1995[99]	8.0			P	Int	Y	Y					
										High	Incons	Dir	Imprec	Insuf

Dir = direct; G = good; Imprec = imprecision; Incons = inconsistent; INCS = intranasal corticosteroid; Insuf = insufficient; Int = intermediate; N = no; P = poor; Pt = patient; RD = risk difference; S-AH = selective antihistamine; SOE = strength of evidence; USPSTF = U.S. Preventive Services Task Force; Y = yes.

[a] Values are not statistically significant unless otherwise indicated. "Favors" indicates avoidance of harm.

[b] The process of harms ascertainment was characterized as active, passive, or intermediate as defined in the Methods section.

[c] Denominator was reports, not patients. Confidence limits not calculated to assess strength of evidence.

Oral Selective Antihistamine Versus Oral Decongestant

Key Points

- All seven trials[101-107] identified were approximately two weeks in duration (range 2 to 2.6 weeks).
- There is moderate strength evidence favoring oral antihistamine rather than oral decongestant to avoid insomnia. This evidence was from four trials,[101, 103-105] each with statistically significant differences in the proportion of patients reporting insomnia. The body of evidence was consistent, precise and associated with medium risk of bias.
- Evidence was insufficient to conclude that either oral antihistamine or oral decongestant is favored to avoid sedation, headache or anxiety.

Synthesis and Evidence Assessment

All seven trials[101-107] reporting efficacy outcomes also reported adverse events. Table 61 displays the risk differences and elements for the synthesis of evidence for this comparison.

Two trials, Schenkel (2002)[106] and Sussman (1999),[107] presented adverse events as percentages of total reports, rather than as percentages of patients. In a third trial,[102] it was unclear whether the reporting unit was the patient or an incident event. These three trials were included in the synthesis of evidence only to assess consistency of effect. Only one trial[105] reported palpitations (risk difference 2 percent, favoring oral antihistamine to avoid palpitations). Synthesis of evidence was not conducted for this outcome.

Sedation was reported by three trials[101, 103, 105] (N=1640) with risk differences ranging from 1 percent in favor of oral antihistamine to 3 percent in favor of oral decongestant; none were statistically significant. The risk of bias was considered medium. Fifty-four percent of the patient sample was in good quality trials[101, 103] that actively ascertained adverse events. Risk differences were inconsistent and imprecise. Evidence was insufficient to conclude that either comparator is favored to avoid sedation.

Headache was reported by four trials[101, 103-105] (N=2038) with risk differences ranging from no difference to 4.9 percent favoring oral antihistamine to avoid headache; none were statistically significant. The risk of bias was considered medium. Fifty-six percent of the patient sample for this adverse event was in two trials[104, 105] that had poor USPSTF quality ratings[104, 105] or inadequate surveillance for adverse events.[105] Risk differences were inconsistent and imprecise. Evidence was insufficient to conclude that either comparator is favored to avoid headache.

Insomnia was reported by four trials[101, 103-105] (N=2038) with risk differences ranging from 6 percent to 11.1 percent favoring oral antihistamine to avoid insomnia; all were statistically significant. The risk of bias was considered medium. Fifty-six percent of the patient sample for this adverse event was in two trials[104, 105] that had poor USPSTF quality ratings[104, 105] or inadequate surveillance for adverse events.[105] Risk differences were consistent and precise. To avoid insomnia, there is moderate strength evidence favoring oral selective antihistamine rather than oral decongestant.

Table 61. Strength of evidence: comparative adverse events for oral selective antihistamine versus oral decongestant

Outcome	Severity	Citation	Favors[a] Oral S-AH RD	Favors[a] Neither RD = 0	Favors[a] Oral Decongestant RD	USPSTF	Active?[b]	Pt Blind?	Assessor Blind?	Risk of Bias	Cons	Dir	Prec	SOE
Sedation	Unspecified	Bronsky,1995[101]	1.0			G	Y	Y	Y					
		Grosclaude,1997[103]			3.0	G	Y	Y	Y					
		Pleskow, 2005[105]	1.0			P	N	Y	Y					
		Schenkel, 2002[106c]			0.1	F	N	Y	Y					
		Sussman,1999[107c]	1.4			G	Y	Y	Y					
										Med	Incons	Dir	Imprec	Insuf
Headache	Unspecified	Bronsky,1995[101]	3.0			G	Y	Y	Y					
		Grosclaude,1997[103]	2.8			G	Y	Y	Y					
		Grubbe, 2009[104]	4.9			P	Y	Y	Y					
		Pleskow, 2005[105]		0		P	N	Y	Y					
		Chervinsky, 2005[102d]			2.0	P	Int	Y	Y					
		Schenkel, 2002[106c]	1.7			F	N	Y	Y					
		Sussman,1999[107c]	5.1			G	Y	Y	Y					
										Med	Incons	Dir	Imprec	Insuf
Insomnia	Unspecified	Bronsky,1995[101]	8.0*			G	Int	Y	Y					
		Grosclaude,1997[103]	11.1*			G	Y	Y	Y					
		Grubbe, 2009[104]	11.0*			P	Y	Y	Y					
		Pleskow, 2005[105]	6.0*			P	N	Y	Y					
		Chervinsky, 2005[102d]	9.0			P	Int	Y	Y					
		Schenkel, 2002[106c]	7.3			F	N	Y	Y					
		Sussman,1999[107c]	11.0			G	Y	Y	Y					
										Med	Cons	Dir	Prec	Mod

Anxiety	Unspecified	Bronsky,1995[101]	3.0	G	Y	Y	Y					
		Grosclaude,1997[103]	2.2*	G	Y	Y	Y					
		Pleskow, 2005[105]	2.0	P	N	Y	Y					
		Schenkel, 2002[106c]	0.3	F	N	Y	Y					
		Sussman,1999[107c]	1.4	G	Y	Y	Y					
								Med	Cons	Dir	Imprec	Insuf

Cons = consistent; Dir = direct; F = fair; G = good; Imprec = imprecision; Incon = inconsistent; Insuf = insufficient; Int = intermediate; Mod = moderate; N = no; P = poor; Prec = precise; Pt = patient; RD = risk difference; S-AH = selective antihistamine; SOE = strength of evidence; USPSTF = U.S. Preventive Services Task Force; Y = yes.

[a] Values are not statistically significant unless otherwise indicated. "Favors" indicates avoidance of harm.

[b] The process of harms ascertainment was characterized as active, passive, or intermediate as defined in the Methods section.

[c] Denominator was reports, not patients. Confidence limits not calculated to assess strength of evidence.

[d] Unclear if denominator was reports or patients. Confidence limits not calculated to assess strength of evidence.

* $p<0.05$, calculated by CER authors.

Anxiety was reported in three trials[101, 103, 105] (N=1640) with risk differences ranging from 2 percent to 3 percent favoring oral antihistamine to avoid anxiety; one result[103] was statistically significant. The risk of bias was considered medium. Fifty-four percent of the patient sample for this adverse event was in good quality trials[101, 103] that actively ascertained adverse events. Risk differences were consistent but imprecise. Seventy-two percent of the patient sample for this adverse event was in trials[101, 105] that reported statistically nonsignificant risk differences. Evidence was insufficient to conclude that either comparator is favored to avoid anxiety.

Oral Selective Antihistamine Versus Oral Leukotriene Receptor Antagonist (Montelukast)

Key Points

- Four[108, 110-112] of nine trials reporting efficacy outcomes also reported adverse events. One[108] was a 4-week trial, and the others were 2 weeks in duration.
- Evidence was insufficient to support the use of either selective oral antihistamine or oral leukotriene receptor antagonist to avoid headache as an adverse outcome. Although the body of evidence included less than half of the trials identified for efficacy, the finding is indirectly supported by the assertions of four other trials[97, 109, 113, 114] that adverse events were similar in frequency between trial arms.

Synthesis and Evidence Assessment

Four[108, 110-112] of nine trials reporting efficacy outcomes also reported adverse events. Four other trials[97, 109, 113, 114] did not report specific events, but included statements suggesting that there were no differences between groups with regard to adverse events. These eight trials were comparable with regard to baseline SAR symptoms (all trials reported baseline nasal symptom scores in the moderate range), and size. One[108] was a 4-week trial, and the others were 2 weeks in duration. However, the trials that reported group level adverse events tended to have higher USPSTF quality ratings (three good, and one poor among those reporting group level outcomes, compared with three poor, and two fair among those not reporting group level outcomes). Table 62 displays the risk differences and elements for the synthesis of evidence for this comparison.

Headache was reported by four trials[108, 110-112] (N=2215) with risk differences ranging from 1 percent in favor of oral selective antihistamine to 3.4 percent in favor of leukotriene receptor antagonist; none were statistically significant. The risk of bias was considered medium. Fifty-one percent of the patient sample for this adverse event was in two trials[110, 112] that had poor USPSTF quality ratings [112] or inadequate surveillance for adverse events,[110] and 20 percent was in a good quality trial[111] that actively ascertained adverse events. Risk differences were inconsistent and imprecise. Evidence was insufficient to conclude that either comparator is favored to avoid headache. This finding is consistent with four trials[97, 109, 113, 114] that did not report group level incidences of adverse events but reported no between-group differences.

Table 62. Strength of evidence: comparative adverse events for oral selective antihistamine versus oral leukotriene receptor antagonist

Outcome	Severity	Citation	Favors[a] Oral S-AH RD	Favors[a] Neither RD = 0	Favors[a] LRA RD	USPSTF	Active?[b]	Pt Blind?	Assessor Blind?	Risk of Bias	Cons	Dir	Prec	SOE
Headache	Unspecified	Baena-Cagnani, 2003[108]		0		G	Int	Y	Y					
		Nayak, 2002[111]	1.0			G	Y	Y	Y					
		Meltzer, 2000[110]			3.4	G	N	Y	Y					
		Philip, 2002[112]			0.3	P	N	Y	Y					
										Med	Incons	Dir	Imprec	Insuf

Dir = direct; G = good; Imprec = imprecision; Incons = inconsistent; Insuf = insufficient; Int = intermediate; LRA = oral leukotriene receptor antagonist; N = no; P = poor; Pt = patient; Prec = precision; RD = risk difference; S-AH = selective antihistamine; SOE = strength of evidence; USPSTF = U.S. Preventive Services Task Force; Y = yes.

[a] Values are not statistically significant unless otherwise indicated. "Favors" indicates avoidance of harm.

[b] The process of harms ascertainment was characterized as active, passive, or intermediate as defined in the Methods section.

Intranasal Corticosteroid Versus Nasal Antihistamine

Key Points

- Eight[115-119, 121] of nine trials that reported efficacy outcomes also reported adverse events. One [116] was a 4-week trial, and the rest were 2 weeks in duration.
- Evidence was insufficient to support the use of either intranasal corticosteroid or nasal antihistamine to avoid any of the following adverse events reported in eight trials: sedation, headache, nasal discomfort, bitter aftertaste, and nosebleeds.

Synthesis and Evidence Assessment

Eight[115-119, 121] of nine trials that reported efficacy outcomes also reported adverse events. Table 63 displays the risk differences and elements for the synthesis of evidence for this comparison.

Two trials[119, 121] presented adverse events as a percentage of total reports, rather than as a percentage of patients. These trials were included in the synthesis of evidence only to assess consistency of effect. Only one trial reported burning or dryness[116] (risk differences 2 percent, favoring nasal antihistamine to avoid dryness, and 4 percent, favoring intranasal corticosteroids to avoid burning). Synthesis of evidence was not conducted for these outcomes.

Sedation was reported by three trials[115, 117, 118] (N=1330) with risk differences ranging from no risk difference to 1.5 percent favoring intranasal corticosteroid to avoid sedation; none were statistically significant. The risk of bias was considered medium. Sixty-seven percent of the patient sample for this adverse event was in a good quality trial[115] that actively ascertained adverse events. Risk differences were inconsistent and imprecise. Evidence was insufficient to conclude that either comparator is favored to avoid sedation.

Headache was reported by four trials[115, 117] (N=1998) with risk differences ranging from 0.7 percent in favor of intranasal corticosteroid to 2.6 percent in favor of nasal antihistamine; none were statistically significant. The risk of bias was considered low. Eighty-five percent of the patient sample for this adverse event was in good quality trials[115] that actively ascertained adverse events. Risk differences were inconsistent and imprecise. Evidence was insufficient to conclude that either comparator is favored to avoid headache.

Nasal discomfort was reported by four trials[115-117] (N=1153) with risk differences ranging from 8 percent in favor of intranasal corticosteroids to 0.7 percent in favor of nasal antihistamine; none were statistically significant. The risk of bias was considered medium. Sixty-nine percent of the patient sample for this adverse event was in good quality trials[115] that actively ascertained adverse events. Risk differences were inconsistent and imprecise. Evidence was insufficient to conclude that either comparator is favored to avoid nasal discomfort.

Bitter aftertaste was reported by six trials[115-117] (N=2178) with risk differences ranging from 2 percent to 6.7 percent favoring intranasal corticosteroid to avoid a bitter aftertaste. Effects were statistically significant in two trials in the same publication.[115] The risk of bias was considered medium. Seventy-eight percent of the patient sample for this adverse event was in good quality trials[115] that actively ascertained adverse events. Risk differences were consistent but imprecise. Evidence was insufficient to conclude that either comparator is favored to avoid a bitter aftertaste.

Table 63. Strength of evidence: comparative adverse events for intranasal corticosteroid versus nasal antihistamine

Outcome	Severity	Citation	Favors[a] INCS RD	Favors[a] Neither RD = 0	Favors[a] Nasal AH RD	USPSTF	Active?[b]	Pt Blind?	Assessor Blind?	Risk of Bias	Cons	Dir	Prec	SOE
Sedation	Unspecified	Carr, 2012 (Trial 3)[115]	0.4			G	Y	Y	Y					
		Hampel, 2010[117]		0		G	N	Y	Y					
		Kaliner, 2009[118]	1.5			P	N	Y	Y					
										Med	Incons	Dir	Imprec	Insuf
Headache	Unspecified	Carr, 2012 (Trial 1)[115]			1.9	G	Y	Y	Y					
		Carr, 2012 (Trial 2)[115]		0		G	Y	Y	Y					
		Carr, 2012 (Trial 3)[115]	0.7			G	Y	Y	Y					
		Hampel, 2010[117]			2.6	G	N	Y	Y					
		Newson-Smith, 1997[119c]			4.8	P	Int	Y	Y					
		Ratner, 2008[121b]	0.1			G	Y	Y	Y					
										Low	Incons	Dir	Imprec	Insuf
Nasal discomfort	Unspecified	Carr, 2012 (Trial 1)[115]	0.9			G	Y	Y	Y					
		Carr, 2012 (Trial 2)[115]	1.0			G	Y	Y	Y					
		Ghimire, 2007[116]	8.0			P	N	Y	Y					
		Hampel, 2010[117]			0.7	G	N	Y	Y					
		Newson-Smith, 1997[119c]			1.2	P	Int	Y	Y					
										Med	Incons	Dir	Imprec	Insuf

Bitter aftertaste	Unspecified	Carr, 2012 (Trial 1)[115]	2.4			G	Y	Y	Y					
		Carr, 2012 (Trial 2)[115]	6.7*			G	Y	Y	Y					
		Carr, 2012 (Trial 3)[115]	4.8*			G	Y	Y	Y					
		Ghimire, 2007[116]	4.0			P	N	Y	Y					
		Hampel, 2010[117]	2.0			G	N	Y	Y					
		Kaliner, 2009[118]	3.1			P	N	Y	Y					
		Newson-Smith, 1997[119c]	6.0			P	Int	Y	Y					
		Ratner, 2008[121b]	6.2			G	Y	Y	Y					
										Med	Cons	Dir	Imprec	Insuf
Nosebleeds	Unspecified	Carr, 2012 (Trial 1)[115]			1.4	G	Y	Y	Y					
		Carr, 2012 (Trial 2)[115]		0		G	Y	Y	Y					
		Carr, 2012 (Trial 3)[115]		0		G	Y	Y	Y					
		Hampel, 2010[117]			1.9	G	N	Y	Y					
		Kaliner, 2009[118]	4.6			P	N	Y	Y					
		Newson-Smith, 1997[119c]	1.2			P	Int	Y	Y					
										Low	Incons	Dir	Imprec	Insuf

Cons = consistent; Dir = direct; G = good; Incons = inconsistent; Imprec = imprecision; Insuf = insufficient; INCS = intranasal corticosteroid; Int = intermediate; Mod = moderate; N = no; P = poor; Pt = patient; RD = risk difference; S-AH = selective antihistamine; SOE = strength of evidence; USPSTF = U.S. Preventive Services Task Force; Y = yes.

[a] Statistical significance as indicated.

[b] The process of harms ascertainment was characterized as active, passive, or intermediate as defined in the Methods section.

[c] Denominator was reports, not patients. Confidence limits not calculated to assess strength of evidence.

* $p<0.05$, calculated by CER authors.

Nosebleeds were reported by five trials.[115, 117, 118] (N=2128) Risk differences ranged from 4.6 percent in favor of intranasal corticosteroid to 1.9 percent in favor of nasal antihistamine; none were statistically significant. The risk of bias was considered low. Eighty percent of the patient sample for this adverse event was in good quality trials[115] that actively ascertained adverse events. Risk differences were inconsistent and imprecise. Evidence was insufficient to conclude that either comparator is favored to avoid nosebleeds.

Intranasal Corticosteroid Versus Nasal Cromolyn

Key Points

- Data for synthesis was available from two small trials[122, 125] with three direct comparisons. One[122] was a 3-week trial, and the other[125] was 8 weeks. Both trials were rated poor quality; one had both passive ascertainment of harms and inadequate patient blinding.
- Evidence was insufficient to support the use of either intranasal corticosteroid or nasal cromolyn to avoid any of the following adverse events: headache, dryness, burning, nasal discomfort, and nosebleeds.

Synthesis and Evidence Assessment

Four trials[122-125] (five direct comparisons) that reported efficacy outcomes also reported adverse events. Table 64 displays the risk differences and elements for the synthesis of evidence for this comparison.

Two trials[123, 124] presented adverse events as a percentage of total reports, rather than as a percentage of patients. These trials were included in the synthesis of evidence only to assess consistency of effect.

Headache was reported in two trials[122, 125] (three comparisons; N=133) with risk differences ranging from 13.4 percent in favor of intranasal corticosteroid to 4.5 percent in favor of nasal cromolyn; none were statistically significant. The risk of bias was considered high; both trials[122, 125] were rated poor quality and one[125] had inadequate patient blinding and ascertained adverse events in a passive fashion. Risk differences were inconsistent and imprecise. Evidence was insufficient to conclude that either comparator is favored to avoid headache.

Dryness was reported in two trials[122, 125] (three comparisons; N=133) with risk differences ranging from 14.5 percent in favor of intranasal corticosteroid to 3.3 percent in favor of nasal cromolyn; none were statistically significant. The risk of bias was considered high; both trials[122, 125] were rated poor quality and one[125] had inadequate patient blinding and ascertained adverse events in a passive fashion. Risk differences were inconsistent and imprecise. Evidence was insufficient to conclude that either comparator is favored to avoid dryness.

Burning was reported in one trial[125] (two comparisons; N=90). Risk differences were 3.3 percent for both intranasal corticosteroid groups compared with nasal cromolyn and favored nasal cromolyn to avoid burning. Neither was statistically significant. The risk of bias was considered high; the trial[125] was rated poor quality, had inadequate patient blinding, and ascertained adverse events in a passive fashion. Risk differences were consistent but imprecise. Evidence was insufficient to conclude that either comparator is favored to avoid burning.

Nasal discomfort was reported in two trials[122, 125] (three comparisons; N=133) with risk differences ranging from 0 percent to 14.3 percent favoring intranasal corticosteroid to avoid nasal discomfort; none were statistically significant. The risk of bias was considered high; both

Table 64. Strength of evidence: comparative adverse events for intranasal corticosteroid versus nasal cromolyn

Outcome	Severity	Citation	Favors[a] INCS RD	Favors[a] Neither RD = 0	Favors[a] Nasal C RD	USPSTF	Active?[b]	Pt Blind?	Assessor Blind?	Risk of Bias	Cons	Dir	Prec	SOE
Headache	Mild	Bjerrum, 1985[122]			4.5	P	Int	Y	Y					
	Unspecified	Welsh, 1987 (BDP)[125d]		0		P	N	N[e]	Y					
		Welsh, 1987 (FLU)[125d]	13.4			P	N	N[e]	Y					
		Lange, 2005[124c]			3.4	P	Int	N	N					
										High	Incons	Dir	Imprec	Insuf
Dryness	Mild	Bjerrum, 1985[122]	14.5			P	Int	Y	Y					
	Unspecified	Welsh, 1987 (BDP)[125d]		0		P	N	N[e]	Y					
		Welsh, 1987 (FLU)[125d]			3.3	P	N	N[e]	Y					
		Bousquet, 1993[123c]	1.1			P	N	Y	Y					
										High	Incons	Dir	Imprec	Insuf
Burning	Unspecified	Welsh, 1987 (BDP)[125d]			3.3	P	N	N[e]	Y					
		Welsh, 1987 (FLU)[125d]			3.3	P	N	N[e]	Y					
		Bousquet, 1993[123c]			1.4	P	N	Y	Y					
										High	Cons	Dir	Imprec	Insuf
Nasal discomfort	Mild	Bjerrum, 1985[122]	14.3			P	Int	Y	Y					
	Unspecified	Welsh, 1987 (BDP)[125d]		0		P	N	N[e]	Y					
		Welsh, 1987 (FLU)[125d]	3.3			P	N	N[e]	Y					
		Bousquet, 1993[123c]			1.6	P	N	Y	Y					
		Lange, 2005[124b]	4.6			P	Int	N	N					
										High	Incons	Dir	Imprec	Insuf

Outcome	Severity	Citation	Favors[a] INCS RD	Favors[a] Neither RD = 0	Favors[a] Nasal C RD	USPSTF	Active?[b]	Pt Blind?	Assessor Blind?	Risk of Bias	Cons	Dir	Prec	SOE
Nosebleed	Mild	Bjerrum, 1985[122]			4.5	P	Int	Y	Y					
	Unspecified	Welsh, 1987 (BDP)[125d]	3.3			P	N	N[e]	Y					
		Welsh, 1987 (FLU)[125d]	3.3			P	N	N[e]	Y					
										High	Cons	Dir	Imprec	Insuf

BDP = Beclomethasone; C = cromolyn; Cons = consistent; Dir = direct; FLU = fluticasone; Imprec = imprecision; Incons = inconsistent, Insuf = insufficient; Int = intermediate; INCS = intranasal corticosteroid; N = no; P = poor; Pt = patient; RD = risk difference; SOE = strength of evidence; USPSTF = U.S. Preventive Services Task Force; Y = yes.

[a] Values are not statistically significant unless otherwise indicated. "Favors" indicates avoidance of harm.

[b] The process of harms ascertainment was characterized as active, passive, or intermediate as defined in the Methods section.

[c] Denominator was reports, not patients. Confidence limits not calculated to assess strength of evidence.

[d] Trial compared nasal cromolyn to two intranasal corticosteroids.

[e] Inadequate patient blinding.

trials[122, 125] were rated poor quality and one[125] had inadequate patient blinding and ascertained adverse events in a passive fashion. Risk differences were inconsistent and imprecise. Evidence was insufficient to conclude that either comparator is favored to avoid nasal discomfort.

Nosebleed was reported in two trials[122, 125] (three comparisons; N=133) with risk differences ranging from 3.3 percent in favor of intranasal corticosteroid to 4.5 percent in favor of nasal cromolyn; none were statistically significant. The risk of bias was considered high; both trials[122, 125] were rated poor quality and one[125] had inadequate patient blinding and ascertained adverse events in a passive fashion. Risk differences were consistent but imprecise. Evidence was insufficient to conclude that either comparator is favored to avoid nasal discomfort.

Intranasal Corticosteroid Versus Oral Leukotriene Receptor Antagonist (Montelukast)

Key Points

- Evidence from three high quality trials[126, 127, 129] was insufficient to support the use of either intranasal corticosteroid or oral leukotriene receptor antagonist to avoid headache or nosebleed. Two trials[126, 129] were 2 weeks in duration, and the third[127] was 4 weeks.

Synthesis and Evidence Assessment

Three[126, 127, 129] of five trials that reported efficacy outcomes also reported adverse events. The trials[97, 128] that did not report adverse events were smaller and included patients with milder symptoms than those that did. Both of these trials were rated poor quality; the three that reported adverse events were rated good quality. Table 65 displays the risk differences and elements for the synthesis of evidence for this comparison.

Headache was reported by all three trials,[126, 127, 129] (N=2014) with risk differences ranging from 0.3 percent to 5 percent favoring intranasal corticosteroid to avoid headache. None of these risk differences were statistically significant. The risk of bias was considered medium. Sixty-three percent of the patient sample for this adverse event was in good quality trials[127, 129] that actively ascertained adverse events. Risk differences were consistent but imprecise. Evidence was insufficient to conclude that either comparator is favored to avoid headache.

Nosebleed was reported by all three trials,[126, 127, 129] (N=2014) with risk differences ranging from 1 percent in favor of intranasal corticosteroid to 1 percent in favor of oral leukotriene receptor antagonist. None of these risk differences were statistically significant. The risk of bias was considered medium. Sixty-three percent of the patient sample for this adverse event was in good quality trials[127, 129] that actively ascertained adverse events. Risk differences were inconsistent and imprecise. Evidence was insufficient to conclude that either comparator is favored to avoid nosebleed.

Table 65. Strength of evidence: comparative adverse events for intranasal corticosteroid versus oral leukotriene receptor antagonist

Outcome	Severity	Citation	Favors[a] INCS RD	Favors[a] Neither RD=0	Favors[a] LRA RD	USPSTF	Active?[b]	Pt Blind?	Assessor Blind?	Risk of Bias	Cons	Dir	Prec	SOE
Headache	Severe	Martin, 2006[126]	0.3			G	Int	Y	Y					
	Moderate	Martin, 2006[126]	2			G	Int	Y	Y					
		Ratner, 2003[129]	2			G	Y	Y	Y					
	Unspecified	Nathan, 2005[127]	5			G	Y	Y	Y					
										Med	Cons	Dir	Imprec	Insuf
Nosebleeds	Moderate	Martin, 2006[126]	1			G	Int	Y	Y					
		Ratner, 2003[129]			1	G	Y	Y	Y					
	Unspecified	Nathan, 2005[127]			1	G	Int	Y	Y					
										Med	Incons	Dir	Imprec	Insuf

Cons = consistent; Dir = direct; G = good; Imprec = imprecision; Insuf = insufficient; Int = intermediate; INCS = intranasal corticosteroid; LRA = oral leukotriene receptor antagonist; Pt = patient; RD = risk difference; SOE = strength of evidence; USPSTF = U.S. Preventive Services Task Force; Y = yes.

[a] Values are not statistically significant unless otherwise indicated. "Favors" indicates avoidance of harm.

[b] The process of harms ascertainment was characterized as active, passive, or intermediate as defined in the Methods section.

Combination Oral Selective Antihistamine Plus Intranasal Corticosteroid Versus Oral Selective Antihistamine

Key Points

- Adverse event reporting in trials included in the efficacy review for this comparison was inadequate to permit analysis.

Synthesis and Evidence Assessment

Of three trials[90, 98, 130] that reported efficacy outcomes, adverse events were assessed in two.[90, 98] However, one[98] of these reported adverse events in the total trial population rather than by treatment arm. The other[90] reported risk differences of 2 percent and 3 percent favoring oral antihistamine monotherapy to avoid burning and nosebleeds, respectively. A risk difference of 4 percent favored combination therapy to avoid headache, and a risk difference of zero was observed for sedation. No differences were statistically significant. The trial used some active adverse event surveillance but was rated poor quality using USPSTF criteria. This single trial provides insufficient evidence to support the use of one treatment over the other to avoid adverse events.

Combination Oral Selective Antihistamine Plus Intranasal Corticosteroid Versus Intranasal Corticosteroid

Key Points

- Adverse event reporting in trials included in the efficacy review for this comparison was inadequate to permit analysis.

Synthesis and Evidence Assessment

All five trials[62, 90, 98, 131, 132] that reported efficacy outcomes reported adverse events. However, one[131] of these used reports (rather than patients) as denominator, one[98] reported adverse events in the total trial population rather than by treatment arm, and two reported adverse events specific to one trial arm only.[62, 132] The remaining trial[90] reported statistically nonsignificant risk differences of 0 percent for sedation, and 4 percent for headache, both favoring combination therapy. Risk differences of 2 percent and 3 percent for burning and nosebleeds, respectively, favored intranasal corticosteroid monotherapy, and neither was statistically significant. The trial used some active adverse event surveillance but was rated poor quality using USPSTF criteria. This single trial provides insufficient evidence to support the use of one treatment over the other to avoid adverse events.

Combination Intranasal Corticosteroid Plus Nasal Antihistamine Versus Intranasal Corticosteroid

Key Points

- All five trials[115, 117, 121] that reported efficacy outcomes also reported adverse events. All trials were 2 weeks in duration.

- Evidence was insufficient to support using either combination intranasal corticosteroid plus nasal antihistamine or intranasal corticosteroid monotherapy to prevent common adverse events including sedation, headache, nasal discomfort, bitter aftertaste, and nosebleed.
- Three[115] of four trials[115, 117] reporting bitter aftertaste (85 percent of the patient sample for this adverse event) used a newly approved (May 2012) formulation that includes a corticosteroid and an antihistamine in the same device. It is unlikely that the new formulation impacted observed effects.

Synthesis and Evidence Assessment

All five trials[115, 117, 121] that reported efficacy outcomes also reported adverse events. Table 66 displays the risk differences and elements for the synthesis of evidence for this comparison.

One trial[121] presented adverse events as a percentage of total reports, rather than as a percentage of patients. This trial was included in the synthesis of evidence only to assess consistency of effect.

Sedation was reported by two trials.[115, 117] (N=1802) there was no difference between treatments in one trial,[117] and a risk difference of 1.1 percent favoring intranasal corticosteroid monotherapy to avoid sedation in the other trial.[115] The 1.1 percent difference was statistically significant. Risk of bias was considered low. Seventy-five percent of the patient sample for this adverse event was in the good quality trial[115] that actively ascertained adverse events. Risk differences were inconsistent and imprecise. Evidence was insufficient to conclude that either comparator is favored to avoid sedation.

Headache was reported by four trials.[115, 117] (N=3000) Risk differences ranged from 1.9 percent in favor of combination therapy to 0.5 percent in favor of intranasal corticosteroid monotherapy, and none were statistically significant. Risk of bias was considered low. Eighty-five percent of the patient sample for this adverse event was in good quality trials[115] that actively ascertained adverse events. Risk differences were inconsistent and imprecise. Evidence was insufficient to conclude that either comparator is favored to avoid headache.

Nasal discomfort was reported by three trials.[115, 117] (N=1657) Risk differences ranged from no difference to 0.6 percent favoring intranasal corticosteroid monotherapy to avoid nasal discomfort, and none were statistically significant. Risk of bias was considered low. Seventy-two percent of the patient sample for this adverse event was in good quality trials[115] that actively ascertained adverse events. Risk differences were inconsistent and imprecise. Evidence was insufficient to conclude that either comparator is favored to avoid nasal discomfort.

Bitter aftertaste was reported by four trials.[115, 117] (N=3000) Risk differences ranged from 1.4 percent to 7.2 percent favoring intranasal corticosteroid monotherapy to avoid a bitter aftertaste. Two of these estimates[115, 117] were statistically significant. Risk of bias was considered low. Eighty-five percent of the patient sample for this adverse event was in good quality trials[115] that actively ascertained adverse events. Risk differences were consistent but imprecise. Forty percent of the patient sample for this adverse event was in trials[115] that reported statistically nonsignificant risk differences. Evidence was insufficient to conclude that either comparator is favored to avoid a bitter aftertaste. Of note, three trials,[115] representing 85 percent of the patient sample for this adverse event, used a newly approved (May 2012) formulation that includes a corticosteroid and an antihistamine in the same device. It is unclear whether the new formulation impacted the observed effects.

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Table 66. Strength of evidence: comparative adverse events for combination intranasal corticosteroid plus nasal antihistamine versus intranasal corticosteroid

Outcome	Severity	Citation	Favors[a] Combo RD	Favors[a] Neither RD=0	Favors[a] INCS RD	USPSTF	Active?[b]	Pt Blind?	Assessor Blind?	Risk of Bias	Cons	Dir	Prec	SOE
Sedation	Unspecified	Carr, 2012 (Trial 3)[115]			1.1*	G	Y	Y	Y					
		Hampel, 2010[117]		0		G	N	Y	Y					
										Low	Incons	Dir	Imprec	Insuf
Headache	Unspecified	Carr, 2012 (Trial 1)[115]	1.9			G	Y	Y	Y					
		Carr, 2012 (Trial 2)[115]			0.5	G	Y	Y	Y					
		Carr, 2012 (Trial 3)[115]		0		G	Y	Y	Y					
		Hampel, 2010[117]	1.3			G	N	Y	Y					
		Ratner, 2008[121c]			1.8	G	N	Y	Y					
										Low	Incons	Dir	Imprec	Insuf
Nasal discomfort	Unspecified	Carr, 2012 (Trial 1)[115]		0		G	Y	Y	Y					
		Carr, 2012 (Trial 2)[115]			0.5	G	Y	Y	Y					
		Hampel, 2010[117]			0.6	G	N	Y	Y					
										Low	Incons	Dir	Imprec	Insuf
Bitter aftertaste	Unspecified	Carr, 2012 (Trial 1)[115]			1.4	G	Y	Y	Y					
		Carr, 2012 (Trial 2)[115]			1.6	G	Y	Y	Y					
		Carr, 2012 (Trial 3)[115]			4.5*	G	Y	Y	Y					
		Hampel, 2010[117]			7.2*	G	N	Y	Y					
		Ratner, 2008[121c]			11.5	G	N	Y	Y					
										Low	Cons	Dir	Imprec	Insuf
Nosebleeds	Unspecified	Carr, 2012 (Trial 1)[115]	1.4			G	Y	Y	Y					
		Carr, 2012 (Trial 2)[115]	0.1			G	Y	Y	Y					
		Carr, 2012 (Trial 3)[115]			0.7	G	Y	Y	Y					
		Hampel, 2010[117]		0		G	N	Y	Y					
										Low	Incons	Dir	Imprec	Insuf

Combo = combination; Dir = direct; G = good; (Im)Prec = (im)precision; (In)Cons=(in)consistent; Insuf = insufficient; INCS = intranasal corticosteroid; Mod = moderate; N = no; Pt = patient; RD = risk difference; S-AH = selective antihistamine; SOE = strength of evidence; USPSTF = U.S. Preventive Services Task Force; Y = yes.

[a] Values are not statistically significant unless otherwise indicated. "Favors" indicates avoidance of harm.

[b] The process of harms ascertainment was characterized as active, passive, or intermediate as defined in the Methods section.

[c] Denominator was reports, not patients. Confidence limits not calculated to assess strength of evidence.

* $p<0.05$, calculated by CER authors.

Nosebleed was reported by four trials.115, 117 (N=3000) Risk differences ranged from 1.4 percent in favor of combination therapy to 0.7 percent in favor of intranasal corticosteroid monotherapy; none were statistically significant. Risk of bias was considered low. Eighty-five percent of the patient sample for this adverse event was in good quality trials115 that actively ascertained adverse events. Risk differences were inconsistent and imprecise. Evidence was insufficient to conclude that either comparator is favored to avoid nosebleed

Combination Intranasal Corticosteroid Plus Nasal Antihistamine Versus Nasal Antihistamine

Key Points

- All five trials[115, 117, 121] that reported efficacy outcomes also reported adverse events. All trials were 2 weeks in duration.
- Evidence from four trials was insufficient to support using either combination intranasal corticosteroid plus nasal antihistamine or nasal antihistamine monotherapy to avoid common adverse events of sedation, headache, nasal discomfort, bitter aftertaste, and nosebleed.
- Three[115] of four trials[115, 117] reporting bitter aftertaste (85 percent of the patient sample for this adverse event) used a newly approved (May 2012) formulation that includes a corticosteroid and an antihistamine in the same device. In these three trials, an older version of nasal antihistamine rather than a newer formulation designed to mitigate bitter aftertaste was used as a comparator.

Synthesis and Evidence Assessment

All five trials[115, 117, 121] that reported efficacy outcomes also reported adverse events. Table 67 displays the risk differences and elements for the synthesis of evidence for this comparison.

One trial[121] presented adverse events as a percentage of total reports, rather than as a percentage of patients. This trial was included in the synthesis of evidence only to assess consistency of effect.

Sedation was reported by two trials.[115, 117] (N=1802) Risk differences were 0 percent and 0.7 percent favoring nasal antihistamine to avoid sedation; neither was statistically significant. Risk of bias was considered low. Seventy-five percent of the patient sample for this adverse event was in a good quality trial[115] that actively ascertained adverse events. Risk differences were inconsistent and imprecise. Evidence was insufficient to conclude that either comparator is favored to avoid sedation.

Headache was reported by four trials.[115, 117] (N=3000) Risk differences ranged from 0.7 percent in favor of combination therapy to 1.3 percent in favor of nasal antihistamine; none were statistically significant. Risk of bias was considered low. Eighty-five percent of the patient sample for this adverse event was in good quality trials[115] that actively ascertained adverse events. Risk differences were inconsistent and imprecise. Evidence was insufficient to conclude that either comparator is favored to avoid headache.

Nasal discomfort was reported by three trials.[115, 117] (N=1657) Risk differences ranged from 0.9 percent in favor of combination therapy to1.3 percent in favor of nasal antihistamine; none were statistically significant. Risk of bias was considered low. Seventy-two percent of the patient sample for this adverse event was in good quality trials[115] that actively ascertained adverse

events. Risk differences were inconsistent and imprecise. Evidence was insufficient to conclude that either comparator is favored to avoid nasal discomfort.

Bitter aftertaste was reported by four trials.[115, 117] (N=3000) Risk differences ranged from 5.1 percent in favor of combination therapy to 5.2 percent in favor of nasal antihistamine. Both extremes were statistically significant. Risk of bias was considered low. Eighty-five percent of the patient sample for this adverse event was in good quality trials[115] that actively ascertained adverse events. Risk differences were inconsistent and imprecise. Thirty-five percent of the patient sample for this adverse event was in trials[115, 117] that reported imprecise risk differences. Evidence was insufficient to conclude that either comparator is favored to avoid a bitter aftertaste. Of note, three[115] of four trials[115, 117] reporting bitter aftertaste (85 percent of the patient sample for this adverse event) used a newly approved (May 2012) formulation that includes a corticosteroid and an antihistamine in the same device. In these three trials, an older version of nasal antihistamine rather than a newer formulation designed to mitigate bitter aftertaste was used as a comparator.

Nosebleed was reported by four trials[115, 117] (N=3000). Risk differences ranged from 0.9 percent in favor of combination therapy to 1.3 percent in favor of nasal antihistamine; none were statistically significant. Risk of bias was considered low. Eighty-five percent of the patient sample for this adverse event was in good quality trials[115] that actively ascertained adverse events. Risk differences were inconsistent and imprecise. Evidence was insufficient to conclude that either comparator is favored to avoid nosebleed.

Table 67. Strength of evidence: comparative adverse events for combination intranasal corticosteroid plus nasal antihistamine versus nasal antihistamine

Outcome	Severity	Citation	Favors[a] Combo RD	Favors[a] Neither RD=0	Favors[a] Nasal AH RD	USPSTF	Active?[b]	Pt Blind?	Assessor Blind?	Risk of Bias	Cons	Dir	Prec	SOE
Sedation	Unspecified	Carr, 2012 (Trial 3)[115]			0.7	G	Y	Y	Y					
		Hampel, 2010[117]		0		G	N	Y	Y					
										Low	Incons	Dir	Imprec	Insuf
Headache	Unspecified	Carr, 2012 (Trial 1)[115]		0		G	Y	Y	Y					
		Carr, 2012 (Trial 2)[115]			0.5	G	Y	Y	Y					
		Carr, 2012 (Trial 3)[115]	0.7			G	Y	Y	Y					
		Hampel, 2010[117]			1.3	G	N	Y	Y					
		Ratner, 2008[121c]			1.7	G	N	Y	Y					
										Low	Incons	Dir	Imprec	Insuf
Nasal discomfort	Unspecified	Carr, 2012 (Trial 1)[115]	0.9			G	Y	Y	Y					
		Carr, 2012 (Trial 2)[115]	0.5			G	Y	Y	Y					
		Hampel, 2010[117]			1.3	G	N	Y	Y					
										Low	Incons	Dir	Imprec	Insuf
Bitter aftertaste	Unspecified	Carr, 2012 (Trial 1)[115]	1			G	Y	Y	Y					
		Carr, 2012 (Trial 2)[115]	5.1*			G	Y	Y	Y					
		Carr, 2012 (Trial 3)[115]	0.4			G	Y	Y	Y					
		Hampel, 2010[117]			5.2*	G	N	Y	Y					
		Ratner, 2008[121c]			5.3	G	N	Y	Y					
										Low	Incons	Dir	Imprec	Insuf
Nosebleeds	Unspecified	Carr, 2012 (Trial 1)[115]	0.9			G	Y	Y	Y					
		Carr, 2012 (Trial 2)[115]	0.1			G	Y	Y	Y					
		Carr, 2012 (Trial 3)[115]			0.7	G	Y	Y	Y					
		Hampel, 2010[117]			1.3	G	N	Y	Y					

Outcome	Severity	Citation	Favors[a] Combo RD	Favors[a] Neither RD=0	Favors[a] Nasal AH RD	USPSTF	Active?[b]	Pt Blind?	Assessor Blind?	Risk of Bias	Cons	Dir	Prec	SOE
										Low	Incons	Dir	Imprec	Insuf

AH = antihistamine; Combo = combination; Cons = consistency; Dir = direct; G = good; Imprec = imprecision; Incons = inconsistent; Insuf = insufficient; INCS = intranasal corticosteroid; N = no; Pt = patient; RD = risk difference; SOE = strength of evidence; USPSTF = U.S. Preventive Services Task Force; Y = yes.

[a] Values are not statistically significant unless otherwise indicated. "Favors" indicates avoidance of harm.

[b] The process of harms ascertainment was characterized as active, passive, or intermediate as defined in the Methods section.

[c] Denominator was reports, not patients. Confidence limits not calculated to assess strength of evidence.

* $p<0.05$, calculated by CER authors.

Combination Oral Selective Antihistamine Plus Oral Decongestant Versus Oral Selective Antihistamine

Key Points

- There is moderate strength evidence to support the use of oral selective antihistamine rather than combination oral selective antihistamine plus oral decongestant to avoid insomnia. This evidence was from four 2-week trials,[101, 103-105] each with statistically significant differences in the proportion of patients reporting insomnia. The body of evidence was consistent, precise and associated with moderate risk of bias.
- Evidence was insufficient to support using either oral antihistamine or oral decongestant to avoid sedation, headache or anxiety.

Synthesis and Evidence Assessment

All seven trials[101-107] that reported efficacy outcomes also reported adverse events. Table 68 displays the risk differences and elements for the synthesis of evidence for this comparison.

Two trials[106, 107] presented adverse events as a percentage of total reports, rather than as a percentage of patients. In a third trial[102] it was unclear if the reporting unit was the patient or an incident event. These three trials were included in the synthesis of evidence only to assess consistency of effect. Only one trial reported palpitations[105] (risk difference 0 percent). One trial[106] reported chest pain in 0.3 percent of reports in the combination arm only. Synthesis of evidence was not conducted for these outcomes.

Sedation was reported by three trials[101, 103, 105] (N=1640) with risk differences ranging from 2 percent in favor of oral selective antihistamine monotherapy to 3 percent in favor of combination therapy; no differences were statistically significant. The risk of bias was considered medium. Fifty-five percent of the patient sample for this adverse event was in good quality trials[101, 103] that actively ascertained adverse events. Risk differences were inconsistent and imprecise. Evidence was insufficient to conclude that either comparator is favored to avoid sedation.

Headache was reported by four trials[101, 103-105] (N=2038) with risk differences ranging from 2 percent in favor of oral selective antihistamine monotherapy to 2.8 percent in favor of combination therapy. No estimates were statistically significant. The risk of bias was considered medium. Fifty-six percent of the patient sample for this adverse event was in poor quality trials,[104, 105] one of which also had inadequate surveillance for adverse events,[105] and forty-four percent was in good quality trials[101, 103] that actively ascertained adverse events. Risk differences were inconsistent and imprecise. Evidence was insufficient to conclude that either comparator is favored to avoid headache.

Insomnia was reported by four trials[101, 103-105] (N=2038) with risk differences ranging from 4 percent to 11.1 percent favoring oral antihistamine monotherapy to avoid insomnia; all were statistically significant. The risk of bias was considered medium. Fifty-six percent of the patient sample for this adverse event was in poor quality trials,[104, 105] one of which also had inadequate surveillance for adverse events,[105] and forty-four percent was in good quality trials[101, 103] that actively ascertained adverse events. Risk differences were consistent and precise. To avoid insomnia, there is moderate strength evidence to support the use of oral antihistamine rather than oral decongestant.

Table 68. Strength of evidence: comparative adverse events for oral selective antihistamine plus oral decongestant versus oral selective antihistamine

Outcome	Severity	Citation	Favors[a] Combo RD	Favors[a] Neither RD	Favors[a] Oral S-AH RD	USPSTF	Active?[b]	Pt Blind?	Assessor Blind?	Risk of Bias	Cons	Dir	Prec	SOE
Sedation	Unspecified	Bronsky, 1995[101]			2	G	Y	Y	Y					
		Grosclaude, 1997[103]	3.0			G	Y	Y	Y					
		Pleskow, 2005[105]			2	P	N	Y	Y					
		Schenkel, 2002[106c]			0.9	F	N	Y	Y					
		Sussman, 1999[107c]			0.5	G	Y	Y	Y					
										Med	Incons	Dir	Imprec	Insuf
Headache	Unspecified	Bronsky, 1995[101]			2	G	Y	Y	Y					
		Grosclaude, 1997[103]	2.8			G	Y	Y	Y					
		Grubbe, 2009[104]	0.6			P	Y	Y	Y					
		Pleskow, 2005[105]	1			P	N	Y	Y					
		Chervinsky, 2005[102d]		0		P	Int	Y	Y					
		Schenkel, 2002[106c]			1.5	F	N	Y	Y					
		Sussman, 1999[107c]			2	G	Y	Y	Y					
										Med	Incons	Dir	Imprec	Insuf
Insomnia	Unspecified	Bronsky, 1995[101]			4*	G	Y	Y	Y					
		Grosclaude, 1997[103]			11.1*	G	Y	Y	Y					
		Grubbe, 2009[104]			6.5*	P	Y	Y	Y					
		Pleskow, 2005[105]			4*	P	N	Y	Y					
		Chervinsky, 2005[102d]			8	P	Int	Y	Y					
		Schenkel, 2002[106c]			4.2	F	N	Y	Y					
		Sussman, 1999[107c]			9.4	G	Y	Y	Y					
										Med	Cons	Dir	Prec	Mod
Anxiety	Unspecified	Bronsky, 1995[101]			4.0*	G	Y	Y	Y					
		Grosclaude, 1997[103]	2.2*			G	Y	Y	Y					
		Pleskow, 2005[105]			1	P	N	Y	Y					
		Schenkel, 2002[106c]			2.1	F	N	Y	Y					

Outcome	Severity	Citation	Favors[a] Combo RD	Favors[a] Neither RD	Favors[a] Oral S-AH RD	USPSTF	Active?[b]	Pt Blind?	Assessor Blind?	Risk of Bias	Cons	Dir	Prec	SOE
		Sussman, 1999[107c]			1.4	G	Y	Y	Y					
										Med	Incons	Dir	Imprec	Insuf

Combo = Combination; Dir = direct; F = fair; G = good; (Im)Prec = (im)precision; (In)Cons = (in)consistent; Insuf = insufficient; Int = intermediate; Mod = moderate; N = no; P = poor; Pt = patient; RD = risk difference; S-AH = selective antihistamine; SOE = strength of evidence; USPSTF = U.S. Preventive Services Task Force; Y = yes.

[a] Values are not statistically significant unless otherwise indicated. "Favors" indicates avoidance of harm.

[b] The process of harms ascertainment was characterized as active, passive, or intermediate as defined in the Methods section.

[c] Denominator was reports, not patients. Confidence limits not calculated to assess strength of evidence.

[d] Unclear if denominator was reports or patients, confidence limits not calculated to assess strength of evidence.

* $p<0.05$, calculated by CER authors.

Anxiety was reported by three trials[101, 103, 105] (N=1640) with risk differences ranging from 4 percent in favor of oral selective antihistamine monotherapy to 2.2 percent in favor of combination therapy; both extremes[101, 103] were statistically significant. The risk of bias was considered medium. Fifty-five percent of the patient sample for this adverse event was in good quality trials[101, 103] that actively ascertained adverse events, and 45 percent was in a poor quality trial[105] that ascertained adverse events in a passive fashion. Risk differences were inconsistent and imprecise. Evidence was insufficient to conclude that either comparator is favored to avoid anxiety.

Key Question 3. Comparative Effectiveness and Adverse Effects of Treatments in Pregnant Women

For the identified comparisons of interest, no comparative trials, observational studies, meta-analyses, or systematic reviews met our inclusion criteria of directly comparing two drug classes used in pregnant women with SAR. We were unable to assess comparative effectiveness and harms of SAR treatments in pregnant women.

Key Question 4. Comparative Effectiveness and Harms of SAR Treatments in Children Younger Than 12 Years of Age

Of 21 treatment comparisons of interest for children, studies that met our inclusion criteria were identified for one, oral selective antihistamine versus oral nonselective antihistamine. For all comparisons, we considered inclusion of studies that reported results for adults and children mixed together. Eight trials that met all other inclusion criteria were identified.[136-143] However, none of these trials provided subgroup analysis by age. Because mixed results would not inform the answer to this Key Question, these studies were not included.

Oral Selective Antihistamine Versus Oral Nonselective Antihistamine

Description of Included Studies

Two RCTs[133, 134] published in 1989 and 1996 were identified. One[134] was a multicenter, 2-week trial in North America (N=126). The other[133] was a 2-week trial in Europe (N=40). The selective antihistamines were cetirizine and loratadine, and the nonselective antihistamines were chlorpheniramine and dexchlorpheniramine. One trial[134] was open-label, and one[133] was assessor-blinded only. One trial[134] was industry-funded, and the other[133] did not report funding source.

The average age of patients was 8.6 years. In both trials, more than 60 percent of patients were male (63 percent to 70 percent). One trial[134] reported information on race, and 82 percent were white. Neither trial required a minimum duration of SAR history; the mean duration of SAR ranged from three to six years. Although both trials required a minimum severity of SAR symptoms, no baseline symptom scores were reported.

The open-label trial[134] assessed individual nasal (congestion and sneezing) and eye (itching and watering) symptoms using a four-point rating scale (0=no symptoms, 3=severe symptoms). The other trial[133] reported only change in total symptom score, comprising both nasal and eye

symptoms. This was not a prespecified outcome of interest and was not abstracted. Neither trial assessed asthma outcomes.

Both trials were rated poor quality.

Effectiveness: Key Points

These results are summarized in Table 69.

- Nasal congestion and sneezing at 2 weeks: Evidence was insufficient to support the use of one treatment over the other based on a single trial with high risk of bias and imprecise results.
- Ocular itching and tearing: Evidence was insufficient to support the use of one treatment over the other based on a single trial with high risk of bias and imprecise results.
- These results are based on trials using one of five oral selective antihistamines (20 percent) and one of twelve oral nonselective antihistamines (eight percent).

Table 69. Strength of evidence: oral selective antihistamine versus oral nonselective antihistamine in children

Outcome	RCTs (Patients)	Risk of Bias	Consistency	Directness	Precision	Overall GRADE
2-week nasal symptoms (congestion, sneezing)	1[134] (126)	High	Unknown (single study)	Direct	Imprecise	Insufficient
2-week eye symptoms (itching, tearing)	1[134] (126)	High	Unknown (single study)	Direct	Imprecise	Insufficient

GRADE = Grading of Recommendations Assessment, Development and Evaluation; RCTs (Patients) = number of randomized controlled trials (number of patients randomized to treatment groups of interest).

Effectiveness: Detailed Synthesis

Nasal symptom outcomes discussed below are summarized in Table 70, and eye symptom outcomes in Table 71.

Nasal Symptoms

One[134] of two trials (N=126) assessed nasal congestion and sneezing at 2 weeks. For nasal congestion, there was a statistically nonsignificant treatment effect of 0.1 on a 0-3 point scale (3 percent of maximum score) that favored nonselective antihistamine. For sneezing, no treatment difference was reported. The trial was rated poor quality due to lack of blinding; therefore, risk of bias was high. Treatment effects for both nasal symptoms were imprecise. The evidence was insufficient to support the use of one treatment over the other for either outcome.

Eye Symptoms

One[134] of two trials (N=126) assessed ocular itching and tearing. For both outcomes, treatment effects were 0.1 on a 0-3 point scale (3 percent of maximum score). Both favored nonselective antihistamine, but neither was statistically significant. The trial was rated poor quality due to lack of blinding; therefore, risk of bias was high. Treatment effects for both ocular symptoms were imprecise. The evidence was insufficient to support the use of one treatment over the other for either outcome.

Table 70. Treatment effects: nasal symptoms–oral selective antihistamine versus oral nonselective antihistamine in children

Outcome[a]	Variance	SS Favors Oral S-AH MD	NSS Favors/NR Oral S-AH MD	Favors Neither MD=0	NSS Favors/NR Oral nS-AH MD	SS Favors Oral nS-AH MD
2-Week Outcomes						
Congestion						
Tinkelman, 1996[134]					0.1 (NSS)	
Sneezing						
Tinkelman, 1996[134]				0		

MD = Mean difference between group mean changes from baseline, nS-AH = nonselective antihistamine, NSS = not statistically significant; NR = p-value not reported; S-AH = selective antihistamine; SS = statistically significant.

[a] Scale 0-3

Table 71. Treatment effects: ocular symptoms–oral selective antihistamine versus oral nonselective antihistamine in children

Outcome[a]	Variance	SS Favors Oral S-AH MD	NSS Favors/NR Oral S-AH MD	Favors Neither MD=0	NSS Favors/NR Oral nS-AH MD	SS Favors Oral nS-AH MD
2-Week Outcomes						
Itchy eyes						
Tinkelman, 1996[134]					0.1[b] (NSS)	
Tearing						
Tinkelman, 1996[134]					0.1[b] (NSS)	

MD = Mean difference between group mean changes from baseline, NSS = not statistically significant; NR = p-value not reported; nS-AH = nonselective antihistamine, S-AH = selective antihistamine; SS = statistically significant.

[a] Scale 0-3

[b] Values obtained from figures using Engauge Digitizer Software

Harms: Key Points

Evidence from two trials[133, 134] was insufficient to support using either oral selective antihistamine or nonselective antihistamine to avoid the adverse event of sedation.

Harms: Synthesis and Evidence Assessment

Both trials[133, 134] reported harms (N=165). Risk differences and elements for the evidence synthesis are displayed in Table 72.

Both trials reported sedation (N=165 patients assessed for harms). In one trial,[133] there was a statistically significant risk difference of 21.1 percent favoring oral selective antihistamine. This trial was rated poor quality due to lack of patient blinding. Assessors also were unblinded, and harms ascertainment was only partially active. In the other trial,[134] the risk difference was 4.3 percent favoring oral selective antihistamine, but this was not statistically significant. This trial was rated poor quality due to lack of blinding and inappropriate analysis of results (not intention to treat). In addition, harms ascertainment was passive.

Based on the quality of the trials, the risk of bias was considered high. Risk differences were consistent but imprecise. Evidence was insufficient to conclude that one treatment is favored to avoid sedation.

Table 72. Risk differences and strength of evidence for harms–oral selective antihistamine versus oral nonselective antihistamine in children

Outcome	Severity	Citation	Favors[a] Oral S-AH RD	Favors[a] Neither RD=0	Favors[a] Oral nS-AH RD	USPSTF	Active?	Pt Blind?	Assessor Blind?	RoB	Cons	Dir	Prec	SOE
Sedation	Moderate	Tinkelman, 1996[134]	4.3			P	N	N	N					
	Unspecified	Boner, 1989[133]	21.1[b]			P	Int	N	Y					
										High	Cons	Dir	Imprec	Insuf

Combo = combination; Cons = consistent; Dir = direct; F = fair; G = good; (Im)Prec = (im)precision; Insuf = insufficient; Int = intermediate; Mod = moderate; N = no; nS-AH = nonselective antihistamine; P = poor; Pt = patient; RD = risk difference; S-AH = selective antihistamine; SOE = strength of evidence; USPSTF = U.S. Preventive Services Task Force; Y = yes.

[a] Statistical significance as indicated.

[b] $p<0.05$, calculated by CER authors.

Discussion

Key Findings and Strength of Evidence

This report reviews 59 randomized, controlled trials (RCTs) of treatments for seasonal allergic rhinitis (SAR) in adults and adolescents, in children younger than 12 years of age, and in pregnant women. In adults and adolescents, oral drug classes studied were selective and nonselective antihistamine, sympathomimetic decongestant, and leukotriene receptor antagonist; nasal drug classes were antihistamine, corticosteroid, and cromolyn. No RCTs or observational studies of intranasal anticholinergic or nasal saline spray were identified. In children, drug classes studied were oral selective and nonselective antihistamine. In this population, no RCTs or observational studies of nasal antihistamine, corticosteroid, or cromolyn; oral leukotriene receptor antagonist; or nasal saline spray were identified. No RCTs or observational studies of SAR treatments in pregnant women were identified.

Key Question 1. Comparative Effectiveness of SAR Treatments in Adults and Adolescents 12 Years of Age or Older

Overview of Results

Twenty-two treatment comparisons of interest were identified. We found studies that satisfied our inclusion criteria for 13 of these. Results for these comparisons are presented in Table 73 and discussed below. For most outcomes, evidence was insufficient to form any comparative effectiveness conclusion. In five comparisons, we found evidence for comparable effectiveness (equivalence) of treatments for at least one outcome (rows 5, 6, 8, 11, and 12 in Table 73), and we found evidence for superior effectiveness of one treatment over another for one outcome in each of two comparisons (row 5 and row 9 in Table 73).

When reviewing Table 73, it is important to keep in mind that the strength of evidence analysis only describes the evidence for each specific treatment comparison. That is, conclusions about equivalence or superiority can be made when two treatments are directly compared. In the absence of direct comparison, neither conclusion is supported. For example, for various nasal symptom outcomes, there was moderate strength evidence for comparable effectiveness (equivalence) of oral selective antihistamine and oral leukotriene receptor antagonist (row 5), and high strength evidence for the comparable effectiveness of intranasal corticosteroid and oral leukotriene receptor antagonist (row 8). This does not support a conclusion of equivalence of oral selective antihistamine and intranasal corticosteroid for nasal symptoms. As shown in row 3, direct evidence from the comparison of oral selective antihistamine to intranasal corticosteroid for the treatment of nasal symptoms was insufficient to form a conclusion about their comparative effectiveness. In contrast, high strength evidence suggests comparable effectiveness of intranasal corticosteroid plus nasal antihistamine combination therapy and each of its components for nasal and eye symptoms (rows 11 and 12). Direct evidence also suggests comparable effectiveness of intranasal corticosteroid and nasal antihistamine for these outcomes (row 6), suggesting comparable effectiveness of all three treatments.

It also is important to keep in mind that:

- Results presented in the summary table, indeed in the entire report, reflect the reporting of data in the literature. Data that were reported with insufficient detail to permit their inclusion in meta-analysis restricted the comparative effectiveness conclusions that could be drawn. Data reported with insufficient detail to assess their quality reduces the strength of the body of evidence. This was particularly evident in three-arm trials in which p-values for comparisons of interest for this review were not the primary comparisons in the trial. It may be that in some cases the reporting of the evidence, rather than the evidence itself, is insufficient to make any conclusion about the comparative effectiveness of two treatments. (See Limitations of the Evidence Base, below.)
- Seven of 13 treatment comparisons (54 percent) had poor representation (less than 50 percent) of at least one drug class compared. Although the Technical Expert Panel (TEP) was unaware of evidence suggesting differential effectiveness within a class, these seven comparisons may not adequately represent the classes of drugs compared, and conclusions are limited to the specific drugs studied. The seven comparisons are listed below with the proportion of drugs represented in each class indicated in parentheses.
    - Oral selective versus oral nonselective antihistamine (40 percent versus 25 percent)
    - Intranasal corticosteroid versus nasal antihistamine (25 percent versus 100 percent)
    - Intranasal corticosteroid versus oral leukotriene receptor antagonist (25 percent versus 100 percent)
    - Combination oral selective antihistamine plus intranasal corticosteroid versus oral selective antihistamine (40 percent of oral selective antihistamines and 25 percent of intranasal corticosteroids)
    - Combination oral selective antihistamine plus intranasal corticosteroid versus intranasal corticosteroid (60 percent of oral selective antihistamines and 25 percent of intranasal corticosteroids)
    - Combination intranasal corticosteroid plus nasal antihistamine versus intranasal corticosteroid (12.5 percent of intranasal corticosteroids and 50 percent of nasal antihistamines)
    - Combination intranasal corticosteroid plus nasal antihistamine versus nasal antihistamine (12.5 percent of intranasal corticosteroids and 50 percent of nasal antihistamines)

For some drug classes, the impact of poor representation may be limited; for example, 25 percent of oral nonselective antihistamines were studied in two comparisons, but this class of drugs is used less often since the advent of newer treatments. Similarly, only one of two oral decongestants was studied (pseudoephedrine), the one that is most commonly used.

In four comparisons, intranasal corticosteroid alone or in combination was poorly represented: In two (versus nasal antihistamine and versus oral leukotriene receptor antagonist), only fluticasone propionate and budesonide were studied. In the other two (combination intranasal corticosteroid plus nasal antihistamine versus each component), only fluticasone propionate was studied. Comparative effectiveness conclusions therefore apply to the specific drugs in each comparison; how well they generalize to other drugs in the same class is uncertain.

Cells marked "Insufficient" indicate insufficient evidence to form a conclusion. As described in the Methods section, conclusions that could be drawn for any outcome depended on the nature of the evidence available:

- For outcomes that had minimal clinically important differences (MCIDs) and meta-analysis was done, conclusions of superiority, equivalence, or insufficient evidence could be made.
- For outcomes that had an MCID and meta-analysis was *not* done, only conclusions of superiority or insufficient evidence could be made.
- For outcomes with no MCID, only conclusions of superiority or insufficient evidence could be made regardless of whether meta-analysis was done.

Of 28 meta-analyses conducted, 26 supported equivalence conclusions. The other two meta-analyses assessed oral selective antihistamine in comparison to intranasal corticosteroid (row 3). In approximately half of the trials identified for this comparison, treatment effects for nasal and eye symptoms were not reported. Therefore, the evidence was imprecise and insufficient to support a comparative effectiveness conclusion of superiority or equivalence for these outcomes. All other "Insufficient" cells indicate insufficient evidence to support only superiority conclusions.

Table 73. Summary of findings and strength of evidence for effectiveness in 13 treatment comparisons: Key Question 1–adults and adolescents

Comparison		Representation[a]	Nasal Symptoms	Eye Symptoms	Asthma Symptoms	Quality of Life
1.	Oral S-AH vs. Oral nS-AH	40% vs. 18%	Insufficient			Insufficient
2.	Oral S-AH vs. Nasal AH	60% vs. azelastine (50%)	Insufficient			Insufficient
3.	Oral S-AH vs. INCS	60% vs. 62.5%	Insufficient	Insufficient		Insufficient
4.	Oral S-AH vs. Oral D	80% vs. pseudoephedrine (50%)	Insufficient	Insufficient		
5.	Oral S-AH vs. LRA	60% vs. montelukast (100%)	Equivalent: Moderate[b]	Equivalent: Moderate[c]	LRA: Moderate[d]	Equivalent: Moderate[e]
6.	INCS vs. Nasal AH	25% vs. 100%	Equivalent: High[f]	Equivalent: High[g]		Insufficient
7.	INCS vs. Nasal C	62.5% vs. cromolyn (100%)	Insufficient			
8.	INCS vs. LRA	25% vs. montelukast (100%)	Equivalent: High[h]		Insufficient	
9.	Oral S-AH + INCS vs. Oral S-AH	40% Oral S-AH, 25% INCS	Insufficient	Insufficient		Oral S-AH + INCS: Low[e]
10.	Oral S-AH + INCS vs. INCS	60% Oral S-AH, 25% INCS	Insufficient	Insufficient		Insufficient
11.	INCS + Nasal AH vs. INCS	FP (12.5%), azelastine (50%)	Equivalent: High[f]	Equivalent: High[g]		Insufficient
12.	INCS + Nasal AH vs. Nasal AH	FP (12.5%), azelastine (50%)	Equivalent: High[f]	Equivalent: High[g]		Insufficient
13.	Oral S-AH + Oral D vs. Oral S-AH	80% Oral S-AH, pseudoephedrine (50%)	Insufficient	Insufficient		

AH = antihistamine; C = cromolyn; D = sympathomimetic decongestant; FP = fluticasone propionate; INCS = intranasal corticosteroid; LRA = leukotriene receptor antagonist; nS-AH = nonselective antihistamine; S-AH = selective antihistamine.

Entries indicate comparative efficacy conclusions supported by the evidence, or insufficient evidence to form a conclusion. Empty cells indicate outcomes that were not assessed.

Conclusions are indicated by Conclusion: Strength of evidence (SOE):

- "Equivalent" indicates sufficient evidence to support a conclusion of equivalence (comparable effectiveness) between compared treatments for the outcome indicated.
- "LRA" and "Oral S-AH + INCS" indicate sufficient evidence to support conclusions of superiority of these treatments over their respective comparators for the indicated outcomes.
- SOE is indicated by Low (low SOE), Moderate (moderate SOE), and High (high SOE).

"Insufficient" indicates insufficient evidence to form a conclusion.

- For the comparison of oral selective antihistamine to intranasal corticosteroid (row 3), evidence was insufficient to form conclusions of superiority or equivalence for nasal and eye symptoms.
- For all other outcomes, "Insufficient" indicates insufficient evidence for conclusions of superiority; equivalence was not assessed.

[a] Representation indicates the proportion of drugs in each class that were studied. For comparisons involving combination therapy (rows 9 through 13), the proportion of the drug class studied as monotherapy is the same as the proportion of that drug class studied in combination therapy. For example, in row 9, two of five oral selective antihistamines (40 percent) were studied as monotherapy, and the same two antihistamines were studied in combination therapy.

[b] Total Nasal Symptom Score at 2-4 weeks.

[c] Total Ocular Symptom Score (eye tearing, itching, redness, and puffiness) at 2-4 weeks.

[d] Rescue medication use at 2 and 4 weeks. For other asthma outcomes (symptoms and forced expired volume in 1 second [FEV_1]), evidence was insufficient to form a comparative effectiveness conclusion.

[e] Rhinitis Quality of Life Questionnaire at 2-4 weeks.

[f] Congestion, rhinorrhea, sneezing, nasal itch and Total Nasal Symptom Score at 2 weeks.

[g] Total Ocular Symptom Score at 2 weeks.

[h] Congestion, rhinorrhea, sneezing, nasal itch and Total Nasal Symptom Score at 2 weeks.

As shown in Table 73, we found:

- High strength evidence for comparable effectiveness (equivalence) of:
    - Combination intranasal corticosteroid plus nasal antihistamine, intranasal corticosteroid monotherapy, and nasal antihistamine monotherapy for nasal and eye symptoms at 2 weeks.
    - Intranasal corticosteroid and oral leukotriene receptor antagonist (montelukast) for nasal symptoms at 2 weeks.
- Moderate strength evidence for comparable effectiveness of oral selective antihistamine and oral leukotriene receptor antagonist for nasal and eye symptoms and for improved quality of life at 2-4 weeks.
- Moderate strength evidence for the use of oral leukotriene receptor antagonist over oral selective antihistamine for reduced asthma rescue medication use at 2-4 weeks.
- Low strength evidence for the use of combination oral selective antihistamine plus intranasal corticosteroid over oral selective antihistamine monotherapy for improved quality of life at 2-4 weeks.

Sensitivity Analysis

These findings and strength of evidence ratings were directly impacted by our choice of the MCID for each outcome. In the absence of well-defined MCIDs for symptom outcomes, we selected an MCID of 30 percent maximum score based on our review of the literature and input from the TEP. In sensitivity analysis, we reduced this value by one third (i.e., to 20 percent maximum score) and found five comparisons affected. Of these five, one conclusion changed (#5 below).

- Oral selective antihistamine versus oral decongestant: eye symptoms at 2 weeks
    - Original conclusion: Insufficient evidence to support the use of one treatment over the other based on two good quality trials[103, 107] (N=890) with low risk of bias and consistent but imprecise treatment effects favoring oral selective antihistamine.
    - Result of sensitivity analysis: One trial[107] (n=436) reported a treatment effect of 25 percent maximum score. This trial[107] represented 49 percent of patients reporting this outcome. Because approximately half of patients would still be in the trial[103] with imprecise results, the body of evidence would remain imprecise.
- Intranasal corticosteroid versus nasal antihistamine: nasal congestion at 2 weeks
    - Original conclusion: High strength of evidence for comparable effectiveness (equivalence) of the treatments based on eight trials[115-119, 121] (N=2443) with low risk of bias and consistent and precise results.
    - Result of sensitivity analysis: One poor quality trial[116] (n=50) reported a treatment effect of 23 percent maximum score favoring intranasal corticosteroid. Because this trial represented 2 percent of patients reporting this outcome, its impact on the overall precision of the body of evidence was minimal, and the body of evidence would remain imprecise.
- Intranasal corticosteroid versus nasal cromolyn: rhinorrhea at 2 weeks
    - Original conclusion: Insufficient evidence to support the use of one treatment over the other based on one poor quality trial[122] (n=43) with high risk of bias and an imprecise treatment effect favoring intranasal corticosteroid.

    - Result of sensitivity analysis: The treatment effect represented 20 percent of maximum score. If this were considered a precise result, the strength of evidence would remain insufficient to support the use of one treatment over the other due to the high risk of bias and unknown consistency of the body of evidence.
- Combination oral selective antihistamine plus intranasal corticosteroid versus oral selective antihistamine monotherapy: total nasal symptom score (TNSS) at 2 weeks
    - Original conclusion: Insufficient evidence to support the use of one treatment over the other based on three trials[90, 98, 130] (N=677) with high risk of bias and consistent but imprecise results.
    - Result of sensitivity analysis: One fair quality trial[98] (n=300) reported a treatment effect of 22 percent maximum score. This trial[98] represented 44 percent of patients reporting this outcome. Because the majority of patients would still be in the trials[90, 130] with imprecise results, the body of evidence would remain imprecise.
- Combination oral selective antihistamine plus oral decongestant versus oral selective antihistamine monotherapy: TNSS at 2 weeks
    - Original conclusion: Insufficient evidence to support the use of one treatment over the other based on one good quality trial[101] (n=438) with low risk of bias and an imprecise treatment effect favoring combination therapy.
    - Result of sensitivity analysis: The treatment effect represented 20 percent of maximum score. If this were considered a precise result, the strength of evidence to support the use of combination oral selective antihistamine plus oral decongestant over oral selective antihistamine monotherapy would be moderate.

Responder Analysis

To demonstrate clinically meaningful treatment effects, the preferred analysis is a responder analysis, in which the outcome of interest is the proportion of patients who reached a predefined minimum threshold of improvement. However, a well-defined MCID is required for a robust responder analysis, and most trials did not use this approach. In meta-analyses of three trials that compared combination intranasal corticosteroid plus nasal antihistamine to both intranasal corticosteroid and nasal antihistamine monotherapy (total N=3150), responder analyses were included.[115] Response was defined as a 50 percent reduction from baseline TNSS on a 0-24 point scale. Resolution was defined as reduction in all individual nasal symptom scores to less than 1.0 on a 0-6 point scale. It is unclear how these thresholds were derived. For the comparison of combination therapy to nasal antihistamine monotherapy, a statistically significantly greater proportion of patients achieved both resolution ($p<0.001$) and response ($p<0.001$) with combination therapy. For the comparison of combination therapy to intranasal corticosteroid monotherapy, a statistically significantly greater proportion of patients achieved resolution with combination therapy ($p=0.033$), but the difference in the proportion of patients achieving response was not statistically significant ($p=0.071$). Correlation of these results with the results presented in the current report is limited by definitions of "response" and "resolution," which did not include MCIDs. Because the published meta-analyses lacked details about the how the analyses were conducted, results could not be replicated. Therefore, these findings do not alter our conclusions of comparable effectiveness (equivalence) of these treatments for nasal symptom outcomes.

Subgroups

We were limited in our ability to address identified subgroups of interest, that is, patients co-diagnosed with asthma or allergic conjunctivitis. For asthma, only the two comparisons of oral leukotriene receptor antagonist (montelukast), to oral selective antihistamine and to intranasal corticosteroid, included asthma outcomes. In one of these, moderate strength evidence supported the superiority of montelukast over oral selective antihistamine for reduction in rescue medication use; for other asthma outcomes assessed in this comparison (asthma symptoms and forced expired volume in 1 second [FEV_1]), evidence was insufficient to form conclusions. In the other comparison, evidence was insufficient to support either intranasal corticosteroid or montelukast for asthma outcomes (symptom-free days, albuterol-free days, morning and evening peak expired flow [PEF], and asthma exacerbations). Eye symptom outcomes were reported in ten treatment comparisons. Of these, conclusions of equivalence of the two treatments were made in four. For each of these comparisons, equivalence also was concluded for nasal symptoms (see Table 73).

We were limited in our ability to address differences in effectiveness between patients with mild symptoms and patients with moderate/severe symptoms. Most trials enrolled patients with moderate/severe baseline SAR symptoms. Those that included patients with mild severity did not report results separately for these patients. Three small trials[122, 128, 130] (total N=81) reported mean baseline TNSS that were in the mild range. Two of these were rated poor quality[122, 128] and favored intranasal corticosteroid over nasal cromolyn[122] and over oral leukotriene receptor antagonist[128] for nasal symptoms. The third[130] (n=27) was a fair quality trial that favored combination oral selective antihistamine plus intranasal corticosteroid over oral selective antihistamine monotherapy for nasal symptoms. Treatment effects ranged from 2 percent to 20 percent of maximum score. The evidence is insufficient to suggest that mild nasal symptoms respond differently than moderate/severe symptoms to the specific treatments compared. However, this conclusion is preliminary until replicated by larger, higher quality trials.

Duration of Treatment

Finally, six trials[88, 120, 123, 125, 128, 131, 132] in four comparisons were longer than 4 weeks in duration. Each of the four comparisons is discussed below. Additionally:

- Because each of the four comparisons involved intranasal corticosteroid, outcomes at 2 weeks and after 2 weeks are compared.
- Two of four other comparisons that involved intranasal corticosteroid included trials of 2 and 4 weeks' duration. These outcomes also are reviewed below.
- The remaining two comparisons that involved intranasal corticosteroid (combination intranasal corticosteroid plus nasal antihistamine versus each component) included trials of 2 weeks' duration only. These trials are not discussed here.

Overall, the evidence is insufficient to suggest that comparative effectiveness at later time points up to 8 weeks differs from effectiveness at 2 to 4 weeks.

Comparisons that included trials longer than 4 weeks:

- Intranasal corticosteroid versus nasal antihistamine: Two poor quality trials[116, 120] (total N=80) favored nasal antihistamine for nasal symptoms at 3, 4, and 5 weeks. Treatment effects ranged from 8 to 17 percent of maximum score. At 2 weeks, high strength evidence supported comparable effectiveness (equivalence) of intranasal corticosteroid and nasal antihistamine for nasal symptoms.

- Intranasal corticosteroid versus nasal cromolyn: Three poor quality trials[122-124] (total N=344) favored intranasal corticosteroid for nasal symptoms at 3 to 6 weeks. Treatment effects ranged from 5 to 16 percent of maximum score. One poor quality trial[125] (n=90) favored intranasal corticosteroid for patient global assessment of symptoms (PGA) at 8 weeks. At 2 weeks, evidence was insufficient to support the use of one treatment over the other for either of these outcomes.
- Intranasal corticosteroid versus oral leukotriene receptor antagonist: Two poor quality trials[127, 128] (total N=602) favored intranasal corticosteroid at 3 to 8 weeks for nasal symptoms. Treatment effects ranged from 4 to 9 percent of maximum score. At 2 weeks, high strength evidence supported comparable effectiveness of intranasal corticosteroid and montelukast for nasal symptoms.
- Combination oral selective antihistamine plus intranasal corticosteroid versus intranasal corticosteroid: Evidence was insufficient to support the use of one treatment over the other for nasal or eye symptoms at 6 and 8 weeks based on one poor quality trial[132] (n=40) and one good quality trial[131] (n=454). At 2 weeks, evidence also was insufficient to support the use of either treatment for these outcomes.

Comparisons involving intranasal corticosteroid that included trials of 2 and 4 weeks' duration:

- Oral selective antihistamine versus intranasal corticosteroid: For nasal and eye symptoms, and quality of life as assessed by the Rhinitis Quality of Life Questionnaire (RQLQ), evidence was insufficient to support either treatment at both 2 weeks and 3 to 4 weeks.
- Combination oral selective antihistamine plus intranasal corticosteroid versus oral selective antihistamine: For nasal and eye symptoms, evidence was insufficient to support the use of either treatment at both 2 and 4 weeks.

Key Question 2. Comparative Harms of SAR Treatments in Adults and Adolescents 12 Years of Age or Older

We identified two comparisons with sufficient evidence to support the use of one treatment over the other in order to avoid harm while treating SAR symptoms. These are shown in Table 74. To avoid insomnia at approximately 2 weeks, moderate strength evidence supported the use of oral selective antihistamine rather than either monotherapy with an oral decongestant or combination therapy with oral selective antihistamine plus oral decongestant. For all other adverse events of interest, evidence to indicate superior harms avoidance with one treatment compared to another was either insufficient or lacking. Because MCIDs for harms outcomes have not been defined, equivalence of treatments compared was not tested and cannot be assumed.

As shown in Table 74, we made 46 harms assessments. Of these, 34 (74 percent) were based on drug class comparisons with less than 50 percent representation for at least one treatment compared. For these 34 assessments, conclusions may be limited to the specific drugs studied. As with effectiveness comparisons, the impact of poor representation may be limited for some drug classes (see "Overview of Results" for Key Question [KQ] 1, above).

We sought comparative information on a wide range of adverse events commonly associated with the pharmacologic classes studied. Conclusions about comparative harms are limited by the nature of the evidence reviewed in this report.

- Included trials lasted at most the duration of the pollen season, which is generally 6 to 8 weeks. Treatment durations were therefore relatively short for consideration of harms. Latent effects or cumulative effects from longer treatment durations are unknown.

Adverse events reported as the proportion of patients experiencing an event are assumed to be constant over time. This method of reporting does not differentiate between a person with a single episode of insomnia and one who experienced it every night of a 2-week trial.
Adverse event frequencies often were not reported for all treatment groups.
Harms assessment was inconsistent in the trials reviewed. Twenty-seven percent of trials indicated that an active method of harms surveillance was used. In contrast to passive surveillance, active surveillance of harms can yield qualitatively and quantitatively different results.[144] However, we had to assume consistency of harms surveillance across trials to synthesize estimates and to consider a body of evidence for comparative review. To mitigate the effects of inconsistent harms surveillance on pooled effects (i.e., meta-analysis), we considered for pooling only events that either were considered severe by investigators or resulted in treatment discontinuation. We found no candidates for meta-analysis in any comparison.
Adverse events collected for this review were categorized as mild, moderate, or severe as they were identified in the source publication, with the exception that all adverse events leading to treatment discontinuation were considered severe.

Table 74. Summary of findings and strength of evidence of harms in 13 treatment comparisons: Key Question 2–adults and adolescents

	Comparison	Headache	Sedation	Nosebleeds	Nasal Discomfort	Bitter Aftertaste	Burning	Anxiety	Insomnia	Palpitations	Dryness	Hypertension	Nasal Candidiasis	Nasal Atrophy	Odor Abnormality	Stinging
1.	Oral S-AH vs. Oral nS-AH	Insuff[b]	Insuff[b]													
2.	Oral S-AH vs. Nasal AH	Insuff[b]	Insuff	Insuff[b]		Insuff[b]										
3.	Oral S-AH vs. INCS	Insuff[b]														
4.	Oral S-AH vs. Oral D	Insuff	Insuff					Insuff	Oral S-AH Moderate[a]							
5.	Oral S-AH vs. LRA	Insuff[b]														
6.	INCS vs. Nasal AH	Insuff[b]	Insuff[b]	Insuff[b]	Insuff[b]	Insuff[b]										
7.	INCS vs. Nasal C	Insuff		Insuff[b]	Insuff		Insuff[b]				Insuff					
8.	INCS vs. LRA	Insuff[b]		Insuff[b]												
9.	Oral S-AH + INCS vs. Oral S-AH	Insuff[b]	Insuff[b]	Insuff[b]			Insuff[b]									
10.	Oral S-AH + INCS vs. INCS	Insuff[b]	Insuff[b]	Insuff[b]			Insuff[b]									
11.	INCS + Nasal AH vs. INCS	Insuff[b]	Insuff[b]	Insuff[b]	Insuff[b]	Insuff[b]										
12.	INCS + Nasal AH vs. Nasal AH	Insuff[b]	Insuff[b]	Insuff[b]	Insuff[b]	Insuff[b]										
13.	Oral S-AH + Oral D vs. Oral S-AH	Insuff	Insuff					Insuff	Oral S-AH Moderate[a]							

C = cromolyn; D = decongestant; INCS = intranasal corticosteroid; LRA = leukotriene receptor antagonist; nS-AH = nonselective antihistamine; S-AH = selective antihistamine.

Entries indicate comparative efficacy conclusions supported by the evidence, or insufficient evidence to form a conclusion. Empty cells indicate outcomes that were not assessed.

Conclusions are indicated by Conclusion: Strength of evidence (SOE):

- "Oral S-AH" indicates sufficient evidence to support conclusions of superiority of oral selective antihistamine over its respective comparators to avoid the indicated harm.
- SOE is indicated by Low (low SOE), Moderate (moderate SOE), and High (high SOE).

"Insuff" indicates insufficient evidence to form a conclusion.

[a] Moderate strength evidence indicates fewer insomnia events at approximately 2 weeks with oral selective antihistamine.

[b] Based on trials that studied less than 50 percent of the drugs in at least one drug class compared.

Combined Evaluation of Key Questions 1 and 2: Comparative Effectiveness and Harms of Treatments in Adults and Adolescents 12 Years of Age or Older

We did not find evidence that any single treatment demonstrated both greater effectiveness and lower risk of harms. Table 75 shows the two comparisons for which there was sufficient evidence on reducing harms to form a conclusion along with the comparative effectiveness results for these comparisons. Moderate strength evidence supported the use of oral selective antihistamine to avoid insomnia associated with sympathomimetic decongestant at approximately 2 weeks (row 1 and row 2), but evidence was insufficient to support the use of one treatment over the other for effectiveness. (Equivalence was not assessed in either comparison due to the inability to conduct meta-analysis.) Similarly, of two treatments shown to be comparatively superior for effectiveness (row 3 and row 4), neither was preferred for harms avoidance.

Table 75. Comparison of efficacy and harms findings for two treatment comparisons

Comparison	Representation[a]	Efficacy Outcome	Harms Outcome
1. Oral S-AH vs. Oral D	80% vs. pseudoephedrine (50%)	Insufficient evidence[b]	Oral S-AH to avoid insomnia: Moderate
2. Oral S-AH vs. Oral LRA	60% vs. montelukast (100%)	Oral LRA for reduced asthma rescue medication use: Moderate	Insufficient evidence[b]
3. Oral S-AH + INCS vs. Oral S-AH	40% Oral S-AH, 25% INCS	Oral S-AH + INCS for improved QoL: Low	Insufficient evidence[b]
4. Oral S-AH + Oral D vs. Oral S-AH	80% Oral S-AH, pseudoephedrine (50%)	Insufficient evidence[b]	Oral S-AH to avoid insomnia: Moderate

AH = antihistamine; D = sympathomimetic decongestant; LRA = leukotriene receptor antagonist; QoL = quality of life; S-AH = selective antihistamine.

Outcome entries indicate Conclusion: Strength of evidence. "Moderate" indicates moderate strength evidence to support the use of oral selective antihistamine over the indicated comparator to avoid insomnia.

[a] Representation indicates the proportion of drugs in each class that were studied.

[b] Insufficient evidence to support conclusions of superiority of one treatment over the other for efficacy or harms outcomes. Equivalence was not tested.

Key Question 3. Comparative Effectiveness and Harms of SAR Treatments in Pregnant Women

For this KQ, we considered only Pregnancy Category B drugs, in which teratogenic effects have not been identified in animal studies or replicated in human studies. Evidence for the assessment of this KQ was lacking. No RCTs, observational studies, systematic reviews, or meta-analyses met the inclusion criteria.

Drugs used for the treatment of SAR have wide therapeutic windows (i.e., across the range of doses at which efficacy is seen, severe adverse events are not expected). Therefore, the choice of SAR treatment in pregnant women may be cautiously informed by comparative effectiveness evidence from the nonpregnant patient population. Because physiologic changes of pregnancy alter drug disposition, generalization of findings from the nonpregnant population to pregnant women requires knowledge of the magnitude and direction of these changes (Table 76). Due to a lack of study in pregnant women, current knowledge does not present a clear picture of safe and

efficacious dosing adjustments of SAR treatments necessary to account for the physiologic changes of pregnancy.[145] The minimum effective dose is generally preferred pregnancy.

Table 76. Physiologic changes in pregnancy and potential effects on drug disposition[145, 146]

Physiologic parameter	Change compared with nonpregnant woman	Potential effect on drug disposition
Plasma volume	↑ approximately 40-50%	↑ Volume of distribution, ↓ peak serum concentrations
Plasma albumin concentration	↓ approximately 15%[a]	Alter protein binding (increase free fraction of protein bound [i.e., weakly acidic or weakly basic] drugs)
Serum pH	↑slightly	May affect protein binding of weakly acidic/basic drugs
Cardiac output	↑30-50%	
Regional blood flow	uterus ↑ kidneys ↑ skin ↑ mammary glands ↑ hepatic↑ up to 160% skeletal muscle ↓	May affect drug distribution and elimination (high extraction ratio drugs)
Glomerular filtration rate	↑ 40-85%	Clearance of drugs eliminated renally
Hepatic metabolizing enzyme activity	N-demethylation ↓ CYP1A2 ↓ CYP2C19 ↓ CYP2C9 ↑ CYP2A6 ↑ CYP2D6 ↑/↓ CYP3A4 ↑	Increase or decrease half-life
Gastric emptying	↓	Drug absorption increased
Gastric pH	↑	Altered depending on pH sensitivity

CYP = Cytochrome P450 isoenzyme.
[a] Plasma concentrations of total protein and α_1-acid glycoprotein, which bind many basic drugs, are relatively unchanged during pregnancy.

Key Question 4. Comparative Effectiveness and Harms of SAR Treatments in Children Younger Than 12 Years of Age

Of 21 treatment comparisons of interest among children, studies that met our inclusion criteria were identified for one, selective versus nonselective oral antihistamine. No observational studies, systematic reviews, or meta-analyses met the required inclusion criteria.

The evidence for effectiveness and for harms was insufficient to support the use of either oral selective antihistamine or nonselective antihistamine for the treatment of nasal or eye symptoms in children younger than 12 years of age (mean age 9 years, range 4 to 12 years). This finding was based on trials that studied 20 percent of oral selective antihistamines and 9 percent of oral nonselective antihistamines used to treat children. As with harms outcomes, a finding of insufficient evidence to support a conclusion of superiority of one treatment over the other does not imply equivalence of the treatments. The evidence for benefit was truly insufficient; equivalence was not assessed.

Findings in Relationship to What Is Already Known

The following three systematic reviews provide current information about the pharmacologic treatment of allergic rhinitis. Each provided a description of the literature search, inclusion and exclusion criteria for identified trials, and quality assessments of included trials. Thus, the risk of bias was considered low for each. Two of the reviews were published before 2010, the cutoff date for potential incorporation of results into this review. Results from the third review were not

incorporated into this review due to methodological differences; for example, the 2010 review was based on previously published systematic reviews, and disease was not limited to SAR. For purposes of comparing our findings to current knowledge, we included high-quality seminal works by relevant groups regardless of publication date.

- Guidelines for the treatment of allergic rhinitis from the international Allergic Rhinitis and Its Impact on Asthma (ARIA) working group, updated in 2010[28]

A 2009 systematic review of treatments for hay fever[147]

A 2008 Practice Parameter on the diagnosis and management of rhinitis from the Joint Task Force on Practice Parameters, representing the American Academy of Allergy, Asthma & Immunology (AAAAI), the American College of Allergy, Asthma and Immunology (ACAAI), and the Joint Council of Allergy, Asthma and Immunology (JCAAI)[3]

A 2010 systematic review of SAR treatments by drug class[41] is not included in this list because quality assessments of included trials were not reported.

Findings from each of these reports are compared with those of this comparative effectiveness review in Table 77. Of 13 comparisons for which we found studies, three were not addressed by the systematic reviews. In two of the remaining ten comparisons, our conclusions agreed with at least one of the systematic reviews (ARIA guidelines in both instances). For five of eight discordant conclusions, other systematic reviews formed comparative effectiveness or harms conclusions, and we found insufficient evidence to do so. The other three discordant conclusions involved intranasal corticosteroid alone or in combination. We concluded comparable effectiveness (equivalence) of the treatments compared, and other systematic reviews concluded comparative superiority of intranasal corticosteroid. The eight discordant conclusions are reviewed below. In all cases, differing conclusions could be attributed to differences in inclusion criteria for trials reviewed.

Discordant conclusions of insufficient evidence:

- Oral selective antihistamine versus oral non-selective antihistamine: ARIA guidelines[28] and the AAAAI practice parameter[3] recommended oral selective antihistamine to avoid harms. ARIA did not provide an evidence profile for this comparison. Evidence to inform AAAAI's recommendation included observational data and comparative studies in healthy volunteers.
- Oral selective antihistamine versus nasal antihistamine: ARIA guidelines[28] recommended oral selective antihistamine for avoidance of harms, such as bitter aftertaste. This review included trials of non-Food and Drug Administration (FDA) approved oral antihistamines (ebastine and levocabastine) and a trial in perennial allergic rhinitis (PAR). The other two reviews[3, 149] reported comparable efficacy of the treatments. One[147] of these conclusions was based on a trial of a non-FDA approved nasal antihistamine (levocabastine) in comparison with a non-FDA approved oral antihistamine (terfenadine). The other[3] included a pharmacodynamic study in an environmental exposure chamber and a trial of combination therapy not identified as an intervention of interest for the present review.
- Oral selective antihistamine versus intranasal corticosteroid: Two reviews[28, 147] found evidence favoring intranasal corticosteroid over mixed oral selective and non-selective antihistamine. One[149] of these included two trials that reported only physiologic outcomes (e.g., nasal airflow), and the other[28] included trials in PAR.
- Intranasal corticosteroid versus nasal cromolyn: The AAAAI practice parameter[3] recommended intranasal corticosteroid for most patients based on a single trial[125] that was one of four trials included in the present review for this comparison.

- Combination oral selective antihistamine plus intranasal corticosteroid versus intranasal corticosteroid: One review[147] reported greater improvement in quality of life with combination therapy than with intranasal corticosteroid monotherapy based on one trial. This trial[62] was one of five trials included in the present review for this comparison.

Discordant conclusions of comparable effectiveness (equivalence):

- Intranasal corticosteroid versus nasal antihistamine: All three reviews supported the use of intranasal corticosteroid based on a systematic review[29] that included patients with PAR.
- Intranasal corticosteroid versus oral leukotriene receptor antagonist: Two reviews[28, 147] found evidence to support the use of intranasal corticosteroid for symptoms of AR[28] and SAR.[147] In both of these, conclusions were based on statistical rather than clinical significance of treatment effects reported by two[128, 129] (in the ARIA guidelines[28]) or four[126-129] (in the 2009 systematic review[149]) of five trials[97, 126-129] included in the present review for this comparison.
- Combination intranasal corticosteroid plus nasal antihistamine versus nasal antihistamine: One review[147] found evidence to support the use of combination therapy over nasal antihistamine (azelastine) monotherapy based on one[121] of five[115, 117, 121] trials included in the present review for this comparison. Four trials[115, 117] were published after the systematic review.[147]

Table 77. Comparison of findings from four systematic reviews of treatments for seasonal allergic rhinitis

Comparison	ARIA[28]	Sheikh[147]	AAAAI[3a]	AHRQ CER	Agreement
1. Oral S-AH vs. Oral nS-AH	Oral S-AH to avoid harms Low quality evidence in AR		Oral S-AH to avoid sedation, performance impairment, and anticholinergic effects B	Insufficient evidence for superiority or harms avoidance	Discordant results
2. Oral S-AH vs. Nasal AH	Oral S-AH to avoid bitter aftertaste Moderate quality evidence in SAR	Mixed oral S-AH and nS-AH comparable to nasal AH for nasal symptoms and harms Moderate-quality evidence	Nasal AH is equal to or superior to oral S-AH for SAR A	Insufficient evidence for superiority or harms avoidance	Discordant results
3. Oral S-AH vs. INCS	INCS preferred over mixed oral S-AH and nS-AH based on efficacy Low quality evidence in SAR	INCS preferred to mixed oral S-AH and nS-AH for nasal symptoms. Comparable efficacy for eye symptoms Low-quality evidence		Insufficient evidence for superiority, equivalence or harms avoidance	Discordant results
4. Oral S-AH vs. Oral D				Oral S-AH to avoid insomnia - Moderate SOE	No comparison
5. Oral S-AH vs. LRA	Comparable for efficacy and harms. Oral AH recommended based on cost Moderate quality evidence in SAR	Low-quality evidence does not permit an efficacy conclusion Comparable for harms		Equivalence for nasal and eye symptoms and QoL; LRA for asthma symptom - Moderate SOE	Agree with ARIA
6. INCS vs. Nasal AH	INCS preferred based on efficacy High quality evidence in mixed SAR/PAR	INCS preferred for nasal symptoms Nasal AH preferred for eye symptoms Very low-quality evidence Bitter taste more common with nasal AH (azelastine) than with INCS (fluticasone)	INCS preferred for treatment of AR A	Equivalence for nasal and eye symptoms - High SOE	Discordant results
7. INCS vs. Nasal C			INCS preferred in most patients with AR; nasal C effective in some patients for prevention and treatment of AR with minimal harms A	Insufficient evidence for superiority or harms avoidance	Discordant results
8. INCS vs. LRA	INCS preferred over LRA based on efficacy Low quality evidence in SAR	INCSA preferred for nasal symptoms High quality evidence Comparable harms		Equivalence for nasal symptoms - High SOE	Discordant results

Comparison	ARIA[28]	Sheikh[147]	AAAAI[3a]	AHRQ CER	Agreement
9. Oral S-AH + INCS vs. Oral S-AH				Oral S-AH + INCS for QoL - Low SOE	No comparison
10. Oral S-AH + INCS vs. INCS		Oral S-AH + INCS for QoL at 2 weeks Low-quality evidence		Insufficient evidence for superiority or harms avoidance	Discordant results
11. INCS + Nasal AH vs. INCS				Equivalence for nasal and eye symptoms - High SOE	No comparison
12. INCS + Nasal AH vs. Nasal AH		INCS + Nasal AH (azelastine) for nasal symptoms at 2 weeks Moderate-quality evidence		Equivalence for nasal and eye symptoms - High SOE	Discordant results
13. Oral S-AH + Oral SD vs. Oral S-AH	Oral AH (mixed S-AH and nS-AH) monotherapy despite greater benefit (small) with combo because harms reported more often with combo Moderate evidence in mixed SAR/PAR	Oral S-AH + oral SD (pseudoephedrine) for nasal symptoms at 2−10 weeks Moderate-quality evidence		Oral S-AH to avoid insomnia - Moderate SOE	Agree with ARIA

AAAAI = American Academy of Allergy, Asthma & Immunology; AH = Antihistamine; AHRQ = Agency for Healthcare Research and Quality; ARIA = Allergic Rhinitis and Its Impact on Asthma; C = cromolyn; CER = comparative effectiveness review; D = decongestant; INCS = intranasal corticosteroid; LRA = leukotriene receptor antagonist; nS-AH = nonselective antihistamine; QoL = quality of life; S-AH = selective antihistamine; SOE = strength of evidence.

[a] Strength of recommendation ratings are based on the level of evidence. An A recommendation is directly based on category I evidence, defined as evidence from meta-analysis of randomized controlled trials or evidence from at least 1 randomized controlled trial. A B recommendation is directly based on category II evidence or extrapolated from category I evidence. Category II evidence is defined as evidence from at least 1 controlled study without randomization or evidence from at least 1 other type of quasi-experimental study.[3]

Applicability

Applicability is assessed in terms of PICOTS—populations, interventions, comparisons, outcomes, timeframes, and settings of care.[79]

Populations: In studies that reported the ethnic-racial make-up of trial participants, most patients were white. Approximately 9 percent were black, 7 percent were Hispanic, and 3 percent were Asian. Adult patients tended to be in their 30s and 40s. Some trials included older patients. This population is representative of many patients with SAR. Results are likely to be generalizable to adults of different ethnicities or ages, although this is not known with certainty. Patients in their seventh or eighth decade of life may require dosage adjustments for reduced renal or liver function and greater vigilance for adverse events, for example, sedating effects.

Most patients had moderate to severe symptoms at baseline and had a minimum 5-year duration of SAR. Evidence from three small trials that studied patients with mild symptoms,[122, 128, 130] was insufficient to suggest that mild nasal symptoms respond differently than moderate/severe symptoms to the specific treatments compared. Only one[130] of these trials reported disease duration; 92 percent of patients had SAR for more than 5 years. Applicability of the findings from this report to patients with mild or recent onset SAR is therefore unknown.

Interventions/Comparisons: The interventions investigated represent treatment options for SAR currently available in the United States. We restricted our search to trials that used FDA-approved drugs at FDA-approved doses. Conclusions may not be applicable to drugs in included drug classes that were not specifically studied (e.g., drugs or doses used in Europe). Additionally, for comparisons with trials studying a small proportion of the drugs in a class, applicability of the findings to other drugs in the class that were not studied is uncertain. We did not assess eye drops for the treatment of eye symptoms associated with SAR. We sought but did not find sufficient comparative trials to address as-needed dosing.

Outcomes: SAR symptoms comprise nasal, eye, ear, palate, and throat symptoms. To maximize comparability across trials, we focused on the most often reported nasal and eye symptom outcomes, which likely enhances generalizability. For patients who experience less common symptoms, such as postnasal drip or ear itching, results from this report may not be generalizable. Outcomes were reported within the time frames of their trials and comparators; for example, nasal outcomes at 2 and 4 weeks were not mixed for trials involving intranasal corticosteroid, but were mixed for trials involving other drugs of more uniform onset and duration of action. It is unclear whether results from shorter intervals are generalizable to longer use, for example, whether treatment effectiveness reported at earlier time points is maintained at later time points and whether the incidence of adverse effects increases with increased duration of exposure.

Timeframes: By limiting diagnosis specifically to SAR, we excluded not only patients with PAR but also those classified according to the new criteria proposed by the ARIA group,[28] that is, those diagnosed with intermittent allergic rhinitis or persistent allergic rhinitis. These categories define overlapping but differing patient populations.[3] Diagnostic categories vary in at least two dimensions: duration of allergen exposure and type of allergen. Because treatments are symptomatic, it is not expected that type of allergen will affect treatment response. However, duration of allergen exposure and, consequently, of treatment exposure may impact the applicability of the findings. For the assessment of treatment effectiveness in real-world settings, we included studies with a 2-week minimum treatment duration during pollen season.[50] Study duration was therefore limited by the natural pollen cycle. We searched for trials of longer

duration to compare short-term (weeks) and longer-term (months) effectiveness and harms, but the few trials of longer than 4 weeks' duration identified prevented definitive conclusions. Similarly, patients who require less than 2 weeks' treatment may experience different effects than those reported here.

Settings: Of all trials identified, only one was not set in Europe or North America. This was a trial of 50 patients conducted in Asia (Nepal).[116] Across all trials, Asian patients represented a minor fraction of patients studied. Generalizability to patients in Asia or to Asian patients in North America or Europe may be limited by differing aeroallergen exposure and by potential genotype differences affecting metabolism of drugs used to treat SAR.

Implications for Clinical and Policy Decisionmaking

Fortunately, SAR is not a life-threatening disease. Consideration of risks and benefits of treatment therefore shifts, from an expectation that adverse events may accompany effective treatments to an appreciation that adverse effects of treatment may be worse than the disease itself. We did not find high strength evidence for differences in effectiveness or adverse effects in any treatment comparison. We did find high strength and moderate strength evidence for comparable effectiveness of several treatments for several outcomes, low strength evidence for superiority of two treatments for two outcomes, and moderate strength evidence for the avoidance of insomnia.

This evidence may be insufficient for policy decisionmaking. For example, although conclusions of comparable effectiveness may suggest that differential costs of treatments are unwarranted, lack of evidence to evaluate comparative harms of these treatments prohibits full assessment of their risk-benefit profiles.

For clinical decisionmaking, conclusions of comparable effectiveness suggest that patient preferences and priorities can contribute significantly to treatment choice. When considering the balance between effectiveness and harms in relatively healthy individuals, potential harms may acquire greater weight.[144]

Limitations of the Comparative Effectiveness Review Process

To narrow the scope of this project to a manageable size, we made several decisions at the start that had downstream consequences. These included:

- We restricted diagnosis to SAR. Given the current state of transition between classification schemes for allergic rhinitis, use of the original scheme may have excluded some trials. However, it is acknowledged that SAR and intermittent allergic rhinitis define different patient populations.[3] We decided to pick one disease to study and then find studies similar enough to compare results. Introducing studies of allergic rhinitis classified according to the newer scheme may have added to the variability of included studies.
- We did not examine every possible treatment comparison. Rather, guided by input from Key Informants and the TEP, we prioritized comparisons that reflect treatment decisions encountered in the clinical setting. It is hoped that we selected, and found evidence to assess, comparisons that are meaningful to users of this report.
- We excluded trials of one drug versus a placebo and focused on direct comparisons only. This decision was based on feasibility concerns given the large scope of the project and

time constraints. Harms assessment was limited by the absence of placebo groups, which can inform adverse event reporting particularly.

- We included FDA-approved drugs only. For the comparison of oral selective antihistamine to oral nonselective antihistamine in particular, this significantly reduced the number of included trials. The majority of these trials used terfenadine or astemizole as the selective antihistamine comparator, neither of which is currently FDA-approved due to postmarketing safety concerns. As a result, only three trials were included for this comparison.
- Our minimum 2-week duration excluded examination of other treatment features that may be important to patients, e.g., onset of action and harms associated with shorter exposure. However, harms associated with the interventions as defined (i.e., minimum 2-week exposure) were included. Trials less than 2 weeks' duration often did not replicate natural methods of exposure to airborne allergens (i.e., used instead environmental exposure chambers, direct application of allergen, or prolonged weekend visits to parks), and results may be less applicable.
- As described below, reporting of efficacy outcomes in SAR research currently is nonstandard. To maximize our ability to compare outcomes across trials, we selected the most commonly used symptom measures, namely the four-symptom TNSS and the three-item total ocular symptom score (TOSS). Data from trials that used variations on these reporting scales could not be incorporated into the report. Symptoms potentially important to patients but seldom assessed (e.g., post-nasal drip, and ear and palate itching) were not included in this review.
- The scope of this report is class comparisons of SAR treatments. As a consequence of this approach, individual drug comparisons were beyond the scope of this report. Also, for comparisons with trials studying a small proportion of the drugs in a class, we were limited in our ability to make conclusions about entire pharmacologic classes, particularly for larger classes such as intranasal corticosteroids and oral nonselective antihistamines. As discussed above (in the Discussion of KQ1), the impact of this limitation may be small for certain drug classes, such as oral nonselective antihistamine, which are less commonly used, and oral decongestant, of which the more commonly used drug was studied.
- Limitations in the quality of trial reporting impacted directly the conclusions that could be drawn and strength of evidence ratings. For example, insufficient group-level data reporting prevented equivalence assessments. Insufficient descriptions of analyses compromised quality ratings. For example, if intention-to-treat (ITT) analysis was not specified, or insufficient patient flow data were provided to determine that an ITT analysis was done, trial quality was rated poor. This was a conservative decision that was warranted. It is hoped that continued implementation of guidelines for trial reporting will address such difficulties.

Limitations of Evidence Base

In their review of SAR treatments, Benninger et al. (2010) conclude that "the reporting of published data should be standardized to permit comparisons among treatments."[41] The following six improvements are cited:

- Standard inclusion criteria for allergic rhinitis based on a unified definition
- Standard stratification of disease severity

- TNSS based on four nasal symptoms (congestion, rhinorrhea, sneezing, and nasal itch) and reported on a 3-point or 4-point severity scale
- Standard ocular data for TOSS
- Standard quality of life data using a validated survey
- Standard age cutoffs (adult studies should include ages > 18 years; adolescents, 12–18 years old; school-age children, 6–11 years old)

In our experience, factors 2, 3, 4, and 6 reduced our ability to draw evidence-based conclusions. Additionally, evidence for efficacy and harms in patients with mild disease was lacking due to enrollment of patients primarily with moderate/severe disease. In fact, standard definitions of mild, moderate, and severe disease in terms of symptom scales do not currently exist. A 4-point scale may be divided into terciles (0-1 mild, 1-2 moderate, 2-3 severe), but this is an empirical division. It is unknown whether the scale is linear in patients' experience.

We could not incorporate several trials that reported only total symptom scores, comprising nasal, eye, ear, and palate symptoms. Standard reporting of the four-symptom TNSS and the three-symptom TOSS would greatly facilitate treatment comparisons. It is surprising that the list above does not include a call for well-defined MCIDs for symptom scales. Although our selection of clinically informed MCIDs permitted us to draw clinically relevant conclusions, validation of the values used (30 percent maximum score) using anchor-based approaches is desirable. Without such well-defined MCIDs, at least three analytic tools important for clinical research–power calculations, non-inferiority margins, and responder analyses–are compromised.

Another methodological issue is the incomplete reporting of results. Examples include:

- Reporting the results of statistical testing for only two arms of a three-arm trial
- Not reporting variance estimates for group-level treatment effects
- Not reporting results for all identified outcomes
- Missing baseline symptom or quality of life scores
- Partial accounting of patient flow through the trial

Adverse event reporting was consistently incomplete. Severity of adverse events was sometimes mentioned, but, as above, lack of standard definitions of severity or a standard adverse event scale currently limits the usefulness of severity descriptions. Adverse events often were not reported by treatment group or were not identified. That is, the proportion of patients experiencing adverse events was at times reported without any description of the adverse events experienced.

We excluded several trials that did not report results by age groups or that formed age groups using non-standard cut points. Defining "adolescent" from age 12 may be arbitrary, but its general adoption would permit greater learning about this age group. FDA commonly uses a cut point of age 12 for dosing of SAR drugs in children and adolescents.

Finally, within the constraints of our inclusion criteria, we identified few to no studies for the assessment of SAR treatments in pregnant women and children. Head-to-head active comparator trials may be ethically difficult in these vulnerable populations unless true equipoise exists. Although we preferred RCTs, we would have included relevant nonrandomized comparative trials, but we found none.

Research Gaps

The greatest need in SAR research is increased methodological rigor. Widely used symptom rating scales require standardization and validation. Lack of anchor-based MCIDs is a major deficiency. Agreed-upon reporting standards for effectiveness and harms outcomes are needed. Agreed-upon classifications of patients by age and standardized definitions of symptom and harms severity also are needed. Study designs that can more efficiently assess the effects of additive therapies are lacking. That is, studies in which all patients are treated with one component of a combination (e.g., oral selective antihistamine) and only those who are resistant receive the second component (e.g., intranasal corticosteroid) may more efficiently isolate the additive effect of the second component. We identified one trial with this design.[148]

Lack of evidence on populations of interest is a research gap. Currently, the majority of trial participants are relatively homogenous: white and middle-aged with moderate/severe SAR symptoms. Inclusion of different races, greater proportions of patients toward both ends of the age spectrum, and patients with mild symptoms may inform our understanding not only of the comparative effectiveness and harms of SAR treatments in different groups, but also of the expression of SAR in various ethnic groups, the natural history of the disease across the life span, and the effect (if any) of early treatment on later symptom expression. As noted above, however, ethical considerations may limit the inclusion of vulnerable populations (e.g., children) in well-designed studies of pharmacologic interventions.

For pregnant women, pregnancy registries and rigorous studies based on the data therein can fill the gap. Additionally, greater understanding of how the physiologic changes of pregnancy affect the magnitude and direction of change in drug disposition may facilitate application of effectiveness and safety findings from the nonpregnant population to pregnant women. This presumes use of Pregnancy Category B drugs to avoid potential known or unknown teratogenic effects of other drugs.

Conclusions

For most treatment comparisons of interest, evidence was insufficient to support conclusions about comparative effectiveness and harms. Of conclusions that could be drawn, most suggested comparable effectiveness of treatments compared. For adults and adolescents over the age of 12 we found:

- High strength evidence for comparable effectiveness (equivalence) of:
    - Combination intranasal corticosteroid (fluticasone propionate) plus nasal antihistamine (azelastine), intranasal corticosteroid monotherapy, and nasal antihistamine monotherapy for nasal and eye symptoms at 2 weeks.
    - Intranasal corticosteroid and oral leukotriene receptor antagonist (montelukast) for nasal symptoms at 2 weeks.
- Moderate strength evidence for comparable effectiveness of oral selective antihistamine and oral leukotriene receptor antagonist for nasal and eye symptoms and for improved quality of life at 2-4 weeks.

In this population, we found evidence for the superiority of:

- Oral selective antihistamine over both oral decongestant and combination oral selective antihistamine plus oral decongestant to avoid insomnia at approximately 2 weeks (moderate strength evidence).

- Oral leukotriene receptor antagonist over oral selective antihistamine for reduced asthma rescue medication use at 2-4 weeks (moderate strength evidence).
- Combination oral selective antihistamine plus intranasal corticosteroid over oral selective antihistamine monotherapy for improved quality of life at 2-4 weeks (low strength evidence).

Conclusions about symptom improvement were based on clinically informed but non-validated MCIDs. Sensitivity analyses supported the conclusions above as well as the use of combination oral selective antihistamine plus oral decongestant over oral selective antihistamine monotherapy for nasal symptoms. The lack of comparative evidence for all drugs within each class limited the applicability of conclusions. Evidence was insufficient or lacking to support any of 48 other identified treatment comparisons of interest among adults and adolescents over the age of 12, pregnant women, and children younger than 12 years of age.

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Abbreviations

AZE: Azelastine
BDP: Beclomethasone dipropionate
BUD: Budesonide
C: Congestion
CET: Cetirizine
CI: Confidence interval
CLM: Clemastine
CHL: Chlorpheniramine
CRS: Cromolyn
DES: Desloratadine
DEX: Dexchlorpheniramine
FEV_1: Forced expired volume in one second
FEX: Fexofenadine
FLU: Flunisolide
FF: Fluticasone furoate
FP: Fluticasone propionate
I: Itching
INCS: Intranasal corticosteroid
LOR: Loratadine
LCT: Levocetirizine
LRA: Leukotriene receptor antagonist
MCID: Minimum clinically important difference
MOD: Moderate
MF: Mometasone furoate
NR: Not reported
NS: Not significant
OLO: Olopatadine
PGA: Patient Global Assessment
PSE: Pseudoephedrine
QoL: Quality of life
R: Rhinorrhea
RCT: Randomized controlled trial
RQLQ: Rhinitis Quality of Life Questionnaire
S: Sneezing
SD: Standard deviation
SE: Standard error
SEV: Severe
TA: Triamcinolone acetonide
TASS: Total asthma symptom score
TNSS: Total nasal symptom score
TOSS: Total ocular symptom score
UNC: Uncertain
UNS: Unspecified
VAS: Visual analog scale

Appendix A. Search Strategies

The following electronic databases were searched on July 18, 2012 for citations:

- MEDLINE® (1948 to July 18, 2012) yielded 1992 records
- EMBASE® (1980 to July 18, 2012) yielded 1621 records
- The Cochrane Library (through July 18, 2012) yielded 731 records

MEDLINE

1. Rhinitis, Allergic, Perennial/
2. Rhinitis, Allergic, Seasonal/
3. Rhinitis/
4. (seasonal or allergic).tw.
5. 3 and 4
6. seasonal rhinitis.tw.
7. allergic rhinitis.tw.
8. (hay fever or hayfever).tw.
9. (sar or par).tw.
10. or/1-2,5-9
11. exp Adrenal Cortex Hormones/ or corticosteroid$.tw.
12. Betamethasone/ or (Betamethasone or Celestone).tw.
13. Cortisone/ or Cortone.tw.
14. exp Dexamethasone/ or (Dexamethasone or Baycadron or Hexadrol or Decadron or Dexium or Dexone or DexPak).tw.
15. exp Hydrocortisone/ or (Hydrocortisone or Cortef or Hydrocortone).tw.
16. Methylprednisolone/ or (Methylprednisolone or medrol).tw.
17. exp Prednisolone/ or (Prednisolone or asmalPred Plus or Millipred or Pediapred or Prelone or Veripred or Flo-Pred or Cotolone or Orapred or Prednoral).tw.
18. Prednisone/ or (Prednisone or Liquid Pred or Deltasone or Meticorten or Orasone or Prednicen or Sterapred or Prednicot).tw.
19. exp Triamcinolone/ or (Triamcinolone or Aristocort).tw.
20. or/11-17
21. exp Administration, Oral/ or oral$.tw.
22. 20 and 21
23. Beclomethasone/ or (Beclomethasone or Beconase or Vancenase).tw.
24. exp Adrenal Cortex Hormones/ or corticosteroid$.tw.
25. Budesonide/ or (Budesonide or Rhinocort).tw.
26. Pregnenediones/ or (Ciclesonide or Omnaris).tw.
27. exp Dexamethasone/ or (Dexamethasone or Dexacort).tw.
28. exp Fluocinolone Acetonide/ or (Flunisolide or Nasalide or Nasarel).tw.
29. exp Androstadienes/ or (Fluticasone or Flonase or Veramyst).tw.
30. (Mometasone or Nasonex).tw.
31. exp Triamcinolone/ or (Triamcinolone or AllerNaze or Nasocort or Tri-nasal).tw.
32. or/23-31
33. Administration, Intranasal/ or (nasal$ or intranasal$).tw.

34. 32 and 33
35. exp Histamine Antagonists/ or antihistamine$.tw.
36. Cetirizine/ or (Cetirizine or Zyrtec or Alleroff or Aller-tec).tw.
37. Loratadine/ or (Loratadine or Desloratadine or Clarinex or Claritin or Triaminic or Agistam or Alavert or Bactimicina allergy or Clear-atadine or Loradamed).tw.
38. Terfenadine/ or (Fexofenadine or Allegra).tw.
39. (Levocetirizine or Xyzal).tw.
40. or/36-39
41. exp Histamine Antagonists/ or antihistamine$.tw.
42. exp Brompheniramine/ or (Brompheniramine or Lodrane or Tridane or Bromaphen or Brovex or B-vex or Tanacof or Bidhist or Bromax or Respa or Brompsiro or Dimetane or Siltane or Vazol or Conex or J-Tan).tw.
43. Carbinoxamine.tw.
44. Pyridines/ or (Carbinoxamine or Carboxine or Cordron or Histuss or Palgic or Pediatex or Pediox or Arbinoxa).tw.
45. Chlorpheniramine/ or (Chlorpheniramine or Chlo-Amine or Chlor-Phen or Krafthist or Chlortan or Ed ChlorPed or P-Tann or Allerlief or Chlor-Al Rel or Myci Chlorped or Pediatan or Ahist or Aller-Chlor or Chlor-Mal or Chlor-Phenit or Diabetic Tussin or Ed Chlor Tan or Ridramin or Teldrin or Uni-Cortrom).tw.
46. Clemastine/ or (Clemastine or Tavist or Allerhist$ or Dayhist$).tw.
47. Cyproheptadine/ or (Cyproheptadine or Periactin).tw.
48. (Dexchlorpheniramine or Polaramine).tw.
49. exp Diphenhydramine/ or (Diphenhydramine or Benadryl or Dytan or Kids-eeze or Allergia$ or Benekraft or Diphenyl or Aler-Dryl or Altaryl or Antihist or Antituss or Beldin or Belix or Bromanate AF or Bydramine or Diphen or Diphenadryl or Diphenyl$ or Dytuss or Elixsure or Hydramine or Nu-med or Pardyl or PediaCare or Scot-Tussin or Syladryl or Silaphen or Tusstat or Theraflu or Ben Tann or Dicopanol or Allermax or Banophen or Diphedryl or Diphenhist or Nervine or Paxidorm).tw.
50. Doxylamine/ or (Doxylamine or Aldex or Doxytex).tw.
51. Promethazine/ or (Promethazine or Phenergan or Pentazine or Promacot).tw.
52. Triprolidine/ or (Triprolidine or Tripohist or Zymine).tw.
53. exp Dibenzoxepins/ or (Olopatadine or Patanase).tw.
54. exp Phthalazines/ or (Azelastine or Astelin or Astepro).tw.
55. or/41-54
56. Ipratropium/ or (Ipratropium or Atrovent).tw.
57. Cromolyn Sodium/ or (cromoglycate or Cromolyn or Nasalcrom).tw.
58. Leukotriene Antagonists/ or (Leukotriene Antagonist$ or Montelukast or Singulair).tw.
59. exp Nasal Decongestants/ or exp Phenylephrine/ or Imidazoles/ or (nasal decongestant$ or Levmetamfetamine or vapo?r inhaler$ or Naphazoline or Privine or Oxymetazoline or Afrin or (Allerest adj3 Nasal) or Dristan or Duramist plus or Four-Way or Mucinex Nasal or Nasin or Neo-Synephrine or Nostrilla or (NTZ adj3 Nasal) or Oxyfrin or Oxymeta or Sinarest or Zicam or Phenylephrine or Tetrahydrozoline or tyzine or (Alconefrin adj2 Decongestant) or Rhinall or 4-way or Sinex or Propylhexedrine or Benzedrex or Xylometazoline or Otrivin).tw.
60. (oral decongestant$ or Ah-chew$ or Gilchew or Phenyl-T or Despec or Lusonal).tw. or exp Pseudoephedrine/ or (Pseudoephedrine or Afrinol or Contac or Efidac or Suphedrine or Decofed or Elixsure or Ephed 60 or Kid Kare or Myfedrine or Q-Fed or Silfedrine or Superfed or Unifed

or Entex or Nasofed or Congest Aid or Sudophed or Cenafed or Congestaclear or Pseudocot or Pseudofed or Pseudotabs or Pseudoval or Ridafed or Seudotabs or Sudafed or Sudodrin or Sudogest or Sudrine).tw.
61. sodium chloride/ or (saline or Altamist or ENTsol or Little Noses or nasal Moist or Ocean or Pretz or Salinex or SaltAire or Deep Sea or Humist or Marine mist or sea Mist or Nasosol or Pediamist or Rhinaris or Sea Soft).tw.
62. (Accuhist or Actacin or Actagen or Actamine or Actedril or Acticon or Actifed or Alacol or Ala-Hist or Alenaze-D or Allan Tannate or Allent or Aller-Chlor or Allercon or AllerDur or Allerest or Allerfrim or Allerx or Altafed or Amerifed or Anamine or Anaplex or Andec or Andehist or Aphedrid or A-Phedrin or Aridex-D or Atridine or Atrogen or Atrohist or Benylin or B-Fedrine or Bi-Tann or BP Allergy or BPM Pseudo or Brexin or Brofed or Brom Tann or Bromadrine or Bromaline or Bromaphedrine or Bromaxefed or BROMDEC or Bromfed or Bromfenex or Bromhist$ or BROMPHEN or C Tan D or Carbaxefed or CARBIC or Carbiset or Carbodec or Carbofed or Cardec or Centergy or Cetiri-d or Chemdec or Chlor Trimeton or Chlorafed$ or Chlordrine or Chlor-Mes or Chlorphedrin or Clorfed or Codimal$ or Coldec or Colfed$ or Cophene or CP Oral or CP Tannic or C-Phed Tannate or Curaler or Cydec or Dallergy or D-Amine or Dayquil Allergy or Deconamine or Decongestamine or De-Congestine or Deconomed or Delsym or Desihist or Dexaphen or Dexophed or Dicel or Dimetapp or Diphentann or Disobrom or Disophrol or Dixaphedrine or Drexophed or Drixomed or Drixoral or D-Tann or Duomine or Duotan or Dura Ron or Durafed or Duralex or Dura-Tap or Duratuss or Dynahist or Ed A-Hist or Endafed or Entre-B or Ex?Dec or Fedahist or Hayfebrol or Hexafed or Hisdec or Histadec or Histafed or Histalet or HistamaxD or Histatab or Hista-Tabs or Histex or Hydro-Tussin or Iofed or Isophen-DF or Klerist-D or Kronofed-A or Lohist or Lortuss or Maldec or Maxichlor or Med-Hist or M-Hist or Mintex or Mooredec or NalDex or Nalfed or Nasohist or ND Clear or NeutraHist or Nohist or Norel LA or Novafed or Novahistine Elixir or Ny-Tannic or Orlenta or Pediachlor or Pharmadrine or Phenabid or PHENAMETH or PHEN-TUSS or Phenyl Chlor Tan or Phenylhistine or Prohist or Pseudoephedrine-BM or Pseubrom or Pseuclor or QDall or Q-Tapp or R?Tann$ or Relera or Rescon or Respahist or Rhinabid or RhinaHist or Ricobid or Ridifed or Rinade$ or Rinate or Robitussin Night$ or Rondamine or Rondec or Rondex or Rymed or Ryna Liquid or Rynatan or Semprex or Seradex or Shellcap or Sildec or Sinuhist or Sonahist or Suclor or SudaHist or Sudal or Sudo Chlor or Suphenamine or SuTan or Tanabid or Tanafed or Tanahist or Tekral or Time-Hist or Touro or Triafed or Triphed or Tri-Pseudo or Triptifed or Trisofed or Tri-Sudo or Trisudrine or Trynate or Ultrabrom or Vazobid or Vazotab or V-Hist or Vi-Sudo or X-Hist or XiraHist or Zinx Chlor$ or Zotex).tw.
63. or/22,34,55,62
64. 10 and 63
65. randomized controlled trial.pt.
66. random$.tw.
67. 65 or 66
68. 64 and 67
69. (animals not humans).sh.
70. 68 not 69
71. limit 70 to english language
72. ("review" or "review academic" or "review tutorial").pt.
73. (medline or medlars or embase or pubmed).tw,sh.
74. (scisearch or psychinfo or psycinfo).tw,sh.

75. (psychlit or psyclit).tw,sh.
76. cinahl.tw,sh.
77. ((hand adj2 search$) or (manual$ adj2 search$)).tw,sh.
78. (electronic database$ or bibliographic database$ or computeri?ed database$ or online database$).tw,sh.
79. (pooling or pooled or mantel haenszel).tw,sh.
80. (retraction of publication or retracted publication).pt.
81. (peto or dersimonian or der simonian or fixed effect).tw,sh.
82. or/73-81
83. 72 and 82
84. meta-analysis.pt.
85. meta-analysis.sh.
86. (meta-analys$ or meta analys$ or metaanalys$).tw,sh.
87. (systematic$ adj5 review$).tw,sh.
88. (systematic$ adj5 overview$).tw,sh.
89. (quantitativ$ adj5 review$).tw,sh.
90. (quantitativ$ adj5 overview$).tw,sh.
91. (quantitativ$ adj5 synthesis$).tw,sh.
92. (methodologic$ adj5 review$).tw,sh.
93. (methodologic$ adj5 overview$).tw,sh.
94. (integrative research review$ or research integration).tw.
95. or/84-94
96. 64 and 95
97. (animals not humans).sh.
98. 96 not 97
99. limit 98 to english language
100. placebo-controlled.tw.
101. (placebo and (control or controlled)).tw.
102. (observational or cohort or case-control or cross-sectional).tw.
103. or/100-102
104. 64 and 103
105. (animals not humans).sh.
106. 104 not 105
107. limit 106 to english language

EMBASE

1. perennial rhinitis/
2. hay fever/
3. rhinitis/
4. (seasonal or allergic).tw.
5. 3 and 4
6. seasonal rhinitis.tw.
7. allergic rhinitis.tw.
8. (hay fever or hayfever).tw.
9. (sar or par).tw.

10. or/1-2,5-9
11. exp corticosteroid/ or corticosteroid$.tw.
12. Betamethasone/ or (Betamethasone or Celestone).tw.
13. Cortisone/ or Cortone.tw.
14. Dexamethasone/ or (Dexamethasone or Baycadron or Hexadrol or Decadron or Dexium or Dexone or DexPak).tw.
15. Hydrocortisone/ or (Hydrocortisone or Cortef or Hydrocortone).tw.
16. Methylprednisolone/ or (Methylprednisolone or medrol).tw.
17. Prednisolone/ or (Prednisolone or asmalPred Plus or Millipred or Pediapred or Prelone or Veripred or Flo-Pred or Cotolone or Orapred or Prednoral).tw.
18. Prednisone/ or (Prednisone or Liquid Pred or Deltasone or Meticorten or Orasone or Prednicen or Sterapred or Prednicot).tw.
19. Triamcinolone/ or (triamcinolone or Aristocort).tw.
20. oral drug administration/ or oral$.tw.
21. or/11-19
22. 20 and 21
23. Beclometasone/ or (Beclomet?asone or Beconase or Vancenase).tw.
24. exp corticosteroid/ or corticosteroid$.tw.
25. Budesonide/ or (Budesonide or Rhinocort).tw.
26. Ciclesonide/ or (Ciclesonide or Omnaris).tw.
27. Dexamethasone/ or (Dexamethasone or Dexacort).tw.
28. Flunisolide/ or (Flunisolide or Nasalide or Nasarel).tw.
29. Fluticasone/ or (Fluticasone or Flonase or Veramyst).tw.
30. mometasone furoate/ or (Mometasone or Nasonex).tw.
31. Triamcinolone/ or (Triamcinolone or AllerNaze or Nasocort or Tri-nasal).tw.
32. intranasal drug administration/ or (nasal$ or intranasal$).tw.
33. or/23-31
34. 32 and 33
35. exp antihistaminic agent/ or antihistamine$.tw.
36. Cetirizine/ or (Cetirizine or Zyrtec or Alleroff or Aller-tec).tw.
37. Loratadine/ or (Loratadine or Desloratadine or Clarinex or Claritin or Triaminic or Agistam or Alavert or Bactimicina allergy or Clear-atadine or Loradamed).tw.
38. Fexofenadine/ or (Fexofenadine or Allegra).tw.
39. Levocetirizine/ or (Levocetirizine or Xyzal).tw.
40. Brompheniramine/ or (Brompheniramine or Lodrane or Tridane or Bromaphen or Brovex or B-vex or Tanacof or Bidhist or Bromax or Respa or Brompsiro or Dimetane or Siltane or Vazol or Conex or J-Tan).tw.
41. Carbinoxamine/ or (Carboxine or Cordron or Histuss or Palgic or Pediatex or Pediox or Arbinoxa).tw.
42. Chlorpheniramine/ or (Chlorpheniramine or Chlo-Amine or Chlor-Phen or Krafthist or Chlortan or Ed ChlorPed or P-Tann or Allerlief or Chlor-Al Rel or Myci Chlorped or Pediatan or Ahist or Aller-Chlor or Chlor-Mal or Chlor-Phenit or Diabetic Tussin or Ed Chlor Tan or Ridramin or Teldrin or Uni-Cortrom).tw.
43. Clemastine/ or (Clemastine or Tavist or Allerhist$ or Dayhist$).tw.
44. Cyproheptadine/ or (Cyproheptadine or Periactin).tw.
45. Dexchlorpheniramine/ or (Dexchlorpheniramine or Polaramine).tw.

46. Diphenhydramine/ or (Diphenhydramine or Benadryl or Dytan or Kids-eeze or Allergia$ or Benekraft or Diphenyl or Aler-Dryl or Altaryl or Antihist or Antituss or Beldin or Belix or Bromanate AF or Bydramine or Diphen or Diphenadryl or Diphenyl$ or Dytuss or Elixsure or Hydramine or Nu-med or Pardyl or PediaCare or Scot-Tussin or Syladryl or Silaphen or Tusstat or Theraflu or Ben Tann or Dicopanol or Allermax or Banophen or Diphedryl or Diphenhist or Nervine or Paxidorm).tw.
47. Doxylamine/ or (Doxylamine or Aldex or Doxytex).tw.
48. Promethazine/ or (Promethazine or Phenergan or Pentazine or Promacot).tw.
49. Triprolidine/ or (Triprolidine or Tripohist or Zymine).tw.
50. Olopatadine/ or (Olopatadine or Patanase).tw.
51. Azelastine/ or (Azelastine or Astelin or Astepro).tw.
52. ipratropium bromide/ or (Ipratropium or Atrovent).tw.
53. cromoglycate disodium/ or (cromoglycate or Cromolyn or Nasalcrom).tw.
54. leukotriene receptor blocking agent/ or (Leukotriene Antagonist$ or Montelukast or Singulair).tw.
55. Decongestive agent/ or Phenylephrine/ or (nasal decongestant$ or Levmetamfetamine or vapo?r inhaler$ or Naphazoline or Privine or Oxymetazoline or Afrin or (Allerest adj3 Nasal) or Dristan or Duramist plus or Four-Way or Mucinex Nasal or Nasin or Neo-Synephrine or Nostrilla or (NTZ adj3 Nasal) or Oxyfrin or Oxymeta or Sinarest or Zicam or Phenylephrine or (Alconefrin adj2 Decongestant) or Rhinall or 4-way or Sinex or Propylhexedrine or Benzedrex or Xylometazoline or Otrivin or tetrahydrozoline or tyzine).tw.
56. Pseudoephedrine/ or (oral decongestant$ or Ah-chew$ or Gilchew or Phenyl-T or Despec or Lusonal or Pseudoephedrine or Afrinol or Contac or Efidac or Suphedrine or Decofed or Elixsure or Ephed 60 or Kid Kare or Myfedrine.tw. or Q-Fed or Silfedrine or Superfed or Unifed or Entex or Nasofed or Congest Aid or Sudophed or Cenafed or Congestaclear or Pseudocot or Pseudofed or Pseudotabs or Pseudoval or Ridafed or Seudotabs or Sudafed or Sudodrin or Sudogest or Sudrine).tw.
57. sodium chloride/ or (saline or Altamist or ENTsol or Little Noses or nasal Moist or Ocean or Pretz or Salinex or SaltAire or Deep Sea or Humist or Marine mist or sea Mist or Nasosol or Pediamist or Rhinaris or Sea Soft).tw.
58. (Accuhist or Actacin or Actagen or Actamine or Actedril or Acticon or Actifed or Alacol or Ala-Hist or Alenaze-D or Allan Tannate or Allent or Aller-Chlor or Allercon or AllerDur or Allerest or Allerfrim or Allerx or Altafed or Amerifed or Anamine or Anaplex or Andec or Andehist or Aphedrid or A-Phedrin or Aridex-D or Atridine or Atrogen or Atrohist or Benylin or B-Fedrine or Bi-Tann or BP Allergy or BPM Pseudo or Brexin or Brofed or Brom Tann or Bromadrine or Bromaline or Bromaphedrine or Bromaxefed or BROMDEC or Bromfed or Bromfenex or Bromhist$ or BROMPHEN or C Tan D or Carbaxefed or CARBIC or Carbiset or Carbodec or Carbofed or Cardec or Centergy or Cetiri-d or Chemdec or Chlor Trimeton or Chlorafed$ or Chlordrine or Chlor-Mes or Chlorphedrin or Clorfed or Codimal$ or Coldec or Colfed$ or Cophene or CP Oral or CP Tannic or C-Phed Tannate or Curaler or Cydec or Dallergy or D-Amine or Dayquil Allergy or Deconamine or Decongestamine or De-Congestine or Deconomed or Delsym or Desihist or Dexaphen or Dexophed or Dicel or Dimetapp or Diphentann or Disobrom or Disophrol or Dixaphedrine or Drexophed or Drixomed or Drixoral or D-Tann or Duomine or Duotan or Dura Ron or Durafed or Duralex or Dura-Tap or Duratuss or Dynahist or Ed A-Hist or Endafed or Entre-B or Ex?Dec or Fedahist or Hayfebrol or Hexafed or Hisdec or Histadec or Histafed or Histalet or HistamaxD or Histatab or Hista-Tabs or Histex

or Hydro-Tussin or Iofed or Isophen-DF or Klerist-D or Kronofed-A or Lohist or Lortuss or Maldec or Maxichlor or Med-Hist or M-Hist or Mintex or Mooredec or NalDex or Nalfed or Nasohist or ND Clear or NeutraHist or Nohist or Norel LA or Novafed or Novahistine Elixir or Ny-Tannic or Orlenta or Pediachlor or Pharmadrine or Phenabid or PHENAMETH or PHEN-TUSS or Phenyl Chlor Tan or Phenylhistine or Prohist or Pseudoephedrine-BM or Pseubrom or Pseuclor or QDall or Q-Tapp or R?Tann$ or Relera or Rescon or Respahist or Rhinabid or RhinaHist or Ricobid or Ridifed or Rinade$ or Rinate or Robitussin Night$ or Rondamine or Rondec or Rondex or Rymed or Ryna Liquid or Rynatan or Semprex or Seradex or Shellcap or Sildec or Sinuhist or Sonahist or Suclor or SudaHist or Sudal or Sudo Chlor or Suphenamine or SuTan or Tanabid or Tanafed or Tanahist or Tekral or Time-Hist or Touro or Triafed or Triphed or Tri-Pseudo or Triptifed or Trisofed or Tri-Sudo or Trisudrine or Trynate or Ultrabrom or Vazobid or Vazotab or V-Hist or Vi-Sudo or X-Hist or XiraHist or Zinx Chlor$ or Zotex).tw.
59. or/22,34-58
60. 10 and 59
61. limit 60 to randomized controlled trial
62. random$.tw.
63. 60 and 62
64. 61 or 63
65. (animal$ not human$).sh,hw.
66. 64 not 65
67. limit 66 to english language
68. exp side effect/
69. side effect$.tw.
70. undesirable effect$.tw.
71. tolerability.tw.
72. exp toxicity/
73. (adverse adj2 (effect$ or reaction$ or event$ or outcome$)).ti.
74. exp adverse drug reaction/
75. or/69-74
76. 60 and 75
77. (animal$ not human$).sh,hw.
78. 76 not 77
79. limit 78 to english language
80. exp review/
81. (literature adj3 review$).ti,ab.
82. exp meta analysis/
83. exp "Systematic Review"/
84. or/80-83
85. (medline or medlars or embase or pubmed or cinahl or amed or psychlit or psyclit or psychinfo or psycinfo or scisearch or cochrane).ti,ab.
86. RETRACTED ARTICLE/
87. 85 or 86
88. 84 and 87
89. (systematic$ adj2 (review$ or overview)).ti,ab.
90. (meta?anal$ or meta anal$ or meta-anal$ or metaanal$ or metanal$).ti,ab.
91. or/88-90

92. 60 and 91
93. (animal$ not human$).sh,hw.
94. 92 not 93
95. limit 94 to english language

Cochrane Library

ID	Search
#1	MeSH descriptor Rhinitis, Allergic, Perennial, this term only
#2	MeSH descriptor Rhinitis, Allergic, Seasonal, this term only
#3	MeSH descriptor Rhinitis, this term only
#4	(seasonal or allergic):ti,ab
#5	(#3 AND #4)
#6	"seasonal rhinitis":ti,ab
#7	"allergic rhinitis":ti,ab
#8	(hay fever or hayfever):ti,ab
#9	(sar or par):ti,ab
#10	(#1 OR #2 OR #5 OR #6 OR #7 OR #8 OR #9)
#11	MeSH descriptor Adrenal Cortex Hormones explode all trees
#12	corticosteroid*:ti,ab
#13	MeSH descriptor Betamethasone, this term only
#14	(Betamethasone or Celestone):ti,ab
#15	MeSH descriptor Cortisone, this term only
#16	Cortone:ti,ab
#17	MeSH descriptor Dexamethasone explode all trees
#18	(Dexamethasone or Baycadron or Hexadrol or Decadron or Dexium or Dexone or DexPak):ti,ab
#19	MeSH descriptor Hydrocortisone explode all trees
#20	(Hydrocortisone or Cortef or Hydrocortone):ti,ab
#21	MeSH descriptor Methylprednisolone, this term only
#22	(Methylprednisolone or medrol):ti,ab
#23	MeSH descriptor Prednisolone, this term only
#24	(Prednisolone or asmalPred Plus or Millipred or Pediapred or Prelone or Veripred or Flo-Pred or Cotolone or Orapred or Prednoral):ti,ab
#25	MeSH descriptor Prednisone, this term only
#26	(Prednisone or Liquid Pred or Deltasone or Meticorten or Orasone or Prednicen or Sterapred or Prednicot):ti,ab
#27	MeSH descriptor Triamcinolone, this term only
#28	(triamcinolone or Aristocort):ti,ab
#29	MeSH descriptor Administration, Oral explode all trees
#30	oral*:ti,ab
#31	(#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29)
#32	(#30 OR #31)
#33	(#31 AND #32)
#34	MeSH descriptor Beclomethasone, this term only

#35 (Beclomet?asone or Beconase or Vancenase):ti,ab
#36 MeSH descriptor Adrenal Cortex Hormones explode all trees
#37 corticosteroid*:ti,ab
#38 MeSH descriptor Budesonide, this term only
#39 (Budesonide or Rhinocort):ti,ab
#40 MeSH descriptor Pregnenediones, this term only
#41 (Ciclesonide or Omnaris):ti,ab
#42 MeSH descriptor Dexamethasone explode all trees
#43 (Dexamethasone or Dexacort):ti,ab
#44 MeSH descriptor Fluocinolone Acetonide explode all trees
#45 (Flunisolide or Nasalide or Nasarel):ti,ab
#46 MeSH descriptor Androstadienes explode all trees
#47 (Fluticasone or Flonase or Veramyst):ti,ab
#48 (Mometasone or Nasonex):ti,ab
#49 MeSH descriptor Triamcinolone explode all trees
#50 (Triamcinolone or AllerNaze or Nasocort or Tri-nasal):ti,ab
#51 MeSH descriptor Administration, Intranasal, this term only
#52 (nasal* or intranasal*):ti,ab
#53 (#34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50)
#54 (#51 OR #52)
#55 (#53 AND #54)
#56 MeSH descriptor Histamine Antagonists explode all trees
#57 antihistamine*:ti,ab
#58 MeSH descriptor Cetirizine, this term only
#59 (Cetirizine or Zyrtec or Alleroff or Aller-tec):ti,ab
#60 MeSH descriptor Loratadine, this term only
#61 (Loratadine or Desloratadine or Clarinex or Claritin or Triaminic or Agistam or Alavert or "Bactimicina allergy" or Clear-atadine or Loradamed):ti,ab
#62 MeSH descriptor Terfenadine, this term only
#63 (Fexofenadine or Allegra):ti,ab
#64 (Levocetirizine or Xyzal):ti,ab
#65 MeSH descriptor Brompheniramine explode all trees
#66 (Brompheniramine or Lodrane or Tridane or Bromaphen or Brovex or B-vex or Tanacof or Bidhist or Bromax or Respa or Brompsiro or Dimetane or Siltane or Vazol or Conex or J-Tan):ti,ab
#67 Carbinoxamine:ti,ab
#68 MeSH descriptor Pyridines, this term only
#69 (Carbinoxamine or Carboxine or Cordron or Histuss or Palgic or Pediatex or Pediox or Arbinoxa):ti,ab
#70 MeSH descriptor Chlorpheniramine, this term only
#71 (Chlorpheniramine or Chlo-Amine or Chlor-Phen or Krafthist or Chlortan or "Ed ChlorPed" or P-Tann or Allerlief or "Chlor-Al Rel" or "Myci Chlorped" or Pediatan or Ahist or Aller-Chlor or Chlor-Mal or Chlor-Phenit or "Diabetic Tussin" or "Ed Chlor Tan" or Ridramin or Teldrin or Uni-Cortrom):ti,ab
#72 MeSH descriptor Clemastine, this term only

#73 (Clemastine or Tavist or Allerhist* or Dayhist*):ti,ab
#74 MeSH descriptor Cyproheptadine, this term only
#75 (Cyproheptadine or Periactin):ti,ab
#76 (Dexchlorpheniramine or Polaramine):ti,ab
#77 MeSH descriptor Diphenhydramine explode all trees
#78 (Diphenhydramine or Benadryl or Dytan or Kids-eeze or Allergia* or Benekraft or or Bydramine or Diphen or Diphenadryl or Diphenyl* or Dytuss or Elixsure or Hydramine or Nu-med or Pardyl or PediaCare or Scot-Tussin or Syladryl or Silaphen or Tusstat or Theraflu or "Ben Tann" or Dicopanol or Allermax or Banophen or Diphedryl or Diphenhist or Nervine or Paxidorm):ti,ab
#79 MeSH descriptor Doxylamine, this term only
#80 (Doxylamine or Aldex or Doxytex):ti,ab
#81 MeSH descriptor Promethazine, this term only
#82 (Promethazine or Phenergan or Pentazine or Promacot):ti,ab
#83 MeSH descriptor Triprolidine, this term only
#84 (Triprolidine or Tripohist or Zymine):ti,ab
#85 MeSH descriptor Dibenzoxepins explode all trees
#86 (Olopatadine or Patanase):ti,ab
#87 MeSH descriptor Phthalazines explode all trees
#88 (Azelastine or Astelin or Astepro):ti,ab
#89 MeSH descriptor Ipratropium, this term only
#90 (Ipratropium or Atrovent):ti,ab
#91 MeSH descriptor Cromolyn Sodium, this term only
#92 (cromoglycate or Cromolyn or Nasalcrom):ti,ab
#93 MeSH descriptor Leukotriene Antagonists, this term only
#94 ("Leukotriene Antagonist*" or Montelukast or Singulair):ti,ab
#95 MeSH descriptor Nasal Decongestants explode all trees
#96 MeSH descriptor Phenylephrine, this term only
#97 (nasal decongestant* or Levmetamfetamine or "vapo?r inhaler*" or Naphazoline or Four-Way or "Mucinex Nasal" or Nasin or Neo-Synephrine or Nostrilla or (NTZ near/3 Nasal) or Oxyfrin or Oxymeta or Sinarest or Zicam or Phenylephrine or (Alconefrin near/2 Decongestant) or Rhinall or 4-way or Sinex or Propylhexedrine or Benzedrex or Xylometazoline or Otrivin or tetrahydrozoline or tyzine):ti,ab
#98 MeSH descriptor Pseudoephedrine, this term only
#99 oral decongestant* or Ah-chew* or Gilchew or Phenyl-T or Despec or Lusonal or Pseudoephedrine or Afrinol or Contac or Efidac or Suphedrine or Decofed or Elixsure or "Ephed 60" or "Kid Kare" or Myfedrine or Q-Fed or Silfedrine or Superfed or Unifed or Entex or Nasofed or Congest Aid or Sudophed or Cenafed or Congestaclear or Pseudocot or Pseudofed or Pseudotabs or Pseudoval or Ridafed or Seudotabs or Sudafed or Sudodrin or Sudogest or Sudrine):ti,ab
#100 MeSH descriptor Sodium Chloride, this term only
#101 (saline or Altamist or ENTsol or "Little Noses" or n"asal Moist" or Ocean or Pretz or Salinex or SaltAire or "Deep Sea" or Humist or "Marine mist" or "sea Mist" or Nasosol or Pediamist or Rhinaris or "Sea Soft"):ti,ab
#102 (Accuhist or Actacin or Actagen or Actamine or Actedril or Acticon or Actifed or Alacol or Ala-Hist or Alenaze-D or "Allan Tannate" or Allent or Aller-Chlor or Allercon or

AllerDur or Allerest or Allerfrim or Allerx or Altafed or Amerifed or Anamine or Anaplex or Andec or Andehist or Aphedrid or A-Phedrin or Aridex-D or Atridine or Atrogen or Atrohist or Benylin or B-Fedrine or Bi-Tann or "BP Allergy" or "BPM Pseudo" or Brexin or Brofed or "Brom Tann" or Bromadrine or Bromaline or Bromaphedrine or Bromaxefed or BROMDEC or Bromfed or Bromfenex or Bromhist* or BROMPHEN or "C Tan D" or Carbaxefed or CARBIC or Carbiset or Carbodec or Carbofed or Cardec or Centergy or Cetiri-d or Chemdec or "Chlor Trimeton" or Chlorafed* or Chlordrine or Chlor-Mes or Chlorphedrin or Clorfed or Codimal* or Coldec or Colfed$ or Cophene or "CP Oral" or "CP Tannic" or C-Phed Tannate or Curaler or Cydec or Dallergy or D-Amine or Dayquil Allergy or Deconamine or Decongestamine or De-Congestine or Deconomed or Delsym or Desihist or Dexaphen or Dexophed or Dicel or Dimetapp or Diphentann or Disobrom or Disophrol or Dixaphedrine or Drexophed or Drixomed or Drixoral or D-Tann or Duomine or Duotan or Dura Ron or Durafed or Duralex or Dura-Tap or Duratuss or Dynahist or Ed A-Hist or Endafed or Entre-B or Ex?Dec or Fedahist or Hayfebrol or Hexafed or Hisdec or Histadec or Histafed or Histalet or HistamaxD or Histatab or Hista-Tabs or Histex or Hydro-Tussin or Iofed or Isophen-DF or Klerist-D or Kronofed-A or Lohist or Lortuss or Maldec or Maxichlor or Med-Hist or M-Hist or Mintex or Mooredec or NalDex or Nalfed or Nasohist or "ND Clear" or NeutraHist or Nohist or "Norel LA" or Novafed or Novahistine Elixir or Ny-Tannic or Orlenta or Pediachlor or Pharmadrine or Phenabid or PHENAMETH or PHEN-TUSS or Phenyl "Chlor Tan" or Phenylhistine or Prohist or Pseudoephedrine-BM or Pseubrom or Pseuclor or QDall or Q-Tapp or R?Tann$ or Relera or Rescon or Respahist or Rhinabid or RhinaHist or Ricobid or Ridifed or Rinade* or Rinate or "Robitussin Night*" or Rondamine or Rondec or Rondex or Rymed or "Ryna Liquid" or Rynatan or Semprex or Seradex or Shellcap or Sildec or Sinuhist or Sonahist or Suclor or SudaHist or Sudal or Sudo Chlor or Suphenamine or SuTan or Tanabid or Tanafed or Tanahist or Tekral or Time-Hist or Touro or Triafed or Triphed or Tri-Pseudo or Triptifed or Trisofed or Tri-Sudo or Trisudrine or Trynate or Ultrabrom or Vazobid or Vazotab or V-Hist or Vi-Sudo or X-Hist or XiraHist or "Zinx Chlor*" or Zotex):ti,ab
#103 (#33 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80 OR #81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89 OR #90 OR #91 OR #92 OR #93 OR #94 OR #95 OR #96 OR #97 OR #98 OR #99 OR #100 OR #101 OR #102)
#104 (#10 AND #103)

Search Strategy for Gray Literature

Regulatory Information

FDA (Drugs@FDA)

Source: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/
Date searched: 4/11/2012
Search strategy: All drugs in review scope searched by generic name
Records: 0

Clinical Trial Registries

ClinicalTrials.gov

Source: http://clinicaltrials.gov/
Date searched: 4/5/2012
Search strategy: Seasonal Allergic rhinitis (category search)
Records: 32

Current Controlled Trials

Source: http://www.controlled-trials.com/
Date searched: 4/12/2012
Search strategy: "Allergic rhinitis" OR (Seasonal AND rhinitis) OR "Hay fever" OR Hayfever OR Pollen
Records: 24

WHO International Clinical Trials Registry Platform Results

Source: http://www.who.int/ictrp/en/
Date searched: 4/5/2012
Search strategy: Allergic rhinitis OR Seasonal OR Rhinitis OR "Hay fever" OR Hayfever OR Pollen
Records: 11

Conference Papers and Abstracts

Conferences and Association Meetings

Source:

- American Academy of Allergy, Asthma & Immunology (AAAAI): www.aaaai.org
- British Society for Allergy and Clinical Immunology (BSACI): www.bsaci.org/

Date searched: 4/5/2012
Search strategy: Not applicable
Records: 1

Scopus

Source: http://www.scopus.com/home.url
Date searched: 4/11/2012
Search strategy: (TITLE-ABS-KEY(seasonal W/2 rhinitis)) OR (TITLE-ABS-KEY("allergic rhinitis")) OR (TITLE-ABS-KEY("hay fever" OR hayfever)) OR (TITLE-ABS-KEY(pollen))) AND (((TITLE-ABS-KEY(corticosteroid* OR betamethasone OR celestone OR cortisone OR cortone OR dexamethasone OR baycadron OR hexadrol OR decadron OR dexium OR dexone OR dexpak OR hydrocortisone OR cortef OR hydrocortone OR methylprednisolone OR medrol OR prednisolone OR "asmalPred Plus" OR millipred OR pediapred OR prelone OR veripred OR flo-pred OR cotolone OR orapred OR prednoral OR prednisone OR liquid pred OR deltasone OR meticorten OR orasone OR prednicen OR sterapred OR prednicot OR triamcinolone OR aristocort)) OR (TITLE-ABS-KEY(beclomethasone OR beconase OR vancenase OR budesonide

OR rhinocort OR ciclesonide OR omnaris OR dexamethasone OR dexacort OR flunisolide OR nasalide OR nasarel OR fluticasone OR flonase OR veramyst OR mometasone OR nasonex OR triamcinolone orallernaze OR nasocort OR tri-nasal)) OR (TITLE-ABS-KEY(antihistamine* OR cetirizine OR zyrtec OR alleroff OR aller-tec OR loratadine OR desloratadine OR clarinex OR claritin OR triaminic OR agistam OR alavert OR bactimicina allergy OR clear-atadine OR loradamed OR fexofenadine OR allegra OR levocetirizine OR xyzal orbrompheniramine OR lodrane OR tridane OR bromaphen OR brovex OR b-vex OR tanacof OR bidhist OR bromax OR respa OR brompsiro OR dimetane OR siltane OR vazol OR conex OR j-tan)) OR (TITLE-ABS-KEY(carbinoxamine OR carboxine OR cordron OR histuss OR palgic OR pediatex OR pediox OR arbinoxa OR chlorpheniramine OR chlo-amine OR chlor-phen OR krafthist OR chlortan OR "Ed ChlorPed" OR p-tann OR allerlief OR "Chlor-Al Rel" OR "Myci Chlorped" OR pediatan OR ahist OR aller-chlor OR chlor-mal OR chlor-phenit OR "Diabetic Tussin" OR "Ed Chlor Tan" OR ridramin OR teldrin OR uni-cortrom)) OR (TITLE-ABS-KEY(clemastine OR tavist OR allerhist* OR dayhist*))) OR ((TITLE-ABS-KEY(cyproheptadine OR periactin)) OR (TITLE-ABS-KEY(diphenhydramine OR benadryl OR dytan OR kids-eeze OR allergia* OR benekraft OR diphenyl OR aler-dryl OR altaryl OR antihist OR antituss OR beldin OR belix OR "Bromanate AF" OR bydramine OR diphen OR diphenadryl OR diphenyl* OR dytuss OR elixsure OR hydramine OR nu-med OR pardyl OR pediacare OR scot-tussin OR syladryl OR silaphen OR tusstat OR theraflu OR "Ben Tann" OR dicopanol OR allermax OR banophen OR diphedryl OR diphenhist OR nervine OR paxidorm)) OR (TITLE-ABS-KEY(doxylamine OR aldex OR doxytex)) OR (TITLE-ABS-KEY(promethazine OR phenergan OR pentazine OR promacot)) OR (TITLE-ABS-KEY(triprolidine OR tripohist OR zymine))) OR ((TITLE-ABS-KEY(olopatadine OR patanase)) OR (TITLE-ABS-KEY(azelastine OR astelin OR astepro)) OR (TITLE-ABS-KEY(ipratropium OR atrovent)) OR (TITLE-ABS-KEY(ipratropium OR atrovent))) OR ((TITLE-ABS-KEY("Leukotriene Antagonist*" OR montelukast OR singulair)) OR (TITLE-ABS-KEY("nasal decongestant*" OR levmetamfetamine OR "vapo?r inhaler*" OR naphazoline OR privine OR oxymetazoline OR afrin OR dristan OR "Duramist plus" OR "Four-Way" OR "Mucinex Nasal" OR nasin OR neo-synephrine OR nostrilla OR oxyfrin OR oxymeta OR sinarest OR zicam OR phenylephrine OR tetrahydrozoline OR tyzine OR rhinall OR 4-way OR sinex OR propylhexedrine OR benzedrex OR xylometazoline OR otrivin)) OR (TITLE-ABS-KEY(allerest W/3 nasal) OR TITLE-ABS-KEY(ntz W/3 nasal) OR TITLE-ABS-KEY(alconefrin adj2 decongestant)) OR (TITLE-ABS-KEY("oral decongestant*" OR ah-chew* OR gilchew OR phenyl-t OR despec OR lusonal)) OR (TITLE-ABS-KEY(pseudoephedrine OR afrinol OR contac OR efidac OR suphedrine OR decofed OR elixsure OR "Ephed 60" OR "Kid Kare" OR myfedrine OR q-fed OR silfedrine OR superfed OR unifed OR entex OR nasofed OR "Congest Aid" OR sudophed OR cenafed OR congestaclear OR pseudocot OR pseudofed OR pseudotabs OR pseudoval OR ridafed OR seudotabs OR sudafed OR sudodrin OR sudogest OR sudrine))) OR ((TITLE-ABS-KEY("sodium chloride" orsaline OR altamist OR "ENTsol" OR "Little Noses" OR "nasal Moist" OR ocean OR pretz OR salinex OR saltaire OR "Deep Sea" OR humist OR "Marine mist" OR "sea Mist" OR nasosol OR pediamist OR rhinaris OR "Sea Soft")) OR (TITLE-ABS-KEY(accuhist OR actacin OR actagen OR actamine OR actedril OR acticon OR actifed OR alacol OR ala-hist OR alenaze-d OR "Allan Tannate" OR allent OR aller-chlor OR allercon OR allerdur OR allerest OR allerfrim OR allerx OR altafed OR amerifed OR anamine OR anaplex OR andec OR andehist OR aphedrid OR a-phedrin OR aridex-d OR atridine OR atrogen OR atrohist OR benylin OR b-fedrine OR bi-tann OR "BP Allergy" OR "BPM Pseudo" OR brexin OR brofed OR "Brom Tann" OR bromadrine OR bromaline OR

bromaphedrine OR bromaxefed OR bromdec OR bromfed OR bromfenex OR bromhist* OR bromphen OR "C Tan D" OR carbaxefed OR carbic OR carbiset OR carbodec OR carbofed OR cardec OR centergy OR cetiri-d OR chemdec OR "Chlor Trimeton" OR chlorafed* OR chlordrine OR chlor-mes OR chlorphedrin OR clorfed OR codimal* OR coldec OR colfed* OR cophene OR "CP Oral" OR "CP Tannic" OR "C-Phed Tannate" OR curaler OR cydec OR dallergy OR d-amine OR "Dayquil Allergy" OR deconamine OR decongestamine OR de-congestine OR deconomed OR delsym OR desihist OR dexaphen OR dexophed OR dicel OR dimetapp OR diphentann OR disobrom OR disophrol OR dixaphedrine OR drexophed OR drixomed OR drixoral OR d-tann OR duomine OR duotan OR "Dura Ron" OR durafed OR duralex OR dura-tap OR duratuss OR dynahist OR "Ed A-Hist" OR endafed OR entre-b OR ex?dec OR fedahist OR hayfebrol OR hexafed OR hisdec OR histadec OR histafed OR histalet OR histamaxd OR histatab OR hista-tabs OR histex OR hydro-tussin OR iofed OR isophen-df OR klerist-d OR kronofed-a OR lohist OR lortuss OR maldec OR maxichlor OR med-hist OR m-hist OR mintex OR mooredec OR naldex OR nalfed OR nasohist OR "ND Clear" OR neutrahist OR nohist OR "Norel LA" OR novafed OR "Novahistine Elixir" OR ny-tannic OR orlenta OR pediachlor OR pharmadrine OR phenabid OR phenameth OR phen-tuss OR "Phenyl Chlor Tan" OR phenylhistine OR prohist OR pse-bm OR pseubrom OR pseuclor OR qdall OR q-tapp OR r?tann* OR relera OR rescon OR respahist OR rhinabid OR rhinahist OR ricobid OR ridifed OR rinade* OR rinate OR "Robitussin Night*" OR rondamine OR rondec OR rondex OR rymed OR "Ryna Liquid" OR rynatan OR semprex OR seradex OR shellcap OR sildec OR sinuhist OR sonahist OR suclor OR sudahist OR sudal OR "Sudo Chlor" OR suphenamine OR "SuTan" OR tanabid OR tanafed OR tanahist OR tekral OR time-hist OR touro OR triafed OR triphed OR tri-pseudo OR triptifed OR trisofed OR tri-sudo OR trisudrine OR trynate OR ultrabrom OR vazobid OR vazotab OR v-hist OR vi-sudo OR x-hist OR xirahist OR "Zinx Chlor*" OR zotex)))) AND (LIMIT-TO(DOCTYPE, "cp"))
Records: 117

Government Documents

AHRQ Effective Health Care Program

Source: http://effectivehealthcare.ahrq.gov/
Date searched: 4/12/2012
Search strategy: Allergies in Health Condition
Records: 2

AHRQ Home Page

Source: http://www.ahrq.gov/
Date searched: 4/16/2012
Search strategy: “seasonal allergic”
Records: 0

NIH Reporter

Source: http://projectreporter.nih.gov/reporter.cfm
Date searched: 4/16/2012
Search strategy: Category: Allergic Rhinitis (Hay Fever), Text search: rhinitis, Text search: seasonal, Text search: "hay fever" OR hayfever

Records: 0

Manufacturer Database

Source: Sanofi
Date posted: 5/7/2012
Search strategy: Not applicable
Records: 80

Source: Merck
Date posted: 5/7/2012
Search strategy: Not applicable
Records: 57

Source: Sunovion
Date posted: 5/7/2012
Search strategy: Not applicable
Records: 39

Source: McNeil
Date posted: 5/7/2012
Search strategy: Not applicable
Records: 160

Appendix B. Excluded Studies

Appendix Table B1. Key to study exclusion coding system

Code	Definition
FLA	Foreign language article
IRD	Incomplete data reported
MAC	Mixed adult and children populations
MSP	Mixed SAR and PAR populations
NDE	Not relevant design
NRC	Not relevant comparator
NRD	Not relevant disease
NRO	Not relevant outcome
UTO	Unable to obtain

Aaronson, N. J. Ehrlich, D. B. Frankel, A. A. Gutman and D. W. Aaronson. Effective oral nasal decongestion. A double-blind, crossover analysis. Annals of Allergy 1968 26(3): 145-50. NRC

Adkins, J. T. Angello, W. E. Cetnarowski, H. M. Druce, K. L. Lampl, M. L. Vandewalker and D. P. H. S. Group. Diphenydramine shows superior efficacy to loratadine in sar. Annals of Allergy, Asthma & Immunology 2001 86(): 136. NDE

Anderson, N. E. Marshall and M. C. Clark. A double-blind controlled trial of disodium cromoglycate in seasonal allergic rhinitis. The Practitioner 1972 208(247): 676-9. NDE

Anon. Azelastin nasal spray more effective than oral desloratadine. Pediatriya 2006 46(3): 65+6. FLA

Aschan. Decongestion of nasal mucous membranes by oral medication in acute rhinitis. A rhinomanometric study to demonstrate synergism between antihistamines and adrenergic substance. Acta Otolaryngol 1974 77(6): 433-8. NRC

Ashe. Oral medications in nasal decongestion. A study among industrial workers. IMS, Industrial medicine and surgery 1968 37(3): 212-4. NRC

Axelsson and B. Lindholm. The effect of triamcinolone acetonide on allergic and vasomotor rhinitis. Acta Oto-Laryngologica 1972 73(1): 64-7. NDE

Bachert and M. Maurer. Safety and efficacy of desloratadine in subjects with seasonal allergic rhinitis or chronic urticaria: Results of four postmarketing surveillance studies. Clinical Drug Investigation 2010 30(2): 109-122. NRC

Badorrek, M. Dick, A. Schauerte, H. Hecker, R. Murdoch, B. Luettig, J. M. Hohlfeld and N. Krug. A combination of cetirizine and pseudoephedrine has therapeutic benefits when compared to single drug treatment in allergic rhinitis. Int J Clin Pharmacol Ther 2009 47(2): 71-7. NDE

Bender and H. Milgrom. Comparison of the effects of fluticasone propionate aqueous nasal spray and loratadine on daytime alertness and performance in children with seasonal allergic rhinitis. Ann Allergy Asthma Immunol 2004 92(3): 344-9. MAC

Bender, D. R. McCormick and H. Milgrom. Children's school performance is not impaired by short-term administration of diphenhydramine or loratadine. J Pediatr 2001 138(5): 656-60. NDE

Bender, S. Berning, R. Dudden, H. Milgrom and Z. V. Tran. Sedation and performance impairment of diphenhydramine and second-generation antihistamines: A meta-analysis. Journal of Allergy and Clinical Immunology 2003 111(4): 770-776. NRD

Bentley, S. Walker, F. Hanotte, C. De Vos and S. R. Durham. A comparison of the effects of oral cetirizine and inhaled beclomethasone on early and late asthmatic responses to allergen and the associated increase in airways hyperresponsiveness. Clin Exp Allergy 1996 26(8): 909-17. NDE

Berger, S. M. Fineman, P. Lieberman and R. M. Miles. Double-blind trials of azelastine nasal spray monotherapy versus combination therapy with loratadine tablets and beclomethasone nasal spray in patients with seasonal allergic rhinitis. Rhinitis Study Groups. Ann Allergy Asthma Immunol 1999 82(6): 535-41. NRC

Berger. Desloratadine reduces seasonal allergic rhinitis symptoms in patients with seasonal allergenic rhinitis and asthma. Journal of Allergy and Clinical Immunology 2001 107(2): S162. NDE

Bhatia, F. M. Baroody, M. deTineo and R. M. Naclerio. Increased nasal airflow with budesonide compared with desloratadine during the allergy season. Arch Otolaryngol Head Neck Surg 2005 131(3): 223-8. NDE

Bousquet, C. Bindslev-Jensen, G. W. Canonica, W. Fokkens, H. Kim, M. Kowalski, A. Magnan, J. Mullol and P. van Cauwenberge. The ARIA/EAACI criteria for antihistamines: an assessment of the efficacy, safety and pharmacology of desloratadine. Allergy 2004 59 Suppl 77(): 4-16. NDE

Bozkurt, G. Karakaya and A. F. Kalyoncu. Seasonal rhinitis, clinical characteristics and risk factors for asthma. International Archives of Allergy and Immunology 2005 138(1): 73-79. NRC

Britton, D. W. Empey, G. C. John, K. A. McDonnell and D. T. Hughes. Histamine challenge and anterior nasal rhinometry: their use in the assessment of pseudoephedrine and triprolidine as nasal decongestants in subjects with hayfever. Br J Clin Pharmacol 1978 6(1): 51-8. NDE

Bronsky, M. Tarpay, D. A. Tinkelman and J. K. Bush. A comparison of two dosing regimens of beclomethasone dipropionate aqueous nasal spray and flunisolide nasal spray in the treatment of acute seasonal rhinitis. Immunology and Allergy Practice 1987 9(5): 165-170. NRC

Brooks. Spectrum of seasonal allergic rhinitis symptom relief with topical corticoid and oral antihistamine given singly or in combination. American Journal of Rhinology 1996 10(3): 193-199. MAC

Brown, C. Engler and J. R. English. A comparative trial of flunisolide and sodium cromoglycate nasal sprays in the treatment of seasonal allergic rhinitis. Clinical Allergy 1981 11(2): 169-73. MAC

Brozek, J. Bousquet, C. E. Baena-Cagnani, S. Bonini, G. W. Canonica, T. B. Casale, R. G. Van Wijk, K. Ohta, T. Zuberbier and H. J. Schunemann. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 Revision. Journal of Allergy and Clinical Immunology 2010 126(3): 466-476. NDE

Bruno, E. Errigo and G. S. Del Giacco. A multicentre study to evaluate the efficacy and safety of BW825C (Acrivastine) in the treatment of seasonal allergic rhinitis. European Review for Medical and Pharmacological Sciences 1986 8 (3)(): 305-317. NRC

Calderon Moises, P. Rodriguez del Rio and P. Demoly. Topical nasal corticosteroids versus oral antihistamines for allergic rhinitis. Calderon Moises A, Rodriguez del Rio Pablo, Demoly Pascal Topical nasal corticosteroids versus oral antihistamines for allergic rhinitis Cochrane Database of Systematic Reviews: Protocols 2010 Issue 1 John Wiley & Sons, Ltd Chichester, UK DOI: 10 1002/14651858 CD008232 2010 (1). NDE

Can, R. Tanac, E. Demir, F. Gulen and A. Veral. Is the usage of intranasal glucocorticosteroids alone in allergic rhinitis sufficient?. Allergy Asthma Proc 2006 27(3): 248-53. MAC

Carroll. Effective use of corticosteroids in allergic rhinitis. Current Therapeutics 1984 25(11): 55-60. NDE

Charpin and D. Vervloet. Treating seasonal rhinitis: Antihistamines or intranasal corticosteroids?. European Respiratory Review 1994 4(20): 256-259. NDE

Cierpiol-Tracz, H. Kawalski, G. Szpyrka, M. Mos and M. Kopacz. Comparative study of the application of sympathomimetic generally and locally as combined with loratadine in the initial therapy of allergic rhinitis in older children. New Medicine 1999 3(): 16-17. NRC

Cingi, K. Gunhan, L. Gage-White and H. Unlu. Efficacy of leukotriene antagonists as concomitant therapy in allergic rhinitis. Laryngoscope 2010 120(9): 1718-23. NRC

Coffman. A controlled trial of disodium cromoglycate in seasonal allergic rhinitis. Br J Clin Pract 1971 25(9): 403-6. NDE

Condemi and J. Lim. Triamcinolone acetonide aqueous nasal spray compared with loratadine in seasonal allergic rhinitis. Annals of Allergy, Asthma and Immunology 1997 78(): 127. Level 4, NDE

Connell, B. O. Williams, S. Allen, A. Cato and J. G. Perkins. A double-blind controlled evaluation of Actifed and its individual constituents in allergic rhinitis. J Int Med Res 1982 10(5): 341-7. NRC

Connell. Effectiveness of topical nasal decongestants. Ann Allergy 1969 27(11): 541-6. NRC

Cordray, J. B. Harjo and L. Miner. Comparison of intranasal hypertonic dead sea saline spray and intranasal aqueous triamcinolone spray in seasonal allergic rhinitis. Ear Nose Throat J 2005 84(7): 426-30. NDE

Corrado, S. Ollier and M. J. Phillips. Histamine and allergen induced changes in nasal airways resistance measured by anterior rhinomanometry: Reproducibility of the technique and the effect of topically administered antihistaminic and anti-allergic drugs. British Journal of Clinical Pharmacology 1987 24(3): 283-292. NDE

Corren. Desloratadine reduces the use of inhaled Beta²-agonists and improves asthma symptoms in patients with seasonal allergic rhinitis ans asthma. Journal of Allergy and Clinical Immunology 2001 107(2): S163. NDE

Costa, M. Amouyal, P. Lambert, D. Ryan, H. J. Schunemann, J. P. Daures, J. Bousquet and P. J. Bousquet. How representative are clinical study patients with allergic rhinitis in primary care?. J Allergy Clin Immunol 2011 127(4): 920-6 e1. NRC

Crim, L. N. Pierre and P. T. Daley-Yates. A review of the pharmacology and pharmacokinetics of inhaled fluticasone propionate and mometasone furoate. Clin Ther 2001 23(9): 1339-54. NDE

Dahl, B. Lange, G. Holtappels, K. F. Lukat and C. Bachert. Effects of cetirizine and fluticasone propionate nasal spray on symptoms and inflammatory mediators of seasonal allergic rhinitis. Allergologie 2004 27(1): 16-25. FLA

Dahl, R. C. Baker and R. Pauwel. Seasonal rhinitis and asthma. Effects of topical nasal and/or orally inhaled Fluticasone Propionate, the SPIRA study (FNM40001). Journal of Allergy and Clinical Immunology 2001 107(2): S154. NDE

D'Ambrosio, S. Gangemi, R. A. Merendino, A. Arena, L. Ricciardi and G. F. Bagnato. Comparative study between fluticasone propionate and cetirizine in the treatment of allergic rhinitis. Allergol Immunopathol (Madr) 1998 26(6): 277-82.

Das. Treatment of allergic rhinitis in children: What's new? (2012): Journal of Paediatrics and Child Health, 48(4), 366. NDE.

Day, M. Briscoe, E. Rafeiro and B. Kramer. Onset of action and symptom relief with cetirizine, loratadine, or placebo in an environmental exposure unit eeu in ragweed-sensitive subjects with seasonal allergic rhinitis sar. Annals of Allergy, Asthma & Immunology 2000 84(): 125. NDE

Day, M. P. Briscoe and J. D. Ratz. Efficacy of levocetirizine compared with montelukast in subjects with ragweed-induced seasonal allergic rhinitis in the Environmental Exposure Unit. Allergy Asthma Proc 2008 29(3): 304-12. NDE

Day, M. P. Briscoe, J. D. Ratz, M. Danzig and R. Yao. Efficacy of loratadine-montelukast on nasal congestion in patients with seasonal allergic rhinitis in an environmental exposure unit. Ann Allergy Asthma Immunol 2009 102(4): 328-38. NDE

Deering, M. J. Derbyshire and P. A. Johnson. An antihistamine-sympathomimetic combination in the treatment of hayfever. Practitioner 1981 225 (1356)(): 929-931. NDE

Delucchi, J. Valenzuela, O. Cofre and A. Martinez. Double-blind comparative trial of ipratropium bromide in chronic vasomotor and allergic rhinitis in children. Revista de Otorrinolaringologia y Cirurgia de Cabeza y Cuello 1984 44(3): 85-88. FLA

Diamond, K. Gerson, A. Cato, K. Peace and J. G. Perkins. An evaluation of triprolidine and pseudoephedrine in the treatment of allergic rhinitis. Ann Allergy 1981 47(2): 87-91. NRC

Dockhorn, B. O. Williams and R. L. Sanders. Efficacy of acrivastine with pseudoephedrine in treatment of allergic rhinitis due to ragweed. Ann Allergy Asthma Immunol 1996 76(2): 204-8. NRC

Dockhorn, E. Meltzer, B. Paull, A. van As, S. Weakley, T. Woehler and P. and Rogenes. Fluticasone propionate aqueous nasal spray given once a day safely controls the symptoms of seasonal allergic rhinitis. Annals of Allergy 1990 64(): 77. NDE

Dolovich, M. Anderson, W. Chodirker, M. Drouin, F. E. Hargreave, J. Hebert, A. Knight, M. O'Conner, P. Small and W. Yang. Fluticasone propionate: a large multicentre trial. Respiratory Medicine 1990 84 Suppl A(): 31-2. NDE

Dorow, R. Aurich and U. Petzold. Efficacy and tolerability of azelastine nasal spray in patients with allergic rhinitis compared to placebo and budesonide. Arzneimittelforschung 1993 43(8): 909-12. NDE

Dorow, S. Thalhofer, R. Aurich and U. and Petzold. Azelastine nasal spray in the treatment of patients suffering from allergic rhinitis - comparison versus placebo and budesonide. Atemwegs- und Lungenkrankheiten 1992 18(11): 501. NDE

Drouin, W. H. Yang, F. Horak, P. H. Van de Heyning, G. H. Kunkel, C. I. Backhouse and M. R. Danzig. Adding loratadine to topical nasal steroid therapy improves moderately severe seasonal allergic rhinoconjunctivitis. Advances in Therapy 1995 12(6): 340-349. NDE

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Appendix C. Evidence Tables

Oral Selective Antihistamine Versus Oral Nonselective Antihistamine

Appendix Table C1. Trial description: oral selective antihistamine versus oral nonselective antihistamine

Author, Year	Location/ Site(s)	Enrollment/ Treatment Duration	Funding/ Author Industry Disclosures	N	Inclusion Criteria	Exclusion Criteria[a]	Rescue Medication Use	Objective Diagnosis	Run-in \Period	Pollen Counts Measured	Patient Blinding	Assessor Blinding
Dockhorn, 1987	N. America Multiple	April 1985 2 weeks	NR NR	220	Minimum SAR severity	SAR meds/- Other meds Chronic asthma Pregnancy	No	•			•	•
Harvey, 1996	N. America Multiple	2 weeks	Industry Yes	86	Minimum SAR severity	SAR meds/+ Pregnancy	Yes	•				•
Kemp, 1987	N. America Multiple	2 weeks	NR NR	209	Minimum SAR severity		No	•			•	•

N = Patients randomized to comparator groups of interest; NR = not reported; SAR = seasonal allergic rhinitis.

[a] +, -, or NR indicates whether FDA-recommended washout periods were required (+), were not required (-), or were not reported (NR) for restricted SAR medications prior to trial entry.

Appendix Table C2. Patient characteristics: oral selective antihistamine versus oral nonselective antihistamine

Author, Year	n	Drug, Dose/Day	Mean Age, years	Sex, % Female	Race, %	Disease Duration, years	Mean Baseline NSS[a]
Dockhorn, 1987	111	Loratadine 10 mg	31 Range: 12-61	21.3	White: 92.6 Other: 7.4	16 Range: 2-48	
	109	Clemastine 2 mg	33 Range: 12-65	24.8	White: 91.4 Other: 8.6	18 Range: 1-55	
Harvey, 1996	43	Cetirizine 5-10mg	35.2 Range: 16.1-64.6	55.8	White: 81.4 Black: 4.7 Hispanic: 11.6 Other: 2.3		
	43	Chlorpheniramine 16mg	34.4 Range: 16.4-68.3	60.5	White: 74.4 Black: 9.3 Hispanic: 11.6 Other: 4.7		
Kemp, 1987	108	Loratadine 10 mg	30 (11) Range :12-62	54.6	Unspecified	17 Range: 1-50	TNSS: 7.5

Author, Year	n	Drug, Dose/Day	Mean Age, years	Sex, % Female	Race, %	Disease Duration, years	Mean Baseline NSS[a]
	101	Clemastine 2 mg	30 (12) Range: 12-64	47.5	Unspecified	16 Range: 1-42	TNSS: 7.3

n = Patients randomized to comparator groups of interest. NSS = nasal symptom score; TNSS = total nasal symptom score.

Values are presented as mean (standard deviation) unless otherwise noted.

[a] TNSS ranges from 0 to 12

Appendix Table C3. USPSTF quality assessment: oral selective antihistamine versus oral nonselective antihistamine

Author, Year	Assembled comparable groups	Maintained comparable groups	Minimal follow-up loss	Measurements equal, valid, and reliable	Interventions clearly defined	Important outcomes considered	Appropriate analysis of results	Overall USPSTF rating
Dockhorn, 1987	Yes	Yes	Yes	Yes	Yes	Yes	No	Poor
Harvey, 1996	No	Uncertain	Yes	No	Yes	Yes	No	Poor
Kemp, 1987	Yes	Uncertain	Uncertain	Yes	Yes	Yes	Yes	Fair

USPSTF = United States Preventive Services Task Force.

Appendix Table C4. Nasal symptom outcomes: change from baseline–oral selective antihistamine versus oral nonselective antihistamine

Author, Year	Drug, Dose/Day	N/n	Time, weeks	TNSS	p
Kemp, 1987	Loratadine 10 mg	108/108	2	-2.8[ab]	NS
	Clemastine 2 mg	101/101		-2.5[ab]	

N/n = Number of patients randomized to comparator groups of interest/number of patients analyzed; NS= non-significant; TNSS = total nasal symptom score. TNSS ranges from 0 to 12.

[a] Values extracted from figures using Engauge Digitizer software.

[b] Values calculated by report author.

Appendix Table C5. Quality of life outcomes–oral selective antihistamine versus oral nonselective antihistamine

Author, Year	Drug, Dose/Day	N/n	Time, weeks	Outcome	Baseline Mean	Change from Baseline	p
Harvey, 1996	Loratadine 10 mg	43/39	2	RQLQ, 0 to 84 scale	87.0	-35.9[a]	<0.05
	Clemastine 2 mg	43/40			89.2	-23.0[a]	

N/n = Number of patients randomized to comparator groups of interest/number of patients analyzed; RQLQ = Rhinitis Quality of Life Questionnaire.

[a] Values calculated by report author.

Oral Selective Antihistamine Versus Nasal Antihistamine

Appendix Table C6. Trial description: oral selective antihistamine versus nasal antihistamine

Author, Year	Location/ Site(s)	Enrollment/ Treatment Duration	Funding/ Author Industry Disclosures	N	Inclusion Criteria	Exclusion Criteria[a]	Rescue Medication Use	Objective Diagnosis	Run-in Period	Pollen Counts Measured	Patient Blinding	Assessor Blinding
Berger, 2003	N. America Multiple	2002 2 weeks	Industry NR	219	Minimum SAR severity and duration	SAR meds/+ Chronic asthma Pregnancy Infection Deformities	No	•	•		•	•
Berger, 2006	N. America Multiple	Spring 2005 2 weeks	Industry Industry	360	Minimum SAR severity and duration	SAR meds/ Other meds Chronic asthma Pregnancy Infection Deformities	No	•	•		•	•
Charpin, 1995	Europe Multiple	2 weeks	NR Industry	136	Minimum SAR severity and duration	SAR meds/+ Other meds Chronic asthma Pregnancy Infection Deformities	No	•			•	•
Corren, 2005	N. America Multiple	2004 2 weeks	NR Industry	307	Minimum SAR severity and duration	SAR meds/ Other meds Chronic asthma Pregnancy Infection Deformities	No	•	•		•	•
Gambardella, 1993	Europe	6 weeks	NR NR	30	Minimum SAR duration		No				•	•

N = Patients randomized to comparator groups of interest; NR = not reported; SAR = seasonal allergic rhinitis.

[a] +, -, or NR indicates whether FDA-recommended washout periods were required (+), were not required (-), or were not reported (NR) for restricted SAR medications prior to trial entry.

Appendix Table C7. Patient characteristics: oral selective antihistamine versus nasal antihistamine

Author, Year	n	Drug, Dose/Day	Mean Age, years	Sex, % Female	Race, %	Disease Duration, years	Mean Baseline NSS[a]
Berger, 2003	111	Desloratadine 5mg	32.6 Range: 12-73	66.7	White: 75.7 Black: 13.5 Asian: 0.9 Other: 9.9		C: 5.12 S: 3.57 R: 4.66 I: 4.31 TNSS: 17.67[b]
	108	Azelastine 4 puffs/nostril	35.9 Range: 12-70	60.2	White: 80.6 Black: 13.0 Asian: 2.8 Other: 3.7		C: 5.07 S: 3.60 R: 4.63 I: 4.40 TNSS: 17.70[b]
Berger, 2006	175	Cetirizine 10mg	34.3 Range: 12-74	56.0	White: 77.7 Black: 8.6 Asian: 4.0 Other: 9.7	18.7	TNSS: 18.7 (3.1)[b]
	179	Azelastine 4 puffs/nostril	35.1 Range: 12-64	59.8	White: 77.7 Black: 5.0 Asian: 5.0 Other: 12.3	18.4	TNSS: 19.1 (3.2)[b]
Charpin, 1995	69	Cetirizine 10mg	30[cd]				
	67	Azelastine 2 puffs/nostril					
Corren, 2005	155	Cetirizine 10mg	35.7 Range: 12-74	60.6	White: 69.0 Black: 19.4 Asian: 3.9 Other: 7.7	20.0 Range: 2-58	C: 5.27 (0.62) S: 3.98 (1.32) R: 4.61 (0.95) I: 4.64 (0.98) TNSS: 18.50 (2.85)[b]
	152	Azelastine 4 puffs/nostril	35.6 Range: 12-74	63.2	White: 70.4 Black: 19.1 Asian: 2.0 Other: 8.6	18.8 Range: 2-51	C: 5.31 (0.62) S: 4.14 (1.25) R: 4.74 (0.97) I: 4.63 (1.14) TNSS: 18.82 (2.86)[b]
Gambardella, 1993	15	Loratadine 10mg	31[cd] Range: 18-55	16.7		Range: 2-31	
	15	Azelastine 560 mcg					

C = Congestion; I = itching; n = patients randomized to comparator groups of interest; NSS = nasal symptom score; R = rhinorrhea; S = sneezing; TNSS = total nasal symptom score.

Values are presented as mean (standard deviation) unless otherwise noted.

[a] Individual symptoms rated on a scale from 0 (no symptoms) to 6 (severe symptoms) except as noted.

[b] TNSS is a sum of AM and PM scores ranging from 0 to 24.

[c] Values are medians.

[d] Overall demographic info provided only.

Appendix Table C8. USPSTF quality assessment: oral selective antihistamine versus nasal antihistamine

Author, year	Assembled comparable groups	Maintained comparable groups	Minimal follow-up loss	Measurements equal, valid, and reliable	Interventions clearly defined	Important outcomes considered	Appropriate analysis of results	Overall USPSTF rating
Berger, 2003	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Berger, 2006	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Charpin, 1995	No	Uncertain	Yes	Yes	Yes	Uncertain	No	Poor
Corren, 2005	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Gambardella, 1993	No	Uncertain	Uncertain	Uncertain	Yes	Yes	No	Poor

USPSTF = United States Preventive Services Task Force.

Appendix Table C9. Nasal symptom outcomes: change from baseline–oral selective antihistamine versus nasal antihistamine

Author, Year	Drug, Dose/Day	N/n	Time, weeks	Congestion	p	Rhinorrhea	p	Sneezing	p	Itching	p	TNSS[a]	p
Berger, 2003	Desloratadine 5mg	111/111	2	-0.82	NR	-0.78	NR	-0.71	NR	-0.78	NR	-3.10	NR
	Azelastine 4 puffs/nostril	108/106		-0.90		-1.00		-0.94		-1.03		-3.88	
Berger, 2006	Cetirizine 10mg	175/175	2		0.049				0.010			-3.9 (4.3)	0.140
	Azelastine 4 puffs/nostril	179/179										-4.6 (4.2)	
Charpin, 1995	Cetirizine 10mg	69[b]	2		0.002[d]		0.044[d]		NS[d]		NS[d]		
	Azelastine 2 puffs/nostril	67[b]											
Corren, 2005	Cetirizine 10mg	155/155	2	-0.96 (1.26)	0.187	-1.00 (1.40)	0.003	-1.29 (1.36)	0.065	-1.09 (1.46)	0.056	-4.32 (4.66)	0.015
	Azelastine 4 puffs/nostril	152/151		-1.13 (1.16)		-1.46 (1.39)		-1.58 (1.49)		-1.39 (1.45)		-5.56 (4.68)	

N/n = Number of patients randomized to comparator groups of interest/number of patients analyzed; NR = not reported; NS= non-significant; TNSS = total nasal symptom score.

Except as noted, entries for each symptom represents the mean change from baseline symptom score using a 0 (no symptom) to 6 (severe symptom) rating scale. Values are presented as mean (standard deviation) unless otherwise noted.

[a] TNSS is a sum of AM and PM scores ranging from 0 to 24.

[b] Only patients analyzed are reported.

[c] Symptoms scored on a 0-100 VAS.

[d] Linear regression of VAS scores over time.

Appendix Table C10. Quality of life outcomes–oral selective antihistamine versus nasal antihistamine

Author, Year	Drug, Dose/Day	N/n	Time, weeks	Outcome	Baseline Mean	Change from Baseline	p
Berger, 2006	Cetirizine 10mg	175/175	2	RQLQ		-1.1	0.002
	Azelastine 4 puffs/nostril	179/179				-1.5	
Charpin, 1995	Cetirizine 10mg	69[a]	2	% Reporting excellent or good response to treatment		67.9[b]	0.87
	Azelastine 2 puffs/nostril	67[a]				68.5[b]	
Corren, 2005	Cetirizine 10mg	155/155	2	RQLQ	3.75 (1.03)	-1.11 (1.18)	0.049
	Azelastine 4 puffs/nostril[b]	152/151			3.69 (1.04)	-1.41 (1.25)	

N/n = Number of patients randomized to comparator groups of interest/number of patients analyzed; RQLQ = Rhinitis Quality of Life Questionnaire.

Values are presented as mean (standard deviation) unless otherwise noted.

[a] Only patients analyzed are reported.

[b] Post-treatment values.

[c] Equivalent to 4 puffs.

Oral Selective Antihistamine Versus Intranasal Corticosteroid

Appendix Table C11. Trial description: oral selective antihistamine versus intranasal corticosteroid

Author, Year	Location/ Site(s)	Enrollment/ Treatment Duration	Funding/ Author Industry Disclosures	N	Inclusion Criteria	Exclusion Criteria[a]	Rescue Medication Use	Objective Diagnosis	Run-in Period	Pollen Counts Measured	Patient Blinding	Assessor Blinding
Andrews, 2009 (Trial 1)	N. America Multi-center	2006 2 weeks	Industry Yes	623	Minimum SAR severity and duration	SAR meds/+ Chronic asthma Pregnancy Infection Deformities	No	•	•	•	•	•
Andrews, 2009 (Trial 2)	N. America Multi-center	2007 2 weeks	Industry Yes	451	Minimum SAR severity and duration	SAR meds/+ Other meds Chronic asthma Pregnancy	No	•	•	•	•	•

Author, Year	Location/ Site(s)	Enrollment/ Treatment Duration	Funding/ Author Industry Disclosures	N	Inclusion Criteria	Exclusion Criteria[a]	Rescue Medication Use	Objective Diagnosis	Run-in Period	Pollen Counts Measured	Patient Blinding	Assessor Blinding
						Infection Deformities						
Anolik, 2008	N. America Multi-center	March 1995 15 days	NR Yes	526	Minimum SAR severity and duration	Chronic asthma Immunotherapy Infection Deformities	No	•	•	•	•	•
Bernstein, 2004	N. America Multi-center	4 weeks	Industry Yes	316	Minimum SAR severity and duration	SAR meds/NR	No	•	•		•	•
Condemi, 2000	N. America Multi-center	4 weeks	Industry Yes	351	Minimum SAR severity and duration	SAR meds/+ Other meds Pregnancy Infection Deformities	No	•	•	•	•	•
Gawchik, 1997	N. America Multi-center	4 weeks	Industry Yes	305	Minimum SAR severity and duration	SAR meds/+ Other meds Immunotherapy Pregnancy Infection		•	•	•	•	•
Gehanno, 1997	Europe Multi-center	March 1991 4 weeks	Industry Yes	114	Minimum SAR severity	SAR meds/+ Pregnancy	Yes	•			•	•
Jordana, 1996	N. America Multi-center	4 weeks	Industry Yes	242		SAR meds/- Pregnancy Infection Deformities	Yes	•	•	•	•	•
Kaszuba, 2001	N. America Single center	August 1999 4 weeks	Industry, NIH No	88	Minimum SAR duration	SAR meds/+ Pregnancy Deformities	No	•		•		
Lu, 2009 (Trial 1)	N. America Multi-center	April 1998 2 weeks	Industry Yes	289	Minimum SAR severity and duration		No	•	•		•	•
Ratner, 1998	N. America Multi-center	2 weeks	Industry Yes	450	Minimum SAR severity and duration	SAR meds/+ Pregnancy Infection Deformities	No	•	•		•	•
Schoenwetter, 1995	N. America Multi-center	4 weeks	Industry Yes	298	Minimum SAR severity and duration	SAR meds/+ Other meds Pregnancy Infection	No	•	•	•	•	•

Author, Year	Location/ Site(s)	Enrollment/ Treatment Duration	Funding/ Author Industry Disclosures	N	Inclusion Criteria	Exclusion Criteria[a]	Rescue Medication Use	Objective Diagnosis	Run-in Period	Pollen Counts Measured	Patient Blinding	Assessor Blinding
						Deformities						
Vervloet, 1997	Europe Multi-center	3 weeks	Industry Yes	238	Minimum SAR severity	SAR meds/+ Immunotherapy Pregnancy Deformities	Yes	•		•	•	•

N = Patients randomized to comparator groups of interest; NIH = National Institutes of Health; NR = not reported; SAR = seasonal allergic rhinitis.

[a] +, -, or NR indicates whether FDA-recommended washout periods were required (+), were not required (-), or were not reported (NR) for restricted SAR medications prior to trial entry.

Appendix Table C12. Patient characteristics: oral selective antihistamine versus intranasal corticosteroid

Author, Year	Drug, Dose/Day	n	Mean Age, years	Sex, % Female	Race, %	Disease Duration, years	Mean Baseline NSS[a]
Andrews, 2009 (Trial 1)	Fexofenadrine 180 mg	311	39.6 (14.63)	64	White: 92 Black: 3 Other: 5	≥2 to <5: 11% ≥5 to <10: 22% ≥10: 67%	TNSS: 9.8 (SE: 0.09)
	Fluticasone furoate 110 mcg	312	37.8 (13.95)	67	White: 86 Black: 8 Other: 6	≥2 to <5: 14% ≥5 to <10: 18% ≥10: 67%	TNSS: 9.8 (SE: 0.09)
Andrews, 2009 (Trial 2)	Fexofenadrine 180 mg	227	34.3 (13.66)	59	White: 80 Black: 19 Other: 2	≥2-<5: 10% ≥5-<10: 19% ≥10: 71%	TNSS: 9.9 (SE: 0.11)
	Fluticasone furoate 110 mcg	224	34.0 (13.55)	68	White: 84 Black: 13 Other: 3	≥2-<5: 8% ≥5-<10: 21% ≥10: 71%	TNSS: 9.7 (SE: 0.10)
Anolik, 2008	Loratadine 10 mg	176	25 (Range: 12-65)	50.3	Unspecified	14 (Range: 2-60)	C: 2.3 S: 1.7 R: 2.1 I: 1.9 TNSS: 7.9 (2.2)
	Mometasone furoate 200 mcg	169	26 (Range: 12-71)	50.6	Unspecified	13 (Range: 2-56)	C: 2.2 S: 1.7 R: 2.1 I: 1.7 TNSS: 7.8 (2.5)
Bernstein, 2004	Loratadine 10 mg	158	80% of patients were between 18 and 64 years old[b]	58-62[b]	White: 80-89[b]		C: 78.3[c] (SE: 1.1)
	Fluticasone propionate 200 mcg	158					C: 79.0[c] (SE: 1.1)
Condemi, 2000	Loratadine	176	32	55[c]	White: 90[b]		C: 2.3

Author, Year	Drug, Dose/Day	n	Mean Age, years	Sex, % Female	Race, %	Disease Duration, years	Mean Baseline NSS[a]
	10 mg		(Range: 12-69)[b]				S: 2.1 R: 2.1 I: 2.0 TNSS: 8.4
	Triamcinolone acetonide 220 mcg	175					C: 2.2 S: 2.0 R: 2.0 I: 2.0 TNSS: 8.2
Gawchik, 1997	Loratadine 10 mg	153	32.6 (12.0)	58	White: 90 Black: 8 Hispanic: 1 Asian: <1	Mean: 17.5 (11.2)	
	Triamcinolone acetonide 220 mcg	152	33.7 (13.0)	57	White: 91 Black: 6 Hispanic: <1 Asian: 2	Mean: 19.1 (12.9)	
Gehanno, 1997	Loratadine 10 mg	57	41.0 (Range: 13-80)	58	Unspecified	<2: 18% 2-5: 49% 6-10: 9% >10: 25%	
	Fluticasone propionate 200 mcg	57	37.0 (Range: 15-70)	53	Unspecified	<2: 16% 2-5: 44% 6-10: 16% >10: 25%	
Jordana, 1996	Loratadine 10 mg	119	Range: 12-17	40.3	Unspecified		
	Fluticasone propionate 200 mcg	121	Range: 12-17	47.1	Unspecified		
Kaszuba, 2001	Loratadine 10 mg[d]	44	30.0[e] (Range: 19-44)	43	White: 57		
	Fluticasone propionate 200 mcg[d]	44	27.5[e] (Range: 18-48)	52	White: 64		
Lu, 2009 (Trial 1)	Loratadine 10 mg	116	34.8 (12.4)	64.7	White: 79.3 Black: 6.9 Hispanic: 8.6 Other: 5.2	18.1 (11.0)	TNSS: 2.11
	Beclomethasone dipropionate 400 mcg[f]	173	34.1 (13.3)	61.3	White: 79.2 Black: 8.1 Hispanic: 8.1 Other: 4.6	17.9 (12.2)	TNSS: 2.03
Ratner, 1998	Loratadine 10 mg	150	40.1 (Range: 15-70)	54	White: 73 Hispanic: 19		TNSS: 300[cg]

Author, Year	Drug, Dose/Day	n	Mean Age, years	Sex, % Female	Race, %	Disease Duration, years	Mean Baseline NSS[a]
					Other: 8		
	Fluticasone propionate 200 mcg	150	40.7 (Range: 13-80)	55	White: 78 Hispanic: 15 Other: 7		TNSS: 290[cg]
Schoenwetter, 1995	Loratadine 10 mg	149	31.2 (11.3)	57	White: 89 Black: 5 Hispanic: 2 Other: <1	17.2 (11.2)	C: 2.07 S: 1.93 R: 1.85 I: 1.95 TNSS: 7.80[h]
	Triamcinolone acetonide 220 mcg	149	31.4 (11.5)	58	White: 91 Black: 4 Hispanic: 2 Other: 3	19.1 (11.6)	C: 2.12 S: 1.94 R: 1.99 I: 1.90 TNSS: 7.95[h]
Vervloet, 1997	Cetirizine 10 mg	118	30 (Range: 12-75)	49.2	Unspecified	<1: 2.54% 1-3: 13.56% 4-8: 38.14% >8: 45.76%	TNSS: 9.36[i] (2.17)
	Fluticasone propionate 200 mcg	120	28 (Range: 12-71)	47.1	Unspecified	<1: 1.68% 1-3: 18.49% 4-8: 31.93% >8: 47.9%	TNSS: 9.23[i] (2.02)

C = congestion; I = itching; n = patients randomized to comparator groups of interest; NSS = nasal symptom score; R = rhinorrhea; S = sneezing; SE = standard error; TNSS = total nasal symptom score.

Values are presented as mean (standard deviation) unless otherwise noted.

[a] Individual nasal symptoms rated on a scale from 0 (no symptoms) to 3 (severe symptoms) except as noted. TNSS ranges from 0 to 12.

[b] Overall demographic info provided only.

[c] Individual symptoms rated on a visual analog scale from 0 to 100. TNSS ranges from 0 to 400.

[d] As-needed (prn) dosing.

[e] Values are medians.

[f] Twice daily (bid) dosing.

[g] Values extracted from figures using Engauge Digitizer software.

[h] Values calculated by report author.

[i] TNSS is the sum of 5 individual symptom scores rated on a scale from 0 (none) to 3 (severe): congestion when waking, daytime congestion, rhinorrhea, sneezing, and nasal itch. TNSS ranges from 0 to 15.

Appendix Table C13. USPSTF quality assessment: oral selective antihistamine versus intranasal corticosteroid

Author, Year	Assembled comparable groups	Maintained comparable groups	Minimal follow-up loss	Measurements equal, valid, and reliable	Interventions clearly defined	Important outcomes considered	Appropriate analysis of results	Overall USPSTF rating
Andrews, 2009 (Trial 1)	Yes	Yes	Yes	Yes	Uncertain	Yes	Yes	Fair
Andrews, 2009 (Trial 2)	Yes	Yes	Yes	Yes	Uncertain	Yes	Yes	Fair
Anolik, 2008	Yes	Yes	Yes	Yes	Yes	Yes	No	Poor
Bernstein, 2004	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Condemi, 2000	No	Uncertain	Yes	Yes	Yes	Yes	Yes	Poor
Gawchik, 1997	No	Uncertain	Yes	Yes	Yes	Yes	No	Poor
Gehanno, 1997	No	Uncertain	Yes	Yes	Yes	Yes	Yes	Poor
Jordana, 1996	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Kaszuba, 2001	No	Uncertain	Yes	No	Yes	Uncertain	No	Poor
Lu, 2009 (Trial 1)	Yes	Yes	Yes	Uncertain	Yes	Yes	No	Poor
Ratner, 1998	Yes	Yes	Yes	Yes	Yes	Uncertain	Yes	Fair
Schoenwetter, 1995	Yes	Yes	Yes	Yes	Yes	Yes	No	Poor
Vervloet, 1997	Yes	Yes	Yes	Yes	Yes	No	No	Poor

USPSTF = United States Preventive Services Task Force

Appendix Table C14. Nasal symptom outcomes: change from baseline–oral selective antihistamine versus intranasal corticosteroid

Author, Year	Drug, Dose/Day	N/n	Time, Weeks	Congestion	p	Rhinorrhea	p	Sneezing	p	Itching	p	TNSS	p
Andrews, 2009 (Trial 1)	Fexofenadrine 180 mg	311/311	2										<0.001
	Fluticasone furoate 110 mcg	312/312											
Andrews, 2009 (Trial 2)	Fexofenadrine 180 mg	227/227	2										<0.001
	Fluticasone furoate 110 mcg	224/244											
Anolik, 2008	Loratadine 10 mg	181/175	2.1	-0.4	NS	-0.4	NS	-0.6	NS	-0.6	NS	-1.9 (2.2)	NS
	Mometasone furoate 200 mcg	176/166		-0.7		-0.7		-0.7		-0.6		-2.7 (2.5)	
Gawchik, 1997	Loratadine 10 mg	153/137	2									-3.6[ab]	<0.05
	Triamcinolone acetonide 220 mcg	152/142										-4.6[ab]	

Author, Year	Drug, Dose/Day	N/n	Time, Weeks	Congestion	p	Rhinorrhea	p	Sneezing	p	Itching	p	TNSS	p
Lu, 2009 (Trial 1)	Loratadine 10 mg	116/115	2									-0.53 (95% CI -0.63, -0.42)	NR
	Beclomethasone dipropionate 400 mcg[c]	173/172										-0.70 (95% CI -0.78, -0.61)	
Ratner, 1998	Loratadine 10 mg	150/150	2									-90[ad]	<0.001
	Fluticasone propionate 200 mcg	150/150										-150[ad]	
Gawchik, 1997	Loratadine 10 mg	153/137	3									-4.1[ab]	NR
	Triamcinolone acetonide 220 mcg	152/142										-5.3[ab]	
Vervloet, 1997	Cetirizine 10 mg	118/118	3									-4.96[e]	<0.001
	Fluticasone propionate 200 mcg	120/119										-7.13[e]	
Bernstein, 2004	Loratadine 10 mg	158/158	4	-25.0[d] (1.9)[f]	≤0.003								
	Fluticasone propionate 200 mcg	158/158		-35.3[d] (1.9)[f]									
Condemi, 2000	Loratadine 10 mg	176/174	4	-0.8 (1.0)	<0.05	-0.9 (1.0)	NS	-0.9 (0.9)	<0.05	-0.9 (0.9)	<0.05	-3.6 (3.2)	<0.05
	Triamcinolone acetonide 220 mcg	175/174		-1.1 (0.9)		-1.1 (0.9)		-1.2 (0.9)		-1.1 (0.8)		-4.4 (2.9)	
Gawchik, 1997	Loratadine 10 mg	153/137	4		<0.02		NS		<0.02		<0.02	-4.4[ab]	<0.02
	Triamcinolone acetonide 220 mcg	152/142										-5.2[ab]	
Gehanno, 1997	Loratadine 10 mg	57/57	4										0.009
	Fluticasone propionate 200 mcg	57/57											
Jordana, 1996	Loratadine 10 mg	119/119	4		<0.001		<0.001		0.001		0.011		
	Fluticasone propionate 200 mcg	121/121											
Kaszuba, 2001	Loratadine 10 mg[g]	44[h]	4		0.02		0.02		0.009				
	Fluticasone	44[h]											

Author, Year	Drug, Dose/Day	N/n	Time, Weeks	Congestion	p	Rhinorrhea	p	Sneezing	p	Itching	p	TNSS	p
	propionate 200 mcg[g]												
Schoenwetter, 1995	Loratadine 10 mg	149/140	4	-0.43 (0.70)	≤0.001	-0.5 (0.72)	≤0.001	-0.68 (0.71)	≤0.001	-0.76 (0.70)	≤0.001		
	Triamcinolone acetonide 220 mcg	149/134		-0.89 (0.79)		-1.05 (0.70)		-1.13 (0.80)		-1.05 (0.78)			

N/n = Number of patients randomized to comparator groups of interest/number of patients analyzed; NR = not reported; NS = non- significant; TNSS = total nasal symptom score.

Except as noted, entries for each symptom represent the mean change from baseline symptom score using a 0 (no symptom) to 3 (severe symptom) rating scale. TNSS ranges from 0 to 12. Values are presented as mean (standard deviation) unless otherwise noted.

[a] Values extracted from figures using Engauge Digitizer software.

[b] Change in symptom scores calculated using end of treatment scores rather than scores averaged over the treatment interval.

[c] Twice daily (BID) dosing.

[d] Individual symptom scores rated on a visual analog scale from 0 (no symptom) to 100 (severe symptom): congestion, rhinorrhea, sneezing, and nasal itch. Maximum TNSS is 400.

[e] TNSS is the sum of 5 individual symptom scores rated on a scale from 0 (no symptom) to 3 (severe symptom): congestion when waking, congestion the rest of the day, rhinorrhea, sneezing, and nasal itch. TNSS ranges from 0 to 15.

[f] Standard error.

[g] As needed (prn) dosing.

[h] Only patients randomized are reported.

Appendix Table C15. Eye symptom outcomes–oral selective antihistamine versus intranasal corticosteroid

Author, Year	Drug, Dose/Day	N/n	Time, Weeks	Outcome	Baseline Mean	Change from Baseline	p
Andrews, 2009 (Trial 1)	Fexofenadrine 180 mg	311/311	2	TOSS (scale 0-9)	7.0 (0.08)[a]		0.106
	Fluticasone furoate 110 mcg	312/312			6.9 (0.08)[a]		
Andrews, 2009 (Trial 2)	Fexofenadrine 180 mg	227/227	2	TOSS (scale 0-9)	7.0 (0.10)[a]		0.002
	Fluticasone furoate 110 mcg	224/224			6.8 (0.10)[a]		
Anolik, 2008	Loratadine 10 mg	181/175	2	Tearing			0.04[b]
	Mometasone furoate 200 mcg	176/166					
Gawchik, 1997	Loratadine 10 mg	153/137	2	Symptoms undefined			NS
	Triamcinolone acetonide 220 mcg	152/142					
Bernstein, 2004	Loratadine 10 mg	158/158	4	TOSS (scale 0-300)	204.3[c] (3.8)[a]	-72.5[c] (5.4)[a]	0.028
	Fluticasone propionate 200 mcg	158/158			209.4[c] (3.8)[a]	-88.7[c] (5.3)[a]	
Condemi, 2000	Loratadine 10 mg	176/174	4	TOSS (scale 0-9)	1.9	-0.9 (1.0)	NS
	Triamcinolone acetonide 220 mcg	175/174			1.9	-0.9 (0.9)	
Gawchik, 1997	Loratadine 10 mg	153/137	4	Symptoms undefined			<0.02
	Triamcinolone acetonide 220 mcg	152/142					
Schoenwetter, 1995	Loratadine 10 mg	149/140	4	Symptoms undefined	1.75	-0.69 (0.69)	NS
	Triamcinolone acetonide 220 mcg	149/134			1.75	-0.80 (0.78)	

N/n = Number of patients randomized to comparator groups of interest/number of patients analyzed; NS = not significant; TOSS = total ocular symptom score.

TOSS is the sum of scores for 3 ocular symptoms (itching, tearing, and redness). Values are presented as mean (standard deviation) unless otherwise noted.

[a] Standard error

[b] Anolik, 2008 assessed ocular itching, tearing, and redness. Baseline and change from baseline values were not provided. One statistically significant result was reported as shown. For ocular itching and redness, INCS was not statistically superior to selective oral antihistamine. P-values not reported.

[c] TOSS is the sum of 3 individual eye symptom scores rated on a visual analog scale from 0 (no symptom) to 100 (severe symptom): itching, tearing, and redness. TOSS ranges from 0 to 300.

Appendix Table C16. Quality of life outcomes–oral selective antihistamine versus intranasal corticosteroids

Author, Year	Drug, Dose/Day	N/n	Time, Weeks	Outcome	Baseline Mean	Change from Baseline	p
Andrews, 2009 (Trial 1)	Fexofenadrine 180 mg	311/311	2	Nocturnal RQLQ	4.3 (SE: 0.06)		<0.001
	Fluticasone furoate 110 mcg	312/312			4.2 (SE: 0.05)		
Andrews, 2009 (Trial 2)	Fexofenadrine 180 mg	227/227	2	Nocturnal RQLQ	4.2 (SE: 0.07)		<0.001
	Fluticasone furoate 110 mcg	224/224			4.1 (SE: 0.07)		
Condemi, 2000	Loratadine 10 mg	176[a]	2	RQLQ	3.79 (0.89)	-1.66[b]	<0.05
	Triamcinolone acetonide 220 mcg	175[a]			3.70 (0.89)	-1.9[b]	
Kaszuba, 2001	Loratadine 10 mg[c]	44[d]	2	RQLQ	2.0[be]	0.0[f]	<0.01
	Fluticasone propionate 200 mcg[c]	44[d]			2.4[be]	-1.0[f]	
Ratner, 1998	Loratadine 10 mg	150/150	2	RQLQ	4.1 (0.1)	-1.3 (0.1)	<0.001
	Fluticasone propionate 200 mcg	150/150			4.1 (0.1)	-2.2 (0.1)	
	Loratadine 10 mg	150/150	2	% signif, mod, or mild improve[g]	--	63.9[b]	<0.001[h]
	Fluticasone propionate 200 mcg	150/150				88.7[b]	
Vervloet, 1997	Cetirizine 10 mg	118[d]	3	PGA: scale 0-100[i]	61.45 (22.75)	-31 (31)	<0.001
	Fluticasone propionate 200 mcg	120[d]			63.50 (21.15)	-51 (26)	
	Cetirizine 10 mg	118[d]		% v. effective/effective[j]	--	64.3	<0.001
	Fluticasone propionate 200 mcg	120[d]				89.5	
Bernstein, 2004	Loratadine 10 mg	158[a]	4	RQLQ			<0.05
	Fluticasone propionate 200 mcg	158[a]					
	Loratadine 10 mg	158[a]	4	% signif, mod, or mild improve[g]	--	64	<0.001
	Fluticasone propionate 200 mcg	158[a]				82	
Condemi, 2000	Loratadine 10 mg	176[a]	4	RQLQ	3.79 (0.89)	-1.97[b]	<0.05
	Triamcinolone acetonide 220 mcg	175[a]			3.70 (0.89)	-2.22[b]	
Gehanno, 1997	Loratadine 10 mg	57/57	4	RQLQ			<0.05
	Fluticasone propionate 200 mcg	57/57					
	Loratadine 10 mg	57/57	4	% v. effective/effective[j]	--	69.2	NS
	Fluticasone propionate 200 mcg	57/57				79.2	
Kaszuba, 2001	Loratadine 10 mg[c]	44[d]	4	RQLQ	2.0[be]	-0.3[f]	<0.05
	Fluticasone propionate 200 mcg[c]	44[d]			2.4[be]	-1.2[f]	

N/n = Number of patients randomized to comparator groups of interest/number of patients analyzed; NS = non-significant; PGA = patient global assessment; RQLQ = Rhinitis Quality of Life Questionnaire; SE = standard error.

Values are presented as mean (standard deviation) unless otherwise noted.

[a] n analyzed not reported.

[b] Values extracted from figures using Engauge Digitizer software.

[c] As needed (prn) dosing.

[d] Only patients randomized reported.

[e] Median.

[f] Values calculated by report author.

[g] 7-point scale: significant, moderate, or mild improvement; no change; mild, moderate, or significant worsening.

[h] P-value calculated by report author using 2x2 chi-square at mild improvement cut point.

[i] Discomfort due to rhinitis was rated on a visual analog scale from 0 (no discomfort) to 100 (worst discomfort ever experienced).

[j] 4-point scale: very effective, effective, slightly effective, ineffective.

Oral Selective Antihistamine Versus Oral Decongestant

Appendix Table C17. Trial description: oral selective antihistamine versus oral decongestant

Author, Year	Location, Site(s)	Enrollment/ Treatment Duration	Funding/ Author Industry Disclosures	N	Inclusion Criteria	Exclusion Criteria	Rescue Medication Use	Objective Diagnosis	Run in Period	Pollen Count	Patient Blinding	Assessor Blinding
Bronsky, 1995	N. America Multiple	Fall 1989 2 weeks	Industry Yes	437	Minimum SAR severity and duration	SAR meds Other meds Chronic asthma Pregnancy Infection	No	•	•	•	•	•
Chervinsky, 2005	N. America Multiple	2 weeks	NR Yes	436	Minimum SAR severity and duration	SAR meds Pregnancy Infection	No	•	•	•	•	•
Grosclaude, 1997	Europe Multiple	March1992 2 weeks	NR Yes	454	Minimum SAR severity and duration	SAR meds Other meds Pregnancy Infection Deformities	Yes	•		•	•	•
Grubbe, 2009	N. America Multiple	2.1 weeks	Industry Yes	398	Minimum SAR severity and duration	SAR meds Chronic asthma Pregnancy Infection Deformities	No	•	•	•	•	•
Pleskow, 2005	N. America Multiple	2000 2 weeks	Industry Yes	749	Minimum SAR severity and duration	SAR meds Pregnancy Infection Deformities	No	•	•	•	•	•
Schenkel, 2002	N.America Multiple	2.1 weeks	Industry NR	682	Minimum SAR duration	SAR meds Chronic asthma Pregnancy	No	•	•		•	•
Sussman,	N.America	2.6 weeks	Industry	436	Minimum	SAR meds	No					

Author, Year	Location, Site(s)	Enrollment/ Treatment Duration	Funding/ Author Industry Disclosures	N	Inclusion Criteria	Exclusion Criteria	Rescue Medication Use	Objective Diagnosis	Run in Period	Pollen Count	Patient Blinding	Assessor Blinding
1999	Multiple		Yes		SAR severity	Pregnancy Infection		•	•	•	•	•

N = Patients randomized to comparator groups of interest; NR = not reported; SAR = seasonal allergic rhinitis.

[a] +, -, or NR indicates whether FDA-recommended washout periods were required (+), were not required (-), or were not reported (NR) for restricted SAR medications prior to trial entry.

Appendix Table C18. Patient characteristics: oral selective antihistamine versus oral decongestant

Author, Year	Drug, Dose/Day	n	Mean Age, years	Sex, % female	Race, %	Disease Duration, years	Mean Baseline NSS[a]
Bronsky., 1995	Loratadine 10 mg	217	Median: 30 Range: 12-60	57.5	White: 87.3 Black: 4.2 Other: 8.5	Median: 15 Range: 1-50	
	Pseudoephedrine 240 mg	220	Median: 28 Range: 12-60	51.2	White: 92.9 Black: 1.9 Other: 5.2	Median: 15 Range: <1-50	
Chervinsky, 2005	Desloratadine 5 mg	214	37	69	Unspecified	19	C: 2.56
	Pseudoephedrine 240 mg	222	36	65	Unspecified	19	C: 2.56
Grosclaude, 1997	Cetirizine 10 mg	231	32 Range: 12-66	52	Unspecified	8	C: 2.28 R: 2.07 S: 2.02 I: 1.76
	Pseudoephedrine 240 mg	223	34 Range: 12-65	51	Unspecified	8	C: 2.24 R: 2.00 S: 1.99 I: 1.79
Grubbe, 2009	Desloratadine 5 mg	198	37 Range: 12-76	65.2	White: 77 Black: 13 Hispanic: 7 Asian: 2 Other: 2	17.9 Range: 2-56	C: 2.50
	Pseudoephedrine 240 mg	200	35 Range: 12-68	62.0	White: 82 Black: 10 Hispanic: 4 Asian: 3 Other: 2.5	18.0 Range: 2-54	C: 2.46
Pleskow, 2005	Desloratadine 5 mg	372	35 Range: 12-76	65.9	White: 80 Black: 12 Hispanic: 7 Asian: <1	18.0 Range: 2-55	

Author, Year	Drug, Dose/Day	n	Mean Age, years	Sex, % female	Race, %	Disease Duration, years	Mean Baseline NSS[a]
					Other: 0		
	Pseudoephedrine 240 mg	377	36 Range: 12-70	65.5	White: 78 Black: 10 Hispanic: 9 Asian: 1 Other: 2	17.9 Range: 2-50	
Schenke, 2002	Desloratadine 5 mg	340	34.8	60	Unspecified	18.3	C: 2.57
	Pseudoephedrine 240 mg	342	34.2	65	Unspecified	17.6	C: 2.54
Sussman, 1999	Fexofenadrine 120 mg	218	34.9 (12.35) Range: 12-64	56.9	White: 85.3 Black: 6.0 Asian: 8.3 Other: 0.5	15.2 (9.79) Range: 2.0-46.2	C: 2.36 (SE 0.03)*
	Pseudoephedrine 240 mg	218	31.7 (11.12) Range: 12-66	58.7	White: 89.0 Black: 4.1 Asian: 5.5 Other: 1.4	15.9 (10.06) Range: 1.0-46.0	C: 2.34 (SE 0.03)

C = congestion; I = itching; n = patients randomized to comparator groups of interest; NSS = nasal symptom score; R = rhinorrhea; S = sneezing; SE = standard error; TNSS = total nasal symptom score.

[a] Individual symptoms rated on a scale from 0 (no symptoms) to 3 (severe symptoms) in all cases except Sussman 1999, where the maximum was 4.

Appendix Table C19. USPSTF quality assessment: oral selective antihistamine versus oral decongestant

Author, year	Assembled comparable groups	Maintained comparable groups	Minimal follow-up loss	Measurements equal, valid, and reliable	Interventions clearly defined	Important outcomes considered	Appropriate analysis of results	Overall USPSTF rating
Bronsky, 1995	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Chervinsky, 2005	Yes	Uncertain	Yes	Yes	Yes	Yes	No	Poor
Grosclaude, 1997	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Grubbe, 2009	Yes	Yes	Yes	Yes	Yes	Yes	No	Poor
Pleskow, 2005	Yes	Yes	Yes	Yes	Yes	Yes	No	Poor
Schenkel, 2002	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Fair
Sussman, 1999	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good

USPSTF = United States Preventive Services Task Force.

Appendix Table C20. Nasal symptom outcomes: change from baseline–oral selective antihistamine versus oral decongestant

Author, Year	Drug, Dose/Day	N/n	Time, weeks	Congestion[a]	p	Rhinorrhea	p	Sneezing	p	Itching	p	TNSS	p
Bronsky, 1995	Loratadine 10 mg	217/212	2	-0.5	NR							-2.3	NR
	Pseudoephedrine 240 mg	220/211		-0.6								-2.4	
Chervinsky, 2005	Desloratadine 5 mg	214/200	2	-0.73	NR								
	Pseudoephedrine 240 mg	222/204		-0.83									
Grosclaude, 1997	Cetirizine 10 mg	231/231	2	-0.85[b]		-0.96[b]		-1.11[b]		-0.86[b]			
	Pseudoephedrine 240 mg	223/223		-1.02[b]		-0.75[b]		-0.79[b]		-0.73[b]			
Grubbe, 2009	Desloratadine 5 mg	198[c]	2	-0.66									
	Pseudoephedrine 240 mg	200[c]		-0.75									
Pleskow, 2005	Desloratadine 5 mg	372[c]	2	-0.74	0.53								
	Pseudoephedrine 240 mg	377[c]		-0.78									
Schenkel, 2002	Desloratadine 5 mg	340/340	2	0.65	NS								
	Pseudoephedrine 240 mg	342/342		0.70									
Sussman, 1999	Fexofenadrine 120 mg	218/218	2.6	-0.4[d]	NS	-0.4[d]		-0.5[d]					
	Pseudoephedrine 240 mg	218/218		-0.5[d]		-0.3[d]		-0.3[d]					

N/n = Number of patients randomized to comparator groups of interest/number of patients analyzed; NR = not reported, NS= non-significant; TNSS = total nasal symptom score.

[a] Mean change from baseline over the entire treatment duration.

[b] Calculated by author using pre/post data.

[c] Only patient randomized are reported.

[d] Values extracted from figures using Engauge Digitizer Software.

Appendix Table C21. Eye symptom outcomes–oral selective antihistamine versus oral decongestant

Author, Year	Drug, Dose/Day	N/n	Time, weeks	Outcome	Baseline mean	Change from baseline	P
Grosclaude, 1997	Cetirizine 10 mg	231/231	2	Itching eyes	1.83	-1.02 [a,c]	NR
	Pseudoephedrine 240 mg	223/223			1.75	-0.81 [a, c]	
Sussman, 1999	Fexofenadrine 120 mg	218/218	2.6	Itchy, watery, red eyes	NR	-0.5 [b,c]	NR
	Pseudoephedrine 240 mg	218/218			NR	-0.4 [b,c]	

N/n = Number of patients randomized to comparator groups of interest/number of patients analyzed; NR = not reported.

[a] 4-point scale: 0, absent; 1, mild; 2, moderate; 3, severe.

[b] 5-point scale: 0, absent; 1, mild; 2, moderate; 3, severe; 4, very severe.

[c] Values obtained using Engauge Digitizer Software.

Appendix Table C22. Quality of life outcomes–oral selective antihistamine versus oral decongestant

Author, year	Drug, Dose/Day	N/n	Time, weeks	Outcome	Baseline mean	End of treatment	P
Bronsky, 1995	Loratadine 10 mg	217/212	2	% Patients reporting good or excellent response to treatment[a]		47[b]	0.25[d]
	Pseudoephedrine 240 mg	220/211				52[c]	

N/n = number of patients randomized to comparator groups of interest/number of patients analyzed.

[a] 5 point scale: 1, excellent; 2, good; 3, fair; 4, poor; 5, treatment failure.

[b] 95/203

[c] 106/202

[d] P-value calculated by report author.

Oral Selective Antihistamine Versus Oral Leukotriene Receptor Antagonist

Appendix Table C23. Trial description: oral selective antihistamine versus leukotriene receptor antagonist

Author, Year	Location, Site(s)	Enrollment/ Treatment Duration	Funding/ Author Industry Disclosures	N	Inclusion Criteria	Exclusion Criteria[a]	Rescue Medication Use	Objective Dx	Run in Period	Pollen Count	Patient Blinding	Assessor Blinding
Baena-Cagnani, 2003	N. America Multiple	4 weeks	NR NR	622	Minimum SAR duration	SAR meds/NR Other meds Pregnancy Infection Deformities	Yes	•	•		•	•
Lombardo, 2006	Europe Single	4 weeks	NR NR	200	Minimum SAR severity and duration	SAR meds/NR Other meds Immunotherapyth erapy Pregnancy Infection Deformities	No	•	•		•	•
Lu, 2009 (Trial 1)	N. America Multiple	April 1998 2 weeks	Industry Yes	228	Minimum SAR severity and duration		No	•	•		•	•
Lu, 2009 (Trial 2)	N. America Multiple	April 1998 2 weeks	Industry Yes	267	Minimum SAR severity and duration		No	•	•		•	•
Meltzer, 2000	N. America Multiple	March1997 2 weeks	Industry Yes	187	Minimum SAR severity and duration	SAR meds/- Other meds Pregnancy Infection	No	•	•	•	•	•
Nayak, 2002	N. America Multiple	September 1999 2 weeks	Industry Yes	456	Minimum SAR severity and duration	SAR meds/- Other meds Pregnancy Infection Deformities	No	•	•	•	•	•
Philip, 2002	N. America Multiple	2000 2 weeks	Industry Yes	950	Minimum SAR severity and duration	SAR meds/NR Pregnancy Infection Deformities	No	•	•	•	•	•
van Adelsberg, 2003 (Trial 1)	N. America Multiple	2001 2 weeks	Industry Yes	693	Minimum SAR severity	SAR meds/NR Other meds Infection	No	•	•	•	•	•

Author, Year	Location, Site(s)	Enrollment/ Treatment Duration	Funding/ Author Industry Disclosures	N	Inclusion Criteria	Exclusion Criteria[a]	Rescue Medication Use	Objective Dx	Run in Period	Pollen Count	Patient Blinding	Assessor Blinding
					and duration	Deformities						
van Adelsberg, 2003 (Trial 2)	N. America Multiple	4 weeks	Industry NR	628	Minimum SAR severity and duration	SAR meds/NR Other meds Infection	No	•	•	•	•	•

N = patients randomized to comparator groups of interest; NR = not reported; SAR = seasonal allergic rhinitis.

[a] +, -, or NR indicates whether FDA-recommended washout periods were required (+), were not required (-), or were not reported (NR) for restricted SAR medications prior to trial entry.

Appendix Table C24. Patient characteristics: oral selective antihistamine versus leukotriene receptor antagonist

Author, Year	n	Drug Dose/Day	Mean Age, years	Sex, % female	Race, %	Disease duration, Years	Mean Baseline NSS[a]
Baena-Cagnani, 2003	311	Desloratadine 5mg	32.3 Range: 15-75	63	White: 82	16.2	
	311	Montelukast 10mg	33.7 Range: 15-71	61	White: 79	17.2	
Lombardo, 2006	96	Levocetirizine 5mg	42 (13) Range: 18-58	39.6	Unspecified	16 (12)	TNSS: 2.12 (0.38)
	104	Montelukast 10mg	Range: 20-56	43.3	Unspecified	14 (12)	TNSS: 2.02 (0.39)
Lu, 2009 (Trial 1)	116	Loratadine 10mg	34.8 (12.4)	64.7	White: 79.3 Black: 6.9 Hispanic: 8.6 Other: 5.2	18.1 (11.0)	TNSS: 2.11
	112	Montelukast 10mg	35.6 (13.1)	62.5	White: 79.5 Black: 5.4 Hispanic: 8.9 Other: 6.3	18.8 (10.7)	TNSS: 2.06
Lu, 2009 (Trial 2)	164	Loratadine 10mg	30.6(10.9)	60.4	White: 89.0 Black: 7.9 Hispanic: 2.4 Other: 0.6	17.3 (10.3)	TNSS: 1.97
	103	Montelukast 10mg	31.1(13.1)	62.1	White: 89.3 Black: 5.8 Hispanic: 1.9 Other: 2.9	19.3 (11.2)	TNSS: 2.03
Meltzer, 2000	92	Loratadine 10mg	Median: 34.5 Range: 15-66	53.3	Unspecified	19 (13)	TNSS: 2.07 (0.41)
	95	Montelukast 10mg	Median: 33 Range: 15-71	57.9	Unspecified	18 (13)	TNSS: 2.12 (0.38)
Nayak, 2002	155	Loratadine 10mg	35 (11)	66	White: 83	18 (13)	TNSS: 2.06 (0.39)

Author, Year	n	Drug Dose/Day	Mean Age, years	Sex, % female	Race, %	Disease duration, Years	Mean Baseline NSS[a]
			Range: 15-65		Black: 10 Hispanic: 4 Asian: 1 Other: 2	Range: 2-60	
	301	Montelukast 10mg	37 (13) Range: 15-82	64	White: 80 Black: 8 Hispanic: 8 Asian: 2 Other: 2	19 (13) Range: 2-65	TNSS: 2.09 (0.44)
Philip, 2002	602	Loratadine 10mg	36 (13) Range: 15-74	65	White: 84 Black: 6 Hispanic: 4 Other: 6	18 (12)	TNSS: 2.06 (0.41)
	348	Montelukast 10mg	37 (13) Range: 15-76	67	White: 83 Black: 6 Hispanic: 4 Other: 8	18 (12)	TNSS: 2.09 (0.44)
van Adelsberg, 2003 (Trial1)	171	Loratadine 10mg	35 (13) Range: 15-72	58	White: 82 Black: 5 Hispanic: 4 Other: 8	18 (12)	TNSS: 2.15 (0.45)
	522	Montelukast 10mg	36 (14) Range: 15-82	62	White: 82 Black: 7 Hispanic: 3 Other: 8	17 (12)	TNSS: 2.10 (0.43)
van Adelsberg, 2003 (Trial 2)	180	Loratadine 10mg	39 (13)	66	White: 81 Black: 13 Hispanic: 2 Other: 4	21 (13)	TNSS: 2.23 (0.44)
	448	Montelukast 10mg	36 (13) Range: 15-82	67	White: 82 Black: 9 Hispanic: 5 Other: 4	19 (12)	TNSS: 2.20 (0.46)

n = Patients randomized to comparator groups of interest, unless otherwise noted; NSS = nasal symptom score; TNSS = total nasal symptom score.

Values are presented as mean (standard deviation) unless otherwise noted.

[a] Individual symptoms rated on a scale from 0 (no symptoms) to 3 (severe symptoms). TNSS scores are the mean of individual symptoms with a maximum score of 3.

Appendix Table C25. USPSTF quality assessment: oral selective antihistamine versus leukotriene receptor antagonist

Author, year	Assembled comparable groups	Maintained comparable groups	Minimal follow-up loss	Measurements equal, valid, and reliable	Interventions clearly defined	Important outcomes considered	Appropriate analysis of results	Overall USPSTF rating
Baena-Cagnani, 2003	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good

Lombardo, 2006	No	Yes	Yes	Yes	Yes	Yes	No	Poor
Lu, 2009 (Trial 1)	Yes	Yes	Yes	Uncertain	Yes	Yes	No	Poor
Lu, 2009 (Trial 2)	Yes	Yes	Yes	Uncertain	Yes	Yes	No	Poor
Meltzer, 2000	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Nayak, 2002	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Philip, 2002	Yes	Yes	Yes	Yes	Yes	Yes	No	Poor
van Adelsberg, 2003 (Trial1)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Fair
van Adelsberg, 2003 (Trial 2)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Fair

USPSTF = United States Preventive Services Task Force.

Appendix Table C26. Nasal symptom outcomes: mean change from baseline–oral selective antihistamine versus leukotriene receptor antagonist

Author, Year	Drug, Dose/Day	N/n	Time, weeks	Congestion	p	Rhinorrhea	p	Sneezing	p	Itching	p	TNSS (95% CI)	p
Lu, 2009 (Trial 1)	Loratadine 10mg	116/115	2									-0.53 (-0.63, -0.42)	NR
	Montelukast 10mg	112/111										-0.36 (-0.46, -0.25)	
Lu, 2009 (Trial 2)	Loratadine 10mg	164/162	2									-0.40 (-0.49, -0.30)	NR
	Montelukast 10mg	103/103										-0.39 (-0.50, -0.27)	
Meltzer, 2000	Loratadine 10mg	92/90	2	-0.33	NR	-0.42	NR	-0.49	NR	-0.45	NR	-0.34 (-0.44, 0.23)	NR
	Montelukast 10mg	95/94		-0.41		-0.49		-0.47		-0.40		-0.36 (-0.47, -0.26)	
Nayak, 2002	Loratadine 10mg	155[a]	2	-0.20	NR	-0.25	NR	-0.33	NR	-0.30	NR	-0.48 (-0.57, -0.40)	NR
	Montelukast 10mg	301[a]		-0.22		-0.28		-0.21		-0.23		-0.52 (-0.58, -0.46)	
Philip, 2002	Loratadine 10mg	602[a]	2	-0.24	NR	-0.24	NR	-0.36	NR	-0.26	NR	-0.50	NR
	Montelukast 10mg	348[a]		-0.13		-0.14		-0.18		-0.12		-0.40	
van Adelsberg, 2003-1	Loratadine 10mg	171/170	2									-0.47 (-0.55, -0.39)	NR
	Montelukast 10mg	522/519										-0.38 (-0.43, -0.33)	
van Adelsberg, 2003-2	Loratadine 10mg	180[a]	2									-0.45 (-0.52, -0.37)	NR
	Montelukast 10mg	448[a]										-0.33 (-0.37, -0.28)	
Lombardo, 2006	Levocetirizine 5mg	96/96	4									-0.43 (-0.47, -0.28)	NR

Author, Year	Drug, Dose/Day	N/n	Time, weeks	Congestion	p	Rhinorrhea	p	Sneezing	p	Itching	p	TNSS (95% CI)	p
	Montelukast 10mg	104/104										-0.34 (-0.39, -0.18)	
van Adelsberg, 2003-2	Loratadine 10mg	180[a]	4									-0.50 (-0.58, -0.42)	NR
	Montelukast 10mg	448[a]										-0.43 (-0.48, -0.38)	

CI =Confidence interval; N/n = number of patients randomized to comparator groups of interest/number of patients analyzed; NR = not reported; TNSS = total nasal symptom score.

Entries for each symptom represent the mean change from baseline symptom score using a 0 (no symptom) to 3 (severe symptom) rating scale. Lombardo, 2006 reported change from baseline using mean scores during week 4 rather than during the entire treatment period.TNSS scores are a mean of individual symptoms with a maximum score of 3 unless otherwise noted.

[a] Only patients randomized reported.

Appendix Table C27. Eye symptom outcomes–oral selective antihistamine versus leukotriene receptor antagonist

Author, Year	Drug, Dose/Day	N/n	Time, weeks	Outcome	Baseline mean	Change from baseline (95%CI)	p
Meltzer, 2000[c]	Loratadine 10mg	92/90	2	TOSS (scale 0-3)	1.41 (0.76)	-0.25 (-0.37, 0.12)	NR
	Montelukast 10mg	95/94			1.47 (0.68)	-0.28 (-0.40, 0.15)	
van Adelsberg, 2003-1	Loratadine 10mg	171/170	2	TOSS (scale 0-3)	1.48 (0.79)	-0.40 (-0.47, -0.32)	NR
	Montelukast 10mg	522/519			1.49 (0.77)	-0.28 (-0.32, -0.23)	
van Adelsberg, 2003-2	Loratadine 10mg	180[a]	2	TOSS (scale 0-3)	1.64 (0.78)	-0.33 (-0.41, -0.26)	NR
	Montelukast 10mg	448[a]			1.64 (0.73)	-0.28 (-0.33, -0.23)	
Lombardo, 2006	Levocetirizine 5mg	96/96	4	TOSS (scale 0-3)	1.45 (0.68)	-0.38 (-0.45, -0.19)	NR
	Montelukast 10mg	104/104			1.36 (0.69)	-0.22 (-0.25, -0.10)	
van Adelsberg, 2003-2	Loratadine 10mg	180[a]	4	TOSS (scale 0-3)		-0.39 (-0.47, -0.31)	NR
	Montelukast 10mg	448[a]				-0.37 (-0.42, -0.31)	

N/n = Number of patients randomized to comparator groups of interest/number of patients analyzed; NR = not reported; TOSS = total ocular symptom score.

Values are presented as mean (standard deviation) unless otherwise noted. TOSS is the mean of scores for 4 ocular symptoms (itching, tearing, redness, and puffiness) using a 0 (no symptom) to 3 (severe symptom) rating scale.

[a] Only patients randomized reported.

Appendix Table C28. Asthma outcomes–oral selective antihistamine versus leukotriene receptor antagonist

Author, year	Drug, Dose/Day	N[a]	Time, weeks	Outcome	Mean Baseline	End of treatment	Mean Change from Baseline	P
Baena-Cagnani, 2003	Desloratadine 5mg	311	2	Triamcinolone acetonide SS	5.17		-1.17	NS
	Montelukast 10mg	311			5.11		-1.26	
Baena-Cagnani, 2003	Desloratadine 5mg	311	2	Rescue		-13.9		0.134

Author, year	Drug, Dose/Day	N[a]	Time, weeks	Outcome	Mean Baseline	End of treatment	Mean Change from Baseline	P
				medication use[b]				
	Montelukast 10mg	311				-16.3		
Baena-Cagnani, 2003	Desloratadine 5mg	311	4	Triamcinolone acetonide SS			-1.36	NS
	Montelukast 10mg	311					-1.52	
Baena-Cagnani, 2003	Desloratadine 5mg	311	4	Rescue medication use[b]		-12.1		0.078
	Montelukast 10mg	311				-15.9		
Baena-Cagnani, 2003	Desloratadine 5mg	311	4	Cough	1.64		-0.48[c]	NS
	Montelukast 10mg	311			1.61		-0.50[c]	
Baena-Cagnani, 2003	Desloratadine 5mg	311	4	Wheeze	1.70		-0.53[c]	NS
	Montelukast 10mg	311			1.71		-0.57[c]	
Baena-Cagnani, 2003	Desloratadine 5mg	311	4	Difficulty breathing	1.82		-0.56[c]	NS
	Montelukast 10mg	311			1.80		-0.62[c]	
Baena-Cagnani, 2003	Desloratadine 5mg	96[d]	4	FEV_1[d]	2.55		-0.15	NS
	Montelukast 10mg	101[d]			2.55		-0.18	

FEV_1 = Forced expired volume in 1 second; NS= non-significant; TA = Triamcinolone acetonide; TASS = total asthma symptom score.

[a] Only patients analyzed reported.

[b] Change in number of puffs of B-agonist use.

[c] Values extracted from figures using Engauge Digitizer software.

[d] In patients with baseline FEV1 <80%.

Appendix Table C29. Quality of life outcomes–oral selective antihistamine versus leukotriene receptor antagonist

Author, Year	Drug, Dose/Day	N/n	Time, weeks	Outcome	Baseline Mean[a]	Change from Baseline (95% CI)	P
2 week outcomes							
Meltzer, 2000[c]	Loratadine 10mg	92/90	2	RQLQ	3.00 (1.02)	-0.9	NR
	Montelukast 10mg	95/94			3.33 (0.98)	-0.9	
Nayak, 2002	Loratadine 10mg	155[b]	2	RQLQ	3.14 (0.98)	-1.09 (-1.26, -0.92)	NR
	Montelukast 10mg	301[b]			3.10 (1.02)	-1.06 (-1.19, 0.93)	
Philip, 2002	Loratadine 10mg	602[b]	2	RQLQ	3.09 (1.03)	-0.99 (-1.08, -0.90)	NR
	Montelukast 10mg	348[b]			3.12 (0.99)	-0.89 (-1.01, -0.77)	

Author, Year	Drug, Dose/Day	N/n	Time, weeks	Outcome	Baseline Mean[a]	Change from Baseline (95% CI)	P
van Adelsberg, 2003-1	Loratadine 10mg	171/170	2	RQLQ	3.24 (0.97)	-0.98 (-1.15, -0.81)	NR
	Montelukast 10mg	522/519			3.22 (1.06)	-0.90 (-1.00, -0.81)	
van Adelsberg, 2003-2	Loratadine 10mg	180[b]	2	RQLQ	3.46 (1.08)	-0.85 (-1.00, -0.70)	NR
	Montelukast 10mg	448[b]			3.41 (1.00)	-0.85 (-0.94, -0.75)	
van Adelsberg, 2003-2	Loratadine 10mg	180[b]	2	PGA[c]		2.30[d] (2.08, 2.52)	NR
	Montelukast 10mg	448[b]				2.43[d] (2.29, 2.57)	
4 week outcomes							
Lombardo, 2006	Levocetirizine 5mg	96/96	4	RQLQ	3.14 (0.95)	0.78	NR
	Montelukast 10mg	104/104			3.09 (0.88)	0.65	
van Adelsberg, 2003-2	Loratadine 10mg	180[b]	4	RQLQ		-1.08 (-1.25, -0.91)	NR
	Montelukast 10mg	448[b]				-1.12 (-1.23, -1.01)	

N/n = Number of patients randomized to comparator groups of interest/number of patients analyzed; NR = not reported; PGA = patient global assessment; RQLQ = Rhinitis Quality of Life Questionnaire.

[a] Values are presented as mean (standard deviation) unless otherwise noted.

[b] Only patients randomized are reported.

[c] PGA of allergic rhinitis was scored on a 0 (best) to 6 (worst) scale.

[d] Values are absolute scores at week 2.

Intranasal Corticosteroid Versus Nasal Antihistamine

Appendix Table C30. Trial description: intranasal corticosteroid versus nasal antihistamine

Author, Year	Location/ Site(s)	Enrollment/ Treatment Duration	Funding/ Author Industry Disclosures	N	Inclusion Criteria	Exclusion Criteria[a]	Rescue Medication Use	Objective Diagnosis	Run-in Period	Pollen Counts Measured	Patient Blinding	Assessor Blinding
Carr, 2012 (Trial 1)	N.America Multiple	March 2008 2 weeks	Industry Yes	415	Minimum SAR severity and duration	SAR meds/- Other meds Chronic asthma Infection Deformities	No	•	•		•	•

Author, Year	Location/ Site(s)	Enrollment/ Treatment Duration	Funding/ Author Industry Disclosures	N	Inclusion Criteria	Exclusion Criteria[a]	Rescue Medication Use	Objective Diagnosis	Run-in Period	Pollen Counts Measured	Patient Blinding	Assessor Blinding
Carr, 2012 (Trial 2)	N.America Multiple	August 2009 2 weeks	Industry Yes	383	Minimum SAR severity and duration	SAR meds/- Other meds Chronic asthma Infection Deformities	No	•	•		•	•
Carr, 2012 (Trial 3)	N.America Multiple	April 2009 2 weeks	Industry Yes	895	Minimum SAR severity and duration	SAR meds/- Other meds Chronic asthma Infection Deformities	No	•	•		•	•
Ghimire, 2007	Asia Single	4 weeks	NR NR	50		SAR meds/NR Other meds Pregnancy Deformities	No				Open Label trial	
Hampel, 2010	N.America Multiple	January 2007 2 weeks	Industry Yes	305	Minimum SAR severity and duration	SAR meds/- Other meds Infection Deformities	No	•	•		•	•
Kaliner, 2009	N.America Multiple	2 weeks	Industry Yes	130	Minimum SAR severity and duration	SAR meds/+ Other meds Chronic asthma Pregnancy Infection Deformities	No	•			Inade-quate	•
Newson-Smith, 1997	Europe Multiple	April 1991 2 weeks	NR Yes	166	Minimum SAR severity and duration	SAR meds/+ Immunotherapy Pregnancy Deformities	No		•		Inade-quate	•
Pelucchi, 1995	Europe	April 1993 6 weeks	NR NR	30	Minimum SAR duration	Chronic asthma Immunotherapy Deformities	Yes	•		•	•	•
Ratner, 2008	N.America Multiple	December 2005 2 weeks	Industry Yes	99	Minimum SAR severity and duration	SAR meds/+ Other meds	No	•	•	•	•	•

N = Patients randomized to comparator groups of interest; NR = not reported.

[a] +, -, or NR indicates whether FDA-recommended washout periods were required (+), were not required (-), or were not reported (NR) for restricted SAR medications prior to trial entry.

Appendix Table C31. Patient characteristics: intranasal corticosteroid versus nasal antihistamine

Author, Year	n	Drug, Dose/Day	Mean Age, years	Sex, % Female	Race, %	Disease Duration, years	Mean Baseline NSS[a]
Carr, 2012 (Trial 1)	207	Fluticasone propionate 200mcg	38.6 (14.1)	61.4	White: 77.8	21.3 (13.5)	C: 5.0 (0.9)[b] S: 4.1 (1.2)[b] R: 4.6 (1.0)[b] I: 4.5 (1.1)[b] TNSS: 18.2 (3.2)[b]
	208	Azelastine 548mcg	36.2 (14.6)	62.5	White: 77.9	21.6 (13.6)	C: 5.1 (0.8)[b] S: 4.0 (1.3)[b] R: 4.5 (1.2)[b] I: 4.5 (1.2)[b] TNSS: 18.2 (3.5)[b]
Carr, 2012 (Trial 2)	189	Fluticasone propionate 200mcg	37.0 (13.6)	64	White: 74.1	21.1 (13.7)	C: 5.0 (0.8)[b] S: 4.2 (1.3)[b] R: 4.6 (1.0)[b] I: 4.8 (0.9)[b] TNSS: 18.6 (2.9)[b]
	194	Azelastine 548mcg	38.2 (13.5)	66	White: 78.9	19.7 (13.1)	C: 5.1 (0.8)[b] S: 4.2 (1.3)[b] R: 4.5 (1.1)[b] I: 4.7 (1.1)[b] TNSS: 18.5 (3.1)[b]
Carr, 2012 (Trial 3)	450	Fluticasone propionate 200mcg	34.2 (14.5)	62.2	White: 79.1	19.6 (12.5)	C: 5.3 (0.7)[b] S: 4.5 (1.2)[b] R: 4.8 (0.9)[b] I: 4.9 (0.9)[b] TNSS: 19.4 (2.4)[b]
	445	Azelastine 548mcg	36.4 (14.8)	60.9	White: 80.2	19.5 (12.9)	C: 5.3 (0.7)[b] S: 4.5 (1.1)[b] R: 4.8 (0.9)[b] I: 4.9 (0.9)[b] TNSS: 19.5 (2.5)[b]
Ghimire, 2007	25	Beclomethasone dipropionate 400mcg					C: 2.2 S: 2.7 R: 2.6
	25	Azelastine 1120mcg	27[cd] Range: 12-69 IQR: 20-30	48	Unspecified		C: 1.8 S: 2.6 R: 2.7
Hampel, 2010	153	Fluticasone propionate 200mcg	38.1 Range: 12-74	66.2	White: 86.1 Black: 10.6 Asian: 2.0 Other: 1.3	18.4 Range: 3-57	TNSS: 18.3[b]

Author, Year	n	Drug, Dose/Day	Mean Age, years	Sex, % Female	Race, %	Disease Duration, years	Mean Baseline NSS[a]
	152	Azelastine 548mcg	39.5 Range: 12-74	63.8	White: 88.8 Black: 9.9 Asian: 0.0 Other: 1.3	19.0 Range: 2-61	TNSS: 18.1[b]
Kaliner, 2009	65	Fluticasone propionate 200mcg	32.48 (10.83) Range: 13-60	47.6	White: 56.3 Black: 18.8 Hispanic: 12.5 Asian: 10.9 Other: 1.6		TNSS: 6.49 (1.66)
	65	Olopatadine 4 puffs/nostril	38.14 (15.25) Range: 12-73	53.1	White: 56.3 Black: 23.4 Hispanic: 12.5 Asian: 6.3 Other: 1.6		TNSS: 6.72 (1.88)
Newson-Smith, 1997	83	Beclomethasone dipropionate 400mcg					
	83	Azelastine 1120mcg	35[cd]		Unspecified		
Pelucchi, 1995	15[e]	Beclomethasone dipropionate 200mcg	26 (8)	38.5	Unspecified		
	15[e]	Azelastine 560mcg	26 (9)	30	Unspecified		
Ratner, 2008	50	Fluticasone propionate 200mcg	37.4 Range: 12-72	70	White: 64.0 Black: 4.0 Hispanic: 26.0 Asian: 6.0 Other: 0	15.7 Range: 3-51	C: 5.5 (0.4)[b] S: 4.3 (1.3)[b] R: 5.0 (1.0)[b] I: 4.8 (1.3)[b] TNSS: 19.6 (2.7)[b]
	49	Azelastine 4 puffs/nostril	38.4 Range: 12-73	55.1	White: 73.5 Black: 10.2 Hispanic: 14.3 Asian: 0 Other: 2.0	19.2 Range: 3-50	C: 5.5 (0.5)[b] S: 4.5 (1.1)[b] R: 4.9 (0.8)[b] I: 4.8 (0.8)[b] TNSS: 19.7 (2.1)[b]

C = congestion; I = itching; n = patients randomized to comparator groups of interest; NSS = nasal symptom score; R = rhinorrhea; S = sneezing; TNSS = total nasal symptom score.

Values are presented as mean (standard deviation) unless otherwise noted.

[a] Individual symptoms rated on a scale from 0 (no symptoms) to 3 (severe symptoms) except as noted. TNSS ranges from 0 to 12.

[b] Individual symptoms rated on a scale from 0 (no symptoms) to 6 (severe symptoms). TNSS is the sum of AM and PM scores and ranges from 0 to 24.

[c] Values are medians.

[d] Overall demographic info provided only.

[e] Only patients randomized are reported.

Appendix Table C32. USPSTF quality assessment: intranasal corticosteroid versus nasal antihistamine

Author	Assembled comparable groups	Maintained comparable groups	Minimal follow-up loss	Measurements equal, valid, and reliable	Interventions clearly defined	Important outcomes considered	Appropriate analysis of results	Overall USPSTF rating
Carr, 2012 (Trial 1)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Carr, 2012 (Trial 2)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Carr, 2012 (Trial 3)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Ghimire, 2007	No	Uncertain	Uncertain	No	Yes	No	No	Poor
Hampel, 2010	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Kaliner, 2009	Yes	Uncertain	Yes	No	Yes	Yes	Yes	Poor
Newson-Smith, 1997	Yes	Yes	Uncertain	No	Yes	Yes	No	Poor
Pelucchi, 1995	No	Uncertain	Yes	Yes	Yes	Yes	No	Poor
Ratner, 2008	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good

USPSTF = United States Preventive Services Task Force.

Appendix Table C33. Nasal symptom outcomes: change from baseline–intranasal corticosteroid versus nasal antihistamine

Author, Year	Drug, Dose/Day	N/n	Time, weeks	Congestion	p	Rhinorrhea	p	Sneezing	p	Itching	p	TNSS	p
Carr, 2012 (Trial 1)	Fluticasone propionate 200mcg	207/207	2	-1.2 (1.3)	NR	-1.3 (1.4)	NR	-1.5 (1.4)	NR	-1.3 (1.3)	NR	-5.0 (4.7)[a]	NR
	Azelastine 548mcg	208/208		-0.9 (1.3)		-1.1 (1.4)		-1.3 (1.3)		-0.9 (1.3)		-4.1 (4.6)[a]	
Carr, 2012 (Trial 2)	Fluticasone propionate 200mcg	189/189	2	-1.1 (1.5)	NR	-1.3 (1.5)	NR	-1.4 (1.5)	NR	-1.2 (1.4)	NR	-5.0 (5.2)[a]	NR
	Azelastine 548mcg	194/194		-1.0 (1.3)		-1.0 (1.3)		-1.3 (1.5)		-1.1 (1.3)		-4.4 (4.6)[a]	
Carr, 2012 (Trial 3)	Fluticasone propionate 200mcg	450/450	2	-1.1 (1.2)	NR	-1.3 (1.4)	NR	-1.5 (1.5)	NR	-1.2 (1.3)	NR	-5.1 (4.7)[a]	NR
	Azelastine 548mcg	445/445		-1.0 (1.2)		-1.2 (1.4)		-1.4 (1.5)		-1.1 (1.4)		-4.5 (4.8)[a]	
Ghimire, 2007	Beclomethasone dipropionate 400mcg	25[bc]	2	-1.8[d]	NR	-2.2[d]	NR	-2.3[d]	NR				
	Azelastine 1120mcg	25[bc]		-1[d]		-2.2[d]		-2.2[d]					
Hampel, 2010	Fluticasone propionate 200mcg	153/151	2	-0.86	NR	-1.15	NR	-0.98	NR	-0.91	NR	-3.84 (4.76)[a]	NR
	Azelastine 548mcg	152/152		-0.75		-0.87		-0.86		-0.82		-3.25 (4.16)[a]	

Kaliner, 2009	**Fluticasone propionate 200mcg**	**65/65**	**2**	**-29.3[e]**	**NS**	**-40.3[e]**	**NS**	**-41[e]**	**NS**	**-42.8[e]**	**NS**	**3.1[d]**	**0.68**
	Olopatadine 4 puffs/nostril	65/65		-22.4[e]		-38.7[e]		-53.9[e]		-29.4[e]		3.2[d]	
Newson-Smith, 1997	Beclomethasone dipropionate 400mcg	83[bc]	2	-0.8	NS	-1	NS	-1	NS	-0.9	NS		
	Azelastine 1120mcg	83[bc]		-0.3		-0.6		-0.6		-0.5			
Pelucchi, 1995	Beclomethasone dipropionate 200mcg	15/13	2										NS
	Azelastine 560mcg	15/10											
Ratner, 2008	Fluticasone propionate 200mcg	50/49	2	-1.1 (1.2)	NR	-1.3 (1.2)	NR	-1.5 (1.5)	NR	-1.3 (1.5)	NR	-5.2 (4.6)[a]	NR
	Azelastine 4 puffs/nostril	49/49		-1.1 (1.5)		-1.1 (1.4)		-1.5 (1.0)		-1.1 (1.4)		-4.8 (4.3)[a]	
Ghimire, 2007	Beclomethasone dipropionate 400mcg	25[bc]	3	-0.3[f]	NR	-0.3[f]	NR	-0.2[f]	NR				
	Azelastine 1120mcg	25[bc]		-0.8[f]		-0.3[f]		-0.2[f]					
Pelucchi, 1995	Beclomethasone dipropionate 200mcg	15/13	3									-3.4[g]	NS
	Azelastine 560mcg	15/10										-4.5[g]	
Ghimire, 2007	Beclomethasone dipropionate 400mcg	25[bc]	4	-0.1[h]	NR	-0.1[h]	NR	-0.1[h]	NS				
	Azelastine 1120mcg	25[bc]		-0.6[h]		-0.1[h]		-0.1[h]					
Pelucchi, 1995	Beclomethasone dipropionate 200mcg	15/13	4									-2.7[i]	NS
	Azelastine 560mcg	15/10										-3.7[i]	
Pelucchi, 1995	Beclomethasone dipropionate 200mcg	15/13	5									-2.1[j]	NS
	Azelastine 560mcg	15/10										-3.5[j]	

N/n = Number of patients randomized/number of patients analyzed; NR = not reported; NS = non-significant; TNSS = total nasal symptom score.

Except as noted, entries for each symptom represent the mean change from baseline symptom score using a 0 (no symptom) to 3 (severe symptom) rating scale. TNSS ranges from 0 to 12.

Values in parentheses are standard deviations.

[a] TNSS is a sum of AM and PM scores ranging from 0 to 24.

[b] Overall demographic info provided only.

[c] Only patients randomized are reported.

[d] Values calculated by report author.

[e] Percent change from baseline.

[f] Endpoint for third week.

[g] Average for third week.

[h] Endpoint for fourth week.

[i] Average for fourth week.

[j] Average for fifth week.

Appendix Table C34. Eye symptom outcomes–intranasal corticosteroid versus nasal antihistamine

Author, Year	Drug, Dose/Day	N/n	Time, weeks	Outcome	Baseline Mean (SD)	Change from Baseline	p
Carr, 2012 (Trial 1) (scale 0-18)	Fluticasone propionate 200mcg	207/207	2	TOSS (scale 0-18)	11.4 (4.4)	-2.6 (3.5)	NR
	Azelastine 548mcg	208/208			11.5 (4.5)	-2.8 (3.8)	
Carr, 2012 (Trial 2) (scale 0-18)	Fluticasone propionate 200mcg	189/189	2	TOSS (scale 0-18)	12.0 (3.8)	-2.7 (3.6)	NR
	Azelastine 548mcg	194/194			11.8 (3.9)	-3.0 (3.3)	
Carr, 2012 (Trial 3) (scale 0-18)	Fluticasone propionate 200mcg	450/450	2	TOSS (scale 0-18)	12.3 (3.6)	-2.8 (3.5)	NR
	Azelastine 548mcg	445/445			12.4 (4.0)	-3.0 (3.8)	
Hampel, 2010 (scale 0-18)	Fluticasone propionate 200mcg	153/151	2	TOSS (scale 0-18)		-2.17	NR
	Azelastine 548mcg	152/152				-2.62	
Kaliner, 2009 (scale 0-9)	Fluticasone propionate 200mcg	65/65	2	TOSS (scale 0-9)	4.18 (1.84)	-1.7[a]	0.6064
	Olopatadine 4 puffs/nostril	65/65			4.25 (2.05)	-1.64[a]	

N/n = Number of patients randomized to comparator groups of interest/number of patients analyzed; NR = not reported; TOSS = total ocular symptom score.

Values in parentheses are standard deviations. TOSS is the sum of scores for 3 ocular symptoms (itching, tearing, and redness).

[a] Values calculated by report author.

Appendix Table C35. Quality of life outcomes–intranasal corticosteroid versus nasal antihistamine

Author, Year	Drug, Dose/Day	N/n	Time, weeks	Outcome	Baseline Mean (SD)	Change from Baseline	p
Hampel, 2010	Fluticasone propionate 200mcg	153/151	2	RQLQ		-1.43	NR
	Azelastine 548mcg	152/152				-1.17	
Ratner, 2008	Fluticasone propionate 200mcg	50/49	2	RQLQ	3.95 (1.14)	-1.47	NR
	Azelastine 4 puffs/nostril	49/49			3.66 (1.13)	-1.21	

N/n = Number of patients randomized to comparator groups of interest/number of patients analyzed; NR = not reported; RQLQ = Rhinitis Quality of Life Questionnaire.

Intranasal Corticosteroid Versus Nasal Cromolyn

Appendix Table C36. Trial description: intranasal corticosteroid versus nasal cromolyn

Author, Year	Location, Site(s)	Enrollment/ Treatment Duration	Funding/ Disclosures	N	Inclusion Criteria	Exclusion Criteria[a]	Rescue Medication Use	Objective Diagnosis	Run in Period	Pollen Count	Patient Blinding	Assessor Blinding
Bjerrum, 1985	Europe Single	3 weeks	Industry NR	43	Minimum SAR duration	Other meds Chronic asthma Pregnancy Infection Deformities	Yes	•	•		•	•
Bousquet, 1993	Europe Multiple	6 weeks	NR Yes	218	Minimum SAR duration	SAR meds/- Pregnancy Infection	Yes	•		•	•	•
Lange, 2005	Europe Single	May 2003 4 weeks	Industry NR	83	Minimum SAR severity and duration	SAR meds/+ Other meds Chronic asthma Infection Deformities	Yes	•	•	•	Open label trial	Open label trial
Welsh, 1987	N.America	July 1984 8 weeks	Industry NR	90	Minimum SAR duration	Pregnancy Deformities	Yes	•	•	•		•

N = Patients randomized to comparator groups of interest; NR = not reported; SAR = seasonal allergic rhinitis.

[a] +, -, or NR indicates whether FDA-recommended washout periods were required (+), were not required (-), or were not reported (NR) for restricted SAR medications prior to trial entry.

Appendix Table C37. Patient characteristics: intranasal corticosteroid versus nasal cromolyn

Author, Year	Drug Dose/Day	N	Mean Age, years	Sex, % female	Race, %	Disease Duration, Years	Mean Baseline TNSS[a]
Bjerrum, 1985	Budesonide 400 mcg[b]	22	29 Range: 15-55	48.9[C]	Unspecified		1.99
	Cromolyn 26 mg[d]	21					3.29
Bousquet, 1993	Fluticasone propionate, 200 mcg[g]	110	32 (12)		Unspecified		
	Cromolyn 20.8 mg[e]	108	32 (12)		Unspecified		
Lange, 2005	Mometasone furoate 200 mcg[e]	41	35.5 (9.6)	56.1	Unspecified		
	Cromolyn 22.4 mg[f]	42	33.5 (8.2)	66.7	Unspecified		
Welsh, 1987	Beclomethasone dipropionate 336 mcg[b]	30	27 Range: 13-50	30.0	Unspecified		
	Flunisolide 200 mcg[b]	30	27 Range: 14-44	26.7	Unspecified		
	Cromolyn 41.6 mg[e]	30	30 Range: 12-48	33.3	Unspecified		

N = Patients randomized to comparator groups of interest; TNSS = total nasal symptom score.

Values are presented as mean (standard deviation) unless otherwise noted.

[a] Individual symptoms rated on a scale from 0 (no symptoms) to 3 (severe symptoms). TNSS ranges from 0 to 12.

[b] Twice daily.

[C] Overall demographic info provided only.

[d] Five times daily.

[e] Once daily.

[f] Four times daily.

[g] Every morning.

Appendix Table C38. USPSTF quality assessment: intranasal corticosteroid versus nasal cromolyn

Author, year	Assembled comparable groups	Maintained comparable groups	Minimal follow-up loss	Measurements equal, valid, and reliable	Interventions clearly defined	Important outcomes considered	Appropriate analysis of results	Overall USPSTF rating
Bjerrum, 1985	No	Yes	Yes	Yes	Yes	Yes	Yes	Poor
Bousquet, 1993	No	No	No	Yes	No	Yes	No	Poor
Lange, 2005	Yes	Yes	Yes	No	Yes	Yes	Yes	Poor
Welsh, 1987	Yes	No	No	No	No	Yes	Yes	Poor

USPSTF = United States Preventive Services Task Force.

Appendix Table C39. Nasal symptom outcomes: change from baseline–intranasal corticosteroid versus nasal cromolyn

Author, Year	Drug, Dose/Day	N/n	Time, weeks	Congestion	p	Rhinorrhea	p	Sneezing	p	Itching	p	TNSS	p
Bjerrum, 1985	Budesonide 400 mcg[a]	22/21	2	-0.22[a]	<0.05	-0.35[a]	<0.01	-0.10[a]	<0.01	-0.06[a]	<0.01	-0.73[a]	<0.01
	Cromolyn 26 mg[c]	21/21		0.13[a]		0.24[a]		0.28[a]		0.15[a]		0.80[a]	
Bjerrum, 1985	Budesonide 400 mcg[a]	22/21	3	-0.15[a]	NS	-0.24[a]	<0.05	-0.01[a]	<0.02	-0.01[a]	<0.02	-0.39[a]	<0.01
	Cromolyn 26 mg[c]	21/21		0.13[a]		0.25[a]		0.26[a]		-0.16[a]		0.80[a]	
Bousquet, 1993	Fluticasone propionate 200 mcg[f]	110/73	6		0.01		0.01		0.02		0.03		
	Cromolyn 20.8 mg[e]	108/87											
Lange, 2005	Mometasone furoate 200 mcg[d]	41/40	4		0.05[b]		<0.01[b]		<0.01[b]		<0.01[b]		<0.01[b]
	Cromolyn, 22.4 mg[e]	42/42											

N/n = Number of patients randomized/number of patients analyzed; NS, not significant; TNSS = total nasal symptom score.

Entries for each symptom represent the mean change from baseline symptom score using a 0 (no symptom) to 3 (severe symptom) rating scale. TNSS ranges from 0 to 12.

[a] Calculated by report author using pre/post data.

[b] Comparisons are between final outcome scores, not change in scores.

Appendix Table C40. Quality of life outcomes: intranasal corticosteroid versus nasal cromolyn

Author, year	Drug, Dose/Day	N/n	Time, weeks	PGA	Result	p
Lange, 2005	Mometasone furoate 200 mcg	41/40	4	% reporting very good/good treatment efficacy[a]	92.3	<0.001[b]
	Cromolyn 22.4 mg	42/42			62.4	
Welsh, 1987	Beclomethasone dipropionate 336 mcg	30/28	8	% reporting substantial symptom control[c]	75.0	<0.001[b]
	Flunisolide 200 mcg	30/30			80.0	
	Cromolyn 41.6 mg	30/28			55.2	

N/n = Number of patients randomized/number of patients analyzed; PGA = patient global assessment.

[a] 4-point scale: very good, good, slight, insufficient.

[b] Statistical testing is over all PGA categories.

[c] 3-point scale: substantial, some, none.

Intranasal Corticosteroid Versus Oral Leukotriene Receptor Antagonist

Appendix Table C41. Trial description: intranasal corticosteroid versus leukotriene receptor antagonist

Author, Year	Location/ Site(s)	Enrollment/ Treatment Duration	Funding/ Author Industry Disclosures	N	Inclusion Criteria	Exclusion Criteria[a]	Rescue Medication Use	Objective Diagnosis	Run-in Period	Pollen Counts Measured	Patient Blinding	Assessor Blinding
Lu, 2009 (Trial 1)	N.America Multiple	April 1998 2 weeks	Industry/ Industry	285	Minimum SAR severity and duration		No	•	•		•	•
Martin, 2006	N.America Multiple	December 2001 2 weeks	Industry/ Industry	736	Minimum SAR severity and duration	SAR meds/NR Other meds Pregnancy Deformities	No	•	•		•	•
Nathan, 2005	N.America Multiple	4 weeks	Industry/ Industry	573	Minimum SAR severity and duration	SAR meds/+ Pregnancy Infection Deformities	Yes	•	•		•	•
Pullerits, 2002	Europe	03/1999 8 weeks	Industry/	29	Minimum SAR duration	Other meds Pregnancy Infection	Yes	•	•	•	•	•

Author, Year	Location/ Site(s)	Enrollment/ Treatment Duration	Funding/ Author Industry Disclosures	N	Inclusion Criteria	Exclusion Criteria[a]	Rescue Medication Use	Objective Diagnosis	Run-in Period	Pollen Counts Measured	Patient Blinding	Assessor Blinding
Ratner, 2003	N.America Multiple	December 2001 2.1 weeks	Industry/ Industry	705	Minimum SAR severity and duration	SAR meds Other meds Pregnancy Deformities	No	•	•		•	•

N = patients randomized to comparator groups of interest; SAR = seasonal allergic rhinitis.

[a] +, -, or NR indicates whether FDA-recommended washout periods were required (+), were not required (-), or were not reported (NR) for restricted SAR medications prior to trial entry.

Appendix Table C42. Patient characteristics: intranasal corticosteroid versus leukotriene receptor antagonist

Author, Year	n	Drug Dose/Day	Mean Age, years	Sex, % Female	Race, %	Disease Duration, years	Mean Baseline NSS
Lu, 2009 (Trial 1)	173	Beclomethasone dipropionate 400 mcg	34.1(13.3)	61.3	White: 79.2 Black: 8.1 Hispanic: 8.1 Other: 4.6	17.9 (12.2)	TNSS: 2.03[a]
	112	Montelukast 10 mg	35.6 (13.1)	62.5	White: 79.5 Black: 5.4 Hispanic: 8.9 Other: 6.3	18.8 (10.7)	TNSS: 2.06[a]
Martin, 2006	367	Fluticasone propionate 200 mcg	39.1 (14.0)	64	Unspecified	15.1 (11.0)	C: 78.0 (0.8)[b] R: 74.9 (0.9)[b] S: 71.9 (1.0)[b] I: 73.3 (0.9)[b] TNSS: 298.2 (2.8)[c]
	369	Montelukast 10 mg	40.3 (13.9)	62	Unspecified	15.2 (11.8)	C: 78.7 (0.8)[b] R: 76.3 (0.9)[b] S: 72.2 (1.0)[b] I: 74.3 (0.9)[b] TNSS: 301.5 (2.8)[c]
Nathan, 2005	291	Fluticasone propionate 200 mcg	35.8 (12.6)	67	White: 76 Black: 11 Hispanic: 11 Asian: 1 Other: 1		C: 71.5 (1.3)[b] R: 65.7 (1.5)[b] S: 59.8 (1.6)[b] I: 63.7 (1.5)[b] TNSS: 260.7 (4.6)[c]
	282	Montelukast 10 mg	34.4 (13.3)	66	White: 77 Black: 11 Hispanic: 8 Asian: 2 Other: 1		C: 73.0 (1.3)[b] R: 66.6 (1.5)[b] S: 62.7 (1.7)[b] I: 66.8 (1.6)[b] TNSS: 269.1 (4.7)[c]
Pullerits, 2002	13	Fluticasone propionate 200 mcg	28.4 (6.4)	46.2	Unspecified	≤5 years: 8% >5 years: 92%	TNSS: 1.5 (1.4)[d]

Author, Year	n	Drug Dose/Day	Mean Age, years	Sex, % Female	Race, %	Disease Duration, years	Mean Baseline NSS
	16	Montelukast 10 mg	28.3 (8.0)	37.5	Unspecified	≤5 years: 25% >5 years: 75%	TNSS: 1.9 (2.1)[d]
Ratner, 2003	353	Fluticasone propionate 200 mcg	38.3 (13.3)	61	Unspecified	Mean: 15.7 (11.8)	C: 77.5 (0.8)[b] R: 75.2 (0.9)[b] S: 71.0 (1.0)[b] I: 72.6 (0.9)[b] TNSS: 296.2 (2.7)[c]
	352	Montelukast 10 mg	38.1 (13.3)	63	Unspecified	Mean: 15.4 (12.1)	C: 78.3 (0.8)[b] R: 75.9 (0.9)[b] S: 72.0 (1.0)[b] I: 72.7 (0.9)[b] TNSS: 298.9 (2.7)[c]

C = Congestion; I = itching; n = patients randomized to comparator groups of interest; R = rhinorrhea; S = sneezing; TNSS = total nasal symptom score.

Values are presented as mean (standard deviation) unless otherwise noted.

[a] TNSS scale 0 (no symptoms) to 3 (severe symptoms) using symptom categories for each symptom, which were then averaged by the investigators.

[b] Individual symptoms scored 0 (no symptoms) to 100 (severe symptoms) using a VAS.

[c] TNSS scored 0-400, sum of each individual 0 to 100 VAS score.

[d] TNSS scored 0 to 16, a summation of each individual symptom scored 0 (no symptoms) to 4 (severe symptoms).

Appendix Table C43. USPSTF quality assessment: intranasal corticosteroid versus leukotriene receptor antagonist

Author, year	Assembled comparable groups	Maintained comparable groups	Minimal follow-up loss	Measurements equal, valid, and reliable	Interventions clearly defined	Important outcomes considered	Appropriate analysis of results	Overall USPSTF rating
Lu, 2009	Yes	Uncertain	Yes	Uncertain	Yes	Yes	No	Poor
Martin, 2006	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Nathan, 2005	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Pullerits, 2002	Yes	Yes	Uncertain	Yes	Yes	Yes	No	Poor
Ratner, 2003	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good

Appendix Table C44. Nasal symptom outcomes: change from baseline–intranasal corticosteroid versus leukotriene receptor antagonist

Author, Year	Drug, Dose/Day	N/n	Time, weeks	Congestion	p	Rhinorrhea	p	Sneezing	p	Itching	p	TNSS	p
Lu, 2009 (Trial 1)	Beclomethasone dipropionate 400 mcg	173/172	2									-0.7 (-0.78, -0.61)	≤0.01
	Montelukast 10 mg	112/111	2									-0.36 (-0.46, -0.25)	

Author, Year	Drug, Dose/Day	N/n	Time, weeks	Congestion	p	Rhinorrhea	p	Sneezing	p	Itching	p	TNSS	p
Martin, 2006	Fluticasone propionate 200 mcg	367/364	2	-31.1 (1.2)	<0.01	-32.9 (1.2)	<0.01	-33.5 (1.2)	<0. 01	-32.8 (1.2)	<0.001	-130.2 (4.7)	<0.01
	Montelukast 10 mg	369/366	2	-23.1 (1.2)		-23.5 (1.2)		-24.9 (1.2)		-25.0 (1.2)		-96.6 (4.7)	
Nathan, 2005	Fluticasone propionate 200 mcg	291/291	2	-24.0 (1.6)	<0.01	-26.5 (1.6)	<0.01	-25.4 (1.6)	<0.01	-24.0 (1.6)	<0.001	-99.1 (5.8)	<0.01
	Montelukast 10 mg	282/282	2	-16.7 (1.6)		-18.7 (1.7)		-19.1 (1.7)		-18.7 (1.6)		-73.0 (6.0)	
Pullerits, 2002	Fluticasone propionate 200 mcg	13[a]	2									-0.1 [c]	NS
	Montelukast 10 mg	16[a]	2									0.7 [c]	
Ratner, 2003	Fluticasone propionate 200 mcg	353/353	2	-31.4 (1.2)	<0.01	-32.6 (1.2)	<0.01	-33.7 (1.2)	<0.01	-32.7 (1.2)	<0.001	-130.3 (4.7)	<0. 01
	Montelukast 10 mg	352/352	2	-22.7 (1.2)		-24.3 (1.2)		-23.7 (1.2)		-23.2 (1.2)		-94.0 (4.7)	
Nathan, 2005	Fluticasone propionate 200 mcg	291/291	4	-29.0 (1.7)	<0.01	-30.7 (1.7)	<0.01	-29.3 (1.7)	<0.01	-28.8 (1.7)	<0.001	-117.0 (6.2)	<0.01
	Montelukast 10 mg	282/282	4	-20.7 (1.7)		-22.7 (1.7)		-23.1 (1.7)		-22.8 (1.7)		-89.1 (6.4)	
Pullerits, 2002	Fluticasone propionate 200 mcg	13[a]	5 [b]									1.1 [d]	NS
	Montelukast 10 mg	16[a]	5[b]									2.5 [d]	
Pullerits, 2002	Fluticasone propionate 200 mcg	13[a]	8 [c]									-0.4 [d]	<0.05
	Montelukast 10 mg	16[a]	8[c]									0.3 [d]	

N/n = Number of patients randomized/number of patients analyzed; NS = non-significant; TNSS = total nasal symptom score.

Values are mean (standard error) change from baseline. Entries for each outcome represent the mean change from baseline symptom score. Martin, 2006, Nathan, 2005, and Ratner, 2003 used a 0 (no symptoms) to 100 (most severe symptoms) VAS to rate each symptom, then summed the symptom scores for TNSS (maximum, 400). Pullerits, 2002 used a 0 (no symptoms) to 4 (severe symptoms) categorical scale for each symptom, then summed the scores for TNSS (maximum, 16). Lu, 2009 used a 0 (no symptoms) to 3 (severe symptoms) to rate each symptom, then averaged the symptom scores for TNSS (maximum, 3).

[a] Only patients randomized are reported.

[b] Average for interval from 3-5 weeks.

[c] Average for interval from 6-8 weeks.

[d] Calculated by report author from pre/post data reported.

Appendix Table C45. Quality of life outcomes: intranasal corticosteroid versus leukotriene receptor antagonist

Author, year	Drug, Dose/Day	N/n	Time, weeks	Outcome	Baseline mean	End of treatment	p
Martin, 2006	Fluticasone propionate 200 mcg	367/364	2	% patients reporting significant or better improvement[a]		42	<0.001
Martin, 2006	Montelukast 10 mg	369/366				24	
Ratner, 2003	Fluticasone propionate 200 mcg	353/353	2	% patients reporting significant improvement[a]		43	<0.001
Ratner, 2003	Montelukast 10 mg	352/352				25	
Nathan, 2005	Fluticasone propionate 200 mcg	291/291	4	% reporting satisfied or better with treatment[a]		69	<0.001
Nathan, 2005	Montelukast 10 mg	282/282				55	

N/n = Number of patients randomized/number of patients analyzed.

[a] 7-point Likert Scale.

Appendix Table C46. Asthma outcomes–intranasal corticosteroid versus leukotriene receptor antagonist

Author, year	Drug, Dose/Day	N/n	Time, weeks	Outcome	Baseline mean (SE)	End of treatment	Mean Change from Baseline	p
Nathan, 2005	Fluticasone propionate 200 mcg	291/250	4	Morning Peak Expiratory Flow, L/min	361.3 (7.4)		+ 34.0 (4.3)	NS
	Montelukast 10 mg	282/247			367.2 (7.4)		+ 31.6 (4.3)	
Nathan, 2005	Fluticasone propionate 200 mcg	291/250	4	Evening Peak Expiratory Flow, L/min	375.3 (7.7)		+ 24.9 (4.0)	NS
	Montelukast 10 mg	282/247			380.8 (7.7)		+ 23.1 (4.0)	
Nathan, 2005	Fluticasone propionate 200 mcg	291/250	4	Symptom Free Days, %	5.3 (1.0)	20.6 (3.3)		NS
	Montelukast 10 mg	282/247			6.8 (1.0)	23.4 (3.2)		
Nathan, 2005	Fluticasone propionate 200 mcg	291/250	4	Days Free of Albuterol Rx, %	17.4 (2.2)	34.8 (3.5)		NS
	Montelukast 10 mg	282/247			18.3 (2.3)	36.4 (3.5)		
Nathan, 2005	Fluticasone propionate 200 mcg	291/250	4	% of patients experiencing asthma exacerbations[a]		<1		NR

Author, year	Drug, Dose/Day	N/n	Time, weeks	Outcome	Baseline mean (SE)	End of treatment	Mean Change from Baseline	p
	Montelukast 10 mg	282/247				1		

N/n = Number of patients randomized/number of patients analyzed; NR = not reported; NS = non-significant; SE = standard error.

[a] Defined by any asthma-related event that required treatment with asthma medications beyond study medications.

Combination Oral Selective Antihistamine Plus Intranasal Corticosteroid Versus Oral Selective Antihistamine

Appendix Table C47. Trial description: combination oral selective antihistamine plus intranasal corticosteroid versus oral selective antihistamine

Author, Year	Location, Site(s)	Enrollment/ Treatment Duration	Funding/ Author Industry Disclosures	N	Inclusion Criteria	Exclusion Criteria	Rescue Rx	Objective Diagnosis	Run in Period	Pollen Count	Patient Blinding	Assessor Blinding
Anolik, 2008	N.America Multiple	March 1995 2.1 weeks	NR Industry	350	Minimum SAR severity and duration	Chronic asthma Immunotherapy Infection Deformities	No	•	•	•	•	•
Ratner, 1998	N.America Multiple	2 weeks	Industry Industry	300	Minimum SAR severity and duration	SAR meds/+ Pregnancy Infection Deformities	No	•	•		•	•
Wilson, 2000	Europe Single	June 1998 4 weeks	Academia NR	27	Minimum SAR severity	Infection	No	•	•	•	•	

N = Patients randomized to comparator groups of interest; NR = not reported.

[a] +, -, or NR indicates whether FDA-recommended washout periods were required (+), were not required (-), or were not reported (NR) for restricted SAR medications prior to trial entry.

Appendix Table C48. Patient characteristics: combination oral selective antihistamine plus intranasal corticosteroid versus oral selective antihistamine

Author, Year	Drug, Dose/Day	N	Mean Age, years	Sex, % female	Race, %	Disease Duration, years	Mean Baseline NSS[a]
Anolik, 2008	Loratadine 10 mg/ Mometasone furoate 200 mcg	169	26 Range: 11-62	50.3	Unspecified	Mean: 14 Range: 2-51	C: 2.3 R: 2.1 S: 1.8 I: 1.8 TNSS: 7.9 (2.0)
	Loratadine 10 mg	181	25 Range: 12-65	50.3	Unspecified	Mean: 14 Range: 2-60	C: 2.3 R: 2.1 S: 1.7 I: 1.9 TNSS: 7.9 (2.2)

Author, Year	Drug, Dose/Day	N	Mean Age, years	Sex, % female	Race, %	Disease Duration, years	Mean Baseline NSS[a]
Ratner, 1998	Loratadine 10 mg/ Fluticasone propionate 200 mcg	150	42.2 Range: 15-78	51	White: 80 Hispanic: 17 Other: 3		TNSS: 290
	Loratadine 10 mg	150	40.1 Range: 15-70	54	White: 73 Hispanic: 19 Other: 8		TNSS: 300
Wilson, 2000	Cetirizine 10 mg/ Mometasone furoate 200 mcg	14	31 (2.7)	64.3	Unspecified		TNSS: 4.8 (0.7)
	Cetirizine 10 mg	13	30 (2.5)	76.9	Unspecified		TNSS: 5.3 (0.8)

C = Congestion; I = itching; n= patients randomized or assigned to comparator groups of interest; NSS = nasal symptom score; R = rhinorrhea; S = sneezing; TNSS = total nasal symptom score.

Values are presented as mean (standard deviation) unless otherwise noted.

[a] Individual symptoms rated on a scale from 0 (no symptoms) to 3 (severe symptoms) for each individual symptom. Morning and evening scores were summed (maximum individual symptom = 6, maximum TNSS = 24).

Appendix Table C49. USPSTF quality assessment: combination oral selective antihistamine plus intranasal corticosteroid versus oral selective antihistamine

Author, year	Assembled comparable groups	Maintained comparable groups	Minimal follow-up loss	Measurements equal, valid, and reliable	Interventions clearly defined	Important outcomes considered	Appropriate analysis of results	Overall USPSTF rating
Anolik, 2008	Yes	Yes	Yes	Yes	Yes	Yes	No	Poor
Ratner, 1998	Yes	Yes	Yes	Yes	Yes	Uncertain	Yes	Fair
Wilson, 2000	Yes	Yes	Uncertain	Yes	Yes	Yes	Yes	Fair

USPSTF = United States Preventive Services Task Force.

Appendix Table C50. Nasal symptom outcomes: change from baseline–combination oral selective antihistamine plus intranasal corticosteroid versus oral selective antihistamine

Author, Year	Drug, Dose/Day	N/n	Time, weeks	Congestion[a]	p versus Combo	Rhinorrhea[a]	p versus Combo	Sneezing[a]	p versus Combo	Itching[a]	p versus Combo	TNSS[a]	p versus Combo
Anolik, 2008	Loratadine 10 mg/ Mometasone furoate 200 mcg	169/166	2[b]	-0.7		-0.7		-0.8		-0.7		-3.0 (2.0)	
	Loratadine 10 mg	181/175		-0.4	<0.05	-0.4	<0.05	-0.6	<0.05	-0.6	<0.05	-1.9 (2.2)	<0.01
Ratner, 1998	Loratadine 10 mg/ Fluticasone propionate 200	150/150	2[c]									-180[e]	

Author, Year	Drug, Dose/Day	N/n	Time, weeks	Congestion[a]	p versus Combo	Rhinorrhea[a]	p versus Combo	Sneezing[a]	p versus Combo	Itching[a]	p versus Combo	TNSS[a]	p versus Combo
	mcg												
	Loratadine 10 mg	150/150										-90[e]	<0.001
Wilson, 2000	Cetirizine 10 mg/ Mometasone furoate 200 mcg	14	2[c]									-3.0[e]	
	Cetirizine 10 mg	13										-1.8[e]	NS
Wilson, 2000	Cetirizine 10 mg/ Mometasone furoate 200 mcg	14	4[d]									-3.7[e]	
	Cetirizine 10 mg	13										-2.8[e]	NS

N/n = Number of patients randomized/number of patients analyzed; TNSS = total nasal symptom score.

[a] All analyses are mean change from baseline.

[b] All symptom assessments averaged over the treatment duration.

[c] Analysis compares change from baseline to symptom assessments averaged over the second week of treatment.

[d] Analysis compares change from baseline to symptom assessments averaged over the fourth week of treatment.

[e] Calculated by study authors from reported means.

Appendix Table C51. Eye symptom outcomes: change from baseline–combination oral selective antihistamine plus intranasal corticosteroid versus oral selective antihistamine

Author, Year	Drug, Dose/Day	N/n	Time, weeks	Outcome	Baseline mean	Change from baseline	p versus Combo
Anolik, 2008	Loratadine 10 mg/ Mometasone furoate 200 mcg	169/166	2	Individual symptoms [a]	NR	NR	
	Loratadine 10 mg	181/175			NR	NR	<0.05
Wilson, 2000	Cetirizine 10 mg/ Mometasone furoate 200 mcg	14	2	TOSS (scale 0-3)	1.6	-1[b]	
	Cetirizine 10 mg	13			2.4	-1.2[b]	NS
Wilson, 2000	Cetirizine 10 mg/ Mometasone furoate 200 mcg	14	4	TOSS (scale 0-3)	1.6	-1.2[b]	
	Cetirizine 10 mg	13			2.4	-1.4[b]	NS

N/n = Number of patients randomized/number of patients analyzed; NR = not reported; NS = non-significant; TOSS = total ocular symptom score.

[a] Includes itchy eyes, watery eyes and red eyes, assessed daily by patients on a 0 (no symptoms) to 3 (severe symptoms) scale. With the exception of stating that all symptoms were and were not statistically different from combination therapy, no assessment means or p values were reported.

[b] Mean differences calculated by study authors.

Appendix Table C52. Quality of life outcomes: combination oral selective antihistamine plus intranasal corticosteroid versus oral selective antihistamine

Author, year	Drug, Dose/Day	N/n	Time, weeks	Outcome	Baseline mean	Change from Baseline	p versus Combo
Ratner, 1998	Loratadine 10 mg/ Fluticasone propionate 200 mcg	150/150	2	RQLQ[a]	4.0 (0.1)	-2.3 (0.1)	<0.001
	Loratadine 10 mg	150/150			4.1 (0.1)	-1.3 (0.1)	
Ratner, 1998	Loratadine 10 mg/ Fluticasone propionate 200 mcg	150/150	2	Global Assessment[b]		75	<0.001
	Loratadine 10 mg	150/150				43	
Wilson, 2000	Cetirizine 10 mg/ Mometasone furoate 200 mcg	14/	8	Global Assessment[c]	NR	NR	NS
	Cetirizine 10 mg	13/			NR	NR	

N/n = Number of patients randomized/number of patients analyzed; NR = not reported; NS = non-siginificant; RQLQ = Rhinitis Quality of Life Questionnaire.

[a] Scores range from 0 (no impairment) to 6 (severely impaired). The minimum clinically important difference is 0.5 points.

[b] Patient rated overall response to therapy after two weeks of treatment. Percent reporting moderate or significant improvement. P value describes overall test comparing groups over the full 7 point Likert scale.

[c] Patients recorded extent to which their symptoms interfered with their daily activity on an 11-point scale (0 = no interference , 10 = maximal interference)

Combination Oral Selective Antihistamine Plus Intranasal Corticosteroid Versus Intranasal Corticosteroid

Appendix Table C53. Trial description: oral selective antihistamine plus intranasal corticosteroid versus intranasal corticosteroid

Author, Year	Location, Site(s)	Enrollment/ Treatment Duration	Funding/ Author Industry Disclosures	N	Inclusion Criteria	Exclusion Criteria[a]	Rescue Medication Use	Objective Diagnosis	Run in Period	Pollen Count	Patient Blinding	Assessor Blinding
Anolik, 2008	N.America Multiple	March 1995 2.1 weeks	NR Industry	345	Minimum SAR severity and duration	Chronic asthma Immunotherapy Infection Deformities	No	•	•	•	•	•
Barnes, 2006	Europe Single	June 2004 2 weeks	Academia Industry	62		SAR meds/- Pregnancy Deformities	Yes	•	•	•	•	•

Benincasa, 1994	Europe Multiple	May 1990 8 weeks	Industry Industry	454	Minimum SAR severity and duration	SAR meds/+ Other meds Pregnancy Infection Deformities	Yes				•	•
Di Lorenzo, 2004	Europe Multiple	April 2001 6 weeks	Health system[b] NR	40	Minimum SAR severity and duration	SAR meds/+ Chronic asthma Pregnancy Infection Deformities	Yes	•		•	•	•
Ratner, 1998	N.America Multiple	2 weeks	Industry Industry	300	Minimum SAR severity and duration	SAR meds/+ Pregnancy Infection Deformities	No	•	•		•	•

N = Patients randomized to comparator groups of interest; NR = not reported; SAR = seasonal allergic rhinitis.

[a] +, -, or NR indicates whether FDA-recommended washout periods were required (+), were not required (-), or were not reported (NR) for restricted SAR medications prior to trial entry.

[b] Ministero Italiano Universita` e Ricerca (MIUR).

Appendix Table C54. Patient characteristics: oral selective antihistamine plus intranasal corticosteroid versus intranasal corticosteroid

Author, Year	Drug, Dose/Day	N	Mean Age, years	Sex, % female	Race, %	Disease Duration, years	Mean Baseline NSS[a]
Anolik, 2008	Loratadine 10 mg/ Mometasone furoate 200 mcg	169	26 Range: 11-62	50.3	Unspecified	14 Range: 2-51	C: 2.3 R: 2.1 S: 1.8 I: 1.8 TNSS: 7.9 (2.0)
	Mometasone furoate 200 mcg	176	26 Range: 12-71	50.6	Unspecified	13 Range: 2-56	C: 2.2 R: 2.1 S: 1.7 I: 1.7 TNSS: 7.8 (2.5)
Barnes, 2006	Levocetirizine 5 mg/ Fluticasone propionate 200 mcg	31	44.9	59.3	Unspecified		C: 1.24 (0.79) R: 1.00 (0.78) S: 1.31 (0.72) I: 1.16 (0.79) TNSS: 4.56 (2.58)
	Fluticasone propionate 200 mcg	31	44.9	59.3	Unspecified		C: 1.24 (0.79) R: 1.00 (0.78) S: 1.31 (0.72) I: 1.16 (0.79) TNSS: 4.56 (2.58)
Benincasa, 1994	Cetirizine 10 mg/ Fluticasone propionate 200 mcg	227	30 Range: 12-66	56	Unspecified	<10: 48% >10: 52%	
	Fluticasone propionate 200 mcg	227	31 Range: 12-80	58	Unspecified	<10: 46% >10: 54%	
Di Lorenzo, 2004	Cetirizine 10 mg/	20	32.8	60	Unspecified	2-4 years: 55%	

Author, Year	Drug, Dose/Day	N	Mean Age, years	Sex, % female	Race, %	Disease Duration, years	Mean Baseline NSS[a]
	Fluticasone propionate 200 mcg		Range: 14-48			5-9 years: 30% 10+ years:15%	
	Fluticasone propionate 200 mcg	20	30.5 Range: 15-50	40	Unspecified	2-4 years: 55% 5-9 years: 25% 10+ years:20%	
Ratner, 1998	Loratadine 10 mg/ Fluticasone propionate 200 mcg	150	42.2 Range: 15-78	51	White: 80 Hispanic: 17 Other: 3		TNSS: 290[b]
	Fluticasone propionate 200 mcg	150	40.7 Range: 13-80	55	White: 78 Hispanic: 15 Other: 7		TNSS: 290[b]

C = Congestion; I = itching; n= patients randomized or assigned to comparator groups of interest; NSS = nasal symptom score; R = rhinorrhea; S = sneezing; TNSS = total nasal symptom score.

Values are presented as mean (standard deviation) unless otherwise noted.

[a] Except as noted, individual symptoms rated on a scale from 0 (no symptoms) to 3 (severe symptoms). Scores were summed (maximum individual symptom = 3, maximum TNSS = 12).

[b] Individual symptoms scored on a 0-100 VAS. TNSS scale is 0-400.

Appendix Table C55. USPSTF quality assessment: oral selective antihistamine plus intranasal corticosteroid versus intranasal corticosteroid

Author, year	Assembled comparable groups	Maintained comparable groups	Minimal follow-up loss	Measurements equal, valid, and reliable	Interventions clearly defined	Important outcomes considered	Appropriate analysis of results	Overall USPSTF rating
Anolik, 2008	Yes	Yes	Yes	Yes	Yes	Yes	No	Poor
Barnes, 2006	Yes	Yes	Yes	Yes	Yes	Yes	No	Poor
Benincasa, 1994	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Di Lorenzo, 2004	No	Yes	Yes	Yes	Yes	Yes	Yes	Poor
Ratner, 1998	Yes	Yes	Yes	Yes	Yes	Uncertain	Yes	Fair

USPSTF = United States Preventive Services Task Force.

Appendix Table C56. Nasal symptom outcomes: change from baseline–oral selective antihistamine plus intranasal corticosteroid versus intranasal corticosteroid

Author, Year	Drug, Dose/Day	N/n	Time, weeks	Congestion[a]	p versus Combo	Rhinorrhea[a]	p versus Combo	Sneezing[a]	p versus Combo	Itching[a]	p versus Combo	TNSS[a]	p versus Combo
Anolik, 2008	Loratadine 10 mg/ Mometasone furoate 200 mcg	169/ 166	2[b]	-0.7		-0.7		-0.8		-0.7		-3.0 (2.0)	
	Mometasone furoate 200 mcg	176/ 166		-0.7	NS	-0.7	NS	-0.7	NS	-0.6	NS	-2.7 (2.5)	NS

Author, Year	Drug, Dose/Day	N/n	Time, weeks	Congestion[a]	p versus Combo	Rhinorrhea[a]	p versus Combo	Sneezing[a]	p versus Combo	Itching[a]	p versus Combo	TNSS[a]	p versus Combo
Barnes, 2006	Levocetirizine 5 mg/ Fluticasone propionate 200 mcg	31/ 27	2[c]	-0.49 (-0.74, -0.24)		-0.40 (-0.66, -0.14)		-0.66 (-0.96, -0.36)		-0.58 (-0.88, -0.28)		-2.13 (-3.04, -1.23)	
	Fluticasone propionate 200 mcg	31/ 27		-0.60 (-0.63, -0.10)	0.005	-0.37 (-0.63, -0.23)	0.1	-0.51 (-0.79, -0.23)	0.54	-0.55 (-0.85, -0.25)	0.06	-2.02 (-2.91, -1.13)	<0.05
Ratner, 1998	Loratadine 10 mg/ Fluticasone propionate 200 mcg	150/ 150	2[c]									-180[e]	
	Fluticasone propionate 200 mcg	150/ 150										-150[e]	<0.05
Di Lorenzo, 2004	Cetirizine 10 mg/ Fluticasone propionate 200 mcg	20/ 20	6[b]										
	Fluticasone propionate 200 mcg	20/ 20			NS		NS		NS		0.003	[f]	0.04
Benincasa, 1994	Cetirizine 10 mg/ Fluticasone propionate 200 mcg	227 /227	8[b]									[f]	
	Fluticasone propionate 200 mcg	227 /227										[f]	NS

N/n = Number randomized/number analyzed; NS = non-significant; TNSS = total nasal symptom score.

[a] All analyses are mean change from baseline.

[b] All symptom assessments averaged over the treatment duration.

[c] Analysis compares change from baseline to symptom assessments averaged over the second week of treatment.

[d] Analysis compares change from baseline to symptom assessments averaged over the fourth week of treatment.

[e] Calculated by study authors from reported means.

[f] Comparative treatment effects were reported, no treatment level change from baseline provided. See Summary table for comparative treatment effects.

Appendix Table C57. Eye symptom outcomes: change from baseline–oral selective antihistamine plus intranasal corticosteroid versus intranasal corticosteroid

Author, Year	Drug, Dose/Day	N/n	Time, weeks	Outcome	Baseline mean	Change from baseline	p versus Combo
Anolik, 2008	Loratadine 10 mg/ Mometasone furoate 200 mcg	169/166	2	Individual symptoms[a]	NR	NR	
	Mometasone furoate 200 mcg	176/166			NR	NR	≤0.03
Benincasa, 1994	Cetirizine 10 mg/ Fluticasone propionate 200 mcg	227/227	8	TOSS (scale 0-10)		[c]	
	Fluticasone propionate 200 mcg	227/227				[c]	NS

N/n = number randomized/number analyzed; NR = not reported; NS = non-significant; TOSS = total ocular symptom score.

[a] Includes itchy eyes, watery eyes and red eyes, assessed daily by patients on a 0 (no symptoms) to 3 (severe symptoms) scale. With the exception of stating that all symptoms were and were not statistically different from combination therapy, no assessment means or p-values were reported.

[b] Mean differences calculated by study authors.

[c] Comparative treatment effects were reported, no treatment level change from baseline provided. See Summary table for comparative treatment effects.

Appendix Table C58. Quality of life outcomes: change from baseline–oral selective antihistamine plus intranasal corticosteroid versus intranasal corticosteroid

Author, year	Drug, Dose/Day	N/n	Time, weeks	Outcome	Baseline mean	Change from Baseline	p versus Combo
Barnes, 2006	Levocetirizine 5 mg/ Fluticasone propionate 200 mcg	31/27	2	Mini RQLQ[a]	2.5 (0.22)	-0.4	NS
	Fluticasone propionate 200 mcg	31/27			2.5 (0.22)	-0.5	
Ratner, 1998	Loratadine 10 mg/ Fluticasone propionate 200 mcg	150/150	2	RQLQ[b]	4.0 (0.1)	-2.3 (0.1)	
	Fluticasone propionate 200 mcg	150/150			4.1 (0.1)	-2.2 (0.1)	NS
Ratner, 1998	Loratadine 10 mg/ Fluticasone propionate 200 mcg	150/150	2	Global Assessment[c]		75	
	Fluticasone propionate 200 mcg	150/150				71	NS

N/n = Number randomized/number analyzed; NS = non-significant; RQLQ = Rhinitis Quality of Life Questionnaire.

Values are presented as mean (standard deviation) unless otherwise noted.

[a] Scores range from 0 (no trouble) to 6 (extremely troubled). Average of 14 questions in 5 domains (activity, practical problems, nose symptoms, eye symptoms and other symptoms).

[b] Scores range from 0 (no impairment) to 6 (severely impaired). The minimum clinically important difference is 0.5 points.

[c] Patient rated overall response to therapy after two weeks of treatment. Percent reporting moderate or significant improvement. P value describes overall test comparing groups over the full 7 point Likert scale.

[d] Patients recorded extent to which their symptoms interfered with their daily activity on an 11-point scale (0 = no interference, 10 = maximal interference).

Combination Intranasal Corticosteroid Plus Nasal Antihistamine Versus Intranasal Corticosteroid and Nasal Antihistamine

Appendix Table C59. Trial description: combination nasal selective antihistamine plus intranasal corticosteroid versus intranasal corticosteroid and nasal antihistamine

Author, Year	Location, Site(s)	Enrollment/ Treatment Duration	Funding/ Author Industry Disclosures	N	Inclusion Criteria	Exclusion Criteria[a]	Rescue Rx	Objective Diagnosis	Run in Period	Pollen Count	Patient Blinding	Assessor Blinding
Carr, 2012 (Trial 1)	N.America Multiple	March 2008 2 weeks	Industry Yes	622	Minimum SAR severity and duration	SAR meds/- Other meds Chronic asthma Infection Deformities	No	•	•		•	•
Carr, 2012 (Trial 2)	N.America Multiple	August 2008 2 weeks	Industry Yes	576	Minimum SAR severity and duration	SAR meds/- Other meds Chronic asthma Infection Deformities	No	•	•		•	•
Carr, 2012 (Trial 3)	N.America Multiple	April 2009 2 weeks	Industry Yes	1343	Minimum SAR severity and duration	SAR meds/- Other meds Chronic asthma Infection Deformities	No	•	•		•	•
Hampel, 2010	N.America Multiple	January 2007 2 weeks	Industry Yes	459	Minimum SAR severity and duration	SAR meds/- Other meds Infection Deformities	No	•	•		•	•
Ratner, 2008	N.America Multiple	December 2005 2 weeks	Industry Yes	151	Minimum SAR severity and duration	SAR meds/+ Other meds	No	•	•	•	•	•

N = patients randomized to comparator groups of interest; SAR = seasonal allergic rhinitis.

[a] +, -, or NR indicates whether FDA-recommended washout periods were required (+), were not required (-), or were not reported (NR) for restricted SAR medications prior to trial entry.

Appendix Table C60. Patient characteristics: combination nasal selective antihistamine plus intranasal corticosteroid versus intranasal corticosteroid and nasal antihistamine

Author, Year	Drug, Dose/Day	N	Mean Age, years	Sex, % female	Race, %	Disease Duration, years	Mean Baseline NSS[a]
Carr, 2012 (Trial 1)	Azelastine 548 mcg/ Fluticasone propionate 200 mcg	207	37.3 (14.1)	68.6	White: 78.3	21.7 (13.2)	C: 5.1 (0.8) R: 4.5 (1.0) S: 4.0 (1.3) I: 4.6 (1.0) TNSS: 18.3 (3.0)

Author, Year	Drug, Dose/Day	N	Mean Age, years	Sex, % female	Race, %	Disease Duration, years	Mean Baseline NSS[a]
	Azelastine 548 mcg	208	36.2 (14.6)	62.5	White: 77.9	21.6 (13.6)	C: 5.1 (0.8) R: 4.5 (1.2) S: 4.0 (1.3) I: 4.5 (1.2) TNSS: 18.2 (3.5)
	Fluticasone propionate 200 mcg	207	38.6 (14.1)	61.4	White: 77.8	21.3 (13.5)	C: 5.0 (0.9) R: 4.6 (1.0) S: 4.1 (1.2) I: 4.5 (1.1) TNSS: 18.2 (3.2)
Carr, 2012 (Trial 2)	Azelastine 548 mcg/ Fluticasone propionate 200 mcg	193	38.8 (14.1)	65.3	White: 79.8	21.5 (13.5)	C: 5.1 (0.9) R: 4.5 (1.1) S: 4.1 (1.3) I: 4.5 (1.1) TNSS: 18.2 (3.3)
	Azelastine 548 mcg	194	38.2 (13.5)	66.0	White: 78.9	19.7 (13.1)	C: 5.1 (0.8) R: 4.5 (1.1) S: 4.2 (1.3) I: 4.7 (1.1) TNSS: 18.5 (3.1)
	Fluticasone propionate 200 mcg	189	37.0 (13.6)	64.0	White: 74.1	21.1 (13.7)	C: 5.0 (0.8) R: 4.6 (1.0) S: 4.2 (1.3) I: 4.8 (0.9) TNSS: 18.6 (2.9)
Carr, 2012 (Trial 3)	Azelastine 548 mcg/ Fluticasone propionate 200 mcg	448	35.6 (14.5)	61.8	White: 81.3	20.4 (13.0)	C: 5.3 (0.7) R: 4.7 (1.0) S: 4.5 (1.2) I: 4.9 (0.9) TNSS: 19.4 (2.4)
	Azelastine 548 mcg	445	36.4 (14.8)	60.9	White: 80.2	19.5 (12.9)	C: 5.3 (0.7) R: 4.8 (0.9) S: 4.5 (1.1) I: 4.9 (0.9) TNSS: 19.5 (2.5)
	Fluticasone propionate 200 mcg	450	34.2 (14.5)	62.2	White: 79.1	19.6 (12.5)	C: 5.3 (0.7) R: 4.8 (0.9) S: 4.5 (1.2) I: 4.9 (0.9) TNSS: 19.4 (2.4)
Hampel, 2010	Azelastine 548 mcg/ Fluticasone propionate 200 mcg	153	39.5 Range: 12-73	63.4	White: 86.3 Black: 9.8 Asian: 2.6 Other: 1.3	18.7 Range: 3-64	TNSS: 18.8 (9-24)[b]
	Azelastine 548 mcg	152	39.5 Range: 12-74	63.8	White: 88.8 Black: 9.9	19.0 Range: 2-61	TNSS: 18.1 (10-24)[b]

Author, Year	Drug, Dose/Day	N	Mean Age, years	Sex, % female	Race, %	Disease Duration, years	Mean Baseline NSS[a]
					Asian: 0.0 Other: 1.3		
	Fluticasone propionate 200 mcg	153	38.1 Range: 12-74	66.2	White: 86.1 Black: 10.6 Asian: 2.0 Other: 1.3	18.4 Range: 3-57	TNSS: 18.3 (8-24)[b]
Ratner, 2008	Azelastine 8 puffs/ Fluticasone propionate 200 mcg	52	36.0 Range: 13-70	63.5	White: 78.8 Black: 3.8 Hispanic: 15.4 Asian: 1.9 Other: 0	16.2 Range: 4-40	C: 5.4 (0.6) R: 4.9 (1.0) S: 4.5 (1.2) I: 4.7 (1.0) TNSS: 19.5 (3.0)
	Azelastine 8 puffs	49	38.4 Range: 12-73	55.1	White: 73.5 Black: 10.2 Hispanic: 14.3 Asian: 0 Other: 2.0	19.2 Range: 3-50	C: 5.5 (0.5) R: 4.9 (0.8) S: 4.5 (1.1) I: 4.8 (0.8) TNSS: 19.7 (2.1)
	Fluticasone propionate 200 mcg	50	37.4 Range: 12-72	70.0	White: 64.0 Black: 4.0 Hispanic: 26.0 Asian: 6.0 Other: 0	15.7 Range: 3-51	C: 5.5 (0.4) R: 5.0 (1.0) S: 4.3 (1.3) I: 4.8 (1.3) TNSS: 19.6 (2.7)

C = Congestion; I = itching; n= patients randomized or assigned to comparator groups of interest; NSS = nasal symptom score; R = rhinorrhea; S = sneezing; TNSS = total nasal symptom score.

Values are presented as mean (standard deviation) unless otherwise noted.

[a] Individual symptoms rated on a scale from 0 (no symptoms) to 3 (severe symptoms) for each individual symptom. Morning and evening scores were summed (maximum individual symptom = 6, maximum TNSS = 24).

[b] Interquartile range.

Appendix Table C61. USPSTF quality assessment: combination nasal selective antihistamine plus intranasal corticosteroid versus intranasal corticosteroid and nasal antihistamine

Author, year	Assembled comparable groups	Maintained comparable groups	Minimal follow-up loss	Measurements equal, valid, and reliable	Interventions clearly defined	Important outcomes considered	Appropriate analysis of results	Overall USPSTF rating
Carr, 2012 (Trial 1)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Carr, 2012 (Trial 2)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Carr, 2012 (Trial 3)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Hampel, 2010	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Ratner, 2008	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good

USPSTF = United States Preventive Services Task Force.

Appendix Table C62. Nasal symptom outcomes: change from baseline–combination nasal selective antihistamine plus intranasal corticosteroid versus intranasal corticosteroid and nasal antihistamine

Author, Year	Drug, Dose/Day	N/n	Time, weeks	Congest[a]	p vs. Combo	Rhino[a]	p vs. Combo	Sneeze[a]	p vs. Combo	Itch[a]	p vs. Combo	TNSS[a]	p vs. Combo
Carr, 2012 (Trial 1)	Azelastine 548 mcg/ Fluticasone propionate 200 mcg	207/ 207	2	-1.3 (1.4)		-1.5 (1.5)		-1.6 (1.6)		-1.3 (1.5)		-5.5 (5.2)	
	Azelastine 548 mcg	208/ 208		-0.9 (1.3)	0.003	-1.1 (1.4)	<0.001	-1.3 (1.3)	0.010	-0.9 (1.3)	0.015	-4.1 (4.6)	0.002
	Fluticasone propionate 200 mcg	207/ 207		-1.2 (1.3)	0.163	-1.3 (1.4)	0.043	-1.5 (1.4)	0.144	-1.3 (1.3)	0.058	-5.0 (4.7)	0.034
Carr, 2012 (Trial 2)	Azelastine 548 mcg/ Fluticasone propionate 200 mcg	193/ 193	2	-1.3 (1.3)		-1.4 (1.5)		-1.7 (1.6)		-1.3 (1.5)		-5.6 (5.2)	
	Azelastine 548 mcg	194/ 194		-1.0 (1.3)	0.002	-1.0 (1.3)	0.058	-1.3 (1.5)	0.066	-1.1 (1.3)	0.093	-4.4 (4.6)	0.032
	Fluticasone propionate 200 mcg	189/ 189		-1.1 (1.5)	0.022	-1.3 (1.5)	0.274	-1.4 (1.5)	0.046	-1.2 (1.4)	0.070	-5.0 (5.2)	0.038
Carr, 2012 (Trial 3)	Azelastine 548 mcg/ Fluticasone propionate 200 mcg	448/ 448	2	-1.2 (1.4)		-1.4 (1.5)		-1.7 (1.6)		-1.3 (1.5)		-5.6 (5.2)	
	Azelastine 548 mcg	445/ 445		-1.0 (1.2)	0.004	-1.2 (1.4)	0.006	-1.4 (1.5)	0.012	-1.1 (1.4)	0.065	-4.5 (4.8)	0.016
	Fluticasone propionate 200 mcg	450/ 450		-1.1 (1.2)	0.106	-1.3 (1.4)	0.170	-1.5 (1.5)	0.014	-1.2 (1.3)	0.142	-5.1 (4.7)	0.129
Hampel, 2010	Azelastine 548 mcg/ Fluticasone propionate 200 mcg	153/ 153	2	-1.24		-1.42		-1.47		-1.22		-5.31 (5.08)	
	Azelastine 548 mcg	152/ 152		-0.75	<0.01	-0.87	<0.01	-0.86	<0.01	-0.82	<0.05	-3.25 (4.16)	<0.01
	Fluticasone propionate 200 mcg	153/ 151		-0.86	<0.01	-1.15	NR	-0.98	<0.01	-0.91	<0.05	-3.84 (4.76)	<0.01
Ratner, 2008	Azelastine 8 puffs[b]/ Fluticasone propionate 200 mcg	52/ 52	2	-1.7 (1.4)		-1.7 (1.6)		-2.1 (1.7)		-1.9 (1.7)		-7.4 (5.6)	
	Azelastine 8 puffs[b]	49/ 49		-1.1 (1.5)	0.02	-1.1 (1.4)	0.02	-1.5 (1.0)	0.04	-1.1 (1.4)	0.009	-4.8 (4.3)	0.008
	Fluticasone propionate 200 mcg	50/ 49		-1.1 (1.2)	0.04	-1.3 (1.2)	0.19	-1.5 (1.5)	0.05	-1.3 (1.5)	0.02	-5.2 (4.6)	0.03

[a] All analyses are mean change from baseline over the entire treatment duration.

[b] Symptoms score twice daily 0 (no symptoms) to 3 (severe symptoms); maximum daily score for individual symptom = 6, for TNSS = 24.

[c] Equivalent to 548 mcg/day

Appendix Table C63. Eye symptom outcomes: change from baseline—combination nasal selective antihistamine plus intranasal corticosteroid versus intranasal corticosteroid and nasal antihistamine

Author, Year	Drug, Dose/Day	N/n	Time, weeks	Outcome	Baseline mean	Change from baseline	p vs. Combo
Carr, 2012 (Trial 1)	Azelastine 548 mcg/ Fluticasone propionate 200 mcg	207/207	2	TOSS (scale 0-18)	11.9 (3.9)	-3.2 (4.0)	
	Azelastine 548 mcg	208/208			11.5 (4.5)	-2.8 (3.8)	0.457
	Fluticasone propionate 200 mcg	207/207			11.4 (4.4)	-2.6 (3.5)	0.097
Carr, 2012 (Trial 2)	Azelastine 548 mcg/ Fluticasone propionate 200 mcg	193/193	2	TOSS (scale 0-18)	11.7 (4.2)	-3.6 (3.9)	
	Azelastine 548 mcg	194/194			11.8 (3.9)	-3.0 (3.3)	0.069
	Fluticasone propionate 200 mcg	189/189			12.0 (3.8)	-2.7 (3.6)	0.009
Carr, 2012 (Trial 3)	Azelastine 548 mcg/ Fluticasone propionate 200 mcg	448/448	2	TOSS (scale 0-18)	12.3 (4.0)	-3.0 (4.0)	
	Azelastine 548 mcg	445/445			12.4 (4.0)	-3.0 (3.8)	0.912
	Fluticasone propionate 200 mcg	450/450			12.3 (3.6)	-2.8 (3.5)	0.247
Hampel, 2010	Azelastine 548 mcg/ Fluticasone propionate 200 mcg	153/153	2	TOSS (scale 0-18)		-3.33	
	Azelastine 548 mcg	152/152				-2.62	NR
	Fluticasone propionate 200 mcg	153/151				-2.17	<0.01

N/n, number randomized/number analyzed

[a] Three symptoms (itchy eyes, watery eyes, red eyes) each scored twice daily on a 0 (no symptoms) to 3 (severe symptoms) scale; maximum daily score = 18.

[b] Mean differences adjusted for center, day, and baseline symptoms.

[c] Mean differences calculated by study authors.

Appendix Table C64. Quality of life outcomes: change from baseline–combination nasal selective antihistamine plus intranasal corticosteroid versus intranasal corticosteroid and nasal antihistamine

Author, year	Drug, Dose/Day	N/n	Time, weeks	Outcome	Baseline mean	Change from Baseline	p vs. Combo
Hampel, 2010	Azelastine 548 mcg/ Fluticasone propionate 200 mcg	153/153	2	RQLQ		1.60	
	Azelastine 548 mcg	152/152				1.17	0.005
	Fluticasone propionate 200 mcg	153/151				1.43	0.29

Ratner, 2008	Azelastine 8 puffs/ Fluticasone propionate 200 mcg	52/52	2	RQLQ	3.93 (1.09)	1.92 (1.46)		
	Azelastine 8 puffs	49/49			3.66 (1.13)	1.21 (1.02)		0.005
	Fluticasone propionate 200 mcg	50/49			3.95 (1.14)	1.47 (1.21)		0.08

Combination Oral Selective Antihistamine Plus Oral Decongestant Versus Oral Selective Antihistamine

Appendix Table C65. Trial description: combination oral selective antihistamine plus oral decongestant versus oral selective antihistamine

Author, Year	Location, Site(s)	Enrollment/ Treatment Duration	Funding/Author Industry Disclosures	N	Inclusion Criteria	Exclusion Criteria	Rescue Medication Use	Objective Diagnosis	Run in Period	Pollen Count	Patient Blinding	Assessor Blinding
Bronsky, 1995	N.America Multiple	Fall 1989 2 weeks	Industry Yes	438	Minimum SAR severity and duration	SAR meds Other meds Chronic asthma Pregnancy Infection	No	•	•	•	•	•
Chervinsky, 2005	N.America Multiple	2 weeks	NR Yes	428	Minimum SAR severity and duration	SAR meds Pregnancy Infection	No	•	•	•	•	•
Grosclaude, 1997	Europe Multiple	March1992 2 weeks	NR Yes	458	Minimum SAR severity and duration	SAR meds Other meds Pregnancy Infection Deformities	Yes	•		•	•	•
Grubbe, 2009	N.America Multiple	2.1 weeks	Industry Yes	398	Minimum SAR severity and duration	SAR meds Chronic asthma Pregnancy Infection Deformities	No	•	•	•	•	•
Pleskow, 2005	N.America Multiple	2000 2 weeks	Industry Yes	744	Minimum SAR severity and duration	SAR meds Pregnancy Infection Deformities	No	•	•	•	•	•
Schenkel, 2002	N.America Multiple	2.1 weeks	Industry NR	676	Minimum SAR duration	SAR meds Chronic asthma Pregnancy	No	•	•		•	•
Sussman, 1999	N.America Multiple	2.4 weeks	Industry Yes	433	Minimum SAR	SAR meds Pregnancy	No	•	•	•	•	•

Author, Year	Location, Site(s)	Enrollment/ Treatment Duration	Funding/Author Industry Disclosures	N	Inclusion Criteria	Exclusion Criteria	Rescue Medication Use	Objective Diagnosis	Run in Period	Pollen Count	Patient Blinding	Assessor Blinding
					severity	Infection						

N = patients randomized to comparator groups of interest; NR = not reported; SAR = seasonal allergic rhinitis.

Appendix Table C66. Patient characteristics: combination oral selective antihistamine plus oral decongestant versus oral selective antihistamine

Author, Year	Drug, Dose/Day	N	Mean Age, years	Sex, % female	Race, %	Disease Duration, years	Mean Baseline NSS[a]
Bronsky, 1995	Loratadine 10 mg/ Pseudoephedrine 240 mg	221	Median: 30 Range: 12-82	53.8	White: 87.3 Black: 5.7 Other: 7.1	Median: 15 Range: 2-47	
	Loratadine 10 mg	217	Median: 30 Range: 12-60	57.5	White: 87.3 Black: 4.2 Other: 8.5	Median: 15 Range: 1-50	
Chervinsky, 2005	Desloratadine 5 mg/ Pseudoephedrine 240 mg	214	36	64	Unspecified	18	C: 2.55
	Desloratadine 5 mg	214	37	69	Unspecified	19	C: 2.56
Grosclaude, 1997	Cetirizine 10 mg/ Pseudoephedrine 240 mg	227	31 Range: 9-65	47	Unspecified	9	C: 2.29 R: 1.99 S: 1.93 I: 1.71
	Cetirizine 10 mg	231	32 Range: 12-66	52	Unspecified	8	C: 2.28 R: 2.07 S: 2.02 I: 1.76
Grubbe, 2009	Desloratadine 5 mg/ Pseudoephedrine 240 mg	200	34.9 Range: 12-74	60.5	White: 81 Black: 12 Hispanic: 4 Asian: 2 Other: 2	19.6 Range: 2-69	C: 2.47
	Desloratadine 5 mg	198	37 Range: 12-76	65.2	White: 77 Black: 13 Hispanic: 7 Asian: 2 Other: 2	17.9 Range: 2-56	C: 2.50
Pleskow, 2005	Desloratadine 5 mg/ Pseudoephedrine 240 mg	372	34 Range: 12-78	59.4	White: 77 Black: 11 Hispanic: 8 Asian: 3 Other: <1	16.5 Range: 2-51	
	Desloratadine 5 mg	372	35 Range: 12-76	65.9	White: 80 Black: 12	18.0 Range: 2-55	

Author, Year	Drug, Dose/Day	N	Mean Age, years	Sex, % female	Race, %	Disease Duration, years	Mean Baseline NSS[a]
					Hispanic: 7 Asian: <1 Other: 0		
Schenkel, 2002	Desloratadine 5 mg Pseudoephedrine 240 mg	336	34.2	64	Unspecified	17.5	C: 2.56
	Desloratadine 5 mg	340	34.8	60	Unspecified	18.3	C: 2.57
Sussman, 1999	Fexofenadrine 120 mg/ Pseudoephedrine 240 mg	215	33.0 (11.41) Range: 13-66	57.7	White: 86.5 Black: 6.0 Asian: 5.6 Other: 1.9	14.9 (9.65) Range: 2.0-55.0	C: 2.32 (SE: 0.03)
	Fexofenadrine 120 mg	218	34.9 (12.35) Range: 12-64	56.9	White: 85.3 Black: 6.0 Asian: 8.3 Other: 0.5	15.2 (9.79) Range: 2.0-46.2	C: 2.36 (SE: 0.03)

C = Congestion; I = itching; n= patients randomized to comparator groups of interest; NSS = nasal symptom score; R = rhinorrhea; S = sneezing, SE = standard error.

Values are presented as mean (standard deviation) unless otherwise noted.

[a] Individual symptoms rated on a scale from 0 (no symptoms) to 3 (severe symptoms) in all cases except Sussman (1999) where the maximum was 4.

Appendix Table C67. USPSTF quality assessment: combination oral selective antihistamine plus oral decongestant versus oral selective antihistamine

Author, year	Assembled comparable groups	Maintained comparable groups	Minimal follow-up loss	Measurements equal, valid, and reliable	Interventions clearly defined	Important outcomes considered	Appropriate analysis of results	Overall USPSTF rating
Bronsky, 1995	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Chervinsky, 2005	Yes	Uncertain	Yes	Yes	Yes	Yes	No	Poor
Grosclaude, 1997	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Grubbe, 2009	Yes	Yes	Yes	Yes	Yes	Yes	No	Poor
Pleskow, 2005	Yes	Yes	Yes	Yes	Yes	Yes	No	Poor
Schenkel, 2002	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Fair
Sussman, 1999	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good

Appendix Table C68. Nasal symptom outcomes: change from baseline–combination oral selective antihistamine plus oral decongestant versus oral selective antihistamine

Author, Year	Drug, Dose/Day	N/n	Time, weeks	Congest[a]	p	Rhino[a]	p	Sneeze[a]	p	Itch[a]	p	TNSS[a]	p
Bronsky, 1995	Loratadine 10 mg/ Pseudoephedrine 240 mg	221/212	2	-0.7								-2.9	NR
	Loratadine 10 mg	217/212		-0.5	≤0.02							-2.3	

Chervinsky, 2005	Desloratadine 5 mg/ Pseudoephedrine 240 mg	214/200	2	-0.92							
	Desloratadine 5 mg	214/200		-0.73							
Grosclaude, 1997	Cetirizine 10 mg/ Pseudoephedrine 240 mg	227/227	2	-1.1	<0.001	-1.09[b]	<0.001	-1.19[b]	<0.01	-0.96[b]	<0.01
	Cetirizine 10 mg	231/231		-0.85[b]		-0.96[b]		-1.11[b]		-0.86[b]	
Grubbe, 2009	Desloratadine 5 mg/ Pseudoephedrine 240 mg	200	2	-0.93	<0.001						
	Desloratadine 5 mg	198[c]		-0.66							
Pleskow, 2005	Desloratadine 5 mg/ Pseudoephedrine 240 mg	372[c]	2	-0.9	≤0.001						
	Desloratadine 5 mg	372[c]		-0.74							
Schenkel, 2002	Desloratadine 5 mg/ Pseudoephedrine 240 mg	336/336	2	0.85	<0.001						
	Desloratadine 5 mg	340/340		0.65							
Sussman, 1999	Fexofenadrine 120 mg/ Pseudoephedrine 240 mg	215/215	2.6	-0.6[d]	0.0005	-0.5[d]	NR	-0.6	NR		
	Fexofenadrine 120 mg	218/218		-0.4[d]		-0.4[d]		-0.5[d]			

N/n, number randomized/number analyzed

[a] Mean change from baseline over the entire treatment duration

[b] Calculated by author using pre/post data

[c] Only patient randomized are reported

[d] Values obtained using Engauge Digitizer Software

Appendix Table C69. Eye symptom outcomes: change from baseline–combination oral selective antihistamine plus oral decongestant versus oral selective antihistamine

Author, Year	Drug, Dose/Day	N/n	Time, weeks	Outcome	Baseline mean	Change from baseline	p
Grosclaude, 1997	Cetirizine 10 mg/ Pseudoephedrine 240 mg	227/227	2	Itching eyes	1.68	-1.01[a]	
	Cetirizine 10 mg	231/231			1.83	-1.02 [a]	NS
Sussman, 1999	Fexofenadrine 120 mg/ Pseudoephedrine 240 mg	215/215	2.6	Itchy, watery, red eyes	NR	-0.6 [b,c]	
	Fexofenadrine 120 mg	218/218			NR	-0.5 [b,c]	NR

N/n, number randomized/number analyzed

[a] 4-point scale: 0, absent; 1, mild; 2, moderate; 3, severe.

[b] 5-point scale: 0, absent; 1, mild; 2, moderate; 3, severe; 4, very severe

[c] Values obtained using Engauge Digitizer Software

Appendix Table C70. Quality of life outcomes: change from baseline–combination oral selective antihistamine plus oral decongestant versus oral selective antihistamine

Author, year	Drug, Dose/Day	N/n	Time, weeks	Outcome	Baseline mean	End of treatment	p
Bronsky, 1995	Loratadine 10 mg/ Pseudoephedrine 240 mg	221/212	2	% patients reporting good or excellent response to treatment[a]		61[b]	0.004[d]
	Loratadine 10 mg	217/212				47[c]	

[a] 5 point scale: 1, excellent; 2, good; 3, fair; 4, poor; 5, treatment failure

[b] 125/204

[c] 95/203

[d] P-value calculated by report author, chi-square test.

Comparative Harms

Appendix Table C71. Comparative harms: oral selective antihistamine versus oral nonselective antihistamine

Author, Year	Treatment Group	N/n	Sedation	Headache
Dockhorn, 1987	Loratadine 10 mg	111/108	MOD: 6.3	MOD: 10.8
			SEV: 0	
	Clemastine 2 mg	109/105	MOD: 19.3	MOD: 9.2
			SEV: 2.8	
Harvey, 1996	Cetirizine 5-10mg	43/39	11.6	
	Chlorpheniramine 16mg	43/40	40.5	
Kemp, 1987	Loratadine 10 mg	108/108	15	11.3
	Clemastine 2 mg	101/101	23	6.8

N/n = Number of patients randomized/number of patients analyzed.

Symptom severity is unspecified unless otherwise noted (MILD, MOD = moderate, or SEV = severe).

Appendix Table C72. Comparative harms: oral selective antihistamine versus nasal selective antihistamine

Author, year	Treatment Group	N/n	Sedation	Headache	Nasal Discomfort	Bitter Aftertaste	Hypertension	Insomnia	Nosebleeds
Berger, 2003[a]	Desloratadine 5mg[b]	111/111	1	3		0			
	Azelastine 4 puffs/nostril[c]	108/106	2	0		11			
Berger, 2006	Cetirizine 10mg	175/175	SEV: 0	SEV: 0			SEV: 0		
			2	2		0			2
	Azelastine 4 puffs/nostril	179/179	SEV: 0.6	SEV: 0.6			SEV: 0.6		
			2	2		7.7			2
Charpin, 1995	Cetirizine 10mg	69[b]	SEV: 1						
			7	1					
	Azelastine 2 puffs/nostril	67[b]	2	1					
Corren, 2005	Cetirizine 10mg	155/155	SEV: 0.6						
			1.9	1	1	1			1
	Azelastine 4 puffs/nostril	152/151						SEV: 0.7	

			1.3	2.6	1.3	3.3				2
Gambardella, 1993	Loratadine 10mg[d]	15	SEV: 0							
	Azelastine 560 mcg[e]	15	SEV: 6.7							

N/n = Number of patients randomized/number of patients analyzed.

Symptom severity is unspecified unless otherwise noted (MILD, MOD = moderate, or SEV = severe).

[a] Other: Chest pain: 0.9, Lightheadedness: 0.9.

[b] 4 discontinuations due to events (headache, pregnancy, cough, elevated blood pressure, fatigue).

[c] 1 AE discontinuation (vomiting and GI distress).

[d] Paper reported that adverse events were not serious but nasal congestion in this group caused 1 person to withdraw from study.

[e] Paper reported that adverse events were not serious but epigastralgia and urticaria in this group caused 1 person to withdraw from study.

Appendix Table C73. Comparative harms: oral selective antihistamine versus intranasal corticosteroids

Author, Year	Treatment Group	N/n	Sedation	Headache	Atrophy	Burning	Anxiety	Nosebleeds	Odor	Fungal
Anolik, 2008	Loratadine 10 mg	181/175	MOD: 2	MOD: 8		MOD: 0		MOD:1		
	Mometasone furoate 200 mcg	176/166	MOD: 1	MOD: 6		MOD: 0		MOD: 1		
Bernstein, 2004	Loratadine 10 mg	158		18						
	Fluticasone propionate 200 mcg	158		17						
Condemi, 2000	Loratadine 10 mg[a]	174		15.3						
	Triamcinolone acetonide 220 mcg[b]	174		14.3						
Gawchik, 1997	Loratadine 10 mg	150/150		18			MOD: NR	MILD: NR		
	Triamcinolone acetonide 220 mcg	150/150		22			MOD: 0.7	MILD: 0.7		
Jordana, 1996	Loratadine 10 mg[c]	119/119		25	0			4		0
	Fluticasone propionate 200 mcg[d]	121/121		42	0			7		0

Ratner, 1998[e]	**Loratadine 10 mg**	**150/150**			**≤1**		
	Fluticasone propionate 200 mcg	150/150					
Schoenwetter, 1995	Loratadine 10 mg	149/140		35			
	Triamcinolone acetonide 220 mcg	149/134		43			
Vervloet, 1997[f]	Cetirizine 10 mg	118	5.1			0.8	
	Fluticasone propionate 200 mcg	120			0.8		

N/n = Number of patients randomized/number of patients analyzed; NR = not reported.

Symptom severity is unspecified unless otherwise noted (MILD, MOD = moderate, or SEV = severe).

[a] 4 patients discontinued the study. They reported 6 adverse events; three of these events (headache, rhinitis, and chest pain) were classified as possibly or probably related to study drug and occurred in one patient.

[b] Three loratadine patients withdrew due to adverse events. They reported one adverse event each, none of which were related to study drug.

[c] Headache separated out as mild/mod/severe but they are n reports, not n patients. There were statistically more headache in Fluticasone propionate group (p=0.003, test type not specified).

[d] Headache separated out as mild/mod/severe but they are n reports, not n patients. There were statistically more headache in Fluticasone propionate group (p=0.003, test type not specified).

[e] Adverse events not reported by treatment group.

[f] Number of reports.

Appendix Table C74. Comparative harms: oral selective antihistamine versus oral decongestant

Author, Year	Treatment Group	N/n	Sedation	Headache	Palpitations	Insomnia	Anxiety
Bronsky, 1995	Loratadine 10 mg	217/212	4	23		1	1
	Pseudoephedrine 240 mg	220/211	5	26		9	4
Chervinsky, 2005[a]	Desloratadine 5 mg	214/200		8		2	
	Pseudoephedrine 240 mg	222/204		6		11	
Grosclaude, 1997	Cetirizine 10 mg	231/231	6.1	4.3		0	0
	Pseudoephedrine 240 mg	226/226	3.1	7.1		11.1	2.2
Grubbe, 2009	Desloratadine 5 mg [bc]	198		7.1		3.0	
	Pseudoephedrine 240 mg[de]	200		12.0		14.0	

Pleskow, 2005	**Desloratadine 5 mg**	**372**	**4**	**6**	**1**	**1**	**1**
	Pseudoephedrine 240 mg	377	5	6	3	7	3
Schenkel, 2002[f]	Desloratadine 5 mg	340/340	2.1	1.5		0.6	0.6
	Pseudoephedrine 240 mg	342/342	2.0	3.2		7.9	0.9
Sussman, 1999[g]	Fexofenadrine 120 mg	218/218	0	7.3	0	1.8	0
	Pseudoephedrine 240 mg	218/218	1.4	12.4	2.8	12.8	1.4

N/n = Number of patients randomized/number of patients analyzed.

Symptom severity is unspecified unless otherwise noted (MILD, MOD = moderate, or SEV = severe).

[a] Unclear if proportions of patients, or reports.

[b] Other: no increased heart rate reported.

[c] No serious or unexpected adverse events reported; 9 patients discontinued due to adverse events.

[d] Other: increased heart rate: 3.0 BPM.

[e] No serious or unexpected adverse events reported; 4 patients discontinued due to adverse events.

[f] Number of reports.

[g] Number of reports.

Appendix Table C75. Comparative harms: oral selective antihistamine versus leukotriene receptor antagonist

Author, year	Treatment Group	N/n	Headache
Baena-Cagnani, 2003	Desloratadine 5mg	311	3.5
	Montelukast 10mg	311	3.5
Nayak, 2002	Loratadine 10mg	155	3
	Montelukast 10mg	301	4
Meltzer, 2000	Loratadine 10mg	92/90	8.7
	Montelukast 10mg	95/94	5.3
Philip, 2002	Loratadine 10mg	602	3.5
	Montelukast 10mg	348	3.2

N/n = Number of patients randomized/number of patients analyzed.

Symptom severity is unspecified unless otherwise noted (MILD, MOD = moderate, or SEV = severe).

Appendix Table C76. Comparative harms: intranasal corticosteroids versus nasal selective antihistamine

Author, Year	Treatment Group	N/n	Sedation	Headache	Dryness	Burning	Nasal Discomfort	Bitter Aftertaste	Nosebleeds
Carr, 2012 (Trial 1)	Fluticasone propionate 200mcg	207/207		2.4			1	1	2.4
	Azelastine 548mcg	208/208		0.5			1.9	3.4	1
Carr, 2012 (Trial 2)	Fluticasone propionate 200mcg	189/189		2.1			0	0.5	1.6
	Azelastine 548mcg	194/194		2.1			1	7.2	1.6
Carr, 2012 (Trial 3)	Fluticasone propionate 200mcg	450/450	0	1.3				0.2	1.1
	Azelastine 548mcg	445/445	0.4	2				5	1.1
Ghimire, 2007	Azelastine 1120mcg	25			4	4	16	4	
	Beclomethasone dipropionate 400mcg	25			12	0	8	0	
Hampel, 2010	Azelastine 548mcg	152/152	0.7	1.3			0	2	2
	Fluticasone propionate 200mcg	153/153	0.7	3.9			0.7	0	3.9
Kaliner, 2009	Olopatadine 4 puffs/nostril	65/65	1.5					3.1	4.6
	Fluticasone propionate 200mcg[a]	65/65	0					0	0
Newson-Smith, 1997	Azelastine 1120mcg[bc]	83		2.4		1.2	0	6	2.4
	Beclomethasone dipropionate 400mcg[de]	83		7.2		2.4	1.2	0	1.2
Ratner, 2008[f]	Azelastine 4 puffs/nostril	49/49		4.1				8.2	
	Fluticasone propionate 200mcg	50/49		4				2	

N/n = Number of patients randomized/number of patients analyzed.

Symptom severity is unspecified unless otherwise noted (MILD, MOD = moderate, or SEV = severe).

[a] Other: Ocular injection: 1.5.

[b] Number of reports. Only bitter aftertaste considered tx-related.

[c] Other: Loss of smell: 0.

[d] Number of reports.

[e] Other: Loss of smell: 1.2.

[f] Sample of reports.

Appendix Table C77. Comparative harms: intranasal corticosteroid versus nasal cromolyn

Author, year	Treatment Group	N/n	Sedation	Headache	Stinging	Dryness	Burning	Nasal Discomfort	Bitter Aftertaste	Nosebleeds
Bjerrum, 1985	Budesonide 400 mcg	22/21		MILD: 4.5		MILD: 4.5		MILD: 0		MILD: 4.5
				SEV: 4.5				SEV: 14.3		SEV: 4.5
	Cromolyn 26 mg	21/21		MILD: 0		MILD: 19		MILD: 14.3		MILD: 0
					SEV: 19		SEV:14.3			
Bousquet, 1993[a]	Fluticasone propionate 200 mcg	110/73					1.4	2.7		
	Cromolyn 20.8 mg	108/87				1.1		1.1		
Lange, 2005[b]	Mometasone furoate 200 mcg	41/40	2.4	43.9				7.3		
	Cromolyn 22.4 mg	42/42	0	40.5				11.9		
Welsh, 1987	Cromolyn 41.6 mg	30/28		16.7		0	0	3.3		3.3
	Flunisolide 200 mcg	30/30		3.3	26.7	3.3	3.3		0	0
	Beclomethasone dipropionate 336 mcg	30/28		16.7	0	0	3.3	3.3		0

N/n = Number of patients randomized/number of patients analyzed.

Symptom severity is unspecified unless otherwise noted (MILD, MOD = moderate, or SEV = severe).

[a] Number of reports.

[b] Percent of events, not patients.

Appendix Table C78. Comparative harms: intranasal corticosteroid versus leukotriene receptor antagonist

Author, Year	Treatment Group	N/n	Headache	Palpitations	Anxiety	Nosebleeds
Martin, 2006	Fluticasone propionate 200 mcg	367/364	MOD: 4			MOD: 3
				SEV: 0.3	SEV: 0.3	
	Montelukast 10 mg	369/366	MOD: 6			MOD: 4
			SEV: 0.3	SEV: 0		
Nathan, 2005	Fluticasone propionate 200 mcg[a]	291/291	9			3
	Montelukast 10 mg[b]	282/282	14			2
Ratner, 2003	Fluticasone propionate 200 mcg[c]	353/353	MOD: 5			MOD: 2
	Montelukast 10 mg[c]	352/352	MOD: 7			MOD: 1

N/n = Number of patients randomized/number of patients analyzed.

Symptom severity is unspecified unless otherwise noted (MILD, MOD = moderate, or SEV = severe).

[a] Adrenal: geometric mean urinary cortisol @ week 4 = 15.67 mcg/24h (n=58).

[b] Adrenal: geometric mean urinary cortisol @ week 4 = 11.99 mcg/24h (n=51).

[c] Nasal signs and symptoms were not captured as adverse events. Most adverse events reported were mild to moderate Sample, these are adverse events reported in >1% in either group. No deaths or serious AEs reported (discontinuations not broken down by treatment allocations).

Appendix Table C79. Comparative harms: combination oral selective antihistamine plus intranasal corticosteroid versus intranasal corticosteroid

Author, Year	Treatment Group	N/n	Sedation	Headache	Burning	Nosebleeds
Anolik, 2008	Mometasone furoate 200 mcg/ Loratadine 10 mg	169/169	MOD: 2	MOD: 4	MOD: 2	MOD: 4
	Mometasone furoate 200 mcg	176/176	MOD: 1	MOD: 6	MOD: 0	MOD: 1
Barnes, 2006	Fluticasone propionate 200 mcg	31/27	3.7			
	Fluticasone propionate 200 mcg / Levocetirizine 5 mg	31/27				MILD: 3.7
Benincasa, 1994[a]	Fluticasone propionate 200 mcg	227/227	SEV: 0.9	SEV: 0.4		
	Fluticasone propionate 200 mcg/ Cetirizine 10 mg	227/227	SEV: 1.3	SEV: 0.4		SEV: 0.4
Ratner, 1998	Loratadine 10 mg	150/150				≤1[b]
	Fluticasone propionate 200 mcg	150/150				
	Loratadine 10 mg/ Fluticasone propionate 200 mcg	150/150				

N/n = Number of patients randomized/number of patients analyzed.

Symptom severity is unspecified unless otherwise noted (MILD, MOD = moderate, or SEV = severe).

[a] Number of reports.

[b] Across all treatment groups. Adverse events are not otherwise broken down by group.

Appendix Table C80. Comparative harms: combination oral selective antihistamine plus intranasal corticosteroid versus oral selective antihistamine

Author, Year	Treatment Group	N/n	Sedation	Headache	Burning	Nosebleeds
Anolik, 2008	Mometasone furoate 200 mcg/ Loratadine 10 mg	169/166	MOD: 2	MOD: 4	MOD: 2	MOD: 4
	Loratadine 10 mg	181/175	MOD: 2	MOD: 8	MOD: 0	MOD: 1
Benincasa, 1994[a]	Fluticasone propionate 200 mcg	227/227	SEV: 1.3	SEV: 0.4		SEV: 0.4
	Fluticasone propionate 200 mcg/ Cetirizine 10 mg	227/227				
Ratner, 1998	Loratadine 10 mg	150/150				≤1[b]

Author, Year	Treatment Group	N/n	Sedation	Headache	Burning	Nosebleeds
	Fluticasone propionate 200 mcg	150/150				
	Loratadine 10 mg/ Fluticasone propionate 200 mcg	150/150				

N/n = Number of patients randomized/number of patients analyzed.

Symptom severity is unspecified unless otherwise noted (MILD, MOD = moderate, or SEV = severe).

[a] Number of reports.

[b] Across all treatment groups. Adverse events are not otherwise broken down by group.

Appendix Table C81. Comparative harms: combination intranasal corticosteroid plus nasal antihistamine versus intranasal corticosteroid

Author, Year	Drug, Dose/Day	N/n	Sedation	Headache	Nasal Discomfort	Bitter Aftertaste	Nosebleeds
Carr, 2012 (Trial 1)	Azelastine 548 mcg/ Fluticasone propionate 200 mcg	207/ 207		0.5	1	2.4	1
	Fluticasone propionate 200 mcg	207/ 207		2.4	1	1	2.4
Carr, 2012 (Trial 2)	Azelastine 548 mcg/ Fluticasone propionate 200 mcg	193/ 193		2.6	0.5	2.1	1.5
	Fluticasone propionate 200 mcg	189/ 189		2.1	0	0.5	1.6
Carr, 2012 (Trial 3)	Azelastine 548 mcg/ Fluticasone propionate 200 mcg	448/ 448	1.1	1.3		4.7	1.8
	Fluticasone propionate 200 mcg	450/ 450	0	1.3		0.2	1.1
Hampel, 2010	Azelastine 548 mcg/ Fluticasone propionate 200 mcg	153/ 153	0.7	2.6	1.3	7.2	3.9
	Fluticasone propionate 200 mcg	153/ 153	0.7	3.9	0.7	0	3.9
Ratner, 2008[a]	Azelastine 8 puffs/ Fluticasone propionate 200 mcg	52/ 52		5.8		13.5	
	Fluticasone propionate 200 mcg	50/ 49		4		2	

N/n = Number of patients randomized/number of patients analyzed.

Symptom severity is unspecified unless otherwise noted (MILD, MOD = moderate, or SEV = severe).

[a] Sample of reports.

Appendix Table C82. Comparative harms: combination intranasal corticosteroid plus nasal antihistamine versus nasal antihistamine

Author, Year	Drug, Dose/Day	N/n	Sedation	Headache	Nasal Discomfort	Bitter Aftertaste	Nosebleeds
Carr, 2012 (Trial 1)	Azelastine 548 mcg/ Fluticasone propionate 200 mcg	207/ 207		0.5	1	2.4	1

	Azelastine 548 mcg	208/ 208		0.5	1.9	3.4	1.9
Carr, 2012 (Trial 2)	Azelastine 548 mcg/ Fluticasone propionate 200 mcg	193/ 193		2.6	0.5	2.1	1.5
	Azelastine 548 mcg	194/ 194		2.1	1	7.2	1.6
Carr, 2012 (Trial 3)	Azelastine 548 mcg/ Fluticasone propionate 200 mcg	448/ 448	1.1	1.3		4.7	1.8
	Azelastine 548 mcg	445/ 445	0.4	2		5.1	1.1
Hampel, 2010	Azelastine 548 mcg/ Fluticasone propionate 200 mcg	153/ 153	0.7	2.6	1.3	7.2	3.9
	Azelastine 548 mcg	152/ 152	0.7	1.3	0	2	2.6
Ratner, 2008[a]	Azelastine 8 puffs/ Fluticasone propionate 200 mcg	52/ 52		5.8		13.5	
	Azelastine 8 puffs	49/ 49		4.1		8.2	

N/n = Number of patients randomized/number of patients analyzed.

Symptom severity is unspecified unless otherwise noted (MILD, MOD = moderate, or SEV = severe).

[a] Sample of reports.

Appendix Table C83. Comparative harms: combination oral selective antihistamine plus oral decongestant versus oral selective antihistamine

Author, Year	Treatment Group	N	Sedation	Headache	Palpitations	Insomnia	Anxiety	Other: Chest Pain
Bronsky, 1995	Loratadine 10 mg/ Pseudoephedrine 240 mg	221/212	6	25		5	5	
	Loratadine 10 mg	217/212	4	23		1	1	
Chervinsky, 2005[a]	Desloratadine 5 mg/ Pseudoephedrine 240 mg	214/200		8		10		
	Desloratadine 5 mg	214/200		8		2		
	Pseudoephedrine 240 mg	222/204		6		11		
Grosclaude, 1997	Cetirizine 10 mg/ Pseudoephedrine 240 mg	230/230	6.1	4.3		0	0	
	Cetirizine 10 mg	231/231	3.1	7.1		11.1	2.2	
Grubbe, 2009	Desloratadine 5 mg/ Pseudoephedrine 240 mg[bc]	200		6.5		9.5		
	Desloratadine 5 mg[de]	198		7.1		3.0		
Pleskow, 2005	Desloratadine 5 mg/ Pseudoephedrine 240 mg	372	6	5	1	5	2	
	Desloratadine 5 mg	372	4	6	1	1	1	
Schenkel, 2002[f]	Desloratadine 5 mg/ Pseudoephedrine 240 mg	336/336	3	3		4.8	2.7	0.3[g]

Author, Year	Treatment Group	N	Sedation	Headache	Palpitations	Insomnia	Anxiety	Other: Chest Pain
	Desloratadine 5 mg	340/340	2.1	1.5		0.6	0.6	
Sussman, 1999[h]	Fexofenadrine 120 mg/ Pseudoephedrine 240 mg	215/215	0	7.3	0	1.8	0	
	Fexofenadrine 120 mg	218/218	1.4	12.4	2.8	12.8	1.4	

N/n = Number of patients randomized/number of patients analyzed.

Symptom severity is unspecified unless otherwise noted (MILD, MOD = moderate, or SEV = severe).

[a] Unclear if proportions of patients, or reports.

[b] Other: Increased heart rate 3.9 BPM.

[c] No serious or unexpected adverse events reported; 7 patients discontinued due to adverse events.

[d] Other: no increased heart rate reported.

[e] No serious or unexpected adverse events reported; 9 patients discontinued due to adverse events.

[f] Number of reports.

[g] Assigned Severe category by abstractor.

[h] Number of reports.

Appendix Table C84. Comparative harms: pediatric oral nonselective antihistamine versus oral selective antihistamine

Author, Year	Treatment Group	N/n	Sedation	Headache	Nosebleeds
Tinkelman, 1996	Cetirizine 10 mg	62/62	MOD: 3.6	MOD: 3.2	
	Chlorpheniramine 2 mg	63/63	MOD: 7.9	MOD: 6.3	
Boner, 1989	Loratadine 5 mg	21			MOD: 9.5
			0		
	Dexchlorpheniramine 3 mg	19			MILD: 10.5
			21.1		

N/n = Number of patients randomized/number of patients analyzed.

Symptom severity is unspecified unless otherwise noted (MILD, MOD = moderate, or SEV = severe).

Comparative Effectiveness and Harms of SAR Treatments in Children Younger Than 12 Years of Age

Appendix Table C85. Trial description: oral selective antihistamine versus oral nonselective antihistamine in children

Author, Year	Location/ Site(s)	Enrollment/ Treatment Duration	Funding/ Author Industry Disclosures	N	Inclusion Criteria	Exclusion Criteria[a]	Rescue Medication Use	Objective Diagnosis	Run-in \Period	Pollen Counts Measured	Patient Blinding	Assessor Blinding
Tinkelman, 1996	N. America Multiple	2 weeks	Industry NR	126	Minimum SAR severity	SAR meds/NR Other meds Infection Deformities	No	•			Open Label trial	
Boner, 1989	Europe	April 1986 2 weeks	Industry Yes	40	Minimum SAR severity	SAR meds/- Chronic asthma Immunotherapy Deformities	No	•		•		

N = Patients randomized to comparator groups of interest; NR = not reported; SAR = seasonal allergic rhinitis.

[a] +, -, or NR indicates whether FDA-recommended washout periods were required (+), were not required (-), or were not reported (NR) for restricted SAR medications prior to trial entry.

Appendix Table C86. Patient characteristics: oral selective antihistamine versus oral nonselective antihistamine in children

Author, Year	n	Drug, Dose/Day	Mean Age, years	Sex, % Female	Race, %	Mean Disease Duration, years	Mean Baseline NSS
Tinkelman, 1996	126	Cetirizine 10 mg[a]	8.6 Range: 6-11	35.5	White: 87.1 Other: 12.9	5.8 (2.6)	NR
		Chlorpheniramine 2 mg	8.7 Range: 6-11	30.2	White: 77.8 Other: 22.2	5.2 (2.6)	NR
Boner, 1989	40	Loratadine 5 mg[a]	7.6 (2.9)	33.3	Unspecified	3.2 (1.3)	NR
		Dexchlorpheniramine 3 mg[a]	7.8 (3.0)	36.8	Unspecified	2.5 (1.8)	NR

n = Patients randomized to comparator groups of interest; NR = not reported; NSS = nasal symptom score.

Values are presented as mean (standard deviation) unless otherwise noted.

[a] Doses were determined based on body weight.

Appendix Table C87. USPSTF quality assessment: oral selective antihistamine versus oral nonselective antihistamine in children

Author, year	Assembled comparable groups	Maintained comparable groups	Minimal follow-up loss	Measurements equal, valid, and reliable	Interventions clearly defined	Important outcomes considered	Appropriate analysis of results	Overall USPSTF rating
Tinkelman, 1996	Yes	Yes	Yes	No	Yes	Uncertain	No	Poor
Boner, 1989	No	Uncertain	Yes	No	Yes	Yes	No	Poor

USPSTF = United States Preventive Services Task Force.

Appendix Table C88. Nasal symptom outcomes: change from baseline–oral selective antihistamine versus oral nonselective antihistamine in children

Author, Year	Drug, Dose/Day	N/n	Time, weeks	Congestion	p	Sneezing	p
Tinkelman, 1996	Cetirizine 10 mg[a]	62/62	2	-0.7	NS	-0.5	NS
	Chlorpheniramine 2 mg	63/63		-0.8		-0.5	

N/n = Number of patients randomized to comparator groups of interest/number of patients analyzed; NS= non-significant.

[a] Dose was determined based on body weight.

Appendix Table C89. Eye symptom outcomes–oral selective antihistamine versus oral nonselective antihistamine in children

Author, Year	Drug, Dose/Day	N/n	Time, weeks	Itching eyes	p	Watering eyes	p
Tinkelman, 1996	Cetirizine 10 mg	62/62	2	-0.6	NS	-0.2	NS
	Chlorpheniramine 2 mg	63/63		-0.7		-0.3	

N/n = number of patients randomized to comparator groups of interest/number of patients analyzed; NS = non-significant.

Appendix D. Data Abstraction Form Elements

Population Form

- Is the reference about adults, children or pregnant women?
    - **Adults**
    - **Children**
    - **Pregnant women**

Study Characteristics Form

- First Author (last name, first name)
- Publication Year
- Study Location
    - North America
    - Europe
    - Asia
    - Other (specify)
    - Multicontinental
- **Does the reference have a single or multiple sites?**
    - **Single**
    - **Multiple**
- **Enrollment month, year- XX/XXXX**
- **Funding**
    - Industry
    - Academia
    - Academia
    - Not reported
    - Other
- **Were author industry relationships disclosed/identified?**
    - **Yes**
    - **No**
    - **Not Reported**
- Study Design
    - RCT
    - Quasi-RCT
    - Controlled (non-randomized) clinical trial
    - Population-based cohort study
    - Case-control study
    - SR/MA
- Intervention N:
    - Total number of patients randomized:
    - Total number of patients analyzed:

- **SAR diagnosis objectively confirmed?**
    - Yes
    - No
- Inclusion criteria:
    - Minimum SAR severity:
    - Minimum SAR duration:
    - Both:
- **Exclusion criteria**:
    - SAR medication restrictions
    - Other medication restrictions
    - Chronic asthma
    - Immunotherapy
    - Pregnancy
    - Respiratory infection
    - Anatomical deformities
    - Sleep apnea
    - Other:
- Other symptom-relieving medications allowed?
    - Yes
    - No
- Duration of treatment (weeks)
- Duration of follow-up (weeks)
    - Number of weeks
    - Not reported
- Were pollen counts measured
    - Yes
    - No
- Blinding
    - Patient
    - Assessor
    - Inadequate patient blinding
    - Inadequate assessor blinding
    - Open-label trial (not blinded)
    - Not reported
- Was a VAS scale used?
- **Interval NSS definitions**
    - Mild
    - Moderate
    - Severe
- **Total nasal symptom scale used**
    - Sum
    - Mean
- **TNSS daily maximum score**

Group Characteristics Form

- **Group**
  - Group One
  - Group Two
  - Group Three
  - Group Four
- Component 1
  - Drug class
    - Intranasal corticosteroid
    - Selective antihistamine, oral
    - Selective antihistamine, nasal
    - Non-selective antihistamine, oral
    - Intranasal anticholinergic
    - Intranasal mast cell stabilizer
    - Oral decongestant
    - Intranasal decongestant
    - Oral LRA
    - Nasal saline
  - Drug dose
  - Frequency
  - Total daily dose
- Component 2
  - Drug class
    - Intranasal corticosteroid
    - Selective antihistamine, oral
    - Selective antihistamine, nasal
    - Non-selective antihistamine, ora
    - Intranasal anticholinergic
    - Intranasal mast cell stabilizer
    - Oral decongestant
    - Intranasal decongestant
    - Oral LRA
    - Nasal saline
  - Drug dose
  - Frequency
  - Total daily dose

Patient Characteristics Form

- Group
  - Group One
  - Group Two
  - Group Three

    - Group Four
- **Patient population**
- **Age**
    - **Mean**
    - **Median**
    - **Range**
    - **SD**
    - **IQR**
- **% Female- XX.X**
- **% Race- XX.X**
    - **Mean**
    - **Median**
    - **Range**
    - **SD**
    - **IQR**
    - **Other**
- **Disease duration (years)**
    - **Mean**
    - **Median**
    - **Range**
    - **SD**
    - **IQR**
    - **Other**

Symptom Outcomes Form

- **Group**
    - Group One
    - Group Two
    - Group Three
    - Group Four
- Total number of patients randomized:
- Total number of patients analyzed:
- Outcome measurement type
    - Reflective
    - Instantaneous
    - AM
    - PM
    - Reflective -AM
    - Reflective -PM
    - Instantaneous -AM
    - Instantaneous -PM
    - Other
    a. Not specified
- Time Point
    - 2 weeks

    - 3 weeks
    - 4 weeks
    - 2 months
    - 3 months
    - 4 months
    - 6 months
    - Other
    - Not specified
- Label
    - Endpoint
    - Overall/Mean
    - Relative
    - Interval/Mean
    - Uncertain
- Outcome
    - **NSS, congestion**
    - **NSS, rhinorrhea**
    - **NSS, sneezing**
    - **NSS, nasal itching**
    - **TNSS**
    - **Asthma**
    - **TOSS**
    - **School performance**
    - **Other medication/rescue med use**
- Outcome measure
    - Pre Mean (SD)
    - Pre Median (range)
    - Post Mean (SD)
    - Post Median (range)
    - Change Mean (SD)
    - Change 95% CI
- Cough mentioned?
    - Yes
    - No
- **Adherence assessed?**
    - **Yes** (% adherence)
    - **No**
- **Are other outcomes available?**

Function and Quality of Life Outcomes Form

- **Group**
    - Group One
    - Group Two
    - Group Three
    - Group Four

- **QoL outcomes mentioned?**
    - **Yes**
    - **No**
- Total number of patients randomized:
- Total number of patients analyzed:
- Time Point
    - 2 weeks
    - 3 weeks
    - 4 weeks
    - 2 months
    - 3 months
    - 4 months
    - 6 months
    - Other
    - Not specified
- **Quality of Life outcomes**
    - **RQLQ**
    - **Mini-RQLQ**
    - **Rhinasthma QLQ**
    - **Nocturnal RQLQ**
    - **SF-36**
    - **PGA**
    - **Epworth**
- Outcome measure
    - Pre Mean (SD)
    - Pre Median (range)
    - Post Mean (SD)
    - Post Median (range)
    - Change Mean (SD)
    - Change 95% CI

Comparisons Form

- **Is a statistical test performed?**
    - Yes
    - No
- **Statistical Test**
    - Kruskal-Wallis
    - Mann Whitney U
    - ANOVA
    - Wilcoxon rank sum test
    - Chi-square
    - T-test
    - ANCOVA
    - Other
- Outcome measurement type

    - Reflective
    - Instantaneous
    - AM
    - PM
    - Reflective -AM
    - Reflective -PM
    - Instantaneous -AM
    - Instantaneous -PM
    - Other
    - Not specified
- Time point
    - Pre
    - 2 weeks
    - 3 weeks
    - 4 weeks
    - 2 months
    - 3 months
    - 4 months
    - 6 months
    - Other
    - Not specified
- Label
    - Endpoint
    - Overall/Mean
    - Relative
    - Interval/Mean
    - Uncertain
- Comparison between groups
    - 1 vs. 2
        - p-value
    - 1 vs. 3
        i. p-value
    - 2 vs. 3
        ii. p-value
    - Multiple group comparisons
        - p-value
- Outcome
    - **NSS, congestion** Mean difference (95% CI)
    - **NSS, sneezing** Mean difference (95% CI)
    - **NSS, rhinorrhea** Mean difference (95% CI)
    - **NSS, nasal itching** Mean difference (95% CI)
    - **TNSS**
    - **Rescue med use** Ratio (95% CI)
    - **TOSS** Mean difference (95% CI)

Function and QoL Comparisons Form

- **Is a statistical test performed?**
    - Yes
    - No
- **Statistical Test**
    - Kruskal-Wallis
    - Mann Whitney U
    - ANOVA
    - Wilcoxon rank sum test
    - Chi-square
    - T-test
    - ANCOVA
    - Other
- Time point
    - Pre
    - 2 weeks
    - 3 weeks
    - 4 weeks
    - 2 months
    - 3 months
    - 4 months
    - 6 months
    - Other
    - Not specified
- Comparison between groups
    - 1 vs. 2
        - p-value
    - 1 vs. 3
        - p-value
    - 2 vs. 3
        - p-value
    - Multiple group comparisons
        - p-value
- **Quality of Life outcomes**
    - Test result (95% CI)
    - **Mini-RQLQ** Test result (95% CI)
    - **RQLQ Rhinasthma QLQ** Test result (95% CI)
    - **Nocturnal RQLQ** Test result (95% CI)
    - **SF-36** Test result (95% CI)
    - **PGA** Test result (95% CI)
    - **Epworth** Test result (95% CI)

Adverse Events Form

- **Group**
    - Group One

    - Group Two
    - Group Three
    - Group Four
- **AEs mentioned?**
    - **Yes**
    - **No**
- N (number analyzed)
- **Type of adverse event by severity**
    - **Mild AEs reported -- % XX.X**
    - **Moderate AEs reported -- % XX.X**
    - **Severe AEs reported -- % XX.X**
    - **Unspecified severity AEs reported -- % XX.X**
        - Sedation
        - Headache
        - Stinging
        - Dryness
        - Burning
        - Impaired work/school performance
        - Odor abnormalities
        - Bitter aftertaste
        - Hypertension
        - Palpitations
        - Insomnia
        - Anxiety
        - Nosebleeds
        - Rhinitis medicamentosa
        - Increased intraocular pressure
        - Cataract formation
        - Nasal septal atrophy
        - Fungal infection
        - Adrenal suppression
        - Hyperglycemia
        - Bone demineralization/fracture
        - Growth delay in children
        - Traffic accidents
        - Nasal discomfort

Study Quality

RCT Quality Assessment (USPSTF)

- **Power calculation reported?**
    - Yes
    - No

- Assembly of comparable groups
    - Yes
    - No
- Maintenance of comparable groups (includes attrition, crossovers, adherence, and contamination)
    - Yes
    - No
    - Uncertain
- Minimal loss to followup (<20% each treatment arm)
    - Yes
    - No
- Interventions comparable/ clearly defined
    - Yes
    - No
    - Uncertain
- All important outcomes considered
    - Yes
    - No
- Appropriate analysis of results (adjustment for potential confounders and intention-to-treat analysis)
    - Yes
    - No
- Overall Rating
    - Good
    - Fair
    - Poor

AE Reporting Quality Assessment, McMaster

- Were the harms pre-defined using standardized or precise definitions?
    - Yes
    - No
    - Uncertain
- Were serious events precisely defined?
    - Yes
    - No
    - Uncertain
- Were severe events precisely defined?
    - Yes
    - No
    - Uncertain
- Was the mode of harms collection specified as active?
    - Yes
    - No
    - Uncertain
- Was the mode of harms collection specified as passive?

    - Yes
    - No
    - Uncertain
- Did the study specify who collected the harms?
    - Yes
    - No
    - Uncertain
- Did the study specify the training or background of who ascertained the harms?
    - Yes
    - No
    - Uncertain
- Did the study specify the timing and frequency of collection of the harms?
    - Yes
    - No
    - Uncertain
- Did the author(s) use standard scale(s) or checklist(s) for harms collection?
    - Yes
    - No
    - Uncertain
- Did the authors specify if the harms reported encompass all the events collected or a selected sample?
    - Yes
    - No
    - Uncertain
- Was the number of participants that withdrew or were lost to follow-up specified for each study group?
    - Yes
    - No
    - Uncertain
- Was the total number of participants affected by harms specified for each study arm?
    - Yes
    - No
    - Uncertain
- Did the author(s) specify the number for each type of harmful event for each study group?
    - Yes
    - No
    - Uncertain
- Did the author(s) specify the type of analyses undertaken for harms data?
    - Yes
    - No
    - Uncertain

Appendix E. United States Preventive Services Task Force (USPSTF) Criteria for Randomized Controlled Trials (RCTs)

Good: Meets all criteria outlined below.

Fair: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential covariates are accounted for. Intention to treat analysis is performed.

Poor: Studies will be graded "poor" if any of the following flaws exists: groups assembled initially are not close to being comparable or maintained throughout the trial; unreliable or invalid measurement instruments are used or not applied at all equally among groups (including not masking outcome assessment); and key covariates are given little or no attention. Intention to treat analysis is lacking.

Criteria

- Initial assembly of comparable groups:
    - For RCTs: potential covariates appropriately distributed
    - For cohort studies: potential confounders controlled
- Maintenance of comparable groups ≈ < 20% loss to follow-up in each arm
- Measurements equal, reliable, and valid
- Interventions comparable and clearly defined
- All important outcomes considered
- Analysis:
    - For RCTs: intention-to-treat, covariate adjustment
    - For cohort studies: adjustment for potential confounders for cohort studies
- Other aspects of analyses appropriate (e.g. missing data, sensitivity analyses)

Appendix F. McMaster Quality Assessment Scale of Harms (McHarm)

Rating

- Were the harms PRE-DEFINED using standardized or precise definitions?
  - Yes
  - No
  - Unsure
- Were SERIOUS events precisely defined?
  - Yes
  - No
  - Unsure
- Were SEVERE events precisely defined?
  - Yes
  - No
  - Unsure
- Were the number of DEATHS in each study group specified OR were the reason(s) for not specifying them given?
  - Yes
  - No
  - Unsure
- Was the mode of harms collection specified as ACTIVE?
  - Yes
  - No
  - Unsure
- Was the mode of harms collection specified as PASSIVE?
  - Yes
  - No
  - Unsure
- Did the study specify WHO collected the harms?
  - Yes
  - No
  - Unsure
- Did the study specify the TRAINING or BACKGROUND of who ascertained the harms?
  - Yes
  - No
  - Unsure
- Did the study specify the TIMING and FREQUENCY of collection of the harms?
  - Yes
  - No

- Unsure

- Did the author(s) use STriamcinolone acetonide NDARD scale(s) or checklist(s) for harms collection?
  - Yes
  - No
  - Unsure
- Did the authors specify if the harms reported encompass ALL the events collected or a selected SAMPLE?
  - Yes
  - No
  - Unsure
- Was the NUMBER of participants that withdrew or were lost to follow-up specified for each study group?
  - Yes
  - No
  - Unsure
- Was the TOTriamcinolone acetonide L NUMBER of participants affected by harms specified for each study arm?
  - Yes
  - No
  - Unsure
- Did the author(s) specify the NUMBER for each TYPE of harmful event for each study group?
  - Yes
  - No
  - Unsure
- Did the author(s) specify the type of analyses undertaken for harms data?
  - Yes
  - No
  - Unsure