Ann Allergy Asthma Immunol xxx (2017) 1–23

Contents lists available at ScienceDirect

Practice Guideline

Treatment of seasonal allergic rhinitis
An evidence-based focused 2017 guideline update

Mark S. Dykewicz, MD; Dana V. Wallace, MD; Fuad Baroody, MD; Jonathan Bernstein, MD; Tim Craig, DO; Ira Finegold, MD; Faith Huang, MD; Desiree Larenas-Linnemann, MD; Eli Meltzer, MD; Gary Steven, MD, PhD; David I. Bernstein, MD; Joann Blessing-Moore, MD; Chitra Dinakar, MD; Matthew Greenhawt, MD, MBA; Caroline C. Horner, MD; David A. Khan, MD; David Lang, MD; John Oppenheimer, MD; Jay M. Portnoy, MD; Christopher R. Randolph, MD; Matthew A. Rank, MD; Workgroup Chair and Cochair: Mark S. Dykewicz, MD; Dana V. Wallace, MD

ARTICLE INFO

Article history:
Received for publication August 9, 2017.
Accepted for publication August 15, 2017.

Guideline Update Objective

Allergic rhinitis (AR) is a prevalent disorder responsible for a significant and often underappreciated health burden for individuals and society (see Burden of Disease section). Guidelines to improve care for patients with AR have been evolving in an effort to respond to the introduction of new treatment approaches, to address the availability of additional studies that compare treatment options, and to incorporate the use of more standardized, evidence-based medicine methods to analyze data and make recommendations.[1-4] As part of a comprehensive review of

Task Force Reviewers: David I. Bernstein, MD; Joann Blessing-Moore, MD; Chitra Dinakar, MD; Matthew Greenhawt, MD, MBA; Carolyn C. Horner, MD; David A. Khan, MD; David Lang, MD; John Oppenheimer, MD; Jay M. Portnoy, MD; Christopher R. Randolph, MD; Matthew A. Rank, MD; and Dana Wallace, MD

Reprints: Natalie Aumann, Joint Task Force on Practice Parameters, 85 W Algonquin Rd, Ste 550, Arlington Heights, IL 60005; E-mail: NAumann@aaaai.org

Disclosures: All members of the Rhinitis Workgroup and the Joint Task Force on Practice Parameters (JTFPP) were required to complete a detailed declaration of interest statement, including all current and future conflicts of interest and past conflicts of interest restricted to 2 years before joining the workgroup and/or the JTFPP. It is believed that excluding all individuals with some degree of potential conflict of interest would prevent the assembly of a workgroup and the JTFPP. The authors therefore allowed members of the workgroup and the JTFPP to have past financial and/or intellectual conflicts of interest. No consequences were attached to the stated interests, but rather the authors insisted on transparency. All members of the workgroup and the JTFPP were allowed to participate in all discussions and had equal weight in formulating the statements. All were allowed equal involvement in data extraction and writing the rationales. The declaration of interest forms are available from www.allergyparameters.org and are updated on a regular basis. A summary of interests disclosed on work group members' conflict of interest disclosure statements (not including information concerning family member interests) can be found in the article's online repository and at www.allergyparameters.org. Completed conflict of interest disclosure statements are available on request. The JTFPP recognizes that experts in a field are likely to have interests that could come into conflict with the development of a completely unbiased and objective practice parameter. To take advantage of that expertise, a process has been developed to prevent potential conflicts from influencing the final document in a negative way. At the workgroup level, all the sections are reviewed by all workgroup members to determine whether the content is appropriate and without apparent bias. If a section is deemed to have apparent bias, it will be appropriately revised without the section author's involvement to remove potential bias. In addition, the entire document is then reviewed by the JTFPP, and any apparent bias is removed at that level. In a final stage of review, the practice parameter is sent for review and comment to invited expert reviewers and the American Academy of Allergy, Asthma, and Immunology and American College of Allergy, Asthma, and Immunology general membership via posting the document on their website.

Disclaimer: The American Academy of Allergy, Asthma, and Immunology (AAAAI) and the American College of Allergy, Asthma, and Immunology (ACAAI) have jointly accepted responsibility for establishing Treatment of Seasonal Allergic Rhinitis: An Evidence-Based Focused 2017 Guideline Update. This is a complete and comprehensive document at the current time. The medical environment is changing, and not all recommendations will be appropriate or applicable to all patients. Because this document incorporated the efforts of many participants, no single individual, including members serving on the Joint Task Force on Practice Parameters (JTFPP), are authorized to provide an official AAAAI or ACAAI interpretation of these practice parameters. Any request for information or interpretation of this practice parameter by the AAAAI or ACAAI should be directed to the executive offices of the AAAAI and the ACAAI. These parameters are not designed for use by the pharmaceutical industry in drug development or promotion. The JTFPP understands that the cost of diagnostic tests and therapeutic agents is an important concern that may appropriately influence the workup and treatment chosen for a given patient. The JTFPP recognizes that the emphasis of our primary recommendations regarding a medication may vary, for example, depending on third-party payer issues and product patent expiration dates. However, because a given test or agent's cost is so widely variable, and there is a paucity of pharmacoeconomic data, the JTFPP generally does not consider cost when formulating practice parameter recommendations. In extraordinary circumstances, when the cost benefit of an intervention is prohibitive as supported by pharmacoeconomic data, commentary may be provided. These parameters are not designed for use by pharmaceutical companies in drug promotion. The JTFPP is committed to ensuring that the Practice

https://doi.org/10.1016/j.anai.2017.08.012

recommendations made in an updated practice parameter on rhinitis published in 2008 by the Joint Task Force on Practice Parameters (JTFPP) of the American Academy of Allergy, Asthma, and Immunology (AAAAI), the American College of Allergy, Asthma, and Immunology (ACAAI), and the Joint Council of Allergy, Asthma, and Immunology, a workgroup of the Joint Task Force was convened to develop this focused guideline document on seasonal allergic rhinitis (SAR) treatment.[4] The Treatment of Seasonal Allergic Rhinitis: An Evidence-Based Focused 2017 Guideline Update is the first AAAAI/ACAAI guideline on rhinitis to use the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach with an explicit declaration and management of potential competing interests of panel members.

Using a modified Delphi process (see Methods section for description of the process), the JTFPP Treatment of Seasonal Allergic Rhinitis: An Evidence-Based Focused 2017 Guideline Update workgroup developed a group of questions that it assessed could be answered with GRADE recommendations.[5] The workgroup ultimately selected 3 questions for systematic review that it judged (1) had clinical importance, (2) had notable new data available since the last practice parameter update, and/or (3) likely had evidence basis for more guidance than provided by a 2013 systematic review on AR by the Agency for Healthcare Research and Quality (AHRQ) document,[6] and (4) could provide an opportunity to promote more cost-effective and/or improved care. The 3 questions addressed by this systematic review and the derived key clinical advice are outlined in Box 1 and Box 2.

This updated SAR guideline is therefore focused. Ultimately, the objective of this guideline document is to highlight several quality improvement opportunities for clinicians in the care of AR and reduce unnecessary cost and variations in care. Emphasizing the evidence-based method used by the workgroup in making its assessments and recommendations; this document is intended to provide guidance to health care professionals for treatment of adult and adolescent patients (≥12-15 years of age) with AR. Even though a number of these treatments are approved for younger children, the application of recommendations to children with AR would be partially based on data extrapolation from adult studies and would therefore be less certain. Recommendations in this document may not be applicable to all populations with AR and should not replace individualization of patient care or clinical judgment. Although the inclusion criteria for analyzed studies was for mild to severe AR, the studies that met all the inclusion criteria included, overwhelmingly, patients with moderate to severe symptoms of SAR. Therefore, these conclusions may not apply to patients with mild SAR. As medical treatment evolves, future data may mandate further revision of these recommendations. In the Discussion section of this document, the workgroup also outlines questions for which further research is required.

Parameters are based on the best scientific evidence that is free of commercial bias. To this end, the parameter development process includes multiple layers of rigorous review. These layers include the work group convened to draft the parameter, the task force reviewers, and peer review by members of each sponsoring society. Although the JTFPP has the final responsibility for the content of the documents submitted for publication, each reviewer's comments were discussed and reviewers received written responses to comments when appropriate. To preserve the greatest transparency regarding potential conflicts of interest, all members of the JTFPP and the practice parameters work groups will complete a standard potential conflict of interest disclosure form, which will be available for external review by the sponsoring organization and any other interested individual. In addition, before confirming the selection of a work group chairperson, the JTFPP will discuss and resolve all relevant potential conflicts of interest associated with this selection. Finally, all members of parameter work groups will be provided a written statement regarding the importance of ensuring that the parameter development process is free of commercial bias. Previously published Practice Parameters of the Joint Task Force on Practice Parameters for Allergy & Immunology are available at http://www.AAAAI.org, http://www.ACAAI.org, or http://www.allergyparameters.org.

Funding Sources: This work was funded by the American Academy of Allergy, Asthma, Immunology and the American College of Allergy, Asthma, and Immunology.

Contributors: The Joint Task Force has made a concerted effort to acknowledge all contributors to this parameter. If any contributors have been excluded inadvertently, the Task Force will ensure that appropriate recognition of such contributions is made subsequently.

Chief Editors: Mark S. Dykewicz, MD, Raymond and Alberta Slavin Endowed Professor in Allergy & Immunology, Professor of Internal Medicine, Chief, Section of Allergy and Immunology, Division of Infectious Diseases, Allergy & Immunology, Department of Internal Medicine, Director, Allergy and Immunology Fellowship Program, Saint Louis University School of Medicine, St. Louis, Missouri; Dana Wallace, MD, Associate Clinical Professor, Department of Medicine, Nova Southeastern University, Davie, Florida.

Workgroup Contributors: Mark S. Dykewicz, MD, Raymond and Alberta Slavin Endowed Professor in Allergy & Immunology, Professor of Internal Medicine, Chief, Section of Allergy and Immunology, Division of Infectious Diseases, Allergy & Immunology, Department of Internal Medicine, Director, Allergy and Immunology Fellowship Program, Saint Louis University School of Medicine, St. Louis, Missouri; Fuad Baroody, MD, Professor of Surgery (Otolaryngology–Head and Neck Surgery) and Pediatrics, The University of Chicago Medicine and the Comer Children's Hospital, Chicago, Illinois; Jonathan Bernstein, MD, Professor of Medicine University of Cincinnati Department of Internal Medicine, Division of Immunology/Allergy Section and Bernstein Allergy Group and Clinical Research Center Partner, Cincinnati, Ohio; Tim Craig, DO, Professor of Medicine and Pediatrics, Distinguished Educator, Chief and Program Director, Allergy Asthma and Immunology, Penn State University, Hershey PA; Ira Finegold, MD Professor of Medicine Icahn School of Medicine at Mount Sinai, NY Chief of Allergy Mount Sinai West, New York, Director Cooke Institute of Allergy; Faith Huang, MD, Allergist Immunologist, Southern California Permanente Medical Group, Downey, California; Desiree Larenas-Linnemann, MD, Staff Investigational Unit, Hospital Médica Sur, Mexico City, Mexico, Head Center of Excellence in Asthma and Allergy, Mexico City, Mexico; Eli Meltzer, MD, Clinical Professor of Pediatrics, Division of Allergy & Immunology, University of California, San Diego, Senior Associate, Allergy & Asthma Medical Group & Research Center, San Diego, California; Gary Steven, MD, PhD, Assistant Clinical Professor of Medicine, MCW, Allergy, Asthma & Sinus Center, Greenfield, Wisconsin.

Patient advocate contributors: Katie Heim, RN, Bernstein Allergy Group, Cincinnati, Ohio; Donna Poland, PhD, Educational Leadership, Past Principal middle school and high school, public and private, University School at Nova Southeastern University, Davie, Florida, Jessica Willworth, RN, Bernstein Allergy Group, Cincinnati, Ohio; Tonya Winders, President and CEO Allergy & Asthma Network, President Global Allergy & Asthma Patient Platform, Vienna, Virginia.

Methodology Group: Jacqueline A. Bartlett, PhD, RN, Director, Evidence Based Practice, Children's Mercy Center of Clinical Effectiveness Kansas City, Missouri.

Task Force Reviewers: David I. Bernstein, MD, Department of Medicine and Environmental Health, Division of Immunology, Allergy, and Rheumatology, University of Cincinnati College of Medicine, Cincinnati, Ohio; Joann Blessing-Moore, MD, Department of Immunology, Stanford University Medical Center, Palo Alto, California; Chitra Dinakar, MD, Clinical Professor, Stanford University School of Medicine Allergy & Asthma Clinical Chief, Stanford, California; Matthew Greenhawt, MD, MBA, MSc, Department of Pediatrics, Children's Hospital Colorado, Section of Allergy and Immunology, University of Colorado School of Medicine, Aurora, Colorado; Caroline C. Horner, MD, Associate Professor, Pediatrics, Division of Pediatric Allergy, Immunology and Pulmonary Medicine, Washington University School of Medicine, St Louis, Missouri; David A. Khan, MD, Department of Medicine, Division of Allergy & Immunology, University of Texas Southwestern Medical Center, Dallas, Texas; David M. Lang, MD, Department of Medicine and Department of Allergy and Clinical Immunology, Respiratory Institute, Cleveland Clinic Foundation, Cleveland, Ohio; John Oppenheimer, MD, Department of Internal Medicine, New Jersey Medical School, Morristown, New Jersey; Jay M. Portnoy, MD, Section of Allergy, Asthma & Immunology, The Children's Mercy Hospital, University of Missouri–Kansas City School of Medicine, Kansas City, Missouri; Christopher Randolph, MD, Center for Allergy, Asthma and Immunology, Yale Hospital, Waterbury, Connecticut; Matthew Rank, MD, Associate Professor Medicine, Mayo Clinic School of Medicine, Scottsdale, Arizona; Dana Wallace, MD, Associate Clinical Professor, Department of Medicine, Nova Southeastern University, Davie, Florida.

Invited Society Reviewers: Anju Peters, MD, Chicago, Illinois; Seong Ho Cho, MD, Tampa, Florida; Maria Slack, MD, Rochester, New York.

Box 1. Key Questions Addressed by This Systematic Review on Seasonal Allergic Rhinitis (SAR)

1. For the initial treatment of moderate to severe SAR in patients who are ≥12 years of age, is there any clinical benefit of using a combination of an oral antihistamine and an intranasal corticosteroid compared with monotherapy with an intranasal corticosteroid?
2. For the initial treatment of moderate to severe SAR in patients who are ≥15 years of age, how does montelukast compare with an intranasal corticosteroid in terms of clinical benefit.
3. For the initial management of moderate to severe SAR in patients who are ≥12 years of age, is there any clinical benefit to using combination therapy with an intranasal corticosteroid and an intranasal antihistamine compared with monotherapy with either agent?

Burden of Illness

The burden of AR is substantial. Surveys that require a physician-confirmed diagnosis of AR report prevalence rates of 14% of US adults and 13% of US children.[7] Adverse consequences on patients' quality of life may include impairment in physical and social functioning, daytime somnolence and fatigue, irritability, depression and attention deficit, learning and memory deficits, loss of productivity at work, sexual dysfunction, and sleep disordered breathing.[7-11] Compared with matched controls, patients with AR have an approximately 2-fold increase in medication costs and a 1.8-fold increase in the number of visits to health care practitioners.[12] Lack of treatment, undertreatment, and nonadherence to treatment have all been found to increase costs.[13] Sequelae of AR add to the disease burden and include headaches, ocular symptoms (itchy watery, red, swollen eyes), earaches, and cough. Epidemiologic surveys have consistently found that AR is an independent risk factor for the development of asthma. US surveys report that 38% of patients with AR have asthma and up to 78% of asthma patients have AR.[14]

Defining AR

AR is an IgE antibody–mediated, inflammatory disease that is characterized by one or more of the following symptoms: nasal congestion, rhinorrhea (anterior and posterior), sneezing, and itching.[3,4]

Box 2. Key Clinical Advice.

For initial treatment of nasal symptoms of seasonal allergic rhinitis in patients ≥12 years of age, clinicians:

- Should routinely prescribe monotherapy with an intranasal corticosteroid rather than a combination of an intranasal corticosteroid with an oral antihistamine.
- Should recommend an intranasal corticosteroid over a leukotriene receptor antagonist (for ≥15 years of age).
- For moderate to severe symptoms, may recommend the combination of an intranasal corticosteroid and an intranasal antihistamine.

Categories of AR

Classifying AR by several characteristics may define an AR subpopulation for clinical trials and assist in the selection of the most appropriate treatment strategies for an individual patient. AR may be classified by (1) temporal pattern and context of exposure to a triggering allergen, (2) frequency and duration of symptoms, and/or (3) severity.

Temporal patterns may be (1) *seasonal* (eg, pollens), (2) *perennial* (year-round exposures, eg, house dust mites), or (3) *episodic environmental* (from allergen exposures not normally encountered in the patient's home or occupational environment, eg, visiting a home with pets not present in an individual's home).[3,4] In the United States, AR traditionally has been categorized as being seasonal AR (SAR) or perennial AR (PAR), a distinction that the US Food and Drug Administration (FDA) uses for regulatory purposes when approving medications for AR. The FDA recognizes that SAR and PAR have similar pathophysiologic and end-organ manifestations, with differences between the 2 entities primarily based on the causes and duration of disease.[15] This distinction between SAR and PAR has some limitations (eg, in most temperate climates, grass sensitive patients have SAR symptoms in relation to seasonal grass pollen seasons, whereas in some warmer/tropical climates, grass sensitive patients may have PAR symptoms to year-round grass pollen seasons). The clinical implications of the distinction between SAR and PAR may be less clear when polysensitized patients have both SAR and PAR.[3,15]

Symptom Frequency

AR symptom frequency has been divided into *intermittent* (<4 days per week or <4 weeks per year) and persistent (>4 days per week and >4 weeks per year).[16] However, this classification has limitations. For example, a patient who has symptoms 3 days per week year-round would be classified as having intermittent AR even though they would closely resemble a patient with persistent AR. According to these definitions, some patients may have persistent symptoms with SAR or intermittent symptoms with PAR.

Severity

AR severity can be classified as being mild (when symptoms are present but are not interfering with quality of life) or more severe (when symptoms are bad enough to interfere with quality of life).[3,4,16] Factors that may lead to a more severe classification include sleep disturbance; impairment of daily, sport, or leisure activities; and impairment of school or work performance.[7]

Overview of AR Treatment

Treatment options for AR include environmental control(s), pharmacologic therapy, and allergen immunotherapy. Complete allergen avoidance for SAR is not possible, and reduction of exposure by limiting time outdoors is generally undesirable and often unrealistic for the patient. Pharmacologic therapy includes antihistamines (intranasal and oral), decongestants (intranasal and oral), corticosteroids (intranasal and oral), intranasal cromolyn, intranasal anticholinergics, and oral leukotriene receptor antagonists (LTRAs). The efficacy of antihistamines, corticosteroids, and LTRAs will be considered in this guideline update.

Oral Antihistamines

Antihistamines target the histamine$_1$ (H_1) receptor and relieve the itching, sneezing, and rhinorrhea of AR.[17] Antihistamines are available as oral (first- and second-generation) and intranasal preparations. First-generation antihistamines (eg, diphenhydramine, chlorpheniramine, and hydroxyzine) cross the blood-brain barrier easily and bind central H_1-receptors abundantly, which

can cause sedation. They also lack specificity because cross-binding also occurs with cholinergic, α-adrenergic, and serotonergic receptors, which can cause dry mouth, dry eyes, urinary retention, constipation, and tachycardia.[18] Cumulative use of first-generation antihistamines with strong anticholinergic properties has been associated with higher risk of dementia.[19] In contrast, second-generation antihistamines (eg, fexofenadine, cetirizine, levocetirizine, loratadine, desloratadine, ebastine, epinastine, and bilastine) are more specific for peripheral H_1-receptors and have limited penetration of the blood-brain barrier, thus reducing sedation.[20]

Intranasal Antihistamines

Intranasal preparations of azelastine[5,21-26] and olopatadine[27] are available in the United States and have a rapid onset of action and may aid in reducing nasal congestion.[28,29] As with oral antihistamines, intranasal antihistamines (INAHs) target the H_1-receptor, but there is evidence that higher nasal tissue levels achieved by intranasal administration have anti-inflammatory effects.[30-34] Sedation and bitter taste have been reported with both preparations.[35]

Intranasal Corticosteroids

Intranasal corticosteroids (INCSs) have potent anti-inflammatory properties that reduce symptoms of sneezing, itching, rhinorrhea, and congestion.[36-39] Limited data suggest that INCSs can also reduce allergic eye symptoms, such as itching, tearing, redness, and puffiness.[40,41] Intranasal, oral, and injectable corticosteroids are available, but oral and injectable preparations are generally not recommended for AR because of the adverse effects of systematically administered corticosteroids. INCSs result in a significant reduction in mediator and cytokine release, thus reducing the recruitment of basophils, eosinophils, neutrophils, and mononuclear cells to nasal secretions.[42-44] Continuous use of INCSs is recommended and is more efficacious than intermittent use,[45,46] but intermittent use of intranasal fluticasone is better than placebo.[47,48] In these studies *intermittent* was defined as required or as needed, whereas *continuous* referred to daily during pollen season. Common adverse effects of INCSs include nasal dryness, burning, stinging, blood tinged secretions, and epistaxis.[49-51] The package inserts for all INCSs recommend monitoring for intraocular pressure, glaucoma, and cataracts; monitoring for growth is also recommended in the pediatric population.

Leukotriene Receptor Antagonists

LTRAs block the cysteinyl leukotriene 1 (CysLT1) receptor. They inhibit leukotrienes, inflammatory mediators produced by mast cells, eosinophils, basophils, macrophages, and monocytes, which contribute to the symptoms of AR.[52,53] Montelukast is the only LTRA approved by the FDA for the treatment of SAR. Montelukast has a good safety profile and has been approved for patients 6 months or older. Potential adverse effects include upper respiratory tract infection and headache.[54] There are postmarketing reports of rare drug-induced neuropsychiatric events, including aggression, depression, suicidal thinking, and behavior.[55-57] As many as 40% of patients with AR have coexisting asthma. Because montelukast has been approved for both rhinitis and asthma, it may be considered in such patients.[4,58-60] The use of more than one medication is observed frequently in patients with AR, especially in patients with moderate or severe disease.[61]

Methods

Overview

The Rhinitis Workgroup that developed this guideline was composed of volunteers from the AAAAI and the ACAAI with a specific interest in the topic and the guideline process. The workgroup first developed a list of clinical questions regarding the use of single or combination medications for the treatment of AR, considering relative efficacy, possible additional efficacy by combining medications, costs, adverse effects, and other related outcomes. The top 3 questions that best addressed relevant and controversial issues were selected for GRADE analysis and are detailed in the Guideline Update Objective section of this document. These 3 questions were also part of the AHRQ 2013 systematic review. The entire JTFPP of the AAAAI and ACAAI reviewed and approved these questions before starting the literature search.

Literature Search: Design and Inclusion and Exclusion Criteria

The updated literature search (dates inclusive of July 18, 2012, to June 29, 2016) used by the Rhinitis Workgroup for the 3 questions considered in this focused systematic review was based on the same search criteria, databases, and inclusion criteria that had been used by the AHRQ's search review up to July 18, 2012,[6] with the exception of including only articles that involved human subjects and limited to those published in the English language. For these 3 specific questions, the AHRQ search criteria included randomized clinical trials (RCTs) of SAR, of at least 2 weeks' duration during active pollen season for all individuals 12 years and older. Systematic reviews and meta-analysis that assessed relevant treatment comparisons, reported an outcome of interest, and were of high quality were included in the search. Nonrandomized trials and comparative observational studies that were blinded and controlled for confounders were also included in the search and were considered for use in the final analysis. Individuals 12 years and older were required to have a minimum 2-year history of SAR of mild to severe degree of severity, consistent with Allergic Rhinitis and Its Impact on Asthma (ARIA) guideline definitions of severity, have a positive percutaneous allergy skin test result within the year before study, and be devoid of any of the predetermined exclusion criteria, as determined by the investigators. Outcomes had to include patient-reported symptom scores and/or validated quality-of-life instruments. Although ocular symptoms are important and often included in SAR studies, there was no requirement that the included trials report ocular symptoms as an outcome measure. A description of the search strategy and criteria used by the AHRQ to update the 2012 literature search for queries 1, 2, and 3 are detailed in Appendix A, Tables 1, 2, and 3.

Literature Search: Databases and Results

For both the AHRQ and Rhinitis Workgroup literature searches, the following databases were searched for RCTs, nonrandomized trials, and comparative observational studies through June 29, 2016: MEDLINE (PubMed and Ovid), EMBASE (Ovid), and Cochrane Central Register of Controlled Trials (CENTRAL). For the AHRQ search of systematic reviews from January 1, 2010, to July 18, 2012, the following additional databases were searched: Cochrane Database of Systematic Reviews, and the Database of Abstracts and Reviews of Effects and the Health Technology Assessment databases of the Centre for Reviews and Dissemination. Articles were limited to those published in the English language. Gray literature through July 18, 2012, was sought by the AHRQ by searching FDA Website, conference abstracts of relevant professional organizations, and the clinical trial registries of the US National Institutes of Health and the World Health Organization. The AHRQ screened titles and abstracts to select full-text articles that were eligible for review. Trained teamed reviewers completed the review in a duplicate manner. These full-text articles were then reviewed for inclusion in the systematic review process. The AHRQ search identified 4,513 records of which 169 were eliminated because they were being duplicate articles, leaving 4,344 articles for a title and

abstract screen. Subsequently, 4,059 references were excluded for not meeting predefined criteria, and 285 were selected for full-text review. These were combined with the 4 articles identified through gray literature and hand search. After removing the references that failed to meet the inclusion criteria, 59 unique trials were identified of which 13 reference articles were used to address the 3 questions in the current systematic review.

The updated Rhinitis Workgroup literature search initially cast a large net for all articles published in regard to rhinitis and treatment with the therapies under consideration. This yielded the following total number of articles: PubMed MEDLINE, 6,536 records; PubMed EMBASE, 140,379; Ovid MEDLINE, 1,316; and Cochrane Trials Registry, 220; for a total of 148,451 articles. After the search terms were combined, the number of possibly relevant references for question 1 was 56, for question 2 was 20, and for question 3 was 40. A summary of the literature search is found in in Appendix A, Tables 4, 5, and 6. The details of the literature search are available in Appendix C. (MEDLINE and Cochrane database printed search with review notes.) Two workgroup members reviewed all abstracts and selected full-text articles. None of the articles met the inclusion criteria that had been established.

Although the extended literature search conducted in 2016 by the JTFPP Rhinitis Workgroup did not uncover any new articles that met the inclusion criteria, based on additional selected reviews by workgroup members, including references identified in other recent rhinitis GRADE analyses, the Rhinitis Workgroup selected 3 additional articles,[62-64] all pertaining to question 1, for review by the methods group. However, these studies were excluded from the final analysis because required data were incomplete because of data reporting issues (see Appendix A, Table 7 for details).

Description of Studies

Thirteen studies are reported as single trials.[65-77] One meta-analysis reported study findings from 3 trials, one of which was also included as a single trial[76] already included in this analysis and therefore was not repeated. Twelve of the studies were randomized, double-blind, placebo-controlled, parallel-group trials,[65,67-78] and one study used a double-blind, placebo-controlled, crossover study design.[66] The measures used in the studies are found in Appendix B, Table 1. Five studies[65,71,72,74,78] disclosed and met the needed sample size to determine significant findings, whereas the remaining studies did not report this value or did not obtain the needed study participants. One study[66] was funded by a grant from the Asthma and Allergy Research Group, whereas the remaining studies received funding from pharmaceutical companies or the members of the study teams were or had been a consultant or speaker for a pharmaceutical company or employees of a pharmaceutical company.

Efficacy and Safety Outcome Assessment: Forest Plots

We chose all variants of nasal with ocular symptom scores, rescue medication score, and Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) as outcome variables of efficacy. Continuous variables, such as nasal symptom scores, were analyzed in forest plots, and, where possible, the results of several trials were grouped. We chose local and systemic symptoms generally linked to AR medication (eg, somnolence for oral antihistamines and nasal bleeding for INCSs) as outcome variables of safety.

Effect Size and Standardized Mean Difference

Often when combining data from a large number of studies, which have outcome variables that are not uniform among the trials (eg, some score nasal symptoms scores of 0–12, others of 0–24), the standardized mean different (SMD) is used to determine effect size. The SMD (Hedges g) is the difference between the 2 means divided by the pooled SD, with a correction for small sample bias. In general, when evaluating SMD, Cohen criteria are used to interpret SMD results, in which 0.2 is considered a small effect, 0.5 a moderate, and 0.8 or higher a large effect. The methods group made a decision to combine the data for all studies that used uniformly reported outcomes, such as total nasal symptom score (TNSS). However, for studies for which outcome variables were not uniform, these studies were evaluated separately; thus, SMD was not used.

Quality Assessment of the Included Studies: Risk of Bias Using GRADE Analysis

An assessment of risk of bias factors (random sequence generation, allocation concealment, blinding adequacy, completeness of data, reporting, and other potential biases) that may contribute to risk of bias was initially conducted independently by 3 reviewers (2 Children's Mercy, Kansas City, evidence-based practice scholars and J.A.B.) based on the Review Manager software criteria. One nonclinician reviewer (J.A.B.) conducted a draft evaluation on the methodologic quality of the evidence based on the GRADE criteria independently. The workgroup and ultimately the Joint Task Force reviewed these draft assessments, applied their assessments of clinical importance for each patient-important outcome, and determined an overall quality of evidence across outcomes. For studies in which there had been incomplete reporting of information that might affect bias assessment, an attempt was made to contact authors to provide additional information. On the basis of additional information received from authors (Appendix B) and the workgroup and JTFPP's assessment of the risk of bias using each end point, a final bias assessment was determined by the JTFPP using the modified Delphi process. The level of methodologic quality for the identified literature is summarized after each clinical question.

Certainty of the Body of Evidence Using GRADE Analysis[79]

For GRADE analysis of the certainty of the evidence, 3 areas were evaluated: inconsistency, indirectness, and imprecision.

Inconsistency: studies are reviewed in terms of populations, interventions, and outcomes for similarity, or consistency, among the compared studies.

Indirectness: analysis occurs around comparisons, populations, and outcomes among intervention studies. Indirectness in comparisons occurs when one drug is compared with placebo and another drug is compared with placebo, but the researchers do not compare the first drug and the second drug in a head-to-head comparison. Indirectness in populations means that the population in which the drug was studied doe not reflect the population in which the study drug would be used. Indirectness of outcome refers to a primary or secondary outcome that does not exactly measure the intended outcome (eg, improved quality of life related to rhinitis measured with the generic quality-of-life tool SP27 instead of the specific RQLQ) and thus is not powered for the outcome of choice.

Imprecision: when too few study participants were enrolled or too few events occurred in the study, imprecision is detected.

The GRADE quality analysis defines the certainty of the evidence. There are 4 levels of evidence:

High: The team is very confident that the true effect lies close to the estimate of the effect.
Moderate: The team is moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low: The team confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.

Very low: The team has very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

The GRADE system for evaluating the quality of evidence (http://gdt.guidelinedevelopment.org/app) defines the elements that guideline writing groups need to consider when evaluating the quality of references that address a specific outcome (ie, change in TNSS). These elements include the risk of bias, described above, as well as the article design (eg, RCT, inconsistency, indirectness, imprecision, and other considerations). Articles are not individually graded for these components but are reviewed overall by the guideline writing group and assigned an overall quality rating. Although some guideline writing groups have tried to develop a point system for grading of individual articles,[80] this is not part of the formal GRADE system and was not used in this systematic review. The methods group used by the JTFPP designed a rating of individual references to assist them in their analysis, focusing on the lowest-quality grade assigned to any individual reference as the grade for all of the references used to answer any single question (Appendix B). However, the JTFPP chose to follow the GRADE handbook and reviewed all articles together to determine the overall quality of the articles for each outcome. Each JTFPP member individually determined the quality rating and using the Delphi method, the JTFPP decided the overall quality assessment for each outcome of interest. This difference in approach to the quality assessment is reflected in the discussion within the Clinical Statement Profile for each of the 3 questions. As the final step, the JTFPP rated each outcome across all studies (ie, for a body of evidence) followed by determining an overall quality of evidence across outcomes, again using the Delphi method. The separate quality assessment tables for each of the 3 questions are included within this document.

GRADE: From Quality of Evidence (Bias, Certainty) to Recommendations

After the quality of evidence is evaluated, the GRADE analysis continues to take into account 3 other factors to finally recommend or suggest in favor or against a certain treatment or action: safety of the intervention, cost, and patient's preference. As such, the GRADE analysis is not only a system focused on grading the level of evidence but also a much more complete system aimed at formulating recommendations, as its acronym indicates.

Throughout the development of this practice parameter, we used the GRADE approach. In formulating the replies to the 3 key questions, we took into account the quality of evidence for treatment efficacy, combining this with patients' safety, achieving adherence, and cost.

Individual subgroups drafted the recommendations and justifications based on the GRADE analysis. Subsequently, all recommendations were reviewed by the workgroup and JTFPP. Both groups were provided the opportunity to comment, propose changes, and approve or disapprove each statement. Consensus was sought and reached for each recommendation's direction and strength. Actual or potential conflicts of interest were disclosed semiannually, and transparency of discussion was maintained. External peer review was through appointed official reviewers and membership at large of the AAAAI and the ACAAI. All comments were discussed by the JTFPP, and revisions made when the workgroup and JTFPP believed this to be appropriate.

Reaching Workgroup Consensus on Statements and Conclusions

The workgroup used a modified Delphi process for the determination of the strength of the recommendation and the statement profile for each question. The Delphi method is a structured, interactive, decision-making process used by a panel of experts to arrive at a consensus when there are differing views and perspectives.[81-83] For any statement or conclusion for which there was a difference of opinion, a modified Delphi method was used. Workgroup members provided anonymous answers via email to the JTFPP administrative director to the questions being considered. The administrative director provided via teleconference an anonymous summary of the experts' answers and reasons they provided for their responses. The workgroup members discussed all the answers and then were encouraged to modify their answers on the next round(s) of email voting and teleconferences until a consensus was reached.

Question 1

I. Clinical Context and Background

When treating patients with AR, clinicians often use a combination of therapies. One common combination is the addition of an oral antihistamine to an INCS when there are persistent symptoms despite the use of the INCS. The previous updated practice parameter for the diagnosis and management of rhinitis by the JTFPP states that the combination had not been proven to provide superior clinical benefit compared with the use of INCS monotherapy but that the combination might provide additional benefit for specific individual symptoms.[4] More recent clinical practice guidelines do not recommend adding an oral antihistamine to an INCS, even if symptoms are incompletely controlled, because added clinical benefit is unlikely.[3,83] Thus, reevaluation of this question, as supported by the published literature, was needed to better advise the clinician on the best way to treat patients who are taking INCSs yet have incomplete symptom control.

Specific care question

For the initial treatment of SAR in patients 12 years or older, is there any clinical benefit of using a combination of an oral antihistamine and an INCS compared with monotherapy with an INCSs?

Summary of analysis

For the treatment of SAR in patients who are 12 years or older, there is no clinical benefit of using a combination of an oral antihistamine and an INCS compared with monotherapy with an INCS.

Studies used for appraisal and synthesis

Eight studies[61-69] dealing with this clinical question were identified, but 3 of these[62-64] were excluded because the data provided in the articles could not be used for analysis. Brooks et al[64] presented the mean change in symptoms in bar graph format only. Can et al[62] provided data as medians and ranges. Modgill et al[63] reported the change in daytime and nighttime symptom scores in box and whiskers graphs (See Appendix B and Table 1 below for characteristics of included studies and Appendix D for risk of bias tables for the individual questions.)

Summary of systematic review and quality assessment of included studies

There was no statistically significant superiority of the combination of an oral antihistamine and an INCS for any of the outcome measures in any of the studies analyzed.

II. Characteristics of Included Studies and Determination of Risk of Bias

The detailed characteristics of each study, including setting, participants entering and completing the study, participant demographics, inclusion and exclusion criteria, power analysis, and intervention, as well as primary and secondary end point outcomes,

are reviewed in the tables in Appendix B. The study duration varied from 2 to 8 weeks as listed in Appendix B. A summary of study characteristics used for the quality assessment is given in Table 1. A separate risk of bias table for question 1 is available for review in Appendix D.

Risk of bias: moderate

On the basis of information provided in the published studies, the workgroup made an initial assessment of the factors that may contribute to the risk of bias (random sequence generation, allocation concealment, blinding adequacy, completeness of data reporting, adequacy of sample size, funding source and other potential biases, eg, failure to submit studies with negative results for publication). After obtaining additional information from the authors, the workgroup updated their assessment of the risk of bias. The detailed author responses for question 1 are included in the footnotes to the risk of bias table in Appendix D. Given this additional information, the workgroup recommended that the risk of bias should be considered moderate. Thereafter, the JTFPP reviewed and agreed that the risk of bias was moderate.

Quality assessment for question 1 references

As detailed in Table 2 and Table 3 below, the workgroup and JTFPP reviewed the elements of assessment, including type of article, risk of bias, imprecision, indirectness, inconsistency, and publication bias for each outcome of interest. The primary outcome was change in TNSS.

Conclusion of quality assessment for primary outcome

Because of a moderate risk of bias that could have affected the imprecision indirectly, the JTFPP thought that the overall quality of these articles was moderate (by Delphi, with 7 indicating moderate and 1 indicating low).

Quality assessment of secondary outcomes

The secondary outcomes differed between the references, and many outcomes were supported by only one reference. Thus, each outcome has its own quality assessment rating. The JTFPP determined that for each of these secondary outcomes, the quality rating was moderate.

Quality assessment for all outcomes (primary and secondary)

Because of a moderate risk of bias that could have affected the imprecision indirectly, the JTFPP thought that the overall quality of these articles was moderate (by Delphi, with 7 indicating moderate and 1 indicating low).

III. Development of Forest Plots Comparing Change in Symptom Score and Adverse Effects

Because the outcome measures used were different in the 5 pooled studies, none of the study findings could be pooled in a forest plot to establish a more confident estimate of effect. See Figures 2–15 in Appendix B for forest plots of individual studies.

IV. Advice for the Clinician

The following Clinical Statement Profile is the combined expert opinion of the workgroup, the JTFPP, and patient advocates based on the GRADE analysis conclusions discussed above. The conclusions reached by the experts are a synthesis of the GRADE analysis of data combined with the collective knowledge and experience of the experts involved. When complete agreement could not be reached, the Delphi method was used.

Clinical Statement Profile for question 1

Clinical statement: For initial treatment of nasal symptoms of SAR in patients 12 years or older, clinicians should routinely prescribe monotherapy with an INCS rather than a combination of oral antihistamines and INCSs. Strength of recommendation as determined by the JTFPP: Strong (by Delphi, 7 voted strong and 1 voted weak).

Quality improvement opportunity: To promote a consistent, systematic, and cost-effective approach for the treatment of the patient with SAR.

GRADE evidence of quality as determined by the JTFPP: Medium (by Delphi, 7 voted medium and 1 voted low).

Expert opinion comment on evidence quality: There were 3 large studies (Anolik[65] [332 patients], Benincasa and Lloyd[67] [454 patients], and Ratner et al[69] [287 patients]) that accounted for more than 90% of the patients studied. The studies by Ratner et al[69] (1998), Barnes et al[66] (2006), and Di Lorenzo et al[68] (2004) failed to disclose the methods used for randomization and allocation

Table 1
Question 1: Summary of Study Characteristics Used for the Quality Assessment

Quality assessment	Study characteristics
GRADE inconsistencies	
Analyzing populations	The populations among the studies are fairly similar.
Analyzing interventions	The study interventions are not consistent in this analysis. One study used mometasone furoate nasal spray, 200 μg/d, as the intranasal corticosteroid and loratadine, 10 mg/d, as the oral antihistamine.[65] Four of the studies used fluticasone propionate aqueous nasal spray, 200 μg/d, as the intranasal corticosteroid; however, 3 different oral antihistamines were used: 1 study[66] used levocetirizine, 5 mg/d; 2 studies[68,72] used cetirizine, 10 mg/d; and 1 study[69] used loratadine, 10 mg/d.
Analyzing outcomes	The outcomes measured were different among the 5 studies. In the first study,[65] the participants self-reported the mean total nasal symptom score. In the second study,[66] the Rhinoconjunctivitis Quality-of-Life Questionnaire, peak nasal inspiratory flow, mean total nasal symptom score, and nitric oxide levels were reported. In the third study,[67] nasal, eye, and headache symptom scores were assessed on a categorical rating scale of 0 to 9. In the fourth study,[68] nasal symptom scores were self-reported by the participant based on a 4-point Likert scale, whereas mean blood eosinophil and nasal lavage eosinophils and subepithelial cells were measured in the laboratory environment (nasal lavage eosinophils and subepithelial cells were reported in box and whiskers graphs and therefore not included in this analysis). In the fifth study,[69] nasal symptom scores in which a visual analogue score based on a range of 0 to 100 was used and measurement performed by a clinician.
GRADE indirectness	
Analyzing comparisons	The studies provide head-to-head comparisons. Four studies[65,67-69] have a placebo arm to compare the intervention of choice to, whereas the third study[66] is a cross-over study design, and therefore the participants act as their own controls.
Analyzing interventions	The interventions tested are of interest to this analysis.
Analyzing outcomes	The outcome of interest is the patient symptom–based measure of nasal symptom scoring. However, 1 study[65] met the identified sample size, 3 studies[66-68] did not report the sample size needed to detect significance, and 1 study[69] reported the sample size needed but did not enroll the needed number of participants.
GRADE imprecision	Two studies[66,69] identified imprecision issues attributable to a small sample size,[66] which leads to a large confidence interval, and 1 study[69] reported the inability to enroll the needed number of participants.

Table 2
Quality Assessment for Question 1[a]

Quality assessment							No. of patients		Effect	
No. of studies	Design	Risk of bias[b]	Inconsistency	Indirectness	Imprecision[c]	Other considerations	INCS and OAH	INCS Alone	Relative (95% CI)	Absolute
Reduction in TNSS[d]										
1 (Anolik[65])	RCT	Not rated individually	No serious inconsistency	No serious indirectness	No serious imprecision[A1]	None	166	166	NA	MD 0.3 lower (0.79 lower to 0.19 higher)
Reduction in TNSS[e]										
1 (Barnes et al[66])	RCT	Not rated individually	No serious inconsistency	No serious indirectness	No serious imprecision[BA]	None	31	31	NA	MD 0.11 lower (1.33 lower to 1.11 higher)
Mean Symptom Scores—Nasal Symptoms[f]										
1 (Benincasa and Lloyd[67])	RCT	Not rated individually	No serious inconsistency	No serious indirectness	No serious imprecision[BE]	None	227	227	NA	MD 0 higher (0.28 lower to 0.28 higher)
Mean Daily Symptom Score[g]										
1 (Di Lorenzo et al[68])	RCT	Not rated individually	No serious inconsistency	No serious indirectness	No serious inprecision[D]	None	20	20	NA	MD 0.2 lower (0.46 lower to 0.06 higher)
Change in Nasal Symptoms Score on Day 14[h]										
1 (Ratner et al[69])	RCT	Not rated individually	No serious inconsistency	No serious indirectness	No serious imprecision[R]	None	145	142	NA	MD 1 higher (23.84 lower to 25.84 higher)
Overall	All RCTs	Moderate risk of bias[b]	No serious inconsistency	No serious indirectness	No serious imprecision	None	NA	NA	NA	NA

Abbreviations: CI, confidence interval; INCS, intranasal corticosteroid; MD, mean difference; NA, not applicable; OAH, oral antihistamine; RCT, randomized clinical trial; TNSS, total nasal symptom score.

[a]For all the studies included in the systematic review, it is not possible to guarantee that there was no publication bias because most of these studies were pharmaceutical sponsored studies.

[b]Risk of bias for all 5 articles: (1) random sequence generation: unclear bias; (2) allocation concealment: unclear bias; (3) blinding of participants and personnel: low risk; (4) incomplete outcome data: unclear to high risk; (5) selection reporting: low risk; and (6) other bias: unclear risk. See risk of bias assessment table in Appendix D for details.

[c]A1, The CIs are wide but effect size is large. Although the CI does include zero and the *P* value is not significant for the combination of the medications (indicating a negative study), this only reinforces the conclusion of this systematic review's recommendation and should not be considered a serious imprecision for guideline development; BA, Small sample size; however, the results follow the conclusion of the larger studies. Although the CI does include zero and the *P* value is not significant for the combination of the medications (indicating a negative study), this only reinforces the conclusion of this systematic review's recommendation and should not be considered a serious imprecision for guideline development; BE, The CI crosses zero, there is a low effect size, and there is no statistically significant difference because the combination and the monotherapy groups are equal. This negative study reinforces the conclusions of this systematic review's recommendation and should not be considered a serious imprecision for guideline development; D, The CIs are wide but effect size is large. Although the CI does include zero and the *P* value is not significant for the combination of the medications (indicating a negative study), this only reinforces the conclusion of this systematic review's recommendation and should not be considered a serious imprecision for guideline development; R, The CI crosses zero, there is a low effect size, and there is no statistically significant difference because the combination and the monotherapy groups are close to equal. This negative study reinforces the conclusions of this systematic review's recommendation and should not be considered a serious imprecision for guideline development.

[d]Follow-up of 2 weeks, measured with patient-rated mean change in TNSS, and better indicated by lower value.

[e]Follow-up of 2 weeks, measured with dairy each morning, and Better indicated by lower value.

[f]Follow-up of 8 weeks, measured with: patient-rated separate symptom scores, and better indicated by lower value.

[g]Follow-up of 8 weeks, measured with patient-rated daily symptom score, and better indicated by lower values.

[h]Follow-up of 2 weeks, measured with clinician-rated nasal symptom score at day 14, and better indicated by lower values.

concealment. Likewise, the studies by Ratner et al[69] and Barnes et al[66] did not discuss blinding of outcome assessment. These studies failed to meet prespecified sample size to detect significance. When contacted, the authors of these 3 studies were unable to provide further details because the study documents were not available. However, the workgroup and JTFPP assessed that it was likely that older studies were designed to incorporate all these quality measures to reduce bias, but this was not described in the published articles, and because of the age of these publications, this information was not available. Because of a moderate risk of bias that could have affected the imprecision indirectly, the JTFPP thought that the overall quality of the evidence of these articles was moderate for the primary end point, TNSS, and for secondary outcomes of interest.

Level of confidence in evidence as determined by the workgroup and JTFPP: Moderate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Benefits: Potential cost saving, improving adherence, reduced adverse effects, greater convenience with INCS monotherapy compared with combination therapy with INCS and oral antihistamine. Promoting effective monotherapy with INCSs will decrease variation in care, with no decrement in the ability to bring symptoms under control, and improve quality of life, including sleep and work and school performance.

Risks, harms, and costs: There is no increased risk or harm from use of monotherapy vs combined therapy, and INCS monotherapy would be less costly than combination therapy.

Benefit-harm assessment: There is a preponderance of benefit over harm for the use of INCSs as monotherapy. Because some oral antihistamines, mainly first-generation antihistamines, may cause sedation or adverse effects, such as dryness of mouth and eyes, constipation, and inhibition of micturition (see Summary Statements 61-63 in the 2008 Rhinitis Practice Parameter Update[4]), monotherapy with INCS would avoid these potential antihistamine-induced adverse effects.

Value judgments: The treatment outcomes assessed in this analysis would be valued as important by most patients.

Intentional vagueness: None.

Role of patient preferences: Some patients may want to begin with dual therapy with the hope or expectation that two drugs should be better than one, even if data do not support this.

Table 3
Question 1: Secondary Outcomes of Interest: Quality of Life, Reduction in TNSS, Eye Symptoms, and Adverse Effects

Quality assessment							No. of patients		Effect		Quality for outcome
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision[a]	Other considerations	INCS and OAH	INCS alone	Relative (95% CI)	Absolute	
Improved Quality of Life[b]											
1 (Barnes et al[66])	RCT	Unclear risk to moderate risk	No serious inconsistency	No serious indirectness	No serious imprecision[BA]	None	31	31	NA	MD 0.12 lower (0.56 lower to 0.32 higher)	Moderate
Reduction in Mean Total Symptom Score[c]											
1 (Anolik[65])	RCT	Low risk	No serious inconsistency	No serious indirectness	No serious imprecision[A]	None	166	166	NA	MD 0.6 lower (1.62 lower to 0.42 higher)	Moderate
Mean Symptom Scores—Eye Symptoms[d]											
1 (Benincasa and Lloyd[67])	RCT	Low to unclear risk	No serious inconsistency	No serious indirectness	No serious imprecision[BE1]	None	227	227	NA	MD 0.2 lower (0.44 lower to 0.04 higher)	Moderate
Symptom-Free Days—Eye Symptoms[e]											
1 (Benincasa and Lloyd[67])	RCT	Low to unclear risk	No serious inconsistency	No serious indirectness	No serious imprecision[BE2]	None	227	227	NA	MD 0.01 higher (0.06 lower to 0.08 higher)	Moderate
Mean Daily Symptom Score[f]											
1 (Di Lorenzo et al[68])	RCT	Low risk	No serious inconsistency	No serious indirectness	No serious imprecision[D]	None	20	20	NA	MD 0.2 lower (0.46 lower to 0.06 higher)	Moderate
Adverse Events											
2 (Anolik[65] and Benincasa and Lloyd[67])	RCT	Low risk	No serious inconsistency	No serious indirectness	No serious imprecision[A&BE]	None	31/393 (7.9%)	24/393 (6.1%) and 6.3%	OR, 1.32 (95% CI, 0.76-2.29)	18 more per 1,000 (from 14 fewer to 69 more) and 19 more per 1,000 (from 14 fewer to 70 more)	Moderate

Abbreviations: CI, confidence interval; INCS, intranasal corticosteroid; MD, mean difference; NA, not applicable; OAH, oral antihistamine; OR, odds ratio; RCT, randomized clinical trial; TNSS, total nasal symptom score.
[a]BA, Small sample size, medium effect size, the CI does include zero and the *P* value is not significant for the combination of the medications (indicating a negative study), and consistent with the findings of the effect on TNSS. This only reinforces the conclusion of this systematic review's recommendation and should not be considered a serious imprecision for guideline development; A, The CIs are wide but effect size is large. Although the CI does include zero and the *P* value is not significant for the combination of the medications (indicating a negative study), this reinforces the conclusion of this systematic review's recommendation and should not be considered a serious imprecision for guideline development; BE1, Narrow CI, barely crosses zero, $P = .10$, not significant but close, and large effect size; BE2, Narrow CI, crosses zero, and low effect size that does not reach statistical significance. Mean difference is close to zero. The results correspond with the results of the effect on the TNSS; D, Moderate CI that barely crosses zero, $P = .14$, and large effect size. The results are consistent with the overall effect on TNSS; A and BE, The CI is wide, effect size is large but there is no statistical significance ($P = .33$), and heterogeneity is moderate with $I^2 = 49\%$. However, a trend toward increased adverse events with combined therapy is noted.
[b]Follow-up of 2 weeks, measured with Rhinoconjunctivitis Quality-of-Life Questionnaire, and better indicated by lower values.
[c]Follow-up of 2 weeks, measured with patient-rated change in total symptom score, and better indicated by lower values.
[d]Follow-up of 8 weeks, measured with patient-rated separate symptom scores, and better indicated by lower values.
[e]Follow-up of 8 weeks, measured with patient-rated separate symptom scores, and better indicated by lower values.
[f]Follow-up of 8 weeks, measured with patient-rated daily symptom score, and better indicated by lower values.

Table 4
Question 2: Summary of Study Characteristics Used for the Quality Assessment[a]

Quality assessment	Study characteristics
GRADE inconsistencies	
Analyzing populations	All the study participants were diagnosed with seasonal allergic rhinitis; in addition, one study's[72] participants were also diagnosed with persistent asthma; however, the workgroup believes that the interventions studied are not influenced by the persistent asthma. The study interventions are consistent in 4 of the 5 included studies.
Analyzing interventions	The study interventions are consistent in 4 of the 5 included studies. One study compared beclomethasone (200 μg intranasally twice daily for a total of 400 μg intranasally daily) vs montelukast (10 mg oral once daily).[70] Three studies[71,73,74] compared the same interventions of fluticasone propionate aqueous nasal spray (200 μg intranasally once daily) vs montelukast (10 mg/d). The study that included participants with persistent asthma compared fluticasone propionate aqueous nasal spray (200 μg intranasally once daily) vs montelukast (10 mg daily) with both arms using fluticasone propionate and salmeterol.[72]
Analyzing outcomes	The outcome measures varied among studies. The researchers used the following: the Composite Symptom Score[70] (Fig 17); mean Daytime Nasal Symptom Score[70] (Fig 18); and the Daytime and Nighttime Symptom Scores based on a 5-point Likert scale[73] (Fig 19) or a 4-point Likert scale.[71,72,74] The 3 studies that used a 4-point Likert scale for the daytime (Fig 20) and nighttime symptom scores (Fig 21) could be pooled in a forest plot to establish a more confident estimate of effect. The study[72] with patients with persistent asthma as the study population also measured morning peak expiratory flow (Fig 22), evening peak expiratory flow (Fig 23), percentage of symptom-free days (Fig 24), and percentage of albuterol-free days (Fig 25). Three of the studies[71,72,74] also reported adverse events.
GRADE indirectness	
Analyzing comparisons	The studies provide head-to-head comparisons of intranasal corticosteroids (beclomethasone[70] or fluticasone propionate aqueous nasal spray[71-74] vs montelukast). The populations reflect the population of choice.
Analyzing interventions	The interventions tested are of interest to this analysis.
Analyzing outcomes	The outcome of interest is the patient symptom–based measure of nasal symptom scoring. Three studies[71,72,74] met the sample size determination to identify significant findings, 1 study[70] did not meet the sample size determination, and 1 study[73] did not disclose the sample size needed.
GRADE imprecision	One study[73] could have had imprecision issues because of a small sample size; however, the confidence interval is not large. The authors do not disclose how many participants were needed to detect significance in 2 of the 5 included studies.[70,73]

[a]See Appendix B for figures referenced in Table 4.

Exclusions: None.

Policy level: Recommendation would be appropriate in the judgment of the authors.

Differences of opinion (workgroup members): There was no difference of opinion.

Expert commentary

This systematic review only addressed treatment of SAR in patients 12 years or older. PAR in any age group was not studied. Furthermore, the included studies might not have been adequately powered to ascertain the lack of effect of the combination. In the study by Benincasa and Lloyd,[67] there was a nonsignificant trend to a reduction in eye symptom scores with combination therapy. In addition, the specific question of whether there is benefit from the addition of an oral antihistamine in patients with residual symptoms despite appropriately dosed INCSs was not studied in 4 of the above 5 citations. Therefore, current available evidence is consistent with, but does not methodologically support, the conclusion that when there are residual symptoms of SAR in a patient using an INCS, there is no clinical benefit to adding an oral antihistamine. Moreover, the lack of superiority of the combination would support the recommendation of switching to an INCS in patients who do not derive clinical benefit from an oral antihistamine alone, as opposed to using add-on therapy. Further properly designed and powered studies to support these conclusions are needed.

Question 2

I. Clinical Context and Background

In choosing therapies for AR, clinicians may choose from several monotherapies, including oral agents, with one option being the LTRA oral montelukast, or an intranasal agent, with one option being INCSs. The previous updated practice parameter for the diagnosis and management of rhinitis by the JTFPP states that oral LTRA have proven useful for SAR and PAR, but based on 2 studies, LTRA were less effective than INCSs.[4] A more recent clinical practice guideline states that clinicians should not offer LTRAs as primary therapy for patients with AR and that INCSs are more effective than LTRAs across the range of allergy symptoms.[3]

Specific care question

In patients with moderate to severe SAR who are 15 years or older, how does montelukast compare with an INCS in terms of clinical benefit?

Summary of analysis

When comparing montelukast with INCSs in patients with SAR who are 15 years or older, INCSs have a greater clinical benefit (see Figs 17–25 in Appendix B) over montelukast based on the reduction of nasal symptoms.

Studies used for appraisal and synthesis

Five studies met the criteria for analysis.[70-74]

Summary of systematic review and quality assessment of included studies

There was a statistically significant clinical benefit of an INCS when compared with montelukast based on a reduction in nasal symptoms in the study population.

II. Characteristics of Included Studies and Determination of Risk of Bias

The detailed characteristics of each study, including setting, participants entering and completing the study, participant demographics, inclusion and exclusion criteria, power analysis, intervention, and primary and secondary end point outcomes, are reviewed in the tables in Appendix B. A summary of study characteristics used for the quality assessment is given in Table 4. A separate risk of bias table for question 2 is available for review in Appendix D. It is possible that for one study[72] there could have been bias based on the fact that individuals with asthma were included and, potentially, improvement in lower airway symptoms could have led to a perception of upper airway improvement.

The workgroup updated the risk of bias for the references reviewed to answer this question after obtaining additional information from the authors. The detailed responses are included in the footnotes to the risk of bias for question 2 studies in Appendix D. Given this additional information, the workgroup recommended that the risk of bias should be considered low. The JTFPP reviewed and agreed that the risk of bias was low.

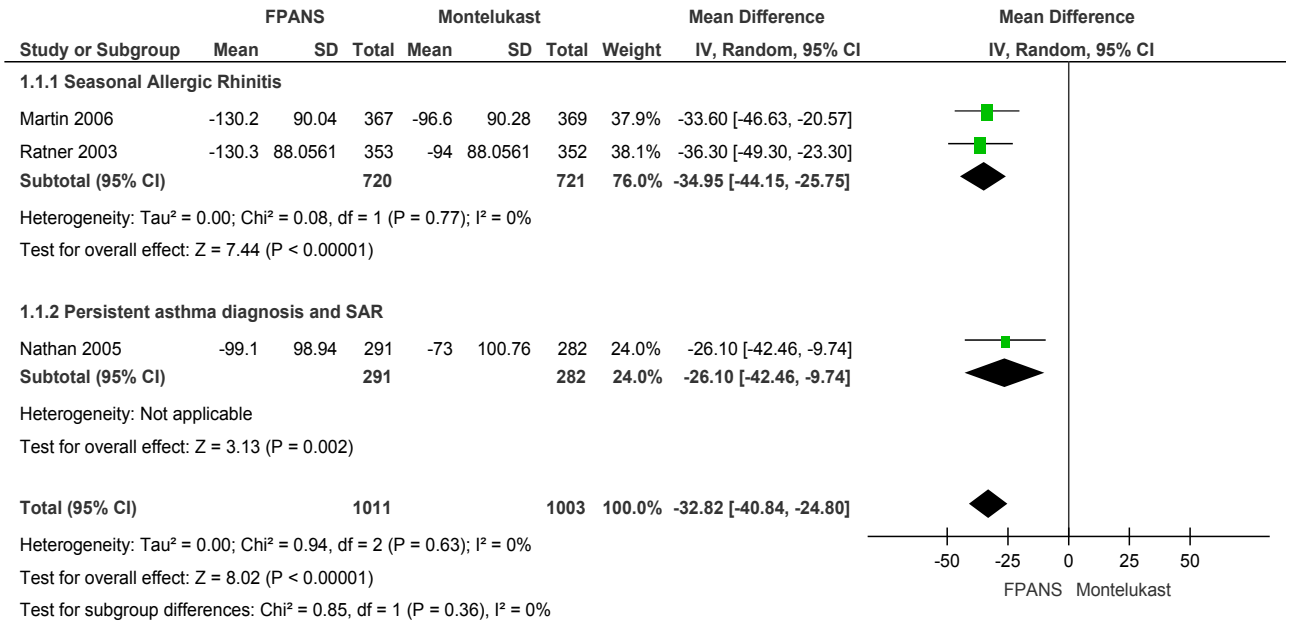

Figure 1. Question 2: Change in mean daytime total nasal symptom score with subgroup analysis. Lower reduction in mean score is better. CI indicates confidence interval; FPANS, fluticasone propionate aqueous nasal spray; SAR, seasonal allergic rhinitis.

III. Development of Forest Plots Comparing Change in Symptom Score and Adverse Effects

Because the 5 included studies did not use the same outcome as defined in Table 3, it was not possible to construct forest plots that would include all studies on one plot. Therefore, individual forest plots were constructed for (1) change in mean composite score,[70] (2) change in mean daytime nasal symptoms score,[70] (3) change in mean daytime nasal symptoms score,[73] (4) change in mean morning peak expiratory flow,[72] (5) change in mean evening peak expiratory flow,[72] (6) percentage change in mean symptom-free days,[72] and (7) percentage change in mean albuterol-free days.[72] These forest plots (Figs 17–19 and 22–25) are available in Appendix B. The forest plots comparing the change in mean daytime nasal symptom scores with subgroup analysis and the change in mean nighttime total nasal symptom score with subgroup analysis are presented in Figure 1 and Figure 2.[71,74] Likewise, the forest plot comparing the adverse events is presented in Figure 3.[71,72,74]

IV. Quality Assessment for Question 2 References

As detailed in Tables 5–9 below, the workgroup and JTFPP reviewed the elements of assessment, including type of article, risk of bias, imprecision, indirectness, inconsistency, and publication bias for each outcome of interest. The primary outcome was change in TNSS.

Conclusion for primary outcome

When all the articles for the primary outcome were considered overall, the quality assessment was good for all categories, and the JTFPP thought that the overall quality of these articles to answer question 2 were high (by Delphi, 8 of 8 voted for high quality).

Secondary outcomes

Secondary outcomes were daytime TNSS and adverse effects.

Conclusion for secondary outcomes

When all the articles for the secondary outcomes were considered overall, the quality assessment was good for all categories, and the JTFPP thought that the overall quality of these articles to answer question 2 was high (by Delphi, 8 of 8 voted for high quality).

Conclusion for all outcomes (primary and secondary)

When all the articles are considered overall, the quality assessment was good for all categories, and the JTFPP thought that the overall quality of these articles to answer question 2 was high (by Delphi, 8 of 8 voted for high quality).

V. Advice for the Clinician

The following Clinical Statement Profile is the combined expert opinion of the workgroup, the JTFPP, and patient advocates based on the GRADE analysis conclusions discussed above. The conclusions reached by the experts are a synthesis of the GRADE analysis of data combined with the collective knowledge and experience of the groups involved. When complete agreement could not be reached, the Delphi method was used.

Clinical Statement Profile for question 2

Clinical statement: For initial treatment of moderate to severe SAR in patients 15 years and older, the clinician should recommend an INCS over an LTRA.

Strength of recommendation as determined by the JTFPP: Strong (by Delphi, 8 of 8 voted for strong).

Quality improvement opportunity: Reduced use of a less effective agent and increased use of a more effective agent.

GRADE evidence of quality as determined by the JTFPP: High (by Delphi, 8 of 8 voted for high).

Expert opinion comment on evidence quality: For the outcome of interest, the day and night TNSSs, the studies by Martin et al, Nathan et al, and Ratner et al compared fluticasone propionate and montelukast. Other studies use different INCSs; thus, one would need to accept previous studies that have found that all INCSs have similar efficacy.[4] When all the articles for the primary outcomes were considered overall, the quality assessment was high for all categories, and the overall quality was assessed to be high.

Level of confidence in evidence by workgroup and JTFPP: High, confident that the true effect lies close to the estimate of the effect.

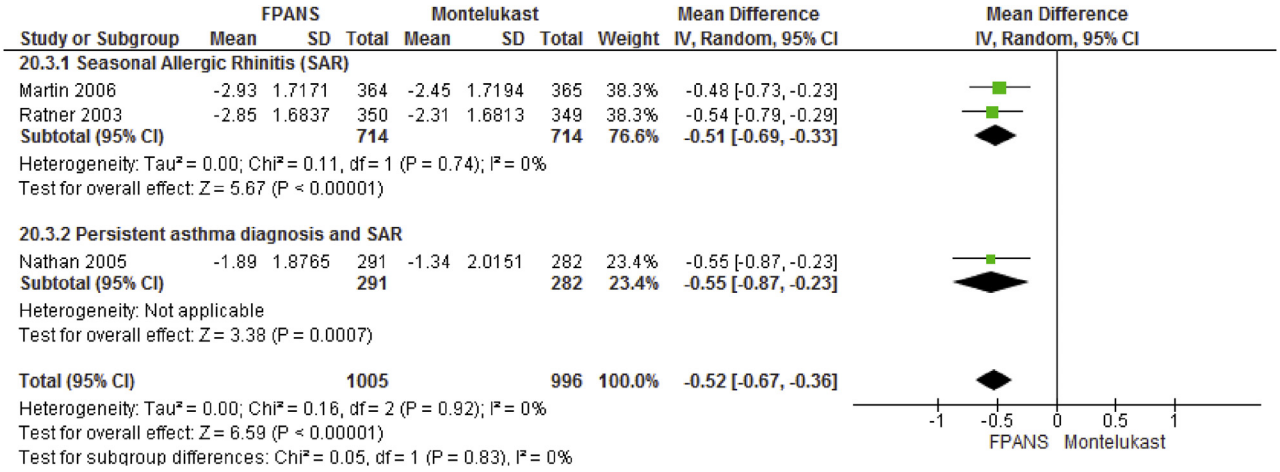

Figure 2. Question 2: Change in mean nighttime total nasal symptom score with subgroup analysis. Lower reduction in mean score is better. CI indicates confidence interval; FPANS, fluticasone propionate aqueous nasal spray; SAR, seasonal allergic rhinitis.

Benefits: Use of the more effective therapy, INCSs, will increase clinical benefit, will decrease variations in care, and should result in a cost saving to society.

Risks, harms, and costs: There was no significant difference in the rate of adverse effects among treatment options. Although local adverse effects are typically minimal with the use of INCSs, nasal irritation and bleeding and, rarely, nasal septal perforation may occur (see Summary Statement 80 in the 2008 Rhinitis Update Practice Parameter[4]). After long-term use in susceptible populations, cataracts, increased intraocular pressure, and glaucoma have been reported, especially when combined with inhaled or oral corticosteroids. Although it is beyond the scope of this review, product labeling recommends that the growth of pediatric patients receiving INCSs should be routinely monitored. The package inserts for all INCSs also recommend monitoring for intraocular pressure, glaucoma, and cataracts.

For montelukast, headache is the most common adverse effect and is reported more frequently than placebo in controlled trials. There are postmarketing reports with montelukast of rare neuropsychiatric events (eg, aggression, depression, suicidal thinking, behavioral changes, dream abnormalities), which appear consistent with a drug-induced effect.[84,85] The cost to society of many INCSs is similar to or even less than that of oral LTRAs. The cost borne by a patient may be similar for generic LTRAs and generic over-the-counter INCSs.

Benefit-harm assessment: There is a preponderance of benefit over harm for the use of INCSs rather than LTRAs unless there are specific contraindications for INCSs.

Value judgments: The treatment outcomes assessed in this analysis would be valued as important by most patients.

Intentional vagueness: None.

Role of patient preferences: Moderate. Some patients do not tolerate or will not accept the use of INCSs based on the method of delivery and/or safety concerns and would prefer oral agents, such as LTRAs, even if less effective.

Exclusions: In patients with a concurrent diagnosis of asthma, an LTRA may be prescribed primarily for asthma and also benefit SAR.

Policy level: Recommendation would be appropriate in the judgment of the authors.

Differences of opinion: None.

Expert commentary

A systematic evidence review found that INCSs are more effective than montelukast for nasal symptom reduction in SAR, although in the study by Nathan et al,[72] the numerically greater improvement in symptom-free days (quality of life) did not reach statistical significance. Although there is not full consensus in the literature about thresholds for a meaningful clinically important difference among treatments, the workgroup and the JTFPP assessed that for the primary end point of TNSS in all studies differences found were clinically meaningful according to recently published criteria.[86] Some patients do not tolerate or will not accept the use of INCSs and would prefer oral agents, such as LTRAs (alone or in combination with oral antihistamines), even if oral

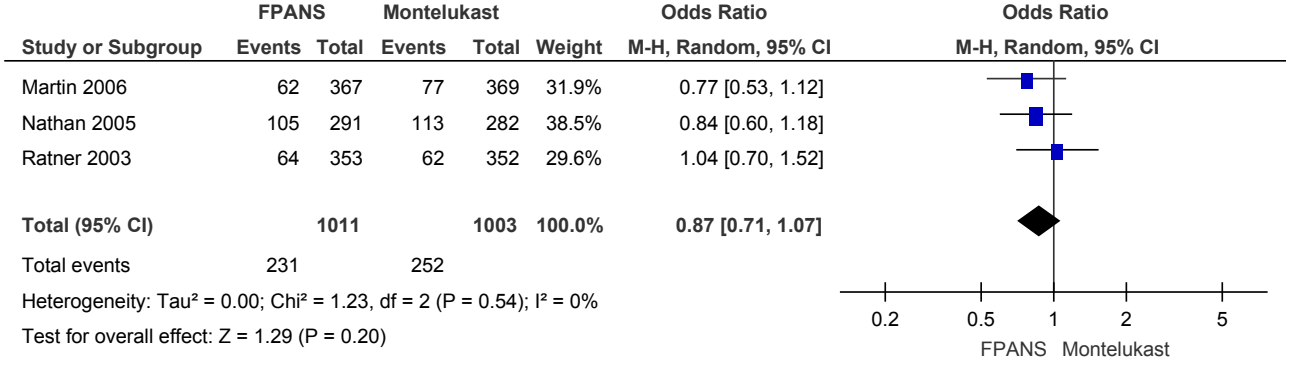

Figure 3. Question 2: Adverse events. Lower reduction in reported events is better. CI indicates confidence interval; FPANS, fluticasone propionate aqueous nasal spray; M-H, Mantel-Haenszel.

Table 5
Question 2: Should Montelukast vs Beclomethasone Be Used for Rhinitis Clinical Benefit?

Quality assessment							No. of patients		Effect	
No. of studies	Design	Risk of bias[a]	Inconsistency[b]	Indirectness	Imprecision	Other considerations	Montelukast	Beclomethasone	Relative (95% CI)	Absolute
Composite Symptoms Score[c]										
1 (Lu et al[70])	RCT	No serious risk of bias	No serious inconsistency[L1]	No serious indirectness	No serious imprecision	None	172	111	NA	MD 0.26 lower (0.37 to 0.15 lower)

Abbreviations: CI, confidence interval; MD, mean difference; NA, not applicable; RCT, randomized clinical trial.
[a]Risk of bias overall for the articles: (1) random sequence generation: low risk of bias; (2) allocation concealment: low risk of bias; (3) blinding of participants and personnel: low risk of bias; (4) incomplete outcome data: low risk of bias; (5) selection reporting: low risk; and (6) other bias: unclear risk of bias. See risk of bias assessment table for question 2 in Appendix D for details.
[b]L1, Although this is the only study that compared montelukast and beclomethasone, the Joint Task Force on Practice Parameters did not believe that this should be considered a serious inconsistency because there is not a significant difference in efficacy between beclomethasone and fluticasone propionate.
[c]Follow-up of 2 weeks, measured with mean daily diary scores for daytime nasal symptoms and nighttime symptoms, and better indicated by lower values.

agents are less effective.[87,88] In patients with a concurrent diagnosis of asthma, an LTRA may be prescribed primarily for asthma and provide benefit for SAR; however, an LTRA would not be the preferred agent for SAR. Montelukast has a specific target, the CysLT1 receptor for cysteinyl leukotrienes (leukotrienes C4, D4, and E4). In asthma there are subpopulations of patients who are high producers of cysteinyl leukotrienes and may respond better to montelukast than to inhaled corticosteroids.[89] It is conceivable (although unproven) that in an analogous fashion in SAR there may be subpopulations that are high producers of cysteinyl leukotrienes and may be more responsive to montelukast, although this possibility is tempered by the finding that in the nose, the CysLT2 receptor, against which montelukast has no activity, is expressed prominently in certain components of nasal tissues.[90] The studies reviewed in this systematic analysis do not specifically answer the question, "If symptoms are not entirely controlled by INCSs, does the addition of montelukast provide benefit?"

Question 3

I. Clinical Context and Background

The JTFPP Rhinitis Practice Parameter Update of 2008[4] (and the original 1998 JTFPP Rhinitis Practice Parameter) states there is high level of evidence that INCSs are the most effective medication class in controlling symptoms of AR (see Summary Statement 74 in the 2008 Rhinitis Updated Practice Parameter[4]) and that INAHs may be considered for use as first-line treatment for allergic and non-AR (see Summary Statement 65 in the 2008 Rhinitis Updated Practice Parameter[4]) but are generally less effective than INCSs for the treatment of AR (see Summary Statement 69 in the 2008 Rhinitis Updated Practice Parameter[4]). The 2008 document also states that, based on limited data that reported an additive benefit, concomitant administration of an INAH with an INCS in separate devices (see Summary Statements 65-69 in the 2008 Rhinitis Updated Practice Parameter[4]) could be considered. However, the question of whether there is an advantage of using an INCS in conjunction with an INAH coadministered in a single device, compared with monotherapy with either of these agents, had not been investigated at the time of publication of the 2008 Rhinitis Updated Practice Parameter. In the interim, studies have been published that compare the effectiveness of combination azelastine and fluticasone administered in a single device to monotherapy with one of these agents. One additional study compares using concomitant administration of the 2 agents in individual devices to monotherapy with each agent. These new studies allow us to answer this question using the GRADE analysis as summarized below.

Specific care questions

For initial treatment of nasal symptoms of SAR in patients with SAR who are 12 years or older, is there any clinical benefit of using the combination of an INAH and an INCS compared with monotherapy with an INCS? For initial treatment of nasal symptoms of SAR in patients with SAR who are 12 years or older, is there any clinical benefit of using the combination of an INAH and an INCS compared with monotherapy with an INAH?

Table 6
Question 2: Should Montelukast vs FPANS Be Used for Rhinitis Clinical Benefit?

Quality assessment							No. of patients		Effect	
No. of studies	Design	Risk of bias[a]	Inconsistency[b]	Indirectness	Imprecision[b]	Other considerations	Montelukast	FPANS	Relative (95% CI)	Absolute
Change in DNSS at 2 Weeks[c]										
1 (Pullerits et al[73])	RCT	No serious risk of bias	Possible serious inconsistency[P1]	No serious indirectness	Serious[P2]	None	13	16	NA	MD 1.2 lower (2.89 lower to 0.49 higher)

Abbreviations: CI, confidence interval; DNSS, daily nasal symptom score; FPANS, fluticasone propionate aqueous nasal spray; MD, mean difference; NA, not applicable; RCT, randomized clinical trial.
[a]Risk of bias overall for the articles: (1) random sequence generation: low risk of bias; (2) allocation concealment: low risk of bias; (3) blinding of participants and personnel: low risk of bias; (4) incomplete outcome data: low risk of bias; (5) selection reporting: low risk; and (6) other bias: unclear risk of bias. See risk of bias assessment table for question 2 in Appendix D for details.
[b]P1, Although this study measured both daytime and nighttime symptoms, it did not determine a combined 24-hour total nasal symptom score. Thus, there was the possibility of some inconsistency compared with the other studies; P2, Small sample size.
[c]Follow-up of 2 weeks, measured with mean of total symptoms score, and better indicated by lower values.

Table 7
Question 2: Should Montelukast vs FPANS Be Used for Rhinitis Clinical Benefit?

Quality assessment							No. of patients		Effect	
No. of studies	Design	Risk of bias[a]	Inconsistency	Indirectness	Imprecision	Other considerations	Montelukast with or without FSC	FPANS with or without FSC	Relative	Absolute
Change in Mean D-TNSS[b]										
3 (Martin et al,[71] Nathan et al,[72] and Ratner et al[74])[c]	RCT	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	1008	1000	NA	MD 32.82 lower (40.86 to 24.78 lower)
Change in Mean N-TNSS[d]										
3 (Martin et al,[71] Nathan et al,[72] and Ratner et al[74])[c]	RCT	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	1,005	996 (20.9%)	NA	MD 0.52 lower (0.67 to 0.36 lower) and 22 fewer per 1000 (from 51 fewer to 11 more)

Abbreviations: CI, confidence interval; D-TNSS, daytime total nasal symptom score; FSC, fluticasone propionate and salmeterol; FPANS, fluticasone propionate aqueous nasal spray; MD, mean difference; NA, not applicable; N-TNSS, nighttime total nasal symptom score; RCT, randomized clinical trial.
[a]Risk of bias overall for the articles: (1) random sequence generation: low risk of bias; (2) allocation concealment: low risk of bias; (3) blinding of participants and personnel: low risk of bias; (4) incomplete outcome data: low risk of bias; (5) selection reporting: low risk; and (6) other bias: unclear risk of bias. See risk of bias assessment table for question 2 in Appendix D for details.
[b]Follow-up of 2 weeks, measured with D-TNSS ranked on 4-point Likert scale, and better indicated by lower values.
[c]All patients had persistent asthma and were taking open-label FSC. The montelukast and FPANS were blinded. The main objective was to investigate the effect of rhinitis therapy on asthma outcomes in patients with both seasonal allergic rhinitis and persistent asthma. However, D-TNSS and individual nasal symptoms were also studied.
[d]Follow-up of 2 weeks, measured with N-TNSS ranked on 4-point Likert scale, and better indicated by lower values.

Table 8
Question 2: Quality Assessment for Daytime Nasal Symptom Scores

Quality assessment							No. of patients		Effect	
No. of studies	Design	Risk of bias[a]	Inconsistency	Indirectness	Imprecision	Other considerations	Montelukast	Beclomethasone	Relative (95% CI)	Absolute
Daytime Nasal Symptom Score[b]										
1 (Lu et al[70])[c]	RCT	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	172	111	NA	MD 0.34 lower (0.47 to 0.21 lower)

Abbreviations: CI, confidence interval; MD, mean difference; NA, not applicable; RCT, randomized clinical trial.
[a]Risk of bias overall for the articles: (1) random sequence generation: low risk of bias; (2) allocation concealment: low risk of bias; (3) blinding of participants and personnel: low risk of bias; (4) incomplete outcome data: low risk of bias; (5) selection reporting: low risk; and (6) other bias: unclear risk of bias. See risk of bias assessment table for question 2 in Appendix D for details.
[b]Follow-up of 2 weeks, measured with daytime total nasal symptom score, and better indicated by lower values.
[c]L, Although this is the only study that compared montelukast and beclomethasone, the Joint Task Force on Practice Parameters did not believe that this should be considered a serious inconsistency because there is not a significant difference in efficacy between beclomethasone and fluticasone propionate.

Table 9
Question 2: Quality Assessment for Adverse Effects[a]

Quality assessment								No. of patients		Effect	
No. of studies	Design	Risk of bias[b]	Inconsistency	Indirectness	Imprecision	Other considerations		Montelukast and FSC	FPANS and FSC	Relative	Absolute
Total Adverse Effects[c]											
3 (Martin et al,[71] Nathan et al,[72] and Ratner et al[74])	RCT	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None		231/1011 (22.8%)	252/1003 (25.1%) and 20.9%	OR, 0.87 (95% CI, 0.71-1.07)	25 fewer per 1,000 (from 59 fewer to 13 more) and 22 fewer per 1,000 (from 51 fewer to 11 more)

Abbreviations: CI, confidence interval; FSC, fluticasone propionate and salmeterol; FPANS, fluticasone propionate aqueous nasal spray; MD, mean difference; NA, not applicable; OR, odds ratio; RCT, randomized clinical trial.
[a]For all the studies reviewed to answer question 2, it is not possible to guarantee that there was no publication bias as most of these studies were pharmaceutical sponsored studies.
[b]Risk of bias overall for the articles: (1) random sequence generation: low risk of bias; (2) allocation concealment: low risk of bias; (3) blinding of participants and personnel: low risk of bias; (4) incomplete outcome data: low risk of bias; (5) selection reporting: low risk; and (6) other bias: unclear risk of bias. See risk of bias assessment table for question 2 in Appendix D for details.
[c]Follow-up of 2 weeks and assessed with count of adverse effects.

Summary of analysis

There appears to be a clinical benefit of using the combination of an INAH[91] and an INCS compared with monotherapy with an INCS as shown in Figures 4 and 5 below based on the reduction of total nasal symptoms. Similarly, there appears to be a clinical benefit of using the combination of an INAH and an INCS compared with monotherapy with an INAH as shown in Figures 6 and 7 below based on the reduction of total nasal symptoms. Although not a primary end point, one study demonstrated reduction of ocular symptoms and improvement in quality of life (Figs 30, 31, 34 and 35 in Appendix B). The primary adverse events identified for the combination therapy were headache, bitter taste, and epistaxis; the combination product contributed to more adverse events than did monotherapy with the INCS or the INAH. Clinicians should discuss with the patient whether the addition of an INAH increased the odds of experiencing an adverse event (Fig 8).

Studies used for appraisal and synthesis

Five relevant studies address this question. In these studies, all study participants evaluated had a diagnosis of SAR.[75-78] Four of these studies used the same treatment arms, which were fluticasone propionate and normal saline vs fluticasone propionate and normal saline, 200 μg/d, plus azelastine, 548 μg (as a single combination spray).[75,76,78] In the fifth study, the same study arms were used, but fluticasone propionate and normal saline was compared with fluticasone propionate and normal saline plus azelastine, 1,100 μg daily (using 2 separate commercially available sprays).[77] Therefore, using 2 separate sprays compared with a single combination spray will double the dose of azelastine delivered. Given the fact that only one study used separate sprays, we are unable to make a statement on the comparative efficacy of combined vs 2 separate sprays of fluticasone propionate and normal saline and azelastine. The reported outcome measure for the first 4 studies was the mean difference in TNSS among groups.[75,76,78] The fifth study reported the least square means of the TNSS.[77] The study by Hampel et al[75] also reported total ocular symptom scores, whereas the study by Ratner et al[77] reported RQLQ, and the study by Meltzer et al,[76] Ratner et al,[77] and Hampel et al[75] also reported total adverse effects. For all the primary end point evaluations for each of these studies, treatment with fluticasone propionate and normal saline and azelastine was more effective than fluticasone propionate and normal saline alone.

Summary of systematic review and quality assessment of included studies

There was a statistically significant clinical benefit in terms of total nasal symptom reduction when using the combination of an INAH and an INCS but with an increase of adverse events.

II. Characteristics of Included Studies and Determination of Risk of Bias

The detailed characteristics of each study, including setting, participants entering and completing the study, participant demographics, inclusion and exclusion criteria, power analysis, intervention, and s primary and secondary end point outcomes, may be reviewed in the tables in Appendix B. A summary of study characteristics used for the quality assessment is given in Table 10. A separate risk of bias table for question 3 is available for review in Appendix D.

The workgroup updated the risk of bias (random sequence generation, allocation concealment, blinding adequacy, completeness of data, reporting, adequacy of sample size, funding source and other potential biases, eg, failure to submit studies with negative findings for publication) that may contribute to risk of bias. The detailed responses are included in the footnotes to the risk of bias for question 3 studies in Appendix D. The workgroup

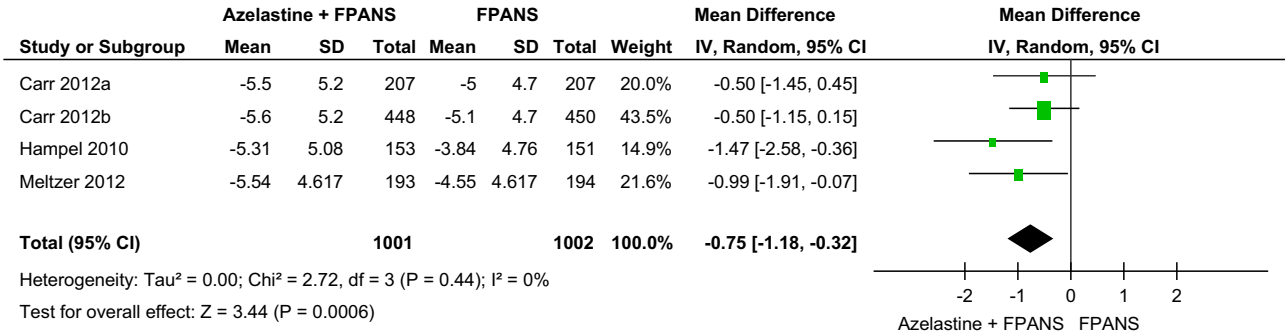

Figure 4. Question 3: Change in mean total nasal symptom score. Lower reduction in mean score is better. CI indicates confidence interval; FPANS, fluticasone propionate aqueous nasal spray.

recommended that the risk of bias should be considered low. The JTFPP reviewed and agreed that the risk of bias was low.

III. Development of Forest Plots Comparing Change in Symptom Score and Adverse Effects

Because the 5 included studies did not all use the same outcome as outlined in Table 10, it was not possible to construct forest plots that would include all studies on one plot. Therefore, individual forest plots were constructed for some studies. Forest plots that compare more than one study are included in this document, whereas all forest plots (Figs 28–36) may be reviewed in Appendix B.

IV: Quality Assessment for Question 3 References

As detailed in Tables 11 and 12 below, the workgroup and the JTFPP reviewed the elements of assessment, including type of article, risk of bias, imprecision, indirectness, inconsistency, and publication bias, and concluded that overall these references were of high quality. The primary outcome was change in TNSS.

Conclusion of quality assessment for primary outcome

When all the articles are considered overall, the quality assessment was good for all categories, and the JTFPP thought that the overall quality of these articles to answer question 3 was high (by Delphi, 8 of 8 voted for high quality).

V. Advice for the Clinician

The following Clinical Statement Profile is the combined expert opinion of the workgroup, the JTFPP, and patient advocates based on the GRADE analysis conclusions discussed above. The conclusions reached by the experts are a synthesis of the GRADE analysis of data combined with the collective knowledge and experience of the experts involved. When complete agreement could not be reached, the Delphi method was used.

Clinical Statement Profile for question 3

Clinical statement: For treatment of nasal symptoms of moderate to severe SAR in patients 12 years or older, the clinician may recommend the combination of an INCS nd an INAH for initial treatment.

Strength of recommendation as determined by the JTFPP: Weak (by Delphi, 8 of 8 voted for weak).

Expert opinion comment on strength of recommendation: Notwithstanding the high-quality evidence and the efficacy advantage of combination therapy, other factors, such as potential adverse effects and increased cost, were carefully considered by the workgroup and the JTFPP when deciding on the strength of recommendation. Although the difference in efficacy was greater when comparing combination therapy with INAH monotherapy than when comparing combination therapy with INCS, this did not significantly affect the strength of the recommendation because either comparison was believed to be a weak recommendation. Although many clinicians likely start with monotherapy and then add a second agent, none of the studies looked at this therapeutic option. Given the qualifying prestudy period and the few weeks of seasonal pollen exposure, it is highly unlikely that a study starting with monotherapy, failing monotherapy, and then moving to combination therapy would be able to be adequately designed and completed. Therefore, this will likely remain a patient-by patient decision that the clinician will need to make.

Quality improvement opportunity: To improve symptom control in patients for initial therapy, there is the potential for greater improvement of symptoms with a combination of an INCS and an INAH compared with monotherapy with either agent.

GRADE evidence of quality as determined by the JTFPP: High (by Delphi, 8 of 8 voted for high quality).

Expert opinion comment on evidence quality: All studies looking at this question used the reflective TNSS, which is, in general, accepted as the best measurement available for determining efficacy of a medication for SAR. Moreover, the FDA accepts the reflective TNSS because there is no better measurement of efficacy

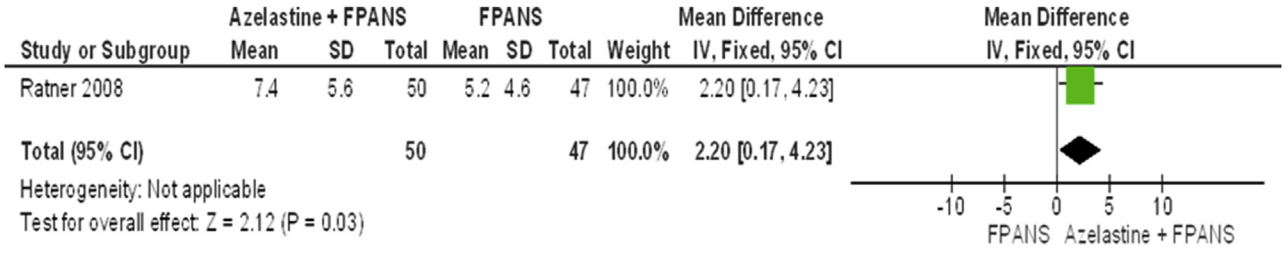

Figure 5. Question 3: Change in least squares mean total nasal symptom score. Higher change is better. CI indicates confidence interval; FPANS, fluticasone propionate aqueous nasal spray.

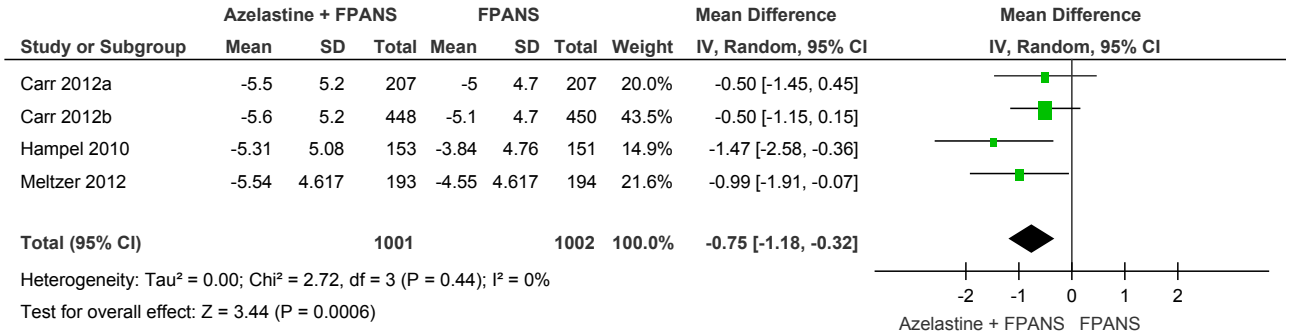

Figure 6. Question 3: Change in mean total nasal symptom score. Lower reduction in mean score is better. CI indicates confidence interval; FPANS, fluticasone propionate aqueous nasal spray.

of medications used to control SAR symptoms. In contrast to most of the studies reported in questions 1 and 2, the authors of the studies under consideration for question 3 reported that they were measuring the reflective TNSS rather than just stating TNSS. It is unclear whether reporting instantaneous TNSS would have been a less subjective measurement.

Level of confidence in evidence by the workgroup and JTFPP: High. There is confidence that the true effect lies close to the estimate of the effect.

Benefits: One can achieve greater control of SAR with combination therapy than with monotherapy of INCS or INAH. The option of using a single intranasal spray device that contains both types of agents provides more convenient administration but with increased cost and, possibly, no greater benefit than the use of 2 separate nasal spray devices each of which contain one type of agent.

Risks, harms, and costs: The addition of an INAH to an INCS increases the potential for harm based on the risk of an adverse effect. Adverse effects include sedation and/or unpleasant taste from INAHs beyond potential nosebleeds from INCSs. Using a single intranasal device that contains 2 medications increases the cost of therapy for most patients. Concurrent therapy with both agents in separate devices is also a greater cost than that of monotherapy with either agent.

Benefit-harm assessment: The benefit of using the combination for patients with conditions not adequately controlled with a single agent outweighs the harm.

Value judgments: The treatment outcomes assessed in this analysis would be valued as important by most patients. Although not the focus of this systematic review, the 2 individual medications are available as single agents in generic form, and their combined cost is significantly lower than the single dual-medication device. Therefore, the physician and patient may discuss the risks and benefits of using 2 single-drug devices rather than the one dual-medication device.

Intentional vagueness: Inadequate response or control allows for some interpretation by clinicians and patients.

Role of patient preferences: High. For initial therapy, some patients may be reluctant to use 2 drug entities with aggregate greater cost when one agent may be sufficient, whereas others may want to begin with 2 agents because of greater likelihood of symptom control. For patients with conditions not well controlled with INCS monotherapy, patients may not want to add an INAH that may cause sedation or taste perversion, whereas patients with conditions not controlled with an INAH may not want to add an INCS because of their concerns regarding safety and adverse events. The relative costs and convenience of using a combination single device vs concurrent therapy with agents in separate devices may also influence patient preference. Because of the increased volume of medication when using 2 separate nasal spray devices concurrently, there should, ideally, be several minutes between the use of the 2 devices to ensure adequate absorption. This will contribute to further inconvenience for the patient and possibly reduce adherence. In the United States, the branded single device combination therapy often requires preapproval for coverage from many pharmacy benefit plans. Higher costs may lead to higher patient expectations. Clinicians should use their expertise in assisting patients to evaluate the best treatment choice through shared decision making in consideration of evidence of benefits, harms, and cost of combination therapy, allowing patients to express their values and preferences and participate in the medical decision-making process.

Exclusions: None.

Policy level: Optional.

Differences of opinion: One workgroup member thought that it would be cost ineffective to recommend combination therapy for initial treatment as an alternative to either of the component monotherapies.

Expert Commentary

In contrast to combination therapy of an INCS and an oral antihistamine (question 1), which did not show any further clinical benefit, combination therapy of an INCS and INAH, as studied in a single device, provides a greater benefit than monotherapy for SAR in the population studied (eg, those 12 years and older). The workgroup and the JTFPP concluded that for the primary end point of TNSS differences found were

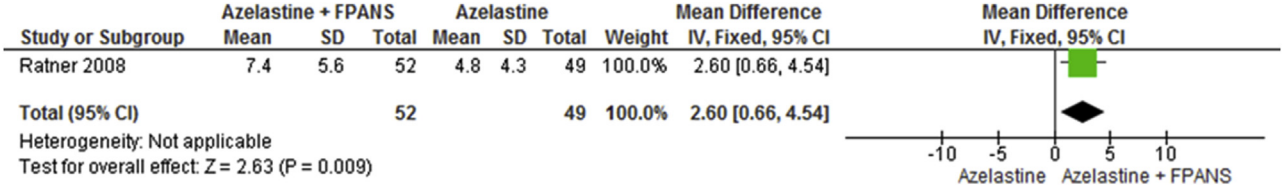

Figure 7. Question 3: Change in least squares mean total nasal symptom score. Higher change in mean is better. CI indicates confidence interval; FPANS, fluticasone propionate aqueous nasal spray.

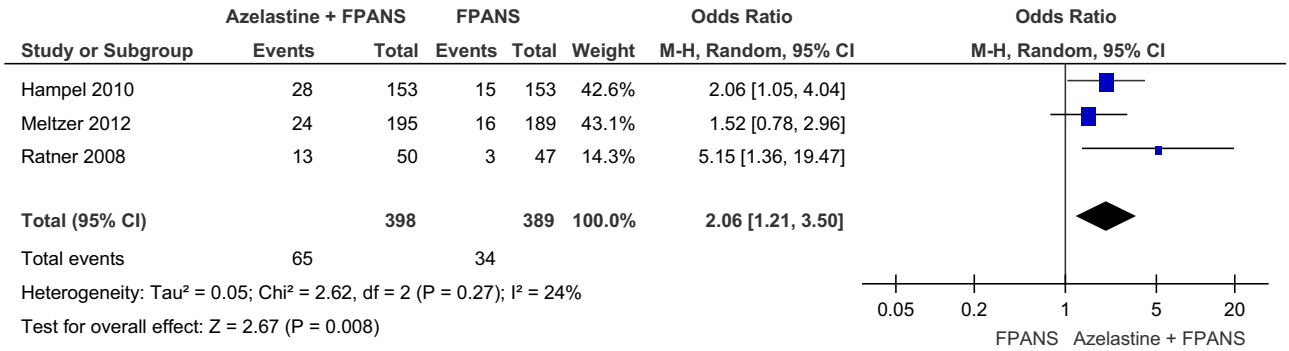

Figure 8. Question 3: Adverse events. Lower reduction in mean score is better. CI indicates confidence interval; FPANS, fluticasone propionate aqueous nasal spray; M-H, Mantel-Haenszel.

clinically meaningful according to recently published criteria.[86] However, for quality-of-life assessments by the RQLQ in placebo-controlled trials, using an established threshold that 0.5 is a clinically meaningful difference, combination therapy did not consistently demonstrate a clinically meaningful difference greater than monotherapies. Combination therapy significantly improved the overall ocular symptoms compared with fluticasone or placebo but not azelastine.[75,76,78] Overall, the number of adverse events in the 6 reported studies was low. Dysgeusia, the most common adverse event, was reported to be more common in azelastine than with the INAH and INCS combination product in 4 of 6 studies and varied between 2.1% and 13.5% of patients in the azelastine and combined INAH and INCS study arms.[75-78] The incidence of epistaxis was similar to or lower in the placebo and treatment arms in 5 of 5 studies.[75,76,78] Somnolence, reported in 2 of 6 studies, varied between 0.4% and 1.1% in the treatment arms that included azelastine. However, higher rates of somnolence have been reported in other studies.[92]

Previously published guidelines[3,4,6,83] have addressed these questions using the same referenced articles. All the guidelines except the AHRQ guidelines recommended adding an INCS to an INAH or adding an INAH to an INCS for better symptom control. The AHRQ concluded that using monotherapy or combination therapy gave equal benefit and, therefore, recommended monotherapy. This discordance (see Discussion section below) demonstrates that using a different analytical approach, the JTFPP and other guideline writing groups conclude that there is high-quality evidence in favor of using the INCS and INAH combination.

Discussion

Although it is likely that most clinicians will think that the answers to the 3 questions asked align closely with their clinical experience for most patients, in select patients the above clinical recommendations may not always apply. Individual patients and their response to treatment may be different and influence the applicability of recommendations. Even strong recommendations do not necessarily represent a legally defined standard of care. Although all the therapeutic options are approved for children younger than 12 years, the studies in this systematic review did not include children; therefore, we cannot make definitive conclusions regarding clinical response in this age group. The clinician may choose, at times, to extrapolate the conclusions reached for the adult population to children. However, method and ease of delivery, concern with long-term adverse effects of some medications, and intolerance of select adverse effects may alter the therapeutic choice in children. The answers to the 3 questions also may not necessarily apply to other populations, such as pregnant and nursing women and senior patients. Physiologic changes during pregnancy can influence rhinitis, and selection of agents must consider safety to the fetus and to the mother (see Summary Statements 98-104 in the 2008 Rhinitis Updated Practice Parameter[4]). In senior patients, rhinitis may also be influenced by age-related physiologic changes, such as cholinergic hyperactivity, anatomical changes, and medications taken for other medical conditions, and patients may be more vulnerable to certain adverse effects (see Summary Statement 106 in the 2008 Rhinitis Updated Practice Parameter[4]).

Table 10
Question 3: Summary of Study Characteristics Used for the Quality Assessment

Quality assessment	Study characteristics
GRADE inconsistencies	
Analyzing populations	All the study participants were diagnosed with seasonal allergic rhinitis.
Analyzing interventions	Four of the studies[75,76,78] used the same study arms of fluticasone propionate aqueous nasal spray, 200 μg/d, vs fluticasone propionate aqueous nasal spray, 200 μg/d, plus azelastine, 548 μg, whereas the fifth study[77] used the same study arms and the dosage of fluticasone propionate aqueous nasal spray remained the same but the dosage of azelastine increased to 1,100 μg/d.
Analyzing outcomes	The outcomes measures reported in the 5 studies were total nasal symptom score as mean difference,[75,76,78] total nasal symptom score as least squares mean,[77] total ocular symptom score,[75] Rhinoconjunctivitis Quality of Life Questionnaire,[77] and total adverse events.[75-77]
GRADE indirectness	
Analyzing comparisons	All the studies compare and provide head-to-head comparisons of an intranasal corticosteroid and an intranasal corticosteroid with an intranasal antihistamine. The populations reflect the population of choice.
Analyzing interventions	The interventions tested are of interest to this analysis.
Analyzing outcomes	The outcome of interest is the patient symptom–based measure of nasal symptom scoring. One study reported the outcomes as least squares mean; therefore, the outcomes from this study needed to be reported separately from the other studies.
GRADE imprecision	One study[77] could have had imprecision issues attributable to a small sample size because the confidence interval is larger than that of the other studies in this group. Sample sizes were an issue in all 5 analyzed studies in that the authors did not indicate the number of participants randomized to each study arm in 2 studies,[78] the authors did not disclose how many participants were needed to detect significance in 2 studies,[75,77] and the number of evaluable participants needed to detect significance was not met in 1 study.[76]

Table 11
Question 3: Does Azelastine and FPANS vs Azelastine Monotherapy Increase Clinical Benefit in Seasonal Allergic Rhinitis?

Quality assessment							No. of patients		Effect	
No. of studies	Design	Risk of bias[a]	Inconsistency	Indirectness	Imprecision	Other considerations	Azelastine and FPANS	Azelastine	Relative (95% CI)	Absolute
Change in TNSS[b]										
4 (Carr et al,[78] Hampel et al,[75] and Meltzer et al[76])	RCT	No serious risk of bias[CHM]	No serious inconsistency	No serious indirectness	No serious imprecision	None	1,001	999	NA	MD 1.3 lower (1.72 to 0.87 lower)
Change in TNSS[c]										
1 (Ratner et al[77])	RCT	No serious risk of bias[R1]	No serious inconsistency	No serious indirectness	No serious imprecision[R2]	None	52	49	NA	MD 2.6 higher (0.66 to 4.54 higher)

Abbreviations: CI, confidence interval; DNSS, daily nasal symptom score; FPANS, fluticasone propionate aqueous nasal spray; MD, mean difference; NA, not applicable; RCT, randomized clinical trial; TNSS, total nasal symptom score.
[a]CHM, Participants in all 4 studies reported reflective TNSS, the US Food and Drug Administration's preferred method of determining drug efficacy in clinical studies. The Joint Task Force on Practice Parameters (JTFPP) does not think that this measurement constitutes a serious risk of bias; R1, Same explanation as CHM; R2, The JTFPP does not consider there to be a significant risk for imprecision. In the study by Ratner et al,[69] 151 individuals were randomized, 150 completed postbaseline diary data, and 147 patients completed the study. Reasons for withdrawal were clearly stated. Although the authors did not indicate within the article the needed sample size before participant enrollment, there was a low dropout rate and statistical significance was reached.
[b]Follow-up of 2 weeks, measured with reflective TNSS, and better indicated by lower values.
[c]Follow-up of 2 weeks, measured with reflective TNSS, and better indicated by higher values.

Table 12
Question 3: Does Azelastine and FPANS vs FPANS Monotherapy Increase Clinical Benefit in Seasonal Allergic Rhinitis?

Quality assessment							No. of patients		Effect	
No. of studies	Design	Risk of bias[a]	Inconsistency	Indirectness	Imprecision[a]	Other considerations	Azelastine and FPANS	FPANS	Relative (95% CI)	Absolute
Change in TNSS[b]										
4 (Carr et al,[78] Hampel et al,[75] and Meltzer et al[76])	RCT	No serious risk of bias[CMM]	No serious inconsistency	No serious indirectness	No serious imprecision	None	1,001	1,002	NA	MD 0.75 lower (1.18 to 0.32 lower)
Change in TNSS[c]										
1 (Ratner et al[77])	RCT	No serious risk of bias[R1]	No serious inconsistency	No serious indirectness	No serious imprecision[R2]	None	50	50	NA	MD 2.2 higher (0.19 to 4.21 higher)

Abbreviations: CI, confidence interval; DNSS, daily nasal symptom score; FPANS, fluticasone propionate aqueous nasal spray; MD, mean difference; NA, not applicable; RCT, randomized clinical trial.
[a]CHM, Participants in all 4 studies reported reflective TNSS, the US Food and Drug Administration's preferred method of determining drug efficacy in clinical studies. The Joint Task Force on Practice Parameters (JTFPP) does not think that this measurement constitutes a serious risk of bias; R1, Same explanation as CHM; R2, The JTFPP does not consider there to be a significant risk for imprecision. In the study by Ratner et al,[69] 151 individuals were randomized, 150 completed postbaseline diary data, and 147 patients completed the study. Reasons for withdrawal were clearly stated. Although the authors did not indicate within the article the needed sample size before participant enrollment, there was a low dropout rate and statistical significance was reached.
[b]Follow-up of 2 weeks, measured with reflective TNSS, and better indicated by lower values.
[c]Follow-up of 2 weeks, measured with reflective TNSS, and better indicated by higher values.

Table 13
Unmet Needs for Allergic Rhinitis Pharmacotherapy

Questions needing answers	Future systematic reviews may be able to answer with current evidence	More research needed—systematic review unlikely to answer at this Time
Benefit of *adding* a second therapeutic agent when the first therapeutic agent fails		X
Difference in efficacy of monotherapy (INCS) vs combination therapy (INCS and INAH) for SAR with and without PAR being present		X
Determination of minimal clinically significant difference in AR TNSS, QOL, and TOSS		X
Efficacy of monotherapy or combination therapy pharmacotherapy for AR in terms of TNSS reduction and/or improvement in QOL when there is concomitant improvement of coexisting asthma (eg, using montelukast)		X
Efficacy of monotherapy (INCS) vs combination therapy (INCS and INAH) for PAR and/or non-AR		X
Efficacy of monotherapy (INCS) vs combination therapy (INCS and INAH) in SAR in children	X	
Efficacy of monotherapy (INCS) vs combination therapy (INCS and INAH) in SAR, PAR, and non-AR in elderly populations and pregnant patients		X
Efficacy of second-generation AH for the management of SAR in children and adults	X	
Comparative efficacy and safety of all currently available INCSs for SAR and PAR in children and adults	X, possibly	
Comparative efficacy and safety of all currently available INAHs for SAR and PAR in children and adults		X
Comparative efficacy and safety of current INAH v. oral AH for PAR in children and adults		X
Efficacy of second-generation oral AH vs INCS for PAR for adults and children		X
Benefit of adding montelukast to an INCS when monotherapy with INCS in SAR and PAR fails in adults and children		X

Abbreviations: AH, antihistamine; AR, allergic rhinitis; INAH, intranasal antihistamine; INCS, inhaled nasal corticosteroids; PAR, perennial allergic rhinitis; QOL, quality of life; SAR, seasonal allergic rhinitis; TNSS, total nasal symptom score; TOSS, Total Ocular Symptom Score.

Evaluation of the Quality of the Trials (Bias and Certainty of Evidence)

Available rhinitis guidelines differ in evaluating and assessing the quality of the evidence. Although the 2008 JTFPP Diagnosis and Management of Rhinitis: An Updated Practice Parameter graded each reference based on study design, the design components and presence and absence for bias were not evaluated.[4] The strength of the recommendations was mostly dependent on the overall study design of the included references. As for the 2015 American Academy of Otolaryngology—Head and Neck Surgery guidelines,[3] even though the team conducted a formal literature search and followed an evidence-based approach in the formulation of recommendations, no structured evaluation of the certainty of the body of evidence and presence or absence of bias was discussed. Both the ARIA 2016 revision[83] and the 2013 AHRQ SAR guidelines[6] used the GRADE approach but arrived at different quality assessment ratings for the same references with different recommendations for the questions being considered. Similar divergence was noted when comparing the ARIA and AHRQ guidelines to this systematic review. As such, the recommendations in this guideline differ from other guidelines.

However, even using a GRADE evidenced-based approach, there are some interesting and perhaps perplexing observations. Most striking is that although the same or similar tools and criteria are used to assess the quality of evidence, there is an element of judgment required in completing the analysis. For example, both the ARIA 2016 revision[83] and the JTFPP Treatment of Seasonal Allergic Rhinitis: An Evidence-Based Focused 2017 Guideline Update used the Cochrane Collaboration Review Manager Software, version 5.3.5.12 for the meta-analysis and the GRADEpro Guideline Development Tool online application (www.gradepro.org) for grading the quality of the evidence, yet the literature for question 1 is overall graded to be low quality by the ARIA 2016 revision methods and to be moderate quality by the JTFPP.

For question 3, the JTFPP methodologists opined that patient reporting of the reflective TNSS was subject to a significant degree of blinding of outcome assessment bias. The workgroup and the JTFPP did not agree with this assessment and, as explained earlier, rated the evidence for question 3 as high. Although one could argue that ideally an objective measurement of clinical response in SAR would be preferred, a reliable, validated objective measurement has yet to be developed. Studies, therefore, rely on an established and validated diary symptom measurement instrument (eg, the reflective TNSS for determining symptom reduction attributed to a clinical intervention). Furthermore, the FDA accepts the reflective TNSS as the most accurate way of determining symptom improvement when considering the approval of a new drug for SAR.[15] Although historically both an instantaneous and reflective TNSS was requested by the FDA, they have, in recent years, only requested to see the reflective TNSS. For questions 1 and 2, the authors also used a 12-hour day and night TNSS. These authors did not describe the reported TNSS as being reflective or instantaneous in the methodologic blinding of outcome assessment. Therefore, these articles were viewed by the JTFPP methodologists to have a low risk of bias. The workgroup and JTFPP concluded that the TNSS and reflective TNSS were, in essence, the same measurement and that using the reflective TNSS did not add significant outcome assessment bias.

Study Inclusion and Limitations

We used the AHRQ-defined literature search and updated it. Our included population is mostly adults with moderate to severe SAR with pollen allergy. Further research will be needed to define whether the conclusions reached in this guideline can be applicable for other patient groups and sensitizations (eg, children and patients with PAR sensitized to house dust mite).

Another potential limitation of this systematic review is the relatively small sample size in most studies. The conclusions may be further biased by not giving due consideration to the sample size when making a quality assessment of the evidence. Furthermore, publication bias of unpublished negative studies and full disclosure of all funding sources for the studies cannot be accurately determined.

When one compares AR treatment guidelines, often using the identical group of references, there are obvious differences in the determination of evidence quality, recommended monotherapy or

combination therapies, the assessment of adverse events, and the strength of the recommendations. The 3 questions addressed in this guideline are, indeed, answered differently, depending on which guideline is used. Guidelines should, therefore, be used as a starting point for the clinician and patient to determine, through shared decision making, what would constitute the optimal treatment for AR at the current time.

Conclusion

In summary, from our review of specific management strategies for AR, the following conclusions are warranted. When monotherapy is being considered, INCSs are a more effective choice than LTRAs. When a patient is already taking an INCS, yet the patient's condition is not optimally controlled, and is considering the addition of an antihistamine, the best additional therapy is an INAH not an oral antihistamine, although the rate of adverse effects with such combination is higher than with an INCS alone. This systematic review and analysis report does not make any statements about oral antihistamines alone as initial treatment for SAR or about the treatment of PAR or mild SAR. On the basis largely of the reviewers' comments, we have added Table 13 (Unmet Needs for Allergic Rhinitis Pharmacotherapy), which addresses examples of unanswered questions and whether current research would likely be able to answer these questions. This systematic review has also brought to the forefront the need of well-designed, nonbiased, appropriately powered AR pharmacotherapy studies that include minimally important clinical differences when evaluating efficacy and adverse events.

Future Directions

As discussed above, perhaps the questions that clinicians really need answered about rhinitis medications alone and in combination have not been addressed. As we visualize and plan the future development of evidence-based documents, the patient and payer perspectives must be thoroughly addressed to provide better real-world recommendations. Such recommendations need to address various areas, such as (1) how patients value the main outcomes of the systematic review findings; (2) what financial resources are required and how certain is the evidence of these required resources; (3) how does the cost-effectiveness of the best drug and combination compare with the patient's current therapy; (4) what is the acceptability of the conclusions by the patient and other stakeholders; (5) how feasible would the recommendation be to implement; and (6) in real-life use, when patients may not be taking medications as regularly as in controlled trials, do guideline-derived treatment recommendations result in improved outcomes for patients? Although some guidelines discuss and reach a conclusion on some or all of these areas, these socioeconomic recommendations are based predominantly on expert opinion by panel members and not on research because of the limited number of articles that address these issues.

Institute of Medicine National Health Care Quality Report Categories

The following is a list of the Institute of Medicine (IOM) national health care quality report categories: IOM care need, getting better, living with illness, IOM domain, effectiveness, patient-centeredness, safety, cost analysis (a formal cost analysis was not performed and published analyses were not reviewed).

Guideline Validation

The method of guideline validation was external peer review or internal peer review.

Internal Review

A first draft of the guideline was sent to AAAAI and ACAAI appointment reviewers, who were asked to comment on the statements and the rationale within free text fields. All these comments and suggestions were discussed during an JTFPP teleconference. The JTFPP liaison to the workgroup coordinated input from the workgroup when needed. For each comment or suggestion, the JTFPP evaluated whether the statement needed to be adapted, again taking into account the balance between desirable and undesirable consequences of the alternative management strategies, the quality of the evidence, and the variability in values and preferences.

External Review

The guideline was posted on the AAAAI, ACAAI, and JTFPP websites for all members and the public at large to review. For each comment or suggestion, the JTFPP evaluated whether the statement needed to be adapted, again taking into account the balance between desirable and undesirable consequences of the alternative management strategies, the quality of the evidence, and the variability in values and preferences.

Benefits and Harms of Implementing the Guideline Recommendations

Potential Benefits

The potential benefit was appropriate management of patients with seasonal allergic rhinitis. See the Advice for the Clinician section for each question in the guideline document for benefits of specific interventions.

Potential Harms

Potential harms included adverse effects associated with treatment. See the Advice for the Clinician section for each question in the guideline document for adverse events of specific interventions.

Qualifying Statements

This clinical practice guideline was designed to facilitate informed decision making on the management of adults with SAR. It was not intended to define a standard of care and should not be construed as such. It should not be interpreted as a prescription for an exclusive course of management.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

No implementation tools were developed.

Supplementary Data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.anai.2017.08.012.

References

[1] Dykewicz MS, Fineman S, Skoner DP, et al. Diagnosis and management of rhinitis: complete guidelines of the Joint Task Force on Practice Parameters in Allergy, Asthma and Immunology. American Academy of Allergy, Asthma, and Immunology. *Ann Allergy Asthma Immunol*. 1998;81(5, pt 2):478–518 (IV).

[2] Brozek JL, Bousquet J, Baena-Cagnani CE, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision. *J Allergy Clin Immunol*. 2010;126:466–476.

[3] Seidman MD, Gurgel RK, Lin SY, et al. Clinical practice guideline: allergic rhinitis executive summary. *Otolaryngol Head Neck Surg*. 2015;152:197–206.

[4] Wallace DV, Dykewicz MS, Bernstein DI, et al. The diagnosis and management of rhinitis: an updated practice parameter. *J Allergy Clin Immunol*. 2008;122(2 suppl):S1–S84 (IV).

[5] Corren J, Storms W, Bernstein J, Berger W, Nayak A, Sacks H. Effectiveness of azelastine nasal spray compared with oral cetirizine in patients with seasonal allergic rhinitis. *Clin Ther*. 2005;27:543–553 (Ib).

[6] Glacy J, Putnam K, Godfrey S, et al. *Treatments for Seasonal Allergic Rhinitis. Comparative Effectiveness Review No. 120 (Prepared by the Blue Cross and Blue Shield Association Technology Evaluation. Evidence-based Practice Center under Contract No. 290-2007-10058-I). Rockville, MD: Agency for Healthcare Research and Quality; July 2013. AHRQ publication 13-EHC098-EF*, https://effectivehealthcare.ahrq.gov/ehc/products/376/1588/allergy-seasonal-report-130711.pdf. Accessed August 7, 2017.

[7] Meltzer EO, Blaiss MS, Naclerio RM, et al. Burden of allergic rhinitis: allergies in America, Latin America, and Asia-Pacific adult surveys. *Allergy Asthma Proc*. 2012;33(suppl 1):S113–S141.

[8] Meltzer EO. Allergic rhinitis: burden of illness, quality of life, comorbidities, and control. *Immunol Allergy Clin North Am*. 2016;36:235–248.

[9] Kirmaz C, Aydemir O, Bayrak P, Yuksel H, Ozenturk O, Degirmenci S. Sexual dysfunction in patients with allergic rhinoconjunctivitis. *Ann Allergy Asthma Immunol*. 2005;95:525–529.

[10] Mullol J, Maurer M, Bousquet J. Sleep and allergic rhinitis. *J Investig Allergol Clin Immunol*. 2008;18:415–419.

[11] Colas C, Galera H, Anibarro B, et al. Disease severity impairs sleep quality in allergic rhinitis (the SOMNIAAR study). *Clin Exp Allergy*. 2012;42:1080–1087.

[12] Nathan RA. The burden of allergic rhinitis. *Allergy Asthma Proc*. 2007;28:3–9.

[13] Schoenwetter WF, Dupclay L Jr, Appajosyula S, Botteman MF, Pashos CL. Economic impact and quality-of-life burden of allergic rhinitis. *Curr Med Res Opin*. 2004;20:305–317 (IV).

[14] Casale TB, Dykewicz MS. Clinical implications of the allergic rhinitis-asthma link. *Am J Med Sci*. 2004;327:127–138.

[15] US Department of Health and Human Services. *Allergic Rhinitis: Developing Drug Products for Treatment Guidance for Industry: Draft Guidelines* 2016. Rockville, MD: Federal Register, http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071293.pdf. Accessed August 7, 2017.

[16] Bousquet J, Khaltaev N, Cruz AA, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA2LEN and AllerGen). *Allergy*. 2008;63(suppl 86):8–160.

[17] Simons FE. Advances in H_1-antihistamines. *N Engl J Med*. 2004;351:2203–2217.

[18] Church MK, Maurer M, Simons FE, et al. Risk of first-generation H(1)-antihistamines: a GA(2)LEN position paper. *Allergy*. 2010;65:459–466.

[19] Gray SL, Anderson ML, Dublin S, et al. Cumulative use of strong anticholinergics and incident dementia: a prospective cohort study. *JAMA Intern Med*. 2015;175:401–407.

[20] Golightly LK, Greos LS. Second-generation antihistamines: actions and efficacy in the management of allergic disorders. *Drugs*. 2005;65:341–384.

[21] Berger W, Hampel F Jr, Bernstein J, Shah S, Sacks H, Meltzer EO. Impact of azelastine nasal spray on symptoms and quality of life compared with cetirizine oral tablets in patients with seasonal allergic rhinitis. *Ann Allergy Asthma Immunol*. 2006;97:375–381.

[22] Horak F, Zieglmayer UP, Zieglmayer R, et al. Azelastine nasal spray and desloratadine tablets in pollen-induced seasonal allergic rhinitis: a pharmacodynamic study of onset of action and efficacy. *Curr Med Res Opin*. 2006;22:151–157.

[23] LaForce CF, Corren J, Wheeler WJ, Berger WE. Efficacy of azelastine nasal spray in seasonal allergic rhinitis patients who remain symptomatic after treatment with fexofenadine. *Ann Allergy Asthma Immunol*. 2004;93:154–159.

[24] Newson-Smith G, Powell M, Baehre M, Garnham SP, MacMahon MT. A placebo controlled study comparing the efficacy of intranasal azelastine and beclomethasone in the treatment of seasonal allergic rhinitis. *Eur Arch Otorhinolaryngol*. 1997;254:236–241.

[25] Ratner PH, Findlay SR, Hampel F Jr, van Bavel J, Widlitz MD, Freitag JJ. A double-blind, controlled trial to assess the safety and efficacy of azelastine nasal spray in seasonal allergic rhinitis. *J Allergy Clin Immunol*. 1994;94:818–825 (Ib).

[26] LaForce C, Dockhorn RJ, Prenner BM, et al. Safety and efficacy of azelastine nasal spray (Astelin NS) for seasonal allergic rhinitis: a 4-week comparative multicenter trial. *Ann Allergy Asthma Immunol*. 1996;76:181–188 (Ib).

[27] Patel D, Garadi R, Brubaker M, et al. Onset and duration of action of nasal sprays in seasonal allergic rhinitis patients: olopatadine hydrochloride versus mometasone furoate monohydrate. *Allergy Asthma Proc*. 2007;28:592–599.

[28] Patel P, D'Andrea C, Sacks HJ. Onset of action of azelastine nasal spray compared with mometasone nasal spray and placebo in subjects with seasonal allergic rhinitis evaluated in an environmental exposure chamber. *Am J Rhinol*. 2007;21:499–503.

[29] Benninger M, Farrar JR, Blaiss M, et al. Evaluating approved medications to treat allergic rhinitis in the United States: an evidence-based review of efficacy for nasal symptoms by class. *Ann Allergy Asthma Immunol*. 2010;104:13–29.

[30] Fukuishi N, Matsuhisa M, Shimono T, et al. Inhibitory effect of olopatadine on antigen-induced eosinophil infiltration and the LFA-1 and Mac-1 expression in eosinophils. *Jpn J Pharmacol*. 2002;88:463–466.

[31] Pipkorn P, Costantini C, Reynolds C, et al. The effects of the nasal antihistamines olopatadine and azelastine in nasal allergen provocation. *Ann Allergy Asthma Immunol*. 2008;101:82–89.

[32] Kempuraj D, Huang M, Kandere-Grzybowska K, et al. Azelastine inhibits secretion of IL-6, TNF-alpha and IL-8 as well as NF-kappaB activation and intracellular calcium ion levels in normal human mast cells. *Int Arch Allergy Immunol*. 2003;132:231–239.

[33] Singh U, Bernstein JA, Haar L, Luther K, Jones WK. Azelastine desensitization of transient receptor potential vanilloid 1: a potential mechanism explaining its therapeutic effect in nonallergic rhinitis. *Am J Rhinol Allergy*. 2014;28:215–224.

[34] Luo X, Ma R, Wu X, et al. Azelastine enhances the clinical efficacy of glucocorticoid by modulating MKP-1 expression in allergic rhinitis. *Eur Arch Otorhinolaryngol*. 2015;272:1165–1173.

[35] *Astelin (azelastine hydrochloride) 2007*, http://www.astelin.com/Astelin.Public/AstelinPi.pdf. Accessed August 7, 2017.

[36] Herman H. Once-daily administration of intranasal corticosteroids for allergic rhinitis: a comparative review of efficacy, safety, patient preference, and cost. *Am J Rhinol*. 2007;21:70–79.

[37] Rodrigo GJ, Neffen H. Efficacy of fluticasone furoate nasal spray vs. placebo for the treatment of ocular and nasal symptoms of allergic rhinitis: a systematic review. *Clin Exp Allergy*. 2011;41:160–170.

[38] Penagos M, Compalati E, Tarantini F, Baena-Cagnani CE, Passalacqua G, Canonica GW. Efficacy of mometasone furoate nasal spray in the treatment of allergic rhinitis: meta-analysis of randomized, double-blind, placebo-controlled, clinical trials. *Allergy*. 2008;63:1280–1291.

[39] Dibildox J. Safety and efficacy of mometasone furoate aqueous nasal spray in children with allergic rhinitis: results of recent clinical trials. *J Allergy Clin Immunol*. 2001;108:S54–S58.

[40] DeWester J, Philpot EE, Westlund RE, Cook CK, Rickard KA. The efficacy of intranasal fluticasone propionate in the relief of ocular symptoms associated with seasonal allergic rhinitis. *Allergy Asthma Proc*. 2003;24:331–337 (Ia).

[41] Bielory L, Chun Y, Bielory BP, Canonica GW. Impact of mometasone furoate nasal spray on individual ocular symptoms of allergic rhinitis: a meta-analysis. *Allergy*. 2011;66:686–693.

[42] Bascom R, Wachs M, Naclerio RM, Pipkorn U, Galli SJ, Lichtenstein LM. Basophil influx occurs after nasal antigen challenge: effects of topical corticosteroid pretreatment. *J Allergy Clin Immunol*. 1988;81:580–589.

[43] Pipkorn U, Proud D, Lichtenstein LM, Kagey-Sobotka A, Norman PS, Naclerio RM. Inhibition of mediator release in allergic rhinitis by pretreatment with topical glucocorticosteroids. *N Engl J Med*. 1987;316:1506–1510 (Ib).

[44] Erin EM, Leaker BR, Zacharasiewicz AS, et al. Single dose topical corticosteroid inhibits IL-5 and IL-13 in nasal lavage following grass pollen challenge. *Allergy*. 2005;60:1524–1529.

[45] Juniper EF, Guyatt GH, O'Byrne PM, Viveiros M. Aqueous beclomethasone diproprionate nasal spray: regular versus "as required" use in the treatment of seasonal allergic rhinitis. *J Allergy Clin Immunol*. 1990;86:380–386.

[46] Juniper EF, Guyatt GH, Archer B, Ferrie PJ. Aqueous beclomethasone dipropionate in the treatment of ragweed pollen-induced rhinitis: further exploration of "as needed" use. *J Allergy Clin Immunol*. 1993;92:66–72.

[47] Jen A, Baroody F, de Tineo M, Haney L, Blair C, Naclerio R. As-needed use of fluticasone propionate nasal spray reduces symptoms of seasonal allergic rhinitis. *J Allergy Clin Immunol*. 2000;105:732–738 (Ib).

[48] Dykewicz MS, Kaiser HB, Nathan RA, et al. Fluticasone propionate aqueous nasal spray improves nasal symptoms of seasonal allergic rhinitis when used as needed (prn). *Ann Allergy Asthma Immunol*. 2003;91:44–48 (Ib).

[49] Maspero JF, Rosenblut A, Finn A Jr, Lim J, Wu W, Philpot E. Safety and efficacy of fluticasone furoate in pediatric patients with perennial allergic rhinitis. *Otolaryngol Head Neck Surg*. 2008;138:30–37.

[50] Meltzer EO, Tripathy I, Maspero JF, Wu W, Philpot E. Safety and tolerability of fluticasone furoate nasal spray once daily in paediatric patients aged 6-11 years with allergic rhinitis: subanalysis of three randomized, double-blind, placebo-controlled, multicentre studies. *Clin Drug Investig*. 2009;29:79–86.

[51] Rosenblut A, Bardin PG, Muller B, et al. Long-term safety of fluticasone furoate nasal spray in adults and adolescents with perennial allergic rhinitis. *Allergy: Eur J Allergy Clin Immunol*. 2007;62:1071–1077.

[52] Nayak A. A review of montelukast in the treatment of asthma and allergic rhinitis. *Expert Opin Pharmacother*. 2004;5:679–686.

[53] Jones TR, Labelle M, Belley M, et al. Pharmacology of montelukast sodium (Singulair), a potent and selective leukotriene D4 receptor antagonist. *Can J Physiol Pharmacol*. 1995;73:191–201.

[54] Kushnir NM. The role of decongestants, cromolyn, guafenesin, saline washes, capsaicin, leukotriene antagonists, and other treatments on rhinitis. *Immunol Allergy Clin North Am*. 2011;31:601–617.

[55] *Updated Information on Leukotriene Inhibitors: Montelukast (marketed as Singulair), Zafirlukast (marketed as Accolate), and Zileuton (marketed as Zyflo and Zyflo CR) 2009 [updated 8.28.09]*, http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm165489.htm. Accessed August 7, 2017.

[56] Holbrook JT, Harik-Khan R. Montelukast and emotional well-being as a marker for depression: results from 3 randomized, double-masked clinical trials. *J Allergy Clin Immunol*. 2008;122:828–829.

[57] Philip G, Hustad C, Noonan G, et al. Reports of suicidality in clinical trials of montelukast. *J Allergy Clin Immunol*. 2009;124:691–696.e6.

[58] Polos PG. Montelukast is an effective monotherapy for mild asthma and for asthma with co-morbid allergic rhinitis. *Prim Care Respir J*. 2006;15:310–311. author reply 1–2.

[59] Price DB, Swern A, Tozzi CA, Philip G, Polos P. Effect of montelukast on lung function in asthma patients with allergic rhinitis: analysis from the COMPACT trial. *Allergy*. 2006;61:737–742.

[60] Price D, Scadding G, Ryan D, et al. The hidden burden of adult allergic rhinitis: UK healthcare resource utilisation survey. *Clin Transl Allergy*. 2015;5:39.

[61] Ngamphaiboon J. Montelukast in general pediatric practices. *J Med Assoc Thai*. 2005;88:S348–S351.

[62] Can D, Tanac R, Demir E, Gulen F, Veral A. Is the usage of intranasal glucocorticosteroids alone in allergic rhinitis sufficient? *Allergy Asthma Proc*. 2006; 27:248–253.

[63] Modgill V, Badyal DK, Verghese A. Efficacy and safety of montelukast add-on therapy in allergic rhinitis. *Methods Findings Exp Clin Pharmacol*. 2010;32: 669–674.

[64] Brooks C, Francom S, Peel B, Chene B, Klatt K. Spectrum of seasonal allergic rhinitis symptom relief with topical corticoid and oral antihistamine given singly or in combination. *Am J Rhinol*. 1996;10:193–199.

[65] Anolik R. Clinical benefits of combination treatment with mometasone furoate nasal spray and loratadine vs monotherapy with mometasone furoate in the treatment of seasonal allergic rhinitis. *Ann Allergy Asthma Immunol*. 2008;100:264–271.

[66] Barnes ML, Ward JH, Fardon TC, Lipworth BJ. Effects of levocetirizine as add-on therapy to fluticasone in seasonal allergic rhinitis. *Clin Exp Allergy*. 2006; 36:676–684 (Ib).

[67] Benincasa C, Lloyd R. Evaluation of fluticasone propionate aqueous nasal spray taken alone and in combination with cetirizine in the prophylactic treatment of seasonal allergic rhinitis. *Drug Investig*. 1994;8:225–233.

[68] Di Lorenzo G, Pacor ML, Pellitteri ME, et al. Randomized placebo-controlled trial comparing fluticasone aqueous nasal spray in mono-therapy, fluticasone plus cetirizine, fluticasone plus montelukast and cetirizine plus montelukast for seasonal allergic rhinitis. *Clin Exp Allergy*. 2004;34:259–267.

[69] Ratner PH, van Bavel JH, Martin BG, et al. A comparison of the efficacy of fluticasone propionate aqueous nasal spray and loratadine, alone and in combination, for the treatment of seasonal allergic rhinitis. *J Fam Pract*. 1998;47:118–125 (Ib).

[70] Lu S, Malice MP, Dass SB, Reiss TF. Clinical studies of combination montelukast and loratadine in patients with seasonal allergic rhinitis. *J Asthma*. 2009;46:878–883.

[71] Martin BG, Andrews CP, Van Bavel JH, et al. Comparison of fluticasone propionate aqueous nasal spray and oral montelukast for the treatment of seasonal allergic rhinitis symptoms. *Ann Allergy Asthma Immunol*. 2006;96:851–857.

[72] Nathan RA, Yancey SW, Waitkus-Edwards K, et al. Fluticasone propionate nasal spray is superior to montelukast for allergic rhinitis while neither affects overall asthma control. *Chest*. 2005;128:1910–1920 (Ib).

[73] Pullerits T, Praks L, Ristioja V, Lotvall J. Comparison of a nasal glucocorticoid, antileukotriene, and a combination of antileukotriene and antihistamine in the treatment of seasonal allergic rhinitis. *J Allergy Clin Immunol*. 2002;109: 949–955 (Ib).

[74] Ratner PH, Howland WC III, Arastu R, et al. Fluticasone propionate aqueous nasal spray provided significantly greater improvement in daytime and nighttime nasal symptoms of seasonal allergic rhinitis compared with montelukast. *Ann Allergy Asthma Immunol*. 2003;90:536–542 (Ib).

[75] Hampel FC, Ratner PH, Van Bavel J, et al. Double-blind, placebo-controlled study of azelastine and fluticasone in a single nasal spray delivery device. *Ann Allergy Asthma Immunol*. 2010;105:168–173.

[76] Meltzer EO, LaForce C, Ratner P, Price D, Ginsberg D, Carr W. MP29-02 (a novel intranasal formulation of azelastine hydrochloride and fluticasone propionate) in the treatment of seasonal allergic rhinitis: a randomized, double-blind, placebo-controlled trial of efficacy and safety. *Allergy Asthma Proc*. 2012;33:324–332.

[77] Ratner PH, Hampel F, Van Bavel J, et al. Combination therapy with azelastine hydrochloride nasal spray and fluticasone propionate nasal spray in the treatment of patients with seasonal allergic rhinitis. *Ann Allergy Asthma Immunol*. 2008;100:74–81.

[78] Carr W, Bernstein J, Lieberman P, et al. A novel intranasal therapy of azelastine with fluticasone for the treatment of allergic rhinitis. *J Allergy Clin Immunol*. 2012;129:1282–1289.e10.

[79] Schünemann H, Santesso N. *How to GRADE the Evidence: The Cochrane Collaboration* 2016, http://training.cochrane.org/. Accessed August 7, 2017.

[80] Brozek JL, Bousquet J, Agache I, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) Guidelines - 2016 Revision. *J Allergy Clin Immunol*. 2017;140: 950–958.

[81] Dalkey N, Helmer O. An experimental application of the DELPHI method to the use of experts. *Manage Sci*. 1963;9:458–467.

[82] Linstone HA, Turoff M. *The Delphi Method: Techniques and Applications*. Reading, MA: Addison-Wesley Publishing Co, Advanced Book Program; 1975.

[83] Brown B. *Delphi Process: A Methodology Used for the Elicitation of Opinions of Experts*. Santa Monica, CA: Rand; 1968.

[84] Merck & Co I. *Highlights of Prescribing Info Singulair, updated. 2016 [cited 2016 10.23.16]*. Available from: https://www.merck.com/product/usa/pi_circulars/s/singulair/singulair_pi.pdf.

[85] Merck & Co Inc. *Singulair (Montelukast Sodium)* 2009. Whitehouse Station, NJ: Merck & Co Inc, http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020829s051_020830s052_021409s028lbl.pdf. Accessed August 7, 2017.

[86] Meltzer EO, Wallace D, Dykewicz M, Shneyer L. Minimal clinically important difference (MCID) in allergic rhinitis: Agency for Healthcare Research and Quality or anchor-based thresholds? *J Allergy Clin Immunol Pract*. 2016;4: 682–688.e6.

[87] Hellings PW, Dobbels F, Denhaerynck K, Piessens M, Ceuppens JL, De Geest S. Explorative study on patient's perceived knowledge level, expectations, preferences and fear of side effects for treatment for allergic rhinitis. *Clin Transl Allergy*. 2012;2:9.

[88] Forbes Consulting Group. *Understanding the Dynamics Surrounding Allergy Suffering and Treatment*. Lexington, MA: Forbes Consuling Group; 2005.

[89] Hasday JD, Meltzer SS, Moore WC, et al. Anti-inflammatory effects of zileuton in a subpopulation of allergic asthmatics. *Am J Respir Crit Care Med*. 2000;161: 1229–1236.

[90] Shirasaki H, Kanaizumi E, Seki N, Fujita M, Kikuchi M, Himi T. Localization and up-regulation of cysteinyl leukotriene-2 receptor in human allergic nasal mucosa. *Allergol Int*. 2013;62:223–228.

[91] Farajzadeh Deroee A, Oweinah J, Naraghi M, et al. Regression of polypoid nasal mucosa after systemic corticosteroid therapy: a proteomics study. *Am J Rhinol Allergy*. 2009;23:480–485.

[92] *DymistaUSPI2015. May 16, 2017*, https://docs.google.com/viewer?url=http%3A%2F%2Fdymista.com%2Fpdf%2FDymistaUSPI.pdf. Accessed August 7, 2017.

Appendix A

Table 1
AHRQ Search Terms and Process

MEDLINE search

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.

(*continued on next page*)

Table 1 (*continued*)

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 Cetirid 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).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

Table 2
USPSTF Criteria for Randomized Controlled Trials

USPSTF Grading and Criteria
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)

Table 3
Deeks Criteria for Nonrandomized Comparative Studies

Deeks criteria for nonrandomized comparative studies
Was sample definition and selection prospective or retrospective?
Were inclusion/exclusion criteria clearly described?
Were participants selected to be representative?
Was there an attempt to balance groups by design?
Were baseline prognostic characteristics clearly described and groups shown to be comparable?
Were interventions clearly specified?
Were participants in treatment groups recruited within the same time period?
Was there an attempt by investigators to allocate participants to treatment groups in an attempt to minimize bias?
Were concurrent/concomitant treatments clearly specified and given equally to treatment groups?
Were outcome measures clearly valid, reliable, and equally applied to treatment groups?
Were outcome assessors blinded?
Was the length of follow-up adequate?
Was attrition below an overall high level (<20%)?
Was the difference in attrition between treatment groups below a high level (<15%)?
Did the analysis of outcome data incorporate a method for handling confounders such as statistical adjustment?

Table 4
Description of the 2016 Search Strategy Literature Search Update for Queries 1,2,3

■ The dataset for analysis was updated to current (as of June 29, 2016) using a modification of the search strategy described in the AHRQ reportE7 and the same electronic databases—MEDLINE, EMBASE, and the Cochrane Library. The following limits were applied: English, human subjects, dates 2012 (only studies published after July 18, 2012, considered) to current (June 29, 2016).
■ The modification involved adding the term human subjects as a limit and simplifying some of the search terms for a more direct approach appropriate to the scope of this article (eg, clinical trial replaced placebo-controlled trial + controlled trial + randomized controlled trial + case cohort study + observational trial + cross-sectional study). The search terms were applied as MeSH descriptors, headers, and/or simple search terms according to the structure of each database, and then combined as shown in Appendix B, Figure 1. Only search terms relevant to the 3 queries were included.
■ Any citations were reviewed for inclusion criteria as noted in the text—seasonal allergic rhinitis, minimum of 2-week trial duration, mild-to-severe disease severity, symptoms scored by TNSS, GRCS, or TSS4, and direct comparisons between treatments as indicated by each query.

Table 5
Description of Searches and Queries

LIMITS: All searches were limited as follows (except as noted above for Embase): English; Human; July 18, 2012 – 06/29/2016; Clinical study (or clinical trial);
Search 1 = allergic rhinitis or seasonal allergic rhinitis or perennial allergic rhinitis or hay fever
Search 2 = intranasal corticosteroid or nasal corticosteroid or intranasal steroid or nasal steroid or beclomethasone or betamethasone or ciclesonide or flucinolone or flunisolide or fluticasone or mometasone or triamcinolone or budesonide
Search 3 = antihistamine or histamine antagonist or H1 histamine antagonist or nonsedating antihistamine or cetirizine or levocetirizine or loratadine or desloratadine or terfenadine or fexofenadine or brompheniramine or chlorpheniramine or dexchlorpheniramine or carbinoxamine or clemastine or diphenhydramine or doxylamine or triprolidine or epinastine or ebastine or bilastine (?)
Search 4 = leukotriene receptor antagonist or montelukast
Search 5 = olopatadine or azelastine or intranasal antihistamine or nasal antihistamine
Search 6 = combination with AND for **Search 1 + Search 2**. This is the base for all queries.
Searches were combined as shown in order to address the queries.
QUERY 1: Oral antihistamine + intranasal corticosteroid vs. intranasal corticosteroid
QUERY 2: Leukotriene receptor antagonist vs. intranasal corticosteroid
QUERY 3: Intranasal antihistamine + intranasal corticosteroid vs. intranasal antihistamine and/or vs. intranasal corticosteroid

Table 6
Citations Returned by Each Search for Dates: July 18, 2012 – 06/29/2016

Search	PUBMED Medline	EMBASE Medline*	OVID Medline	Cochrane Trials Registry	Total
Search 1	461	482	84	66	1093
Search 2	3094	77830	948	118	81,990
Search 3	2312	50033	178	26	52,549
Search 4	524	10920	86	7	11537
Search 5	145	1114	28	3	1290
Total Search 1-5	6536	140379	1316	220	147,366
Search 6 = Searches 2 + 1	102	59	14	18	193 (allergic rhinitis and INS)
Query 1 = Searches 6 + 3	34	20	2	0	56 references reviewed by 2 workgroup members and none fulfilled inclusion criteria.
Query 2 = Searches 6 + 4	7	12	0	1	20 references reviewed by 2 workgroup members and none fulfilled inclusion criteria.
Query 3 = Searches 6 + 5	32	5	1	2	40 references reviewed by 2 workgroup members and none fulfilled inclusion criteria.

*__Note:__ The large numbers in EMBASE is due to the way terms are set up in the updated search database. EMBASE does a very broad search of terms in all fields including MeSH headings and keywords.

Table 7
References Excluded From Analysis: Missing Reporting Data

Question being answered	Reference	Reason for exclusion
Question # 1: INCS alone or combined with oral AH	Brooks, Francom (4)	The mean change in symptoms was presented in bar graph format only
Question # 1: INCS alone or combined with oral AH	Can, Tanac (5)	Data presented only as median's and minimum/maximum ranges
Question # 1: INCS alone or combined with oral AH	Modgill, Badyal (3)	The change in daytime and nighttime symptom scores was only reported in box and whiskers graphs

Appendix B

Fifteen studies answer the following three questions:

1. Is there any clinical benefit of adding an oral antihistamine to an intranasal corticosteroid?[1–5] (see pages 6 through 26)
2. How does montelukast compare to an INCS in terms of clinical benefit?[6–10] (see pages 27 through 44)
3. Is there any clinical benefit to adding an intranasal antihistamine (INAH) to an intranasal corticosteroid?[11–15] (see pages 45 through 61)

Included studies

Thirteen studies are reported as single trials.[1–10,13–15] One meta-analysis reported study findings from three trials, one of these trials is a single trial[14] already included in this analysis and therefore not repeated. The findings from the other two studies in the meta-analysis are reported separately as MP4002[11] and MP4006[12]. Twelve of the studies were randomized, double-blind, placebo-controlled, parallel-group trials[1,3-15] and one study used a double blind, placebo-controlled crossover study design.[2] The measures used in the studies are found in Table 1. Five studies[1,7,8,10,11] disclosed and met the needed sample size to determine significant findings while the remaining studies either did not report this value or they did not obtain the needed study participants. One study[2] was funded by a grant from the Asthma and Allergy Research Group while the remaining studies received funding from pharmaceutical companies or the members of the study teams were or have been a consultant/speaker for a pharmaceutical company or employees of a pharmaceutical company.

Updated: 11/8/16

Table 1
Measures Used in the Studies

Study	Measures used	How measure was used	Outcome assessor
Anolik[1]	Total Nasal Symptom Score (TNSS)	Nasal symptoms (nasal congestion, sneezing, rhinorrhea, and nasal itching) were recorded twice daily on a four point Likert scale of 0 to 3 (0 indicates no symptoms; 1, mild symptoms; 2, moderate symptoms; and 3, severe symptoms) and then averaged.	Self-report by participant
Barnes, Ward, Fardon, Lipworth[2]	Total Nasal Symptom Score (TNSS)	Nasal symptoms (nasal congestion, sneezing, rhinorrhea, and nasal itching) were recorded once daily on a four point Likert scale of 0 to 3 (0 indicates no symptoms; 1, mild symptoms; 2, moderate symptoms; and 3, severe symptoms) and then summed attaining a TNSS range of 0 to 12.	Self-report by participant
Barnes, Ward, Fardon, Lipworth[2]	Rhinoconjunctivitis Quality-of-Life Questionnaire (mini-RQLQ)	Validated instrument with 14 items measuring five domains (activities, practical problems, nose, eye and other symptoms). Participants score each item for the preceding week as an integer from 0 (not troubled) to 6 (extremely troubled). The Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) score is the average of all question scores. The authors do not report where the instrument is completed.	Self-report by participant
Barnes, Ward, Fardon, Lipworth[2]	Domiciliary morning peak nasal inspiratory flow rate (PNIF)	Participant tests every morning and takes the best reading out of three attempts	Self-report by participant
Barnes, Ward, Fardon, Lipworth[2]	Nasal nitric oxide levels (NO)	Airway eosinophilic inflammation marker	Sample acquired at each visit
Benincasa, Lloyd[3]	Nasal, Eye, and Headache Symptoms	Symptoms, were assessed on daily diary cards for week 3 to 8 on a 10-point categorical rating scale: 0 = no symptoms, 1-3 = mild symptoms, 4-6 = moderate symptoms, 7-9 = severe symptoms	Self-report by participant
Di Lorenzo, Pacor, Pellitteri, Morici, Di Gregoli, Lo Bianco, Ditta, Martinelli, Candore, Mansueto, Rini, Corrocher, Caruso[4]	Symptoms Score	Nasal symptoms included nasal blockage on waking and during the day, rhinorrhea, sneezing and itching. Eye symptoms included watering and/or irritation. Nasal congestion was scored as follows: (0) not present; (1) slightly difficult breathing through the nose; (2) moderately difficult breathing through the nose; (3) very difficult or impossible breathing through the nose. Any other recorded symptom was scored as follows: (0) none; (1) mild (occasionally present); (2) moderate (rather frequent); (3) severe (persistent).	Self-report by participant
Di Lorenzo, Pacor, Pellitteri, Morici, Di Gregoli, Lo Bianco, Ditta, Martinelli, Candore, Mansueto, Rini, Corrocher, Caruso[4]	Mean blood eosinophil counts	The eosinophils were counted in a Fuchs Rosenthal chamber after staining. Results were expressed as eosinophils x 10^{-3} μL	Venous blood sample was collected
Di Lorenzo, Pacor, Pellitteri, Morici, Di Gregoli, Lo Bianco, Ditta, Martinelli, Candore, Mansueto, Rini, Corrocher, Caruso[4]	Percentage of eosinophils in nasal lavage	Nasal eosinophil counts were performed on nasal lavage after the sample was cytocentrifuged and fixed with ethyl alcohol and Wright-Giemsa stain.	Nasal lavage performed
Ratner, van Bavel, Martin, Hampel, Howland, Rogenes, Westlund, Bowers, Cook[5]	Nasal Symptoms Score	Visual Analog Scale from 0 (no symptoms) to 100 (maximum symptom severity) for each of the four nasal symptoms (nasal congestion, sneezing, rhinorrhea, and nasal itching) and then summed together	Clinician rated on days 0, 7, 14
Lu, Malice, Dass, Reiss[6]	Composite Symptom Score	Nasal symptoms (nasal congestion, sneezing, rhinorrhea, and nasal itching) were recorded twice daily on a four point Likert scale of 0 to 3 (0 indicates no symptoms; 1, mild symptoms; 2, moderate symptoms; and 3, severe symptoms) and then averaged	Self-report by participant
Martin, Andrews, van Bavel, Hampel, Klein, Prillaman, Faris, Philpot[7] Nathan, Yancey, Waitkus-Edwards, Prillaman, Stauffer, Philpot, Dorinsky, Nelson[8] Ratner, Howland, Arastu, Philpot, Klein, Baidoo, Faris, Rickard[10]	Daytime Total Nasal Symptom Score (D-TNSS)	Visual Analog Scale from 0 (no symptoms) to 100 (maximum symptom severity) were recorded twice daily for each of the four nasal symptoms (nasal congestion, sneezing, rhinorrhea, and nasal itching) and then summed together to obtain a D-TNSS.	Self-report by participant
Martin, Andrews, van Bavel, Hampel, Klein, Prillaman, Faris, Philpot[7] Nathan, Yancey, Waitkus-Edwards, Prillaman, Stauffer, Philpot, Dorinsky, Nelson[8]	Nighttime-Total Nasal Symptom Scores (N-TNSS)	A four point Likert scales of 0 to 3 and summing the symptom values of nasal congestion on awakening (0, not noticeable; 3, bothersome most of the time or very bothersome some of the time); difficulty in going to sleep due to nasal symptoms (0, not at all; 3, very); and nighttime awakenings due to nasal symptoms (0, not at all; 3, I felt like I was awake all night) and then summed together to obtain a N-TNSS.	Self-report by participant
Nathan, Yancey, Waitkus-Edwards, Prillaman, Stauffer, Philpot, Dorinsky, Nelson[8]	Peak Expiratory Flow	Peak Flowmeter (Mini-Wright; Clement Clark; London, UK) measurements (best effort of three attempts) obtained in the morning and evening before taking any medications.	Self-report by participant
Nathan, Yancey, Waitkus-Edwards, Prillaman, Stauffer, Philpot, Dorinsky, Nelson[8]	% of symptom-free days		Self-report by participant
Nathan, Yancey, Waitkus-Edwards, Prillaman, Stauffer, Philpot, Dorinsky, Nelson[8]	% of albuterol-free days		Self-report by participant
Pullerits, Praks, Ristioja, Lotvall[9]	Daytime and Nighttime Symptoms	A five point Likert scale of 0 to 4 and defined the scoring differently for nasal congestion than previous studies (0, breathing through the nose freely and easily; 1, slight difficulty breathing through the nose; 2, moderate difficulty breathing through the nose; 3, severe difficulty breathing through the nose; and 4, breathing through the nose is very difficult or impossible) and sneezing, rhinorrhea, and nasal itching (0 indicates no symptoms; 1, mild symptoms; 2, moderate symptoms; 3, severe symptoms; and 4, very severe symptoms)	Self-report by participant

(*continued on next page*)

Table 1 (*continued*)

Study	Measures used	How measure was used	Outcome assessor
Pullerits, Praks, Ristioja, Lotvall[9]	Epithelial change in Eosinophils & Sub epithelial change in Eosinophils	The area of epithelium and the sub epithelium were measured with an image-analysis system and the number of positively stained cells per square millimeter was calculated.	Nasal biopsies obtained
Carr, Bernstein, Lieberman, Meltzer, Bachert, Price, Munzel, Bousquet[11,12] Hampel, Ratner, Van Bavel, Amar, Daftary, Wheeler, Sacks[13] Meltzer, LaForce, Ratner, Price, Ginsberg, Carr[14] Ratner, Hampel, Van Bavel, Amar, Daftary, Wheeler, Sacks[15]	Total Nasal Symptom Score (TNSS)	Nasal symptoms (nasal congestion, sneezing, rhinorrhea, and nasal itching) were recorded twice daily on a four point Likert scale of 0 to 3 (0 indicates no symptoms; 1, mild symptoms; 2, moderate symptoms; and 3, severe symptoms) and then summed attaining a TNSS range of 0 to 24.	Self-report by participant

Quality Assessment of the Included Studies

An assessment of risk of bias factors (random sequence generation, allocation concealment, blinding adequacy, completeness of data, reporting and other potential biases) that may contribute to risk of bias was conducted independently by three reviewers (two Children's Mercy, Kansas City, Evidence Based Practice Scholars and J.A.B.) based on the Review Manager software criteria (See Figs 1, 16, and 27). Red indicates high risk of bias, yellow represents unclear risk of bias, and green indicates low risk of bias. An evaluation on the methodological quality of the evidence based on the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) criteria was conducted independently by one reviewer (J.A.B.). An assessment of the risk of bias for the individual studies and level of methodological quality for the identified literature is summarized after each clinical question.

GRADE Analysis[16]

For GRADE analysis to occur, five areas between studies are evaluated: Risk of Bias, Inconsistency, Indirectness, Imprecision and Publication Bias. To measure inconsistencies between studies, studies are reviewed related to populations, interventions, and outcomes. Populations, interventions, and outcomes are reviewed for similarity, or consistency, between the compared studies. To measure indirectness between intervention studies analysis occurs around comparisons, interventions, and use of surrogate outcomes. Comparisons between one drug to placebo and another drug to placebo but the researchers do not compare the first drug to the second drug in a head to head comparison. Outcome refers to is the study powered for the outcome of choice. To measure imprecision between studies occurs when too few study participants were enrolled or too few events occurred in the study.

Using the GRADE analysis leads to the identification of the quality of the evidence. There are four levels of evidence:

High → The team is very confident that the true effect lies close to that of the estimate of the effect
Moderate → The team is moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low → The team confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low → The team has very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Abbreviations found in text: FPANS = Fluticasone propionate aqueous nasal spray; qd = daily

Specific Care Question:
Is there any clinical benefit of adding an oral antihistamine to an intranasal corticosteroid?

Summary from The Office of Evidence Based Practice:
There is not any clinical benefit to add an oral antihistamine to an intranasal corticosteroid (see Figs 2–14).
However, the confidence in the effect estimate is limited this due to the low quality of the literature: The true effect may be substantially different from the estimate of the effect with additional research.

EBP Scholar's responsible for analyzing the literature:
Teresa Bontrager, RN, BSN, MSNed, CPEN
Jeanette Higgins, RN, MSN, CPNP
David Keeler, RN, BSN, CPN
Kimberly Lucas, RRT-NPS
Joyce McCollum, RN, CNOR
Rebecca Palmer, RN, MSN
Ashley Schuyler, RRT-NPS

EBP team member responsible for reviewing, synthesizing, and developing this literature: Jacqueline A. Bartlett, PhD, RN

Method Used for Appraisal and Synthesis: The Cochrane Collaborative computer program, Review Manager (RevMan 5.3.5), was used to synthesize the five* included studies.[1-5]

***Note:** This analysis was to include three additional studies[17-19]; however, these studies were excluded from the analysis due to the data provided in the article was unable to be tabled within this analysis due to the following data reporting issues:

- Brooks, Francom, Peel, Chene, Klott [19] presented the mean change in symptoms in bar graph format only.
- Can, Tanac, Demir, Gulen, Veral [17] provided data as medians and minimum/maximum ranges.
- Modgill, Badyal, Verghese [18] reported the change in daytime and nighttime symptom scores in box and whiskers graphs.

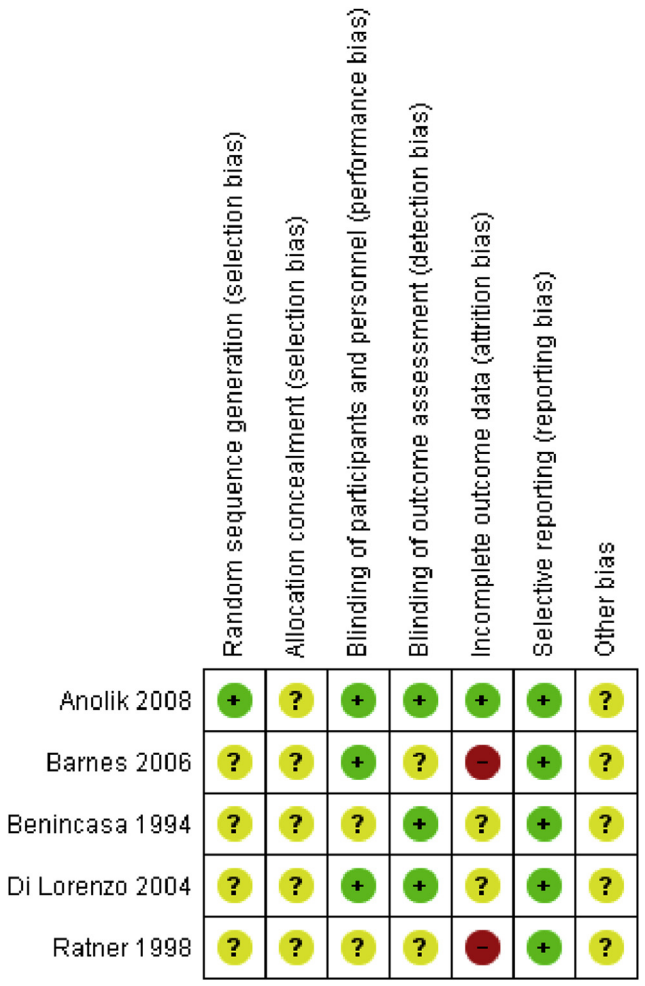

Figure 1. Risk of Bias for Question #1 Studies

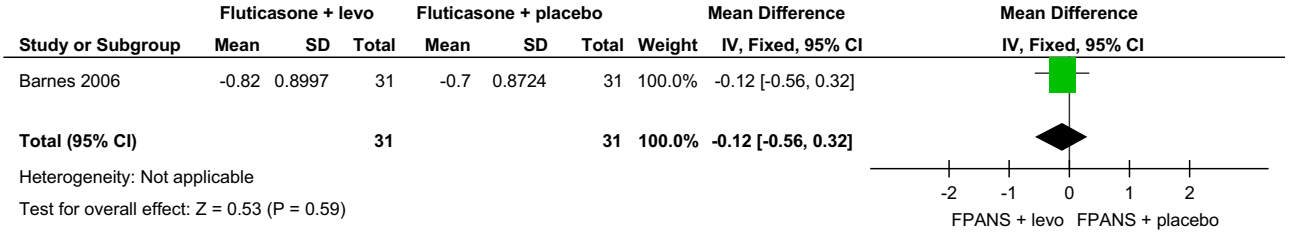

Figure 2. Reduction in Mean Rhinoconjunctivitis Quality-of-Life Questionnaire (mini-RQLQ) (lower [-] reduction in mini-RQLQ score is better)

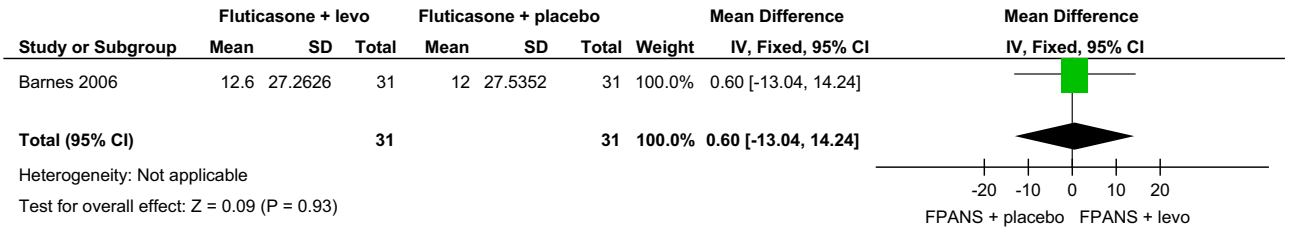

Figure 3. Increase in Mean Domiciliary Morning Peak Nasal Inspiratory Flow Rate (higher [+] mean is better)

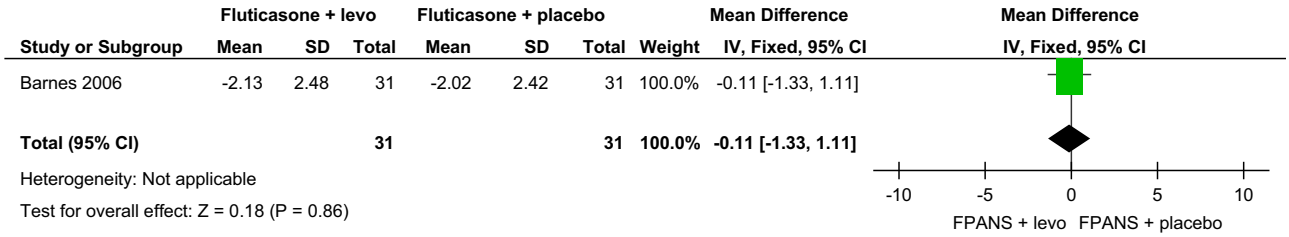

Figure 4. Reduction in Mean Morning Total Nasal Symptoms Score (lower [-] reduction in mean score is better)

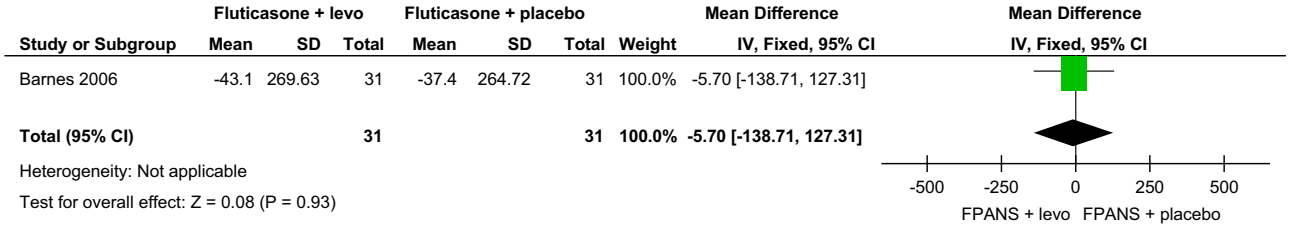

Figure 5. Decrease Mean Nasal Nitric Oxide Levels (lower [-] reduction in mean score is better)

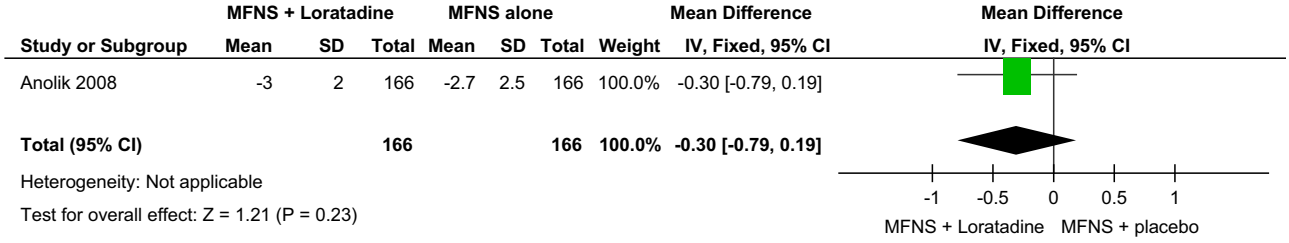

Figure 6. Reduction in Mean Total Nasal Symptoms Score (lower [-] reduction in mean score is better)

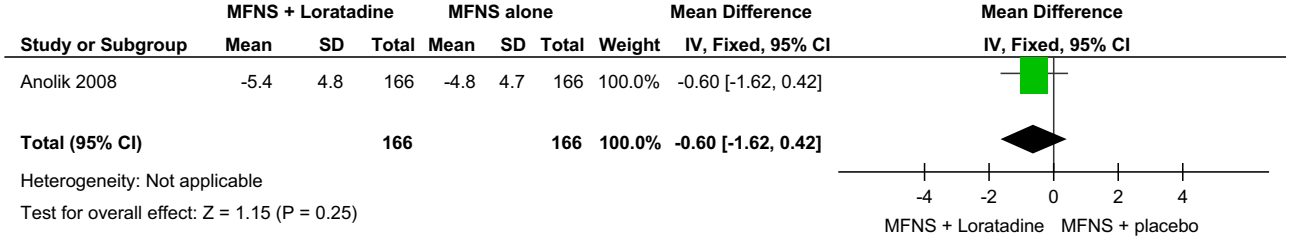

Figure 7. Reduction in Mean Total Symptom Score (lower [-] reduction in mean score is better)

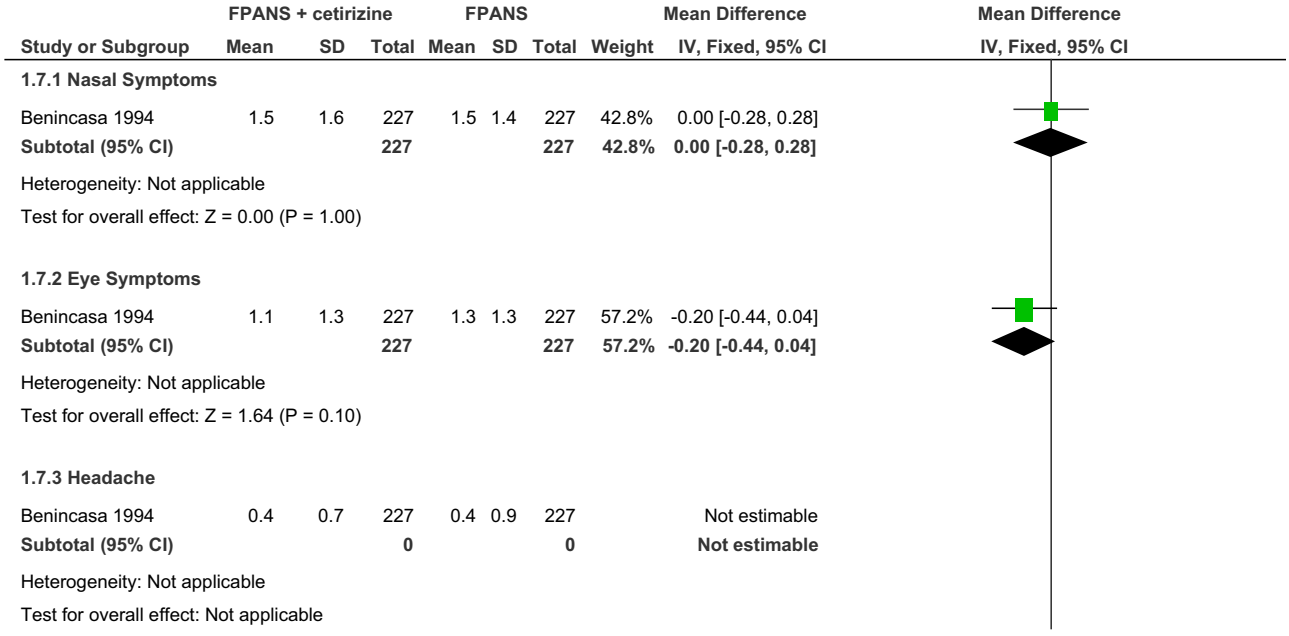

Figure 8. Reduction in Mean Symptom Scores (lower [-] reduction in mean score is better)

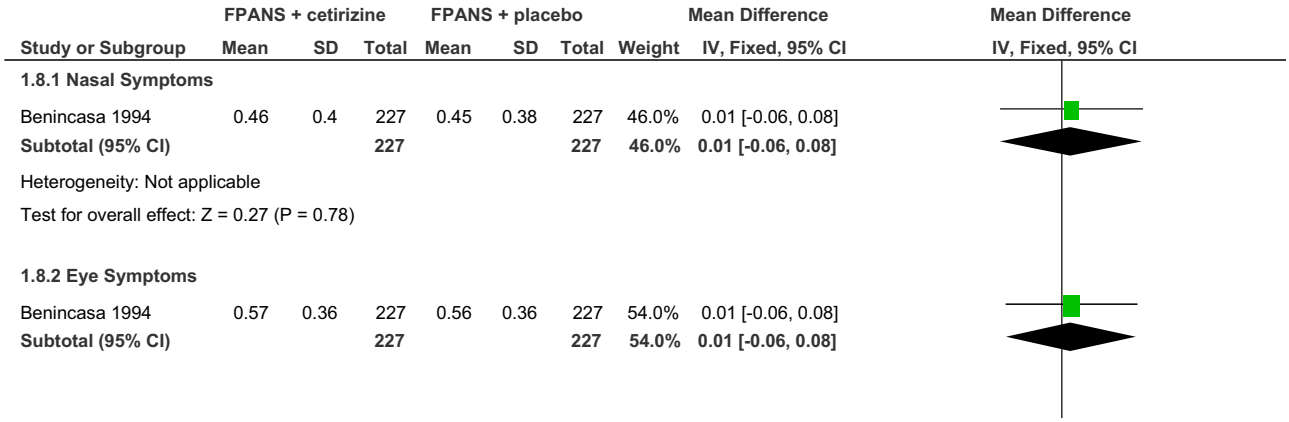

Figure 9a. Reduction in Mean Nasal and Eye Symptom-free Days (higher [+] symptom-free days is better)

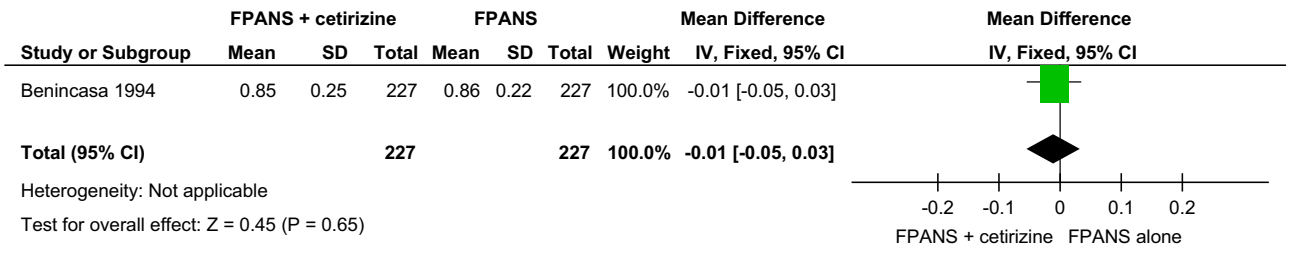

Figure 9b. Reduction in Headache Symptom-free Days (higher [+] symptom-free days is better)

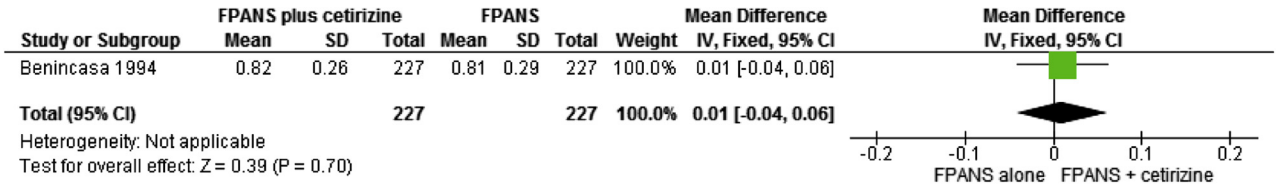

Figure 10. Proportion of Mean Days Rescue Medications Not Needed (higher [+] proportion is better)

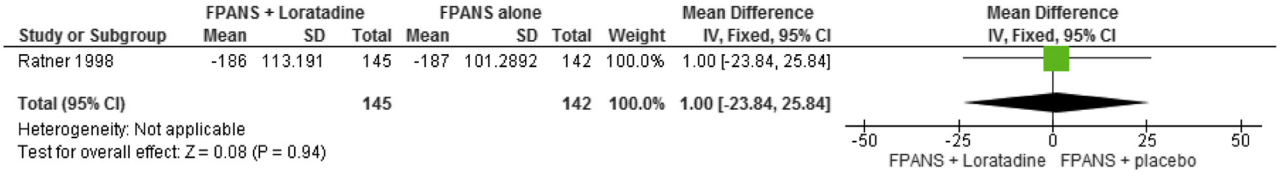

Figure 11. Change in Mean Nasal Symptom Score as Measured by Clinician (lower [-] reduction in mean score is better)

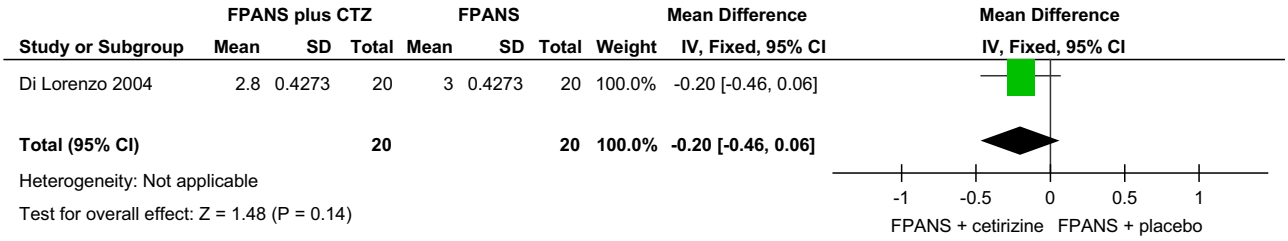

Figure 12. Change in Mean Daily Symptom Score (lower [-] reduction in mean score is better)

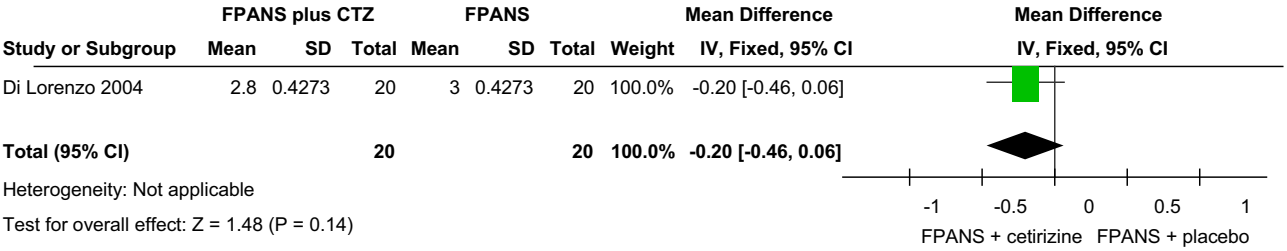

Figure 13. Reduction in Mean Daytime Symptom Score (lower [-] reduction in mean score is better)

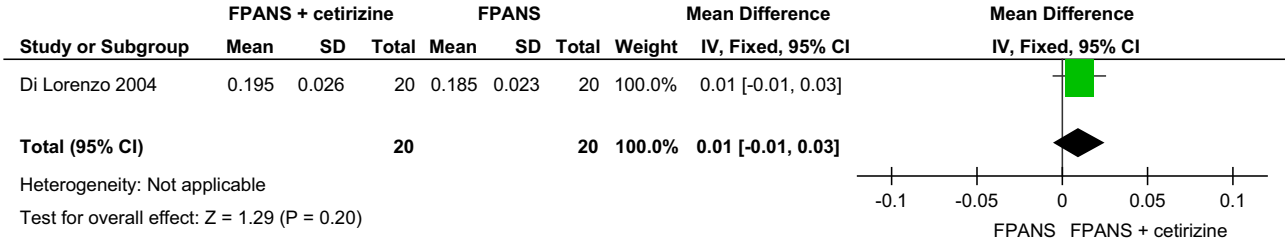

Figure 14. Reduction in Mean Blood Eosinophil Counts (lower [-] reduction in mean score is better)

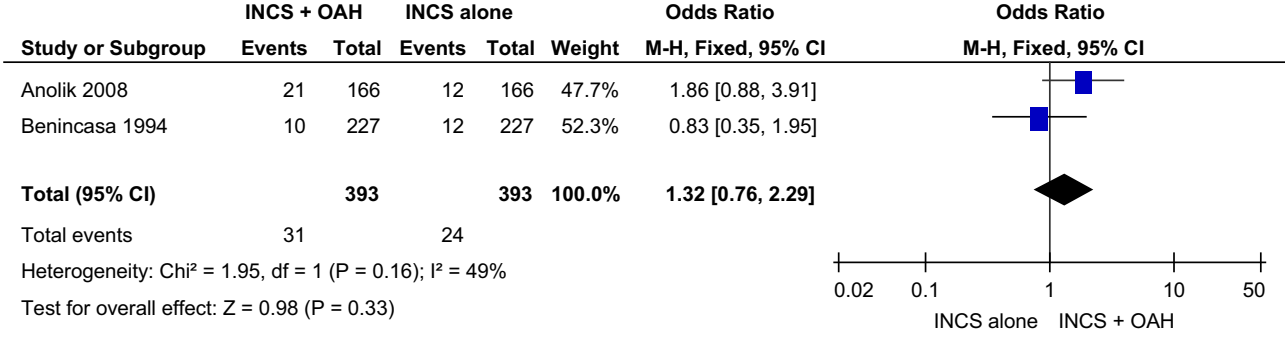

Figure 15. Adverse events (lower [-] reduction in mean score is better)

Author(s): J. A. Bartlett
Date: 2016-07-25
Question #1: Is there clinical benefit to adding an oral antihistamine to an intranasal corticosteroid?

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	INCS + OAH	INCS alone	Relative (95% CI)	Absolute	
Improved quality of life (follow-up 2 weeks; measured with: Mini-RQLQ; Better indicated by lower values)											
1 (Barnes[2])	RCT	very serious[F1]	serious[F2]	no serious indirectness	serious[F3]	none	31	31	-	MD 0.12 lower (0.56 lower to 0.32 higher)	⊕OOO VERY LOW
Increase in mean Peak Nasal Inspiratory Flow Rate (follow-up 2 weeks; measured with: In-check PNIF meter; Better indicated by lower values)											
1 (Barnes[2])	RCT	very serious[F1]	serious[F2]	no serious indirectness	serious[F3]	none	31	31	-	MD 0.6 higher (13.04 lower to 14.24 higher)	⊕OOO VERY LOW
Reduction in Total Nasal Symptom Score (follow-up 2 weeks; measured with: Diary each morning; Better indicated by lower values)											
1 (Barnes[2])	RCT	very serious[F1]	serious[F2]	no serious indirectness	serious[F3]	none	31	31	-	MD 0.11 lower (1.33 lower to 1.11 higher)	⊕OOO VERY LOW
Reduction in nasal Nitric Oxide (nNO) Levels (follow-up 2 weeks; measured with: Niox nitric oxide analyzer; Better indicated by lower values)											
1 (Barnes[2])	RCT	very serious[F1]	serious[F2]	no serious indirectness	serious[F3]	none	31	31	-	MD 5.7 lower (138.71 lower to 127.31 higher)	⊕OOO VERY LOW
Reduction in Total Nasal Symptom Score (TNSS) (follow-up 2 weeks; measured with: Patient-rated average change in TNSS; Better indicated by lower values)											
1 (Anolik[1])	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[F4]	none	166	166	-	MD 0.3 lower (0.79 lower to 0.19 higher)	⊕⊕⊕O MODERATE
Reduction in mean Total Symptom Score (follow-up 2 weeks; measured with: Patient-rated change in TSS; Better indicated by lower values)											
1 (Anolik[1])	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[F4]	none	166	166	-	MD 0.6 lower (1.62 lower to 0.42 higher)	⊕⊕⊕O MODERATE
Mean Symptom Scores - Nasal Symptoms (follow-up 8 weeks; measured with: Patient-rated separate symptom scores; Better indicated by lower values)											
1 (Benincasa[3])	RCT	very serious[F5]	no serious inconsistency	no serious indirectness	serious[F6]	none	227	227	-	MD 0 higher (0.28 lower to 0.28 higher)	⊕OOO VERY LOW
Mean Symptom Scores - Eye Symptoms (follow-up 8 weeks; measured with: Patient-rated separate symptom scores; Better indicated by lower values)											
1 (Benincasa[3])	RCT	very serious[F5]	no serious inconsistency	no serious indirectness	serious[F6]	none	227	227	-	MD 0.2 lower (0.44 lower to 0.04 higher)	⊕OOO VERY LOW
Symptom-free Days - Nasal Symptoms (follow-up 8 weeks; measured with: Patient-rated separate symptom scores; Better indicated by lower values)											
1 (Benincasa[3])	RCT	very serious[F5]	no serious inconsistency	no serious indirectness	serious[F7]	none	227	227	-	MD 0.01 higher (0.06 lower to 0.08 higher)	⊕OOO VERY LOW
Symptom-free Days - Eye Symptoms (follow-up 8 weeks; measured with: Patient-rated separate symptom scores; Better indicated by lower values)											
1 (Benincasa[3])	RCT	very serious[F5]	no serious inconsistency	no serious indirectness	serious[F7]	none	227	227	-	MD 0.01 higher (0.06 lower to 0.08 higher)	⊕OOO VERY LOW
Symptom free days - Headache (follow-up 8 weeks; measured with: Patient-rated separate symptom scores; Better indicated by lower values)											
1 (Benincasa[3])	RCT	very serious[F5]	no serious inconsistency	no serious indirectness	serious[F7]	none	227	227	-	MD 0.01 lower (0.05 lower to 0.03 higher)	⊕OOO VERY LOW
Proportion of Days Rescue Medications were not Needed (follow-up 8 weeks; measured with: Patient-rated separate symptom scores; Better indicated by lower values)											
1 (Benincasa[3])	RCT	very serious[F5]	no serious inconsistency	no serious indirectness	serious[F4]	none	227	227	-	MD 0.01 higher (0.04 lower to 0.06 higher)	⊕OOO VERY LOW
Change in Nasal Symptom Score (NSS) - Day 14 (follow-up 2 weeks; measured with: Clinician-rated NSS at day 14; Better indicated by lower values)											
1 (Ratner[5])	RCT	very serious[F8]	no serious inconsistency	no serious indirectness	very serious[F9]	none	145	142	-	MD 1 higher (23.84 lower to 25.84 higher)	⊕OOO VERY LOW

(*continued on next page*)

(*continued*)

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	INCS + OAH	INCS alone	Relative (95% CI)	Absolute	
Mean Daily Symptom Score (DSS) (follow-up 8 weeks; measured with: Patient-rated DSS; Better indicated by lower values)											
1 (Di Lorenzo[4])	RCT	serious[F10]	no serious inconsistency	no serious indirectness	serious[F4]	none	20	20	-	MD 0.2 lower (0.46 lower to 0.06 higher)	⊕⊕OO LOW
Mean blood eosinophil counts (follow-up 8 weeks; measured with: Fuchs Rosenthal chamber; Better indicated by lower values)											
1 (Di Lorenzo[4])	RCT	serious[F10]	no serious inconsistency	no serious indirectness	serious[F4]	none	20	20	-	MD 0.01 higher (0.01 lower to 0.03 higher)	⊕⊕OO LOW
Adverse events											
2 (Anolik[1]; Benincasa[3])	RCT	very serious[F5]	no serious inconsistency	no serious indirectness	very serious[F4,5]	none	31/393 (7.9%)	24/393 (6.1%)	OR 1.32 (0.76 to 2.29)	18 more per 1000 (from 14 fewer to 69 more)	⊕OOO VERY LOW
								6.3%		19 more per 1000 (from 14 fewer to 70 more)	

F1: Random sequence generation, allocation concealment, blinding of outcome assessment and a wash out time period was not reported by authors. In addition four participants withdrew from the study and authors did not disclose how many subjects were needed from the power analysis to detect improvement.
F2: One study identified for this outcome.
F3: Small sample size.
F4: The confidence interval includes zero (0).
F5: Authors did not disclose how randomization, allocation concealment, blinding of participants and personnel occurred.
F6: The confidence interval for nasal symptoms includes zero (0) and for headache the mean difference is not estimable.
F7: The confidence interval for nasal and eye symptoms and headache include zero (0).
F8: Authors do not disclose how randomization, sequence generation, allocation concealment, blinding of participants and study personnel or outcome assessment occurred.
F9: Sample size needed to detect significance was not met and confidence interval includes zero (0).
F10: Authors do not describe how random sequence generation and allocation concealment occurred. A power analysis was completed but the authors.

Characteristics of included studies:

Anolik[1]

Methods	Randomized, double-blind, placebo-controlled, parallel-group trial
Participants	**Setting:** 18 medical centers in every region of the United States except the Pacific Coast **Randomized into study:** *N = 702* • **Group 1:** mometasone furoate nasal spray (MFNS) + loratadine n = 169; • **Group 2:** MFNS alone n = 176; • **Group 3:** Loratadine alone n = 181; • **Group 4:** Placebo n = 176 **Completed Study:** *N = 672* • **Group 1:** MFNS + loratadine n = 166; • **Group 2:** MFNS alone n = 166; • **Group 3:** Loratadine alone n = 175; • **Group 4:** Placebo n = 165 **Gender, males:** • Group 1: 84 • Group 2: 87 • Group 3: 90 • Group 4: 91 **Age, years (mean):** • **Group 1:** 11-62 (26) • **Group 2:** 12-71 (26) • **Group 3:** 12-65 (25) • **Group 4:** 12-66 (26) **Inclusion Criteria:** • At least 12 years old • 2-year clinical history of seasonal allergic rhinitis (SAR) • Symptoms of active disease • Positive skin prick test results in the past year • Good health • No clinically significant disease (except SAR) • No clinically significant abnormalities on a screening electrocardiogram **Exclusion Criteria:** • Rhinitis medicamentosa • Nasal candidiasis • Nasal structural abnormalities

(*continued on next page*)

(*continued*)

Methods	Randomized, double-blind, placebo-controlled, parallel-group trial
	• History of frequent rhinosinusitis or chronic purulent postnasal drip • Asthma if long-term use of inhaled or systemic corticosteroids required • Immunotherapy (unless taking a stable maintenance dose for ≥1 month) **Power Analysis:** 160 evaluable patients per treatment group to measure primary outcomes
Interventions	• **Group 1:** MFNS 200 μg/d plus loratadine 10 mg/d • **Group 2:** MFNS 200 μg/d plus placebo tablet • **Group 3:** Placebo nasal spray plus loratadine 10 mg/d • **Group 4:** Placebo nasal spray plus placebo tablet ○ Received first dose of study medication (nasal spray and tablet) at baseline visit 2 (study day 1) under supervision in the physician's office to ensure proper use of nasal spray and correct recording of data on diary cards. ○ For the remaining 14 days of the study, patients self-administered treatments ○ All doses taken in the morning on awakening, on an empty stomach, and after recording symptom severity. ○ Symptoms were recorded again in the evening, approximately 12 hours later.
Outcomes	**Primary outcomes:** • Improvement from baseline in averaged morning and evening scores averaged to generate the Total Nasal Symptom Score (TNSS) which includes (nasal discharge, stuffiness, sneezing and itching) • Improvement from baseline in Total Symptom Score (TSS) which is the TNSS plus total nonasal symptom scores (eye tearing, eye redness, eye itching, ear/palate itching). **Safety outcome:** • Adverse effects
Notes	Patients who qualified for study entry had nasal congestion that was at least moderate (score ≥2) with a total nasal symptom score (TNSS) of at least 6 and a total symptom score (TSS), consisting of the total nonnasal symptom score and the TNSS, of at least 11 at the screening and baseline visits

Risk of bias table

Bias	Scholars' judgment	Support for judgement
Random sequence generation (selection bias)	Low risk	Separate randomization schedules were prepared for each center
Allocation concealment (selection bias)	Unclear risk	Authors did not provide information on allocation concealment
Blinding of participants and personnel (performance bias)	Low risk	Patients were randomly assigned to 1 of 4 treatment groups in a 1:1:1:1 ratio
Blinding of outcome assessment (detection bias)	Low risk	Subjects were blinded to the treatment arm and they recorded symptoms before the morning doses of study medications as an evaluation of symptom severity and again in the evening. Efficacy variables: TNSS (nasal discharge plus stuffiness plus sneezing plus itching), TSS and adverse events. The variables measured were not identified as being reflexive in nature.
Incomplete outcome data (attrition bias)	Low risk	Even though there were dropouts in the study, the researchers overenrolled subjects, allowing the researchers to attain study power.
Selective reporting (reporting bias)	Low risk	
Other bias	Unclear risk	Primary author was a consultant/speaker for Schering-Plough and a principal investigator for Schering-Plough Research Institute

Barnes, Ward, Fardon, Lipworth[2]

Methods	Randomized Control Trial- double blind placebo-controlled crossover study
Participants	**Setting:** Dundee area, Scotland; June and July 2004 **Number Randomized:** $N = 31$ **Number who completed the study:** $N = 27$ **Gender:** 11 men, 16 women **Age, mean ± SD:** Men: 45.9 ± 15 Women: 44.2 ± 15.9 **Inclusion criteria:** • Minimum of 16 years of age • Seasonal (intermittent or persistent) allergic rhinitis (AR) • Skin prick-positive responses to grass pollen **Exclusion criteria:** • Any other conditions affecting nasal airway patency, including septal deviation greater than 50% and grade 2 polyps (extending below the upper edge of the inferior turbinate) • Pregnancy • Lactating females • Any medical condition or screening bleed result that might compromise participant safety **Power Analysis:** the authors do not disclose how many subjects were needed to detect significance

(*continued on next page*)

(*continued*)

Methods	Randomized Control Trial- double blind placebo-controlled crossover study
Interventions	**Group 1:** Fluticasone, two sprays each nostril (200 μg/d), and one tablet of levocetirizine 5 mg **Group 2:** Fluticasone, two sprays each side (200 μg/d) and placebo• Fourteen day run-in occurred in which all usual therapy was stopped • Participants were allowed to use sodium cromoglicate nasal spray and eye drops as rescue medication • Rescue medications were to be avoided 24 hours before each visit • All participants received two weeks of the combination therapy and two weeks of monotherapy in a randomized order
Outcomes	**All 4 outcomes were measured or calculated for baseline (visit 2) and after each treatment period (visits 3 and 4)** • Juniper mini Rhino conjunctivitis Quality-of-Life Questionnaire (mini-RQLQ)–validated quality of life instrument with 14 items. Participant scores for the previous week on a scale of 0-6 and analyzed as the average of all the items • Domiciliary morning peak nasal inspiratory flow rate (PNIF)–participant tests every morning and takes the best reading out of three attempts • Domiciliary morning total nasal symptoms score (TNS)–Morning score for nasal run, blockage, itch and sneeze on a scale of 0-3, score range 0 to 12 • Nasal nitric oxide levels (NO)–airway eosinophilic inflammation marker, test at each visit
Notes	**Adverse events:** 1 minor epistaxis (during combination period), 1 URTI, 1 lethargy (during monotherapy). Study funded by Asthma and Allergy Research Group (grant), no financial support from pharmaceutical industry

Risk of bias table

Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Unclear risk	Authors did not describe how this occurred other than the participants were randomized.
Allocation concealment (selection bias)	Unclear risk	Authors did not provide this information
Blinding of participants and personnel (performance bias)	Low risk	An independent pharmacy encapsulated both tablets in an identical manner to blind the study participants and personnel
Blinding of outcome assessment (detection bias)	Unclear risk	Authors did not provide this information
Incomplete outcome data (attrition bias)	High risk	Four participants withdrew from the study; Authors did not disclose how many subjects were needed from the power analysis to detect improvement; results indicated per protocol analysis performed.
Selective reporting (reporting bias)	Low risk	Study protocol is listed and reported
Other bias	Unclear risk	A wash out time period was not reported by authors after crossover between treatment 1 and 2

Benincasa, Lloyd[3]

Methods	Randomized, double-blind, placebo-controlled, parallel-group trial
Participants	**Setting:** Multicenter (64 general practices) study in UK; May - July 1990 **Randomized into study:** *N = 454* **Group 1:** $n = 227$ **Group 2:** $n = 227$ **Completed Study:** $N = 454$ **Group 1:** $n = 227$ **Group 2:** $n = 227$ **Gender, males (%):** **Group 1:** 95 (42) **Group 2:** 99 (44) **Age, years (mean):** **Group 1:** 12-80 (31) **Group 2:** 12-66 (30) **Inclusion Criteria:**• At least 12 years old • 2-year clinical history of seasonal allergic rhinitis (SAR) • Participants with at least two of the following symptoms (one of the symptoms hat to be a nasal symptom): sneezing, nasal itching, runny nose, nasal congestion, eye watering/irritation and headache **Exclusion Criteria:** • Participants who had received: ○ a prescription for the treatment of an upper or lower respiratory infection within the past 2 weeks ○ treatment for SAR in the past week ○ intranasal or oral corticosteroids or ketotifen or sodium cromoglycate with the previous 4 weeks ○ astemizole in the last 6 weeks, depot corticosteroids within 8 weeks or desensitization injections to grass pollen in the previous 6 months • Nasal surgery with the last 2 months, • Nasal infections • Nasal structural abnormalities (polyps, septal deviation, hypertrophy of turbinates) • History of frequent rhinosinusitis • Serious concomitant disease • Taking concomitant medication that could interfere with the interpretation of study results

(*continued on next page*)

(*continued*)

Methods	Randomized, double-blind, placebo-controlled, parallel-group trial
	• Recurrent conjunctivitis • Wearing soft contact lenses • Pregnant or lactating females
Interventions	**Power Analysis:** the authors do not disclose how many subjects were needed to detect significance **Group 1:** FPANS 200 μg/d plus cetirizine 10 mg/d **Group 2:** FPANS 200 μg/d plus placebo tablet ○ Medication was taken for 8 weeks and reassessed at 3 and 8 weeks ○ Daily nasal and eye symptoms were recorded All participants received Otrivine-Antistin® for use for "troublesome" eye symptoms
Outcomes	**Primary outcomes:** • Improvement in symptom-free days • Improvement in symptom scores **Safety outcome:** • Adverse effects
Notes	Nasal and Eye Symptoms, along with headache symptoms, were assessed on daily diary cards for week 3 to 8 inclusive on a 10-point categorical rating scale: • 0 = no symptoms, • 1-3 = mild symptoms • 4-6 = moderate symptoms • 7-9 = severe symptoms

Risk of bias table

Bias	Scholars' judgment	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Authors did not disclose how randomization occurred
Allocation concealment (selection bias)	Unclear risk	Authors did not disclose how allocation was concealed
Blinding of participants and personnel (performance bias)	Unclear risk	Authors did not disclose how blinding of participants and personnel occurred
Blinding of outcome assessment (detection bias)	Low risk	Participants self-report symptoms on daily symptoms cards; the variables measured were not identified as being reflexive in nature.
Incomplete outcome data (attrition bias)	Unclear risk	Authors provide "missing data" for each analysis but they do not indicate how missing data was accounted for
Selective reporting (reporting bias)	Low risk	Authors reported intention to treat analysis occurred
Other bias	Unclear risk	Study funded by Allen and Hanburys Ltd a British pharmaceutical manufacturer absorbed by GlaxoSmithKline

Di Lorenzo, Pacor, Pellitteri, Morici, Di Gregoli, Lo Bianco, Ditta, Martinelli, Candore, Mansueto, Rini, Corrocher, Caruso[4]

Methods	Randomized, double-blind, double dummy, placebo-controlled, parallel group
Participants	**Setting:** Outpatient Clinic (Palermo, Italy) and a University Hospital (Verona, Italy), Spring of 2001. **Randomized into study:** N = 100 Group 1: $n = 20$ Group 2: $n = 20$ Group 3: $n = 20$ Group 4: $n = 20$ Group 5: $n = 20$ **Completed Study:** N = 100 Group 1: $n = 20$ Group 2: $n = 20$ Group 3: $n = 20$ Group 4: $n = 20$ Group 5: $n = 20$ **Gender, (number of males):** Group 1: 12 Group 2: 8 Group 3: 6 Group 4: 9 Group 5: 6 **Age, range in years (mean):** **Group 1:** 11-50 (30.5) **Group 2:** 14-48 (32.8) **Group 3:** 12-48 (27.1)

(*continued on next page*)

(*continued*)

Methods	Randomized, double-blind, double dummy, placebo-controlled, parallel group
	Group 4: 20-44 (34.3) **Group 5:** 14-37 (34.2) **Inclusion Criteria:** • Clinical history of allergic rhinitis • Positive skin prick test response of moderate to severe for Parietaria pollen • At least 2 years duration symptoms during Parietaria season **Exclusion Criteria:** • Taken the following drugs: ○ Long-acting histamine antagonists within the past 6 week ○ Inhaled, intranasal, or systemic corticosteroid ○ Inhaled sodium cromoglycate within the past 4 weeks • Infection of the paranasal sinuses • Infection of the upper or lower respiratory tract • Asthma • Nasal surgery within the past year • Structural nasal abnormalities • Concurrent diseases that could interfere with the validity of the study results • Pregnant or lactating females **Power Analysis:** the authors do not disclose how many subjects were needed to detect significance on the primary assessment of efficacy. A power analysis on post hoc comparisons was performed however the authors do not identify what the numbers of subjects were needed to detect significance in the secondary assessments.
Interventions	**Group 1:** FPANS, 200 μg/d plus cetirizine placebo in the morning and Montelukast placebo in the evening **Group 2:** FPANS, 200 μg/d plus cetirizine 10 mg in the morning and Montelukast placebo in the evening **Group 3:** FPANS, 200 μg/d plus cetirizine placebo in the morning and Montelukast 10mg in the evening **Group 4:** FPANS placebo plus cetirizine 10 mg in the morning and Montelukast 10mg in the evening **Group 5:** FPANS placebo plus cetirizine placebo in the morning and Montelukast placebo in the evening • The treatment period started before the beginning of the pollen season. • Patients were treated for 6 weeks. • Each patient attended the clinics on four different occasions. ○ This included an initial clinical visit. ○ A second visit after 3 weeks of treatment ○ Final visit after 6 weeks of treatment (visit 3) ○ Two weeks after the end of the treatment period (follow-up, visit 4). • At visit 1 symptom scores of rhinitis were assessed by patients by means of a visual analogical scale (0–12), and nasal lavage was performed. ○ Enrolled patients received a daily record diary for nasal and eye symptoms. • Two centers documented local daily pollen counts throughout the study period.
Outcomes	**Primary outcome:** 1. Mean difference between the treatments for TSS (Total Symptom Score out of 12) 2. Mean difference between the treatments for nasal congestion on waking, nasal congestion daily, rhinorrhea, sneezing, and nasal itching (out of 3) **Secondary outcome:** 1. Mean blood eosinophil counts 2. Percentage of eosinophils in nasal lavage 3. Eosinophil cationic protein in nasal lavage
Notes	• Patients were instructed to record their daily symptoms on diary cards. • Nasal symptoms included nasal blockage on waking and during the day, rhinorrhea, sneezing and itching. Eye symptoms included watering and/or irritation. • Nasal congestion was scored as follows: (0) not present; (1) slightly difficult breathing through the nose; (2) moderately difficult breathing through the nose; (3) very difficult or impossible breathing through the nose. • Any other recorded symptom was scored as follows: (0) none; (1) mild (occasionally present); (2) moderate (rather frequent); (3) severe (persistent). • Rescue medications included levocabastine nasal spray (50 mg per puff) and sodium cromoglycate eye-drops. The study was supported by grants and received no support from the pharmaceutical industry.

Risk of bias table

Bias	Scholars' judgment	Support for judgment
Random sequence generation (selection bias)	Unclear risk	Authors did not describe how random sequence generation occurred other than noting the participants were randomized.
Allocation concealment (selection bias)	Unclear risk	Authors did not provide this information
Blinding of participants and personnel (performance bias)	Low risk	The investigators and patients were blinded. The pharmacist used empty bottle of fluticasone propionate prepared PLA of nasal spray using saline solution.
Blinding of outcome assessment (detection bias)	Low risk	Participants self-report symptoms on daily symptoms cards; the variables measured were not identified as being reflexive in nature.
Incomplete outcome data (attrition bias)	Unclear risk	Authors report power analysis completed but do not disclose how many subjects were needed to detect significance
Selective reporting (reporting bias)	Low risk	Study protocol is listed and reported
Other bias	Low risk	The study was supported by grants and received no support from the pharmaceutical industry.

Ratner, van Bavel, Martin, Hampel, Howland, Rogenes, Westlund, Bowers, Cook[5]

Methods	Randomized, double-blind, placebo-controlled, parallel-group control trial
Participants	**Setting**: 5 study sites in south central Texas (90% of enrolled participants were from a primary care physician's office or were under no medical care for their rhinitis symptoms. Less than 10% were recruited from allergist practices.); December 2005 – February 2006 **Randomized into Study**: $N = 600$ **Group 1:** $n = 150$ **Group 2:** $n = 150$ **Group 3:** $n = 150$ **Group 4:** $n = 150$ **Completed Study:** $N = 569$ Group 1: 142 Group 2: 142 Group 3: 145 Group 4: 140 **Gender** (%male) Group 1: 45 Group 2: 46 Group 3: 49 Group 4: 41 **Mean Age years** Group 1: 40.7 Group 2: 40.1 Group 3: 42.2 Group 4: 42 **Inclusion Criteria:** • Male and non-pregnant females • 12 years of age and older • Diagnosed with moderate to severe seasonal allergic rhinitis based on the criteria below: 1. Positive (2+ reaction, scored on a scale of 0-4, defined as a wheal diameter at lease 3 mm greater than diluent control) skin test reaction to mountain cedar (Juniperus ashei) allergen within 12 months. 2. Appearance of the nasal mucosa consistent with a diagnosis of seasonal allergic rhinitis 3. History of seasonal onset and offset of symptoms for at least two previous mountain cedar pollen seasons. 4. Moderate to severe symptoms of rhinitis evidenced by patient diary card ratings during a run-in. **Exclusion Criteria:** • Use of the following medications prior to the screening visit within the time interval specified below ○ Treatment with loratadine within 1 week ○ Astemizole within 6 weeks ○ Cromolyn sodium within 2 weeks ○ Over-the-counter or prescription medications that could affect rhinitis symptomatology (eg, nasal decongestants) within 72 hours. ○ Inhaled, intranasal, or systemic corticosteroids within 1 month • Septal deviation (blockage greater than 50%) or nasal polyp that could obstruct penetration of an intranasal spray • History of nasal septal surgery or nasal septal perforation • Clinically significant physical examination findings at screening • Candidal infection • Pregnant or lactating • Condition or impairment that might affect their ability to complete the study or provide informed consent **Power Analysis:** 150 evaluable participants per treatment group
Interventions	**Group 1:** FPANS 200 μg (50 μg per spray; two sprays per nostril) plus one placebo capsule once daily at 8 AM. **Group 2:** Placebo nasal spray (two sprays per nostril) plus one encapsulated loratadine 10-mg tablet once daily at 8 AM. **Group 3:** FPANS 200 μg (50 μg per spray; two sprays per nostril) plus one encapsulated loratadine 10-mg tablet once daily at 8 AM **Group 4:** Placebo spray (two sprays per nostril) plus one placebo capsule once daily at 8 AM
Outcomes	**Primary outcome:**Efficacy expressed as Nasal Symptoms Score [**NSS**]. The Visual Analog Scale ranged from 0 (no symptoms) to 100 (maximum symptom severity) for each of the four nasal symptoms (nasal congestion, sneezing, rhinorrhea, and nasal itching) and then summed together. Note: this score based on clinician evaluations at day 0, 7 and 14 **Secondary outcomes (not reported in this analysis):** Decreased score on Rhino conjunctivitis Quality of Life Questionnaire [RQLQ]. Note: participants completed this questionnaire at baseline and day 14 Safety (Incidence of adverse events)–authors did not provide data to quantify as a dichotomous variable
Notes	• Symptomatic participants began the 7-30 day run-in period immediately after screening. • Asymptomatic participants recorded their allergy symptoms associated with mountain cedar as soon as they began so that the run-in period could be initiated. • Most frequently reported drug-related adverse events: blood in nasal mucus, epistaxis, and xerostomia • During the study, participants were not allowed to use other medications affecting rhinitis

Risk of bias table

Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Unclear risk	Study is randomized, but authors did not disclose the sequence generation.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not disclosed by the authors.
Blinding of participants and personnel (performance bias)	Unclear risk	Described as a double-blind, double-dummy study, but details were not disclosed by the authors.
Blinding of outcome assessment (detection bias)	Unclear risk	Clinician assessed the primary outcome at day 0, 7, 14
Incomplete outcome data (attrition bias)	High risk	Sample size was not met to detect significance

(*continued on next page*)

(*continued*)

Bias	Authors' judgment	Support for judgment
Selective reporting (reporting bias)	Low risk	Outcomes intended to be studied were reviewed.
Other bias	Unclear risk	Study funded by grant from Glaxo Wellcome Inc. pharmaceutical company

Specific Care Question:
How does Montelukast compare to an inhaled corticosteroid in terms of clinical benefit?

Plain Language Summary from The Office of Evidence Based Practice:
When comparing Montelukast to inhaled corticosteroids it appears inhaled corticosteroids has a greater clinical benefit (see Figs 17–25), over Montelukast, based on the reduction of symptoms. Primarily three of the studies answering this question were high quality evidence,[7,9,10] however with the inclusion of the very low quality study[6] the body of literature was downgraded to very low quality.[20] The confidence in the effect estimate is limited for the outcomes reported. Additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.

EBP Scholar's responsible for analyzing the literature:
Jennifer Foley, RT(R)(N), CNMT
Dan Heble, PharmD
Jeanette Higgins, RN, MSN, CPNP
David Keeler, RN, BSN, CPN
Kay Hoffsommer, LCSW, LMSW, CCM
Kimberly Lucas, RRT-NPS
Helen Murphy, BHS RRT AE-C
Robert Rhodes, MHA, RRT-NPS
Kim Robertson, MBA, MT-BC
Ashley Schuyler, RRT-NPS

EBP team member responsible for reviewing, synthesizing, and developing this literature:
Jacqueline A. Bartlett, PhD, RN

Method Used for Appraisal and Synthesis:

The Cochrane Collaborative computer program, Review Manager (RevMan 5.3.5), was used to synthesize the five included studies.[6-10]

Note: The epithelial change in eosinophils and sub epithelial cells reported in Pullerits, Praks, Ristioja, Lotvall[9] was unable to be included in this analysis as the authors report the results in a box and whiskers graph.

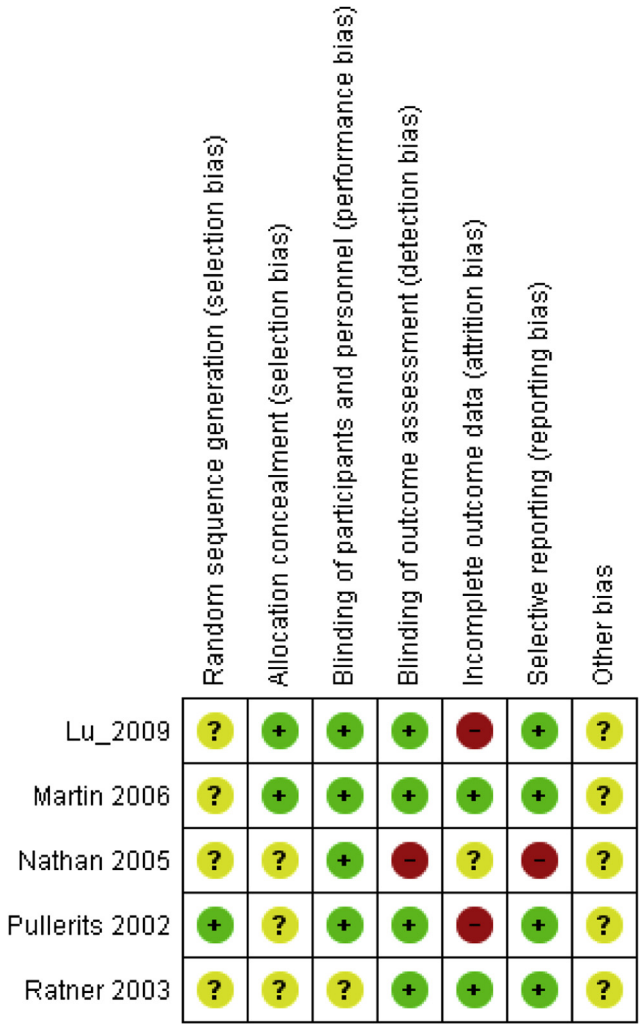

Figure 16. Risk of Bias for Question #2 Studies

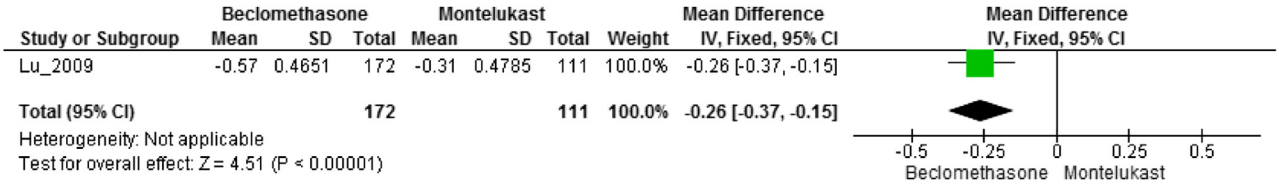

Figure 17. Change in Mean Composite Score (lower [-] reduction in mean score is better)

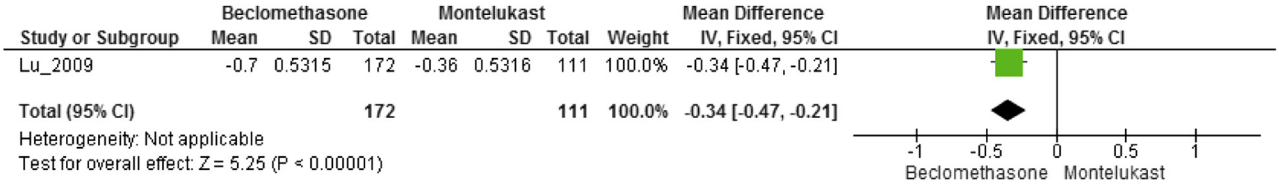

Figure 18. Change in Mean Daytime Nasal Symptoms Score (lower [-] reduction in mean score is better)

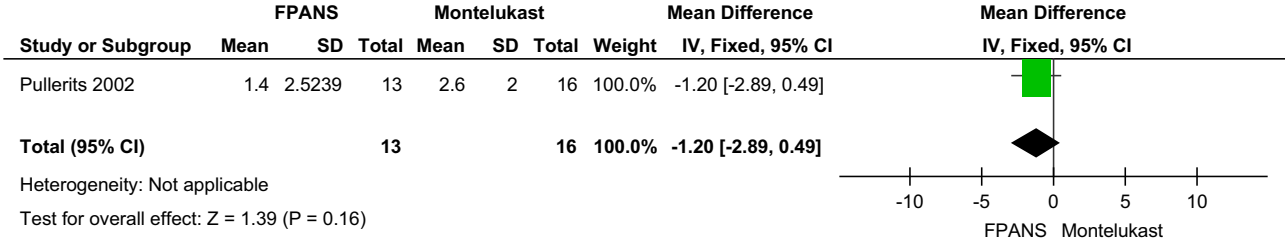

Figure 19. Change in Mean Daytime Nasal Symptom Score (lower [-] reduction in mean score is better)

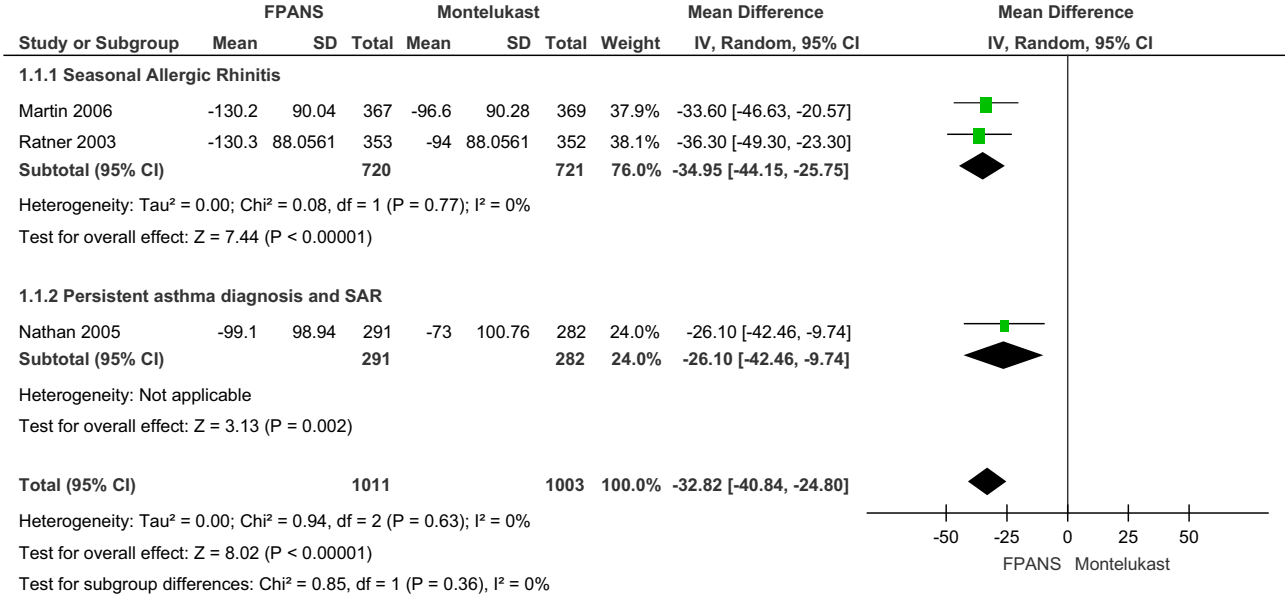

Figure 20. Change in Mean D-TNSS (Daytime-Total Nasal Symptom Score) With Subgroup Analysis (lower [-] reduction in mean score is better)

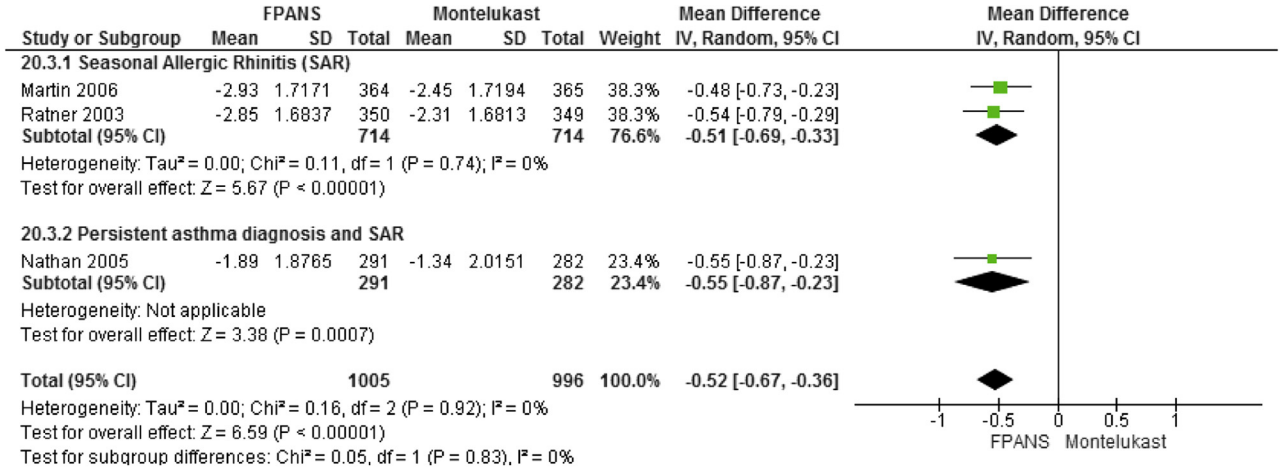

Figure 21. Change in Mean N-TNSS (Nighttime-Total Nasal Symptom Score With Subgroup Analysis (lower [-] reduction in mean score is better)

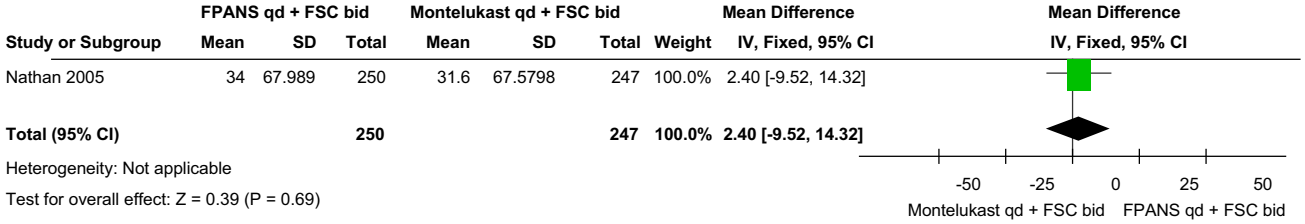

Figure 22. Change in Mean Morning Peak Expiratory Flow (higher [+] mean is better)

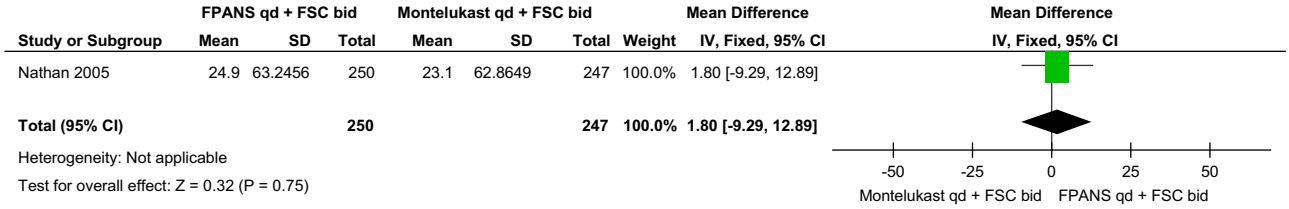

Figure 23. Change in Mean Evening Peak Expiratory Flow (higher [+] mean is better)

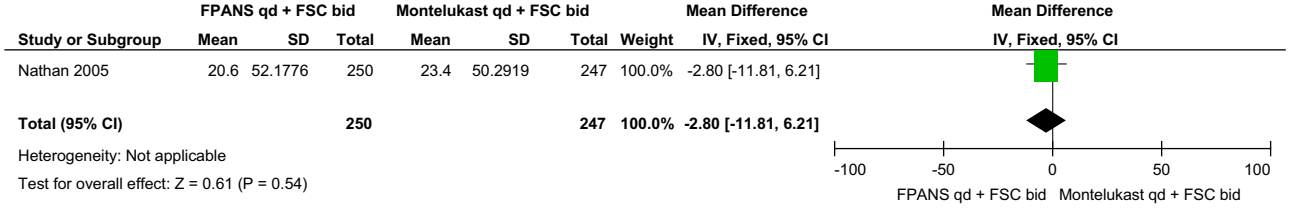

Figure 24. Percentage Change in Mean Symptom-free Days (higher [+] percentage change in mean is better)

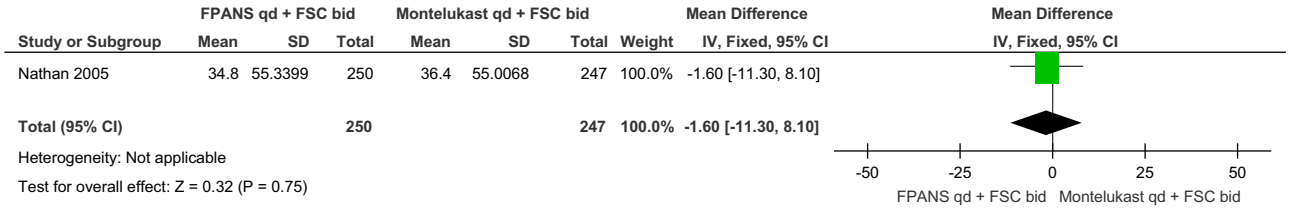

Figure 25. Percentage Change in Mean Albuterol-free Days (higher [+] percentage change in mean is better)

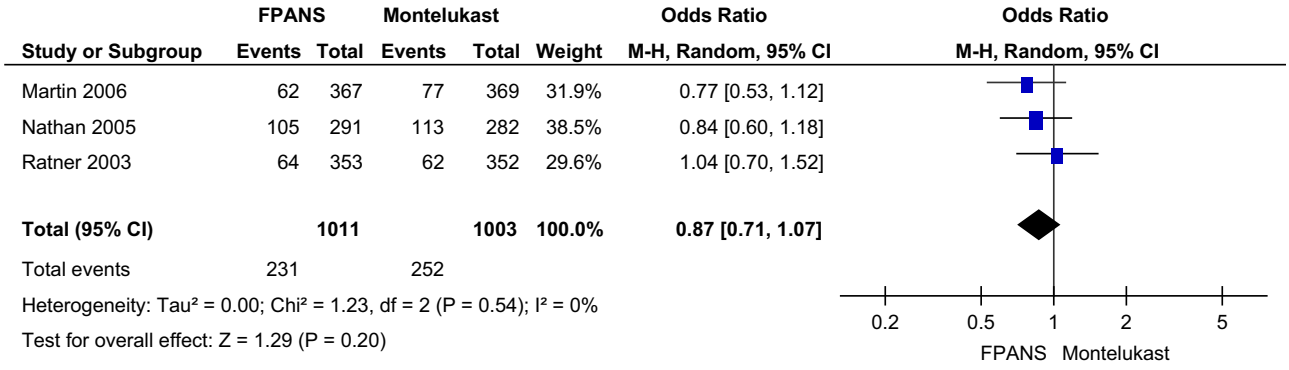

Figure 26. Adverse events (lower [-] reduction in reported events is better)

Question: Should Montelukast vs Beclomethasone be used for rhinitis clinical benefit?

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Montelukast	Beclomethasone	Relative (95% CI)	Absolute	
Composite Symptoms Score (follow-up 2 weeks; measured with: Average of daily diary scores for Daytime Nasal Symptoms and Nighttime Symptoms; Better indicated by lower values)											
1 (Lu[6])	RCT	Very serious[F1]	Serious[F2]	No serious indirectness	No serious imprecision	None	172	111	-	MD 0.26 lower (0.37 to 0.15 lower)	⊕OOO VERY LOW
Daytime Nasal Symptoms Score (follow-up 2 weeks; measured with: Daytime Nasal Symptoms Score; Better indicated by lower values)											
1 (Lu[6])	RCT	Very serious[F1]	Serious[F2]	No serious indirectness	No serious imprecision	None	172	111	-	MD 0.34 lower (0.47 to 0.21 lower)	⊕OOO VERY LOW

F1: Authors do not disclose how randomization occurred, nor was the sample size met to detect significance.
F2: One study identified for this outcome.

Question: Should Montelukast vs FPANS be used for rhinitis clinical benefit?

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Montelukast	FPANS	Relative (95% CI)	Absolute	
Change in DNSS at 2 weeks (follow-up 2 weeks; measured with: Average of total symptoms scored; Better indicated by lower values)											
1 (Pullerits[9])	RCT	No serious risk of bias	Serious[F1]	No serious indirectness	Serious[F2]	None	13	16	-	MD 1.2 lower (2.89 lower to 0.49 higher)	oplus; ⊕OO LOW

F1: One study[9] evaluated this outcome.
F2: Small sample size.

Question: Should Montelukast + FSC vs FPANS +FSC be used for rhinitis clinical benefit?

Quality assessment							No. of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Montelukast + FSC	FPANS + FSC	Relative	Absolute	
Change in mean D-TNSS (follow-up 2 weeks; measured with: Daytime Total Nasal Symptom Score each symptom ranked on four point Likert scale; Better indicated by lower values)											
3 (Martin,[7] Nathan,[8] Ratner[10])	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	1008	1000	-	MD 32.82 lower (40.86 to 24.78 lower)	⊕⊕⊕⊕ HIGH
Change in mean N-TNSS (follow-up 2 weeks; measured with: Nighttime Total Nasal Symptom Score each symptom ranked on four point Likert scale; Better indicated by lower values)											
3 (Martin,[7] Nathan,[8] Ratner[10])	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	1005	996	-	MD 0.52 lower (0.67 to 0.36 lower)	⊕⊕⊕⊕ HIGH
Change in mean Morning PEF (follow-up 2 weeks; measured with: Peak Expiratory Flow recorded every morning by patient; Better indicated by higher values)											
1 (Nathan[8])	RCT	Serious[F1]	Serious[F2]	no serious indirectness	Serious[F3]	none	250	247	-	MD 2.4 higher (9.52 lower to 14.32 higher)	⊕OOO VERY LOW
Change in mean Evening PEF (follow-up 2 weeks; measured with: Peak Expiratory Flow recorded every morning by patient; Better indicated by higher values)											
1 (Nathan[8])	RCT	Serious[F1]	Serious[F2]	no serious indirectness	Serious[F3]	none	250	247	-	MD 1.8 higher (9.29 lower to 12.89 higher)	⊕OOO VERY LOW
Change in Percentage of asthma symptom-free days (follow-up 7 days; measured with: Assessed by patient; Better indicated by higher values)											
1 (Nathan[8])	RCT	Serious[F1]	Serious[F2]	no serious indirectness	Serious[F3]	none	250	247	-	MD 2.8 lower (11.81 lower to 6.21 higher)	⊕OOO VERY LOW
Change in Percentage of albuterol-free days (follow-up 7 days; measured with: Assessed by patient; Better indicated by higher values)											
1 (Nathan[8])	RCT	Serious[F1]	Serious[F2]	no serious indirectness	Serious[F3]	none	250	247	-	MD 1.6 lower (11.3 lower to 8.1 higher)	⊕OOO VERY LOW
Total Adverse Effects (follow-up 2 weeks; assessed with: Count of Adverse Effects)											
3 (Martin,[7] Nathan,[8] Ratner[10])	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	231/1011 (22.8%)	252/1003 (25.1%) 20.9%	OR 0.87 (0.71 to 1.07)	25 fewer per 1000 (from 59 fewer to 13 more) 22 fewer per 1000 (from 51 fewer to 11 more)	⊕⊕⊕⊕ HIGH

F1: Per protocol analysis performed on this outcome.
F2: One study (Nathan et al., 2005) measured this outcome.
F3: Confidence interval includes the line of no difference.

Characteristics of included studies:

Lu, Malice, Dass, Reiss[6]

Methods	Randomized, double-blind, placebo-controlled, parallel-group trial
Participants	**Setting**: 17 US sites; April-June 1998 **Randomized into Study**: $N = 632$ Group 1: $n = 57$ Group 2: $n = 174$ Group 3: $n = 173$ Group 4: $n = 112$ Group 5: $n = 116$ **Completed Study**: $N = 617$ total Group 1: $n = 55$ Group 2: $n = 168$ Group 3: $n = 172$ Group 4: $n = 107$ Group 5: $n = 115$ **Age, Mean ± SD**: **Group 1:** 35.1 ± 13.8 **Group 2:** 34.0 ± 12.7 **Group 3:** 34.1 ± 13.3 **Group 4:** 35.6 ± 13.1 **Group 5:** 34.8 ± 12.4 **Gender (%male)**: Group 1: 36.8 Group 2: 38.5 Group 3: 38.7 Group 4: 37.5 Group 5: 35.3 **Inclusion Criteria**: • 15-85 years of age • ≥ 2-year documented clinical history of SAR (seasonal allergic rhinitis) • Positive skin test (wheal ≥ 3mm greater than saline control) to 1 of the allergens in the study season • Minimal predefined level of daytime nasal symptoms (predefined level not disclosed by authors) **Exclusion Criteria**: Not disclosed by authors **Power Analysis**: 550 evaluable participants needed between the Montelukast + loratadine group and placebo group, the authors do not disclose how many participants were needed to detect significance for the Montelukast and beclomethasone comparison.
Interventions	Prior to study participants received a 1-week placebo run-in then participants were randomized to one of the following study arms: **Group 1:** Placebo: not described **Group 2:** Montelukast 10mg oral once daily + loratadine 10mg oral once daily **Group 3:** Beclomethasone 200 μg intranasal twice daily **Group 4:** Montelukast 10mg oral once daily **Group 5:** Loratadine 10mg oral once daily
Outcomes	**Primary endpoint** • *Composite Symptom Score*: Average of Daytime Nasal Symptom Score (DNSS) + Nighttime Symptoms Score • Clinical adverse experiences unable to compare between Montelukast + loratadine and Placebo as the authors combined all study arm adverse events and reported as a total percentage **Secondary endpoints** (outcomes not included in analysis)**:** • DNSS, Daytime Eye Symptoms Score • Nighttime Symptoms Score • Individual symptoms of the DNSS (Nasal congestion, Rhinorrhea, Pruritus and Sneezing, each symptom rated on a 4-point scale of 0 = none to 3 = severe) • Patient's and Physician's Global Evaluations of AR • Rhino conjunctivitis Quality-of-Life Score

Risk of bias table

Bias	Scholars' judgment	Support for judgment
Random sequence generation (selection bias)	Unclear risk	Method of randomization not disclosed by authors
Allocation concealment (selection bias)	Low risk	Participants randomized to treatment group based on a computerized allocation system
Blinding of participants and personnel (performance bias)	Low risk	Double-blind active-treatment period
Blinding of outcome assessment (detection bias)	Low risk	Participants self-report symptoms on daily symptoms cards; the variables measured were not identified as being reflexive in nature.
Incomplete outcome data (attrition bias)	High risk	Several instances of quantitative data missing based on the author's qualitative statements; the group n's in Table 2 are not reflective of intention to treat analysis, however low risk of bias would have been assigned as the randomized and analyzed numbers are very close. High risk was assigned due to the sample size was not met to detect significance between the study arms.
Selective reporting (reporting bias)	Low risk	
Other bias	Unclear risk	Study funded by Employees of Merck & Co., Inc.

Martin, Andrews, van Bavel, Hampel, Klein, Prillaman, Faris, Philpot[7]

Methods	Randomized, double-blind, placebo-controlled, parallel-group trial
Participants	**Setting:** 4 outpatient allergy clinics in south central Texas (December 11, 2001-February 15, 2002) **Number Randomized**: $N = 736$ **Group 1:** $n = 367$ **Group 2:** $n = 369$ **Number who completed the study:** *actual n unknown* **Group 1:** Author's state approximately 95% completed study arm **Group 2:** Author's state approximately 95% completed **Gender (% Male)**: **Group 1:** 36% **Group 2:** 38% **Age, mean ± SD** **Group 1:** 39.1 ± 14.0 **Group 2:** 40.3 ± 13.9 **Inclusion criteria:** • Male or female, • Minimum 15 years old • Lived in south central Texas, • Diagnosis of SAR (seasonal allergic rhinitis) ○ clinical history of SAR with seasonal onset and offset of nasal allergy symptoms during each of the past 2 **mountain cedar** allergy seasons ○ a positive skin prick test reaction (wheal at least 3 mm greater than the diluent control) to **mountain cedar** allergen within 12 months of visit 1 **Exclusion criteria**:• History of severe physical obstruction of the nose, • Nasal septal surgery or perforation, • Significant respiratory disease, • Long term or concurrent use of tricyclic anti-depressants, • Hypersensitivity to study drugs, sensitivity to aspirin or other NSAIDS, • Exposure to study drug within last 30 days, • Positive pregnancy test **Power analysis:** 338 evaluable participants per treatment group
Interventions	**Interventions were self-administered in the evening:** **Group 1:** fluticasone propionate aqueous nasal spray, 200 μg daily + oral placebo **Group 2:** Montelukast tablets, 10 mg daily + nasal spray placebo
Outcomes	**Primary endpoint** Mean change from baseline in *daytime total nasal symptom scores* (**D-TNSS**) • D-TNSS (daytime total nasal symptom scores) consisted of the sum of four D-INSS using a VAS 0-100 ○ nasal congestion ○ nasal itching ○ rhinorrhea ○ sneezing **Secondary endpoints** Mean change from baseline in nighttime total nasal symptom scores (**N-TNSS**) (not included in this analysis) • **N-TNSS** (*nighttime total nasal symptom scores*) consisted of the sum of 3 N-INSS (*nighttime individual nasal symptom scores*) evaluated on a 4-point scale from 0-3 (0 = none, 3 = very) ○ nasal congestion on awakening ○ difficulty in going to sleep due to nasal symptoms ○ nighttime awakening due to nasal symptom

Risk of bias table

Bias	Scholars' judgment	Support for judgment
Random sequence generation (selection bias)	Unclear risk	Authors state that participants were randomized to one of two groups, but do not state how sequence generation occurred
Allocation concealment (selection bias)	Low risk	Authors state that the placebo interventions matched the actual intervention
Blinding of participants and personnel (performance bias)	Low risk	Authors do not disclose this but if the placebo interventions matched the actual intervention the risk was low
Blinding of outcome assessment (detection bias)	Low risk	Participants self-report symptoms on daily symptoms cards; the variables measured were not identified as being reflexive in nature.
Incomplete outcome data (attrition bias)	Low risk	All efficacy analyses were formed on the intent-to-treat population; however, the Week 1-2 results in Table 1 do not account for 100% of the population therefore per protocol analysis was performed, low risk assigned as the authors overenrolled participants and the sample size was powered appropriately with dropouts.
Selective reporting (reporting bias)	Low risk	All outcomes measures stated were reported
Other bias	Unclear risk	Study funded by GlaxoSmithKline, the maker of fluticasone propionate aqueous nasal spray (FNM40194).

Nathan, Yancey, Waitkus-Edwards, Prillaman, Stauffer, Philpot, Dorinsky, Nelson[8]

Methods	Randomized, double-blind, placebo-controlled, parallel-group trial
Participants	**Setting:** 92 investigative sites in the United States (a collection time frame not disclosed) **Randomization into Study**: $N = 863$ **Group 1:** $n = 291$ **Group 2:** $n = 282$ **Group 3:** $n = 290$ **Completed Study:** $N = 805$ **Age, mean ± SD:** **Group 1:** 35.8 ± 12.6 **Group 2:** 34.4 ± 13.3 **Group 3:** 35.7 ± 14.0 **Gender (% male):** Group 1: 33% Group 2: 34% Group 3: 28% **Inclusion Criteria**: • Minimum 15 years old • History of Seasonal allergic rhinitis (SAR) for at least two allergy seasons • Positive skin test response during screening to the relevant seasonal allergen • Diagnosis of persistent asthma (as defined by the American Thoracic Society) and receiving daily asthma treatment for at least three months preceding the study • Met both asthma and rhinitis symptom criteria during screening **Exclusion Criteria:** • Use of anti-inflammatory medications to control nasal symptoms for 4 weeks prior to or at any time during the study • Use of oral, intranasal, ocular or parenteral corticosteroids and leukotriene modifiers 4 weeks prior to the screening visit • Received more than 2 courses of oral or parenteral corticosteroids within 6 months of screening. • Additional medications excluded prior to screening and throughout the study including: ○ intranasal or ocular Cromolyn ○ short and long-acting antihistamines ○ nasal decongestants ○ intranasal anticholinergics ○ pregnancy and/or lactation ○ history life-threatening asthma ○ asthma hospitalization within 6 months of screening ○ significant concurrent diseases including: ○ recent respiratory tract infection ○ recent nasal surgery or anatomic defects of the nose such as a deviated septum or nasal septal perforation **Power Analysis:** 244 evaluable participants per treatment group for primary outcomes
Interventions	**Participants self-administered two sprays per nostril and one capsule in the evening during the study period, all participants were provided with a FSC inhaler:** **Group 1:** FPANS 200 μg qd + placebo capsule + FSC 100/50 μg bid **Group 2:** Over-encapsulated montelukast tablets 10 mg qd + vehicle placebo aqueous nasal spray + FSC 100/50 μg bid **Group 3:** Placebos for both active treatments-self-administered 2 sprays per nostril and one capsule in the evening + FSC 100/50 μg bid For all study groups pre-study asthma medications, with the exception of albuterol hydrofluoroalkane, were discontinued after randomization.
Outcomes	**Primary outcomes:** • **Daytime Total Nasal Symptom Score (D-TNSS):** Change in baseline at 2 and 4 weeks (only 2 week change reported in this analysis) ○ **D-TNSS:** the sum of reflexive daytime individual nasal symptom (D-INSS) scores, assessed in evening by participants before self-administered medication, regarding the following: ■ nasal congestion ■ rhinorrhea ■ sneezing ■ nasal itching • Peak Expiratory Flow (PEF) ○ Change in baseline **Secondary outcomes (not included in this analysis):** • Nighttime Total Nasal Symptom Score (N-TNSS): Change in baseline at 2 and 4 weeks ○ **N-TNSS** = sum of individual night time symptom score assessed each morning: ■ nasal congestion on awakening ■ difficulty in going to sleep because of nasal symptoms ■ night time awakenings because of nasal symptoms

Risk of bias table

Bias	Scholars' judgment	Support for judgment
Random sequence generation (selection bias)	Unclear risk	Method of randomization not specified by authors.
Allocation concealment (selection bias)	Unclear risk	Authors do not disclose how allocation concealment occurred.
Blinding of participants and personnel (performance bias)	Low risk	Authors share that participants received either a placebo capsule or a vehicle placebo aqueous nasal spray or both of these.
Blinding of outcome assessment (detection bias)	High risk	Participants reflexively self-recorded outcomes every 12 hours in a diary; authors did not disclose the ranges for the D-INSS (Daytime Individual Nasal Symptom) nor the D-TNSS (Daytime Total Nasal Symptom Score).
Incomplete outcome data (attrition bias)	Unclear risk	Authors did not identify how missing data resolution occurred; authors met power analysis
Selective reporting (reporting bias)	High risk	Primary outcomes: • Intention to treat analysis performed on reflexive D-TNSS (Daytime Total Nasal Symptom Score). • Per protocol analysis performed on Peak Expiratory Flow (PEF)
Other bias	Unclear risk	Study funded by GlaxoSmithKline (GSK), Research Triangle Park, NC. Primary investigator Nathan and Nelson are consult speakers and recipient of research grants for GSK. All other authors/investigators are employees of GSK. Drugs manufactured by GSK involved in the study.

Pullerits, Praks, Ristioja, Lotvall[9]

Methods	Randomized, double-blind, placebo-controlled, parallel-group trial
Participants	**Setting:** University hospital in Sweden; (March through August 1999) **Number randomized:** $N = 62$ Group 1: $n = 13$ Group 2: $n = 16$ Group 3: $n = 15$ Group 4: $n = 18$ **Number completed**: 62 participants **Gender**: 58% male **Age, mean ± SD:** **Group 1:** 28.4 ± 6.4 **Group 2:** 28.3 ± 8 **Group 3:** 30.1 ± 9.9 **Group 4:** 29.8 ± 10.4 **Inclusion criteria:**• Age between 15 and 50 years • Known history of allergic rhinitis during the grass pollen season for at least 2 previous seasons (confirmed via skin allergy testing) **Exclusion criteria:**• Positive allergy skin test to area tree pollens • Perennial rhinitis • Concurrent purulent nasal infection • Use of steroids during the course of the study • Presence of any serious or unstable concurrent disease • Positive pregnancy test **Power analysis:** the authors do not disclose how many participants were needed to detect significance
Interventions	**Study consisted of 5 patient visits:** • **Visit #1:** Assessment of each participants eligibility • **Visit #2:** Participants received record cards for recording daily nasal symptoms (nasal congestion, sneezing, rhinorrhea and nasal itching), provided samples for nasal biopsy, hematology, and urinalysis • **Visit #3:** Participants allocated to treatment groups **Group 1:** intranasal fluticasone 50 μg/accuation, Dose = 2 accuations per nostril per day [200 μg/day]; plus placebos **Group 2:** montelukast 10 mg per day; plus placebos **Group 3:** montelukast 10 mg per day; loratadine 10 mg per day; placebo nasal spray **Group 4:** placebos • **Visit #4:** nasal biopsy (during the peak of pollen season) • **Visit #5:** Follow-up visit (1 month after the end of pollen season) Participants were instructed to start treatment 2 to 3 weeks before the beginning of the grass pollen season • Treatment lasted for 50 days and all medications were administered in the morning • Participants were provided with rescue drugs: loratadine tablets and cromoglycate eye drops; any rescue medications was to be recorded on the daily record card
Outcomes	The mean total daily symptom score was calculated and used in the analysis. Primary outcome: Participants recorded nasal symptom scores: • Nasal blockage symptoms scoring began with this visit, using the following scale: ■ 0 - Breathing through nose freely and easily ■ 1 - Slight difficulty breathing through nose ■ 2 - Moderate difficulty breathing through nose ■ 3 - Severe difficulty breathing through nose ■ 4 - Breathing through nose is very difficult or impossible • Sneezing, rhinorrhea, and nasal itching scoring began with this visit, using the following scale:

(*continued on next page*)

(*continued*)

Methods	Randomized, double-blind, placebo-controlled, parallel-group trial
	■ 0 - None ■ 1 - Mild ■ 2 - Moderate ■ 3 - Severe ■ 4 - Very severe
Notes	• Total grass pollen counts during the study period were 17%-33%

Risk of bias table

Bias	Scholars' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Computer-generated allocation schedule
Allocation concealment (selection bias)	Unclear risk	Author's did not disclose
Blinding of participants and personnel (performance bias)	Low risk	Authors share that participants received either a placebo capsule or a vehicle placebo aqueous nasal spray or both of these.
Blinding of outcome assessment (detection bias)	Low risk	Participants self-report symptoms on daily symptoms cards; the variables measured were not identified as being reflexive in nature.
Incomplete outcome data (attrition bias)	High risk	Authors did not disclose the needed sample size
Selective reporting (reporting bias)	Low risk	Intention to treat analysis occurred
Other bias	Unclear risk	Study funded by GlaxoSmithKline (study FNM40012)

Ratner, Howland, Arastu, Philpot, Klein, Baidoo, Faris, Rickard[10]

Methods	Randomized, double-blind, placebo-controlled, parallel-group trial
Participants	**Setting:** 5 clinical investigational sites in south central Texas, during the mountain cedar allergy season from December 12, 2001 to February 26, 2002 for 15 days **Randomized into Study:** $N = 705$ **Group 1:** $n = 353$ **Group 2:** $n = 352$ **Completed Study** $N = 692$ **Group 1:** $n = 345$ **Group 2:** $n = 347$ **Age, mean ± SD** **Group 1:** 38.3 ± 13.3 **Group 2:** 38.1 ± 13.3 **Gender (% male)** Group 1: 39% Group 2: 37% **Inclusion Criteria** • Minimum 15 years old • Resides in south central Texas where the allergen is prevalent • D-TNSS (Daytime Total Nasal Symptom Score) of at least 200 of 400 on the visual analog scale (VAS) for at least 4 of the 7 days immediately before visit 2 • Diagnosis of seasonal allergic rhinitis (SAR) based on: ○ Clinical history of SAR with seasonal onset and offset of nasal allergy symptoms during each of the last two mountain cedar allergy seasons ○ Positive skin test reaction to mountain cedar allergen ■ test performed within the last 12 months of visit 1 ■ wheal diameter at least 3mm greater than diluent control using 1:20 (w:v) glycerinated solution **Exclusion Criteria** • Participants with severe physical obstruction of the nose • History of nasal septal surgery or perforation • Significant respiratory disease • Chronic or concurrent use of tricyclic antidepressants • History of hypersensitivity to either study drug • Sensitivity to aspirin or other non-steroidal anti-inflammatory drugs • Exposure to an investigational study within 30 days of visit 1 • Positive pregnancy test • Previous or concurrent use of any prescription or over the counter medications that may have affected: ○ the results of the skin test ○ nasal rhinitis symptomology during the screening or treatment period ○ evaluation of the effectiveness of the study medication **Power Analysis•** 150 evaluable participants per treatment group

(*continued on next page*)

(*continued*)

Methods	Randomized, double-blind, placebo-controlled, parallel-group trial
Interventions	**Screening Evaluations:** • Visit 1 ○ Initial screening ■ concurrent medication evaluation, medical history, skin testing (if not done within 12 months of visit) ○ Those who qualified based on initial assessment completed a physical exam, pregnancy test, nasal spray technique demonstration and given diary cards • Visit 2 ○ Diary cards reviewed ○ Those with D-TNSS (Daytime Total Nasal Symptom Score) of at least 200 of 400 on the visual analog scale (VAS) for at least 4 of the 7 days immediately were randomly assigned to study drug: **Group 1:** fluticasone propionate aqueous nasal spray 200 ug once daily **Group 2:** montelukast 10 mg once daily ○ Both study groups had the medication administered in the evening • Visit 3 and 4 ○ Similar procedures as visit 2 **Subject Documentation on Diary Cards to:** • Evaluate day (before bed) and night (immediately after waking in morning) • Record daily use of study drugs on same diary card • Record nonrhinitis symptoms/conditions between study visits and any medications used to treat them Diaries reviewed at visits in relation to the subject's previously existing adverse events (AE) and concurrent medical conditions • Any medical symptoms/conditions not documented previously were assessed as either: "not clinically significant" or an AE. • Normal allergic rhinitis symptoms were not considered AE
Outcomes	**Primary Outcome:** • Fluticasone versus montelukast ○ Subject rated daytime total nasal symptom scores (D-TNSS) and individual daytime nasal symptoms scores (D-INSS) averaged over weeks 1 to 2 (days 2 to15) Primary efficacy endpoint, the sum of the four daytime individual symptom scores • Adverse events **Secondary Outcomes (not included in this analysis)** • Fluticasone versus montelukast ○ subject rated nighttime total nasal symptoms score (N-TNSS) and nighttime individual nasal scores (N-INSSs) averaged over weeks 1 to 2 (days 2 to 15) ○ At the end of the study, a seven point categorical scale ranging from significant improvement (1) to significant worsening (7) was used for subject rated overall evaluation of response to therapy for relieving daytime nasal symptoms over the entire treatment period
Notes	• Only one population was defined for this study, the intent to treat (ITT), which consisted of all participants who were assigned to treatment. The ITT population was used for all efficacy analysis and for all safety, background, and demographic summaries. • AE reported in both study arms: headache, diarrhea, gastric upset, nausea, sore throat, epistaxis, and fever

Risk of bias table

Bias	Scholars' judgment	Support for judgment
Random sequence generation (selection bias)	Unclear risk	Authors did not disclose randomization process
Allocation concealment (selection bias)	Unclear risk	Authors did not disclose allocation concealment
Blinding of participants and personnel (performance bias)	Unclear risk	Authors did not disclose blinding process
Blinding of outcome assessment (detection bias)	Low risk	Participants self-report symptoms on daily symptoms cards; the variables measured were not identified as being reflexive in nature.
Incomplete outcome data (attrition bias)	Low risk	Intent to treat analysis performed
Selective reporting (reporting bias)	Low risk	Reported on all outcomes
Other bias	Unclear risk	Study funded by GlaxoSmithKline, the maker of fluticasone nasal spray.

Specific Care Question:
Is there any clinical benefit to adding an intranasal antihistamine (INAH) to an intranasal corticosteroid?

Plain Language Summary from The Office of Evidence Based Practice:
There appears to be a clinical benefit when intranasal antihistamine is added to an intranasal corticosteroid (see Figs 28–36) based on the reduction of total nasal symptoms or ocular symptoms. Clinicians should discuss with the patient that the addition of an INAH may increase the odds of experiencing an adverse event (see Fig 36). The primary adverse events identified were headache, bitter taste or epistaxis.

Due to the low quality of the literature, the confidence in the effect estimate is limited for the outcomes reported. Additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.

EBP Scholar's responsible for analyzing the literature:
Jennifer Foley, RT(R)(N), CNMT
Kori Hess, PharmD
Kimberly Lucas, RRT-NPS
Ashley Schuyler, RRT-NPS

EBP team member responsible for reviewing, synthesizing, and developing this literature: Jacqueline A. Bartlett, PhD, RN

Method Used for Appraisal and Synthesis:
The Cochrane Collaborative computer program, Review Manager (RevMan 5.3.5), was used to synthesize the five included studies.[11-15]

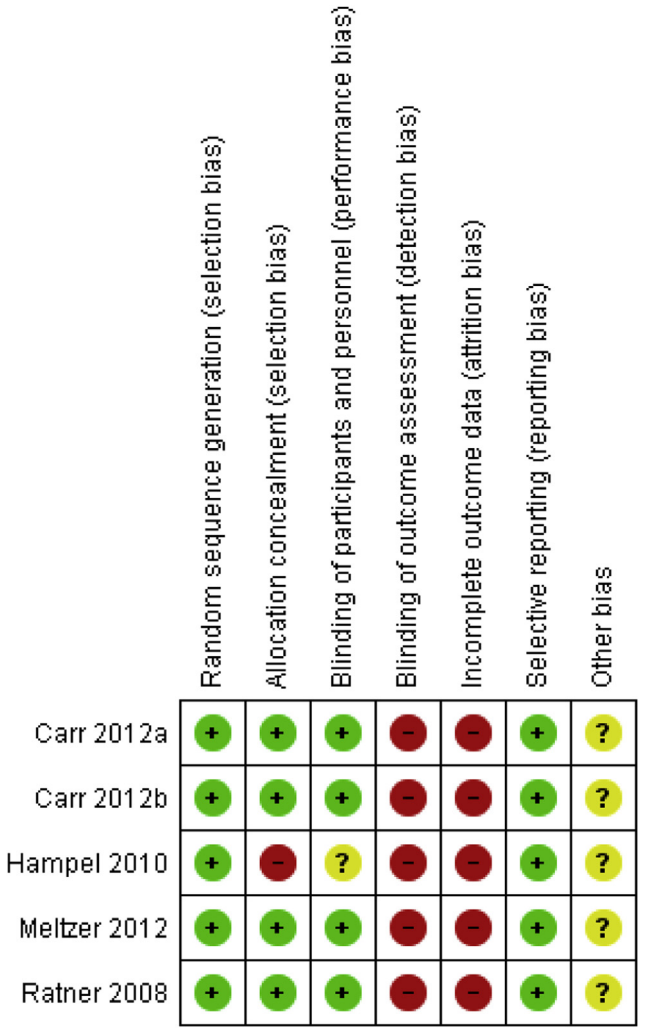

Figure 27. Risk of Bias for Question #3 Studies

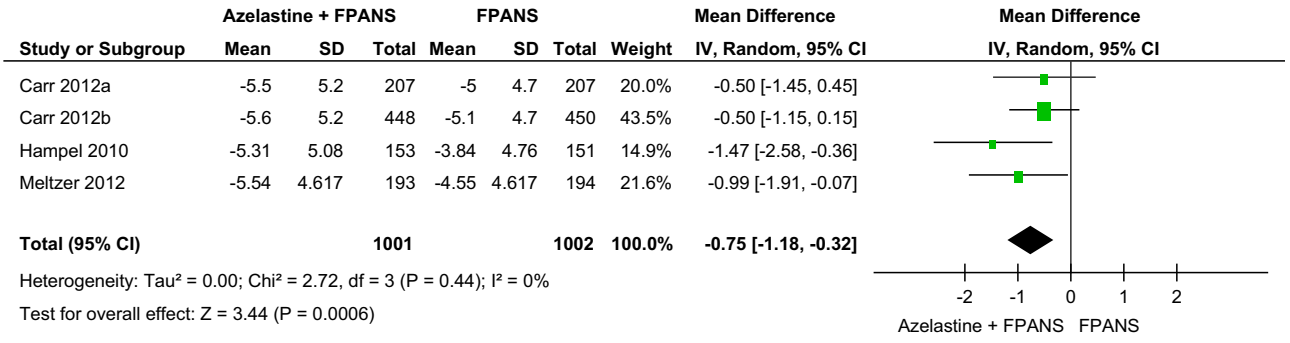

Figure 28. Change in Mean Total Nasal Symptom Score (TNSS) (lower [-] reduction in mean score is better)

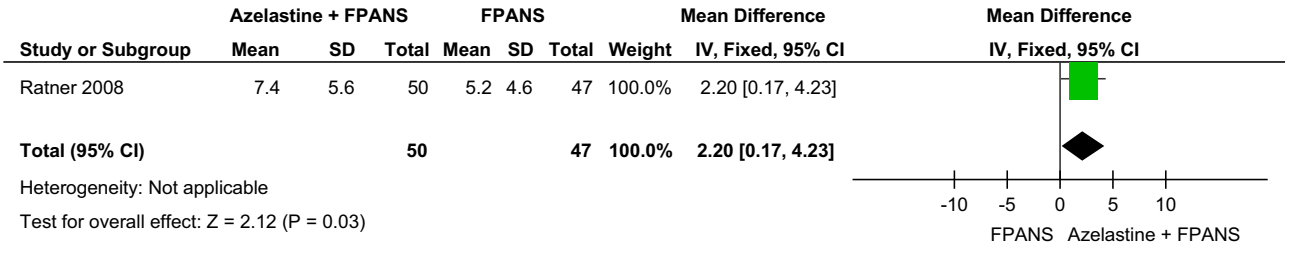

Figure 29. Change in Least Squares Mean Total Nasal Symptom Score (TNSS) (higher [+] change is better)

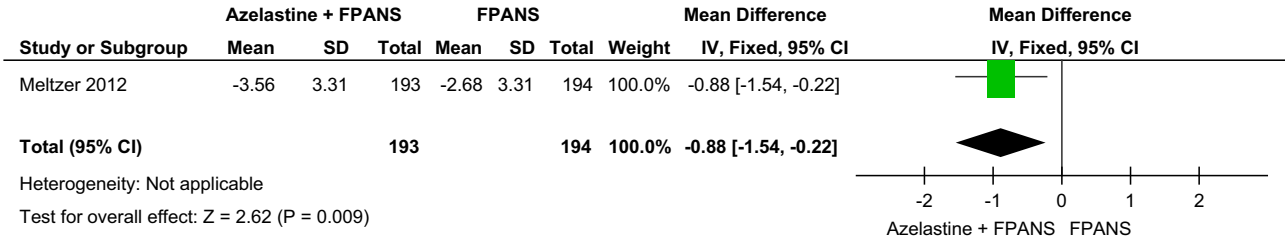

Figure 30. Change in Mean Total Ocular Symptom Score (TOSS) (lower [-] reduction in mean score is better)

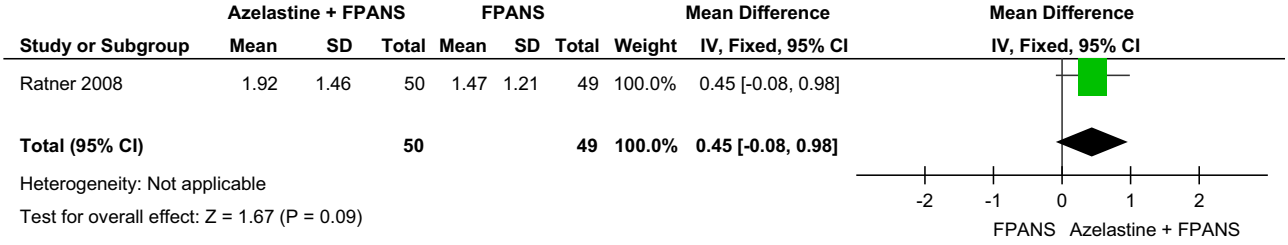

Figure 31. Change in Mean RQLQ (higher [+] change in mean is better)

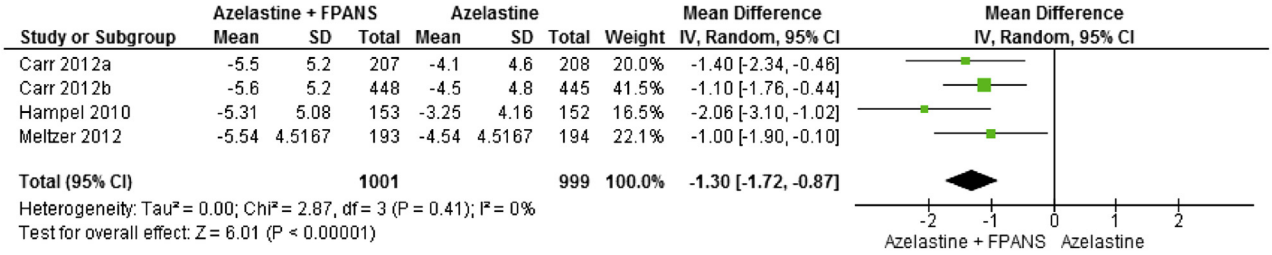

Figure 32. Change in Mean Total Nasal Symptom Score (TNSS) (lower [-] reduction in mean score is better)

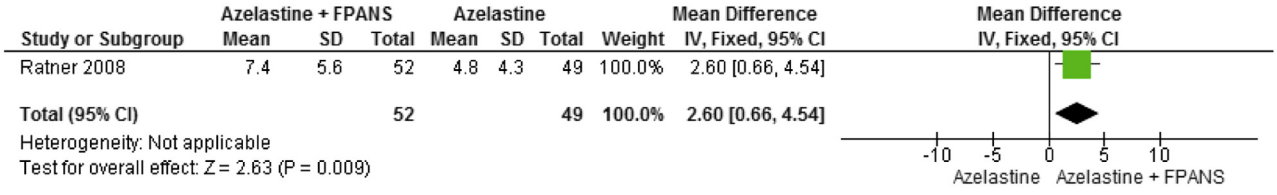

Figure 33. Change in Least Squares Mean Total Nasal Symptom Score (TNSS) (higher [+] change in mean is better)

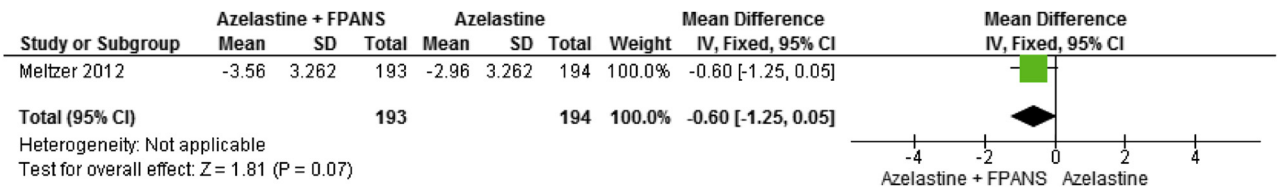

Figure 34. Change in Mean Total Ocular Symptom Score (TOSS) (lower [-] reduction in mean score is better)

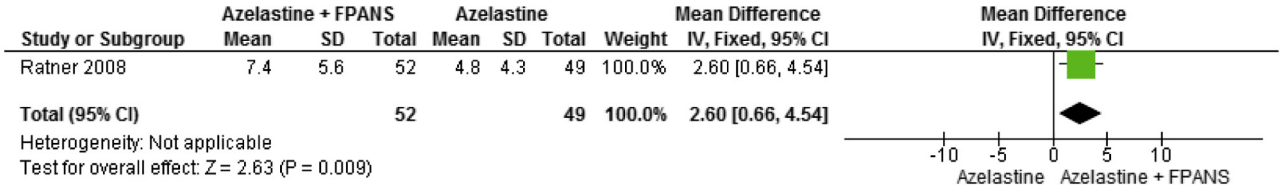

Figure 35. Change in Mean RQLQ (higher [+] change in mean is better)

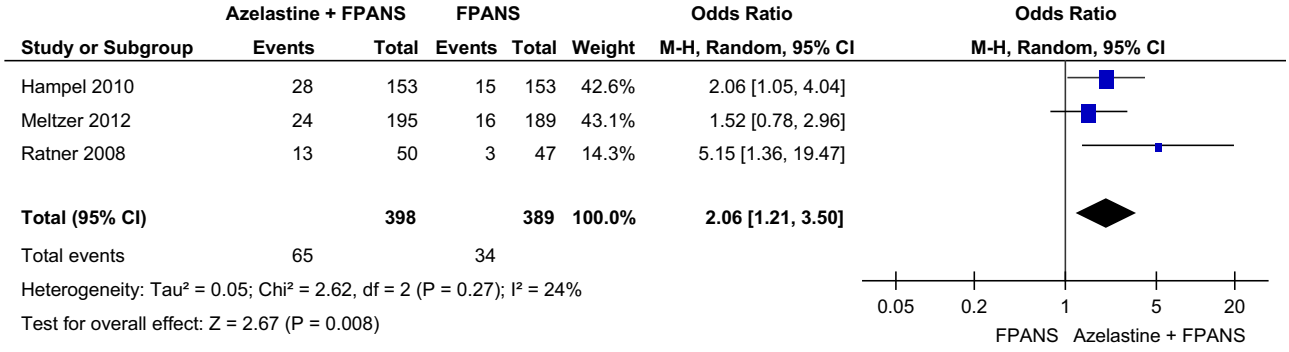

Figure 36. Adverse Events (lower [-] reduction in mean score is better)

Question: Azelastine + FPANS vs Azelastine to increase clinical benefit

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Azelastine + FPANS	Azelastine	Relative (95% CI)	Absolute	
Change in TNSS (follow-up 2 weeks; measured with: TNSS; Better indicated by lower values)											
4 (Carr[11,12]; Hampel[13]; Meltzer[14])	RCT	Serious[F1]	Serious[F1]	No serious indirectness	No serious imprecision	none	1001	999	-	MD 1.3 lower (1.72 to 0.87 lower)	⊕⊕OO LOW
Change in TNSS (follow-up 2 weeks; measured with: reflective TNSS; Better indicated by higher values)											
1 (Ratner[15])	RCT	Serious[F2]	No serious inconsistency	No serious indirectness	Serious[F3]	none	52	49	-	MD 2.6 higher (0.66 to 4.54 higher)	⊕⊕OO LOW

F1: Participants in all four studies reported rTNSS.
F2: Participants in study reported rTNSS.
F3: Needed sample size was not disclosed by the authors.

Question: Azelastine + FPANS vs FPANS to increase clinical benefit

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Azelastine + FPANS	FPANS	Relative (95% CI)	Absolute	
Change in TNSS (follow-up 2 weeks; measured with: reflexive TNSS scale; Better indicated by lower values)											
4 (Carr[11,12]; Hampel[13]; Meltzer[14])	RCT	Serious[F1]	Serious[F1]	No serious indirectness	No serious imprecision	None	1001	1002	-	MD 0.75 lower (1.18 to 0.32 lower)	⊕⊕OO LOW
Change in TNSS (follow-up 2 weeks; measured with: reflective TNSS score; Better indicated by higher values)											
1 (Ratner[15])	RCT	Serious[F2]	No serious inconsistency	No serious indirectness	Serious[F3]	None	50	50	-	MD 2.2 higher (0.19 to 4.21 higher)	⊕⊕OO LOW

F1: Participants in all four studies reported rTNSS.
F2: Participants in study reported rTNSS.
F3: Needed sample size was not disclosed by the authors.

Characteristics of included studies:

Carr, Bernstein, Lieberman, Meltzer, Bachert, Price, Munzel, Bousquet[11]

Methods	Randomized, double-blind, placebo-controlled, parallel-group trial, MP4002
Participants	**Setting:** not disclosed by meta-analyses (MA) authors **Number randomized:** $N = 832$ (From supplemental study materials) • Unable to determine participants randomized per study arm **Completed Study:** $N = 831$ **Gender:** 36.1% male **Age, mean ± SD:** **Group 1:** 37.3 ± 14.1 **Group 2:** 38.6 ± 14.1 **Group 3:** 36.2 ± 14.6 **Group 4:** 37.3 ± 16.0 **Inclusion criteria:** • Males and females • 12 years and older with minimum 2 year history of moderate-to-severe seasonal allergic rhinitis (SAR) • SAR reflective total nasal symptom score (rTNSS) of at least 8 of 12, with a congestion score of 2 or 3 during screening • Significant current clinical rhinitis symptomatology • Positive skin prick test response to relevant pollen **Exclusion criteria:** • Erosion, ulceration, or septal perforation or another disease (such as sinusitis, rhinitis medicamentosa, polyposis, respiratory tract infection [within 14 days of screening]) • Asthma except intermittent asthma • Significant pulmonary disease • Symptomatic cardiac conditions • Taking concomitant medication that could interfere with the interpretation of study results **Power analysis:** 195 evaluable participants per treatment group
Interventions	The study comprised a 7-day, single-blind, placebo lead-in period and a 14-day treatment period with 3 study visits at days 1, 7, and 14. On visit 2 (day 1), eligible participants were randomized to 14 days of treatment (1 spray per nostril twice daily) with the following: **Group 1:** azelastine 0.1% + fluticasone (novel formulation of 137 μg of azelastine/50 μg of FP) **Group 2:** azelastine nasal spray (137 μg) **Group 3:** FP (50 μg) nasal spray **Group 4:** vehicle placebo nasal spray. Doses were separated by approximately 12 hours. Participants recorded application times and symptom scores in a diary.
Outcomes	**Primary outcomes:** **Total Nasal Symptom Score (TNSS)** ○ Sum of the morning and evening overall change from baseline in 12-hour Total Nasal Symptom Score (TNSS) over the entire 14-day treatment period (sum of the individual nasal symptoms of congestion, itching, rhinorrhea, and sneezing) ○ All nasal and ocular symptoms were scored by participants twice daily on each treatment day according to a 4-point scale: ■ Score of 0 was defined as none (no symptoms present) ■ Score of 1 was defined as mild (mild symptoms that do not interfere with any activity) ■ Score of 2 was defined as moderate (slightly bothersome symptoms that slightly interfere with activity/nighttime sleep) ■ Score of 3 was defined as severe (bothersome symptoms that interfere with activity/nighttime sleep). ○ Therefore the maximum Total Nasal Symptom Score (TNSS) or instantaneous total nasal symptom score (iTNSS) was 24 (4 symptoms × score of 3 × 2 for morning + evening). • **Adverse events**
Notes	Smokers were not excluded from the study.

Risk of bias table

Bias	Scholars' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Randomized and balanced by study site in blocks of 4.
Allocation concealment (selection bias)	Low risk	A blind randomization code was maintained at a central site apart from the sponsor and study centers.
Blinding of participants and personnel (performance bias)	Low risk	Individual nasal spray bottles were identity masked such that both participants and study personnel were blind to treatment assignment. The active controls comprised the individual components of MP29-02 in the same vehicle, pump volume, and device. Study blinding was preserved at the study sites until all participants completed the study and the database had been locked.
Blinding of outcome assessment (detection bias)	High risk	Participants reflexively self-recorded outcomes every 12 hours in a diary
Incomplete outcome data (attrition bias)	Low risk	Intention to treat analysis occurred. In supplemental study materials, the authors disclose the ITT population of $N = 831$ which does not reflect the number of randomized participants $N = 832$. Low risk assigned as the total population analyzed was within one; sample size met power analysis
Selective reporting (reporting bias)	Low risk	
Other bias	Unclear risk	Study funded by Meda Pharmaceuticals, Inc.

Carr, Bernstein, Lieberman, Meltzer, Bachert, Price, Munzel, Bousquet[12]

Methods	Randomized, double-blind, placebo-controlled, parallel-group trial, MP4006
Participants	**Setting:** not disclosed by meta-analyses (MA) authors **Number randomized:** $N = 1801$ (From supplemental study materials • Unable to determine participants randomized per study arm **Completed Study:** $N = 1791$ **Gender:** 38.7% male **Age, mean ± SD:** **Group 1:** 35.6 ± 14.5 **Group 2:** 34.2 ± 14.5 **Group 3:** 36.4 ± 14.8 **Group 4:** 34.7 ± 14.1 **Inclusion criteria:** • Males and females • 12 years and older with minimum 2 yearr history of moderate-to-severe seasonal allergic rhinitis (SAR) • SAR reflective total nasal symptom score (rTNSS) of at least 8 of 12, with a congestion score of 2 or 3 during screening • Significant current clinical rhinitis symptomatology • Positive skin prick test response to relevant pollen **Exclusion criteria:** • Erosion, ulceration, or septal perforation or another disease (such as sinusitis, rhinitis medicamentosa, polyposis, respiratory tract infection [within 14 days of screening]) • Asthma except intermittent asthma • Significant pulmonary disease • Symptomatic cardiac conditions • Taking concomitant medication that could interfere with the interpretation of study results **Power analysis:** 450 evaluable participants per treatment group
Interventions	The study comprised a 7-day, single-blind, placebo lead-in period and a 14-day treatment period with 3 study visits at days 1, 7, and 14. On visit 2 (day 1), eligible participants were randomized to 14 days of treatment (1 spray per nostril twice daily) with the following: **Group 1:** azelastine 0.1% + fluticasone (novel formulation of 137 μg of azelastine/50 μg of FP) **Group 2:** azelastine nasal spray (137 μg) **Group 3:** FP (50 μg) nasal spray **Group 4:** vehicle placebo nasal spray. Doses were separated by approximately 12 hours. Participants recorded application times and symptom scores in a diary.
Outcomes	**Primary outcome:** • Total Nasal Symptom Score (TNSS) ○ sum of the morning and evening overall change from baseline in 12-hour Total Nasal Symptom Score (TNSS) over the entire 14-day treatment period (sum of the individual nasal symptoms of congestion, itching, rhinorrhea, and sneezing) ○ All nasal and ocular symptoms were scored by participants twice daily on each treatment day according to a 4-point scale: ■ Score of 0 was defined as none (no symptoms present) ■ Score of 1 was defined as mild (mild symptoms that do not interfere with any activity) ■ Score of 2 was defined as moderate (slightly bothersome symptoms that slightly interfere with activity/nighttime sleep) ■ Score of 3 was defined as severe (bothersome symptoms that interfere with activity/nighttime sleep). ○ Therefore the maximum Total Nasal Symptom Score (TNSS) or instantaneous total nasal symptom score (iTNSS) was 24 (ie, 4 symptoms × score of 3 × 2 for morning + evening). • Adverse events
Notes	Smokers were not excluded from the study.

Risk of bias table

Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Randomized and balanced by study site in blocks of 4.
Allocation concealment (selection bias)	Low risk	A blind randomization code was maintained at a central site apart from the sponsor and study centers.
Blinding of participants and personnel (performance bias)	Low risk	Individual nasal spray bottles were identity masked such that both participants and study personnel were blind to treatment assignment. The active controls comprised the individual components of MP29-02 in the same vehicle, pump volume, and device. Study blinding was preserved at the study sites until all participants completed the study and the database had been locked.
Blinding of outcome assessment (detection bias)	High risk	Participants reflexively self-recorded outcomes every 12 hours in a diary
Incomplete outcome data (attrition bias)	High risk	Intention to treat analysis occurred. In supplemental study materials, the authors disclose the ITT population of $N = 1791$ which does not reflect the number of randomized participants $N = 1801$; sample size not met
Selective reporting (reporting bias)	Low risk	
Other bias	Unclear risk	Study funded by Meda Pharmaceuticals, Inc.

Hampel, Ratner, Van Bavel, Amar, Daftary, Wheeler, Sacks[13]

Methods	Randomized, double-blind, placebo-controlled, parallel-group trial
Participants	**Setting:** 6 investigational sites in Texas (not specified) during January and February 2007 **Number randomized:** $N = 610$ **Group 1:** $n = 153$ **Group 2:** $n = 152$ **Group 3:** $n = 151$ **Group 4:** $n = 151$ **Completed Study:** • 577 participants completed all 14 days of the study, authors report intention to treat analysis occurred based on $N = 607$ for efficacy analysis with the authors imputing the last observation carried forward and $N = 609$ for safety analysis **Gender:** 34.8 %male **Age in years, mean (range):** **Group 1:** 39.5 (12-73) **Group 2:** 39.5 (12-74) **Group 3:** 38.1 (12-74) **Group 4:** 39.9 (12-75) **Inclusion criteria:** • Males and females • ≥ 12 yrs and older with minimum 2 year history of allergy to Texas mountain cedar pollen confirmed by positive prick-puncture skin test within past 12 months • Participants were required to have a minimum total nasal symptom score (TNSS) severity score of 8 AND nasal congestion score of 2 or 3 on at least 3 separate symptom assessments to proceed to RCT. **Exclusion criteria:** • Receiving concomitant treatment that could interfere with interpretation of the study results (examples not given) • Presence of nasal mucosal erosion, • Nasal ulceration • Nasal septal perforation at screening or randomization, • Other nasal diseases likely to affect deposition of intranasal medication (sinusitis, rhinitis medicamentosa, clinically significant polyposis, or nasal structural abnormalities), • Nasal surgery or sinus surgery within previous year, or • More than 3 episodes per year of chronic sinusitis **Power analysis:** the authors do not disclose how many participants were needed to detect significance
Interventions	Placebo lead-in for five days was followed by 14-day double-blind treatment period in which qualified participants were randomized to one of 4 treatment groups: **Group 1:** Azelastine 0.1% + fluticasone, one spray per nostril twice daily for a daily total dosage of 548 μg of azelastine hydrochloride and 200 μg of fluticasone propionate **Group 2:** Azelastine 0.1%, one spray per nostril twice daily for a daily dosage total of 548 μg of azelastine hydrochloride **Group 3:** Fluticasone, one spray per nostril twice daily for a daily dosage total of 200 μg of fluticasone propionate **Group 4:** Azelastine-fluticasone vehicle placebo, one spray per nostril
Outcomes	**Primary Outcome:** • change in Total Nasal Symptom Score (TNSS) from Day 1 (baseline) to Day 14 (intent-to-treat; missing data imputed using last observation carried forward) ○ Individual symptoms of the Total Nasal Symptom Score (TNSS) were scored on a 4-point Likert scale (the maximum combined morning and evening TNSS was 24), where ■ 0 = no symptoms ■ 1 = mild symptoms ■ 2 = moderate symptoms ■ 3 = severe symptoms • For the Total Nasal Symptom Score (TNSS) the SD for placebo group was not provided by the authors therefore the methodologist is unable to build comparison tables for the following: ○ Azelastine + fluticasone versus Placebo ○ Fluticasone versus Placebo ○ Azelastine versus Placebo • For the Total Ocular Symptom Score (TOSS) ○ It is uncertain if the authors' use of imputed data observation is clinically useful as the methodologist is uncertain if symptoms worsen over time. ○ If a placebo subject's last observation was on day one of the intervention was five and they stopped documenting observations five would be used for the remainder of the study for this participant.
Notes	• **Adverse events were:** Dysgeusia, epistaxis, headache, pharyngolaryngeal pain, nasal discomfort, nausea

Risk of bias table

Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Computer generated randomization schedule
Allocation concealment (selection bias)	High risk	Authors did not disclose how allocation was concealed
Blinding of participants and personnel (performance bias)	Unclear risk	Double-blind, additional efforts to maintain blinding not discussed
Blinding of outcome assessment (detection bias)	High risk	Participants reflexively self-recorded outcomes every 12 hours in a diary
Incomplete outcome data (attrition bias)	High risk	Authors did not disclose how many participants were needed from the power analysis to detect significance; In supplemental study materials, the authors disclose the ITT population of $N = 607$ which does not reflect the number of randomized participants $N = 610$.
Selective reporting (reporting bias)	Low risk	
Other bias	Unclear risk	Study funded by Med Pointe Pharmaceuticals, Somerset, New Jersey

Meltzer, LaForce, Ratner, Price, Ginsberg, Carr[14]

Methods	Randomized, double-blind, placebo-controlled, parallel-group trial
Participants	**Setting:** Conducted during fall 2008 allergy season at 41 investigational sites distributed throughout the major geographic regions of the United States **Number randomized:** $N = 779$ **Group 1:** $n = 195$ **Group 2:** $n = 194$ **Group 3:** $n = 189$ **Group 4:** $n = 201$ **Number who completed study:** 739, however 776 had at least one postbaseline efficacy evaluation and were included for primary analysis (intent-to-treat); 778 for safety analysis **Age in years, mean (range):** **Group 1:** 38.8 (12-73) **Group 2:** 38.2 (12-77) **Group 3:** 37.0 (12-72) **Group 4:** 37.2 (12-68) **Gender:** 36% male **Inclusion criteria:**• Male and female participants • $\geq$ 12 years of age with moderate-to-severe SAR per Allergic Rhinitis and Its Impact on Asthma (ARIA) guidelines • Positive skin prick test to a local, prevalent, seasonal allergen within the past year • 12-hr Total Nasal Symptom Score (TNSS) of at least 8 at a minimum of three assessments during the lead-in period (day -7 to 1) **Exclusion criteria:**• Any evidence of mucosal erosion, ulceration, or septal perforation • Any clinically significant nasal disease or structural abnormality • Nasal or sinus surgery in the previous year • Pregnant or nursing women • Disease or medical condition that could interfere with interpretation of the trial results (examples not given) **Power analysis:** 195 evaluable participants per treatment group
Interventions	7 day single-blind placebo lead-in (1 spray each nostril twice daily); participants recorded rTNSS scores twice daily. Participants who met severity criteria (see inclusion) randomized to 2 week treatment period in one of four treatment groups: **Group 1:** Azelastine + fluticasone, one spray per nostril twice daily for a daily total dosage of 548 μg of azelastine hydrochloride and 200 μg of fluticasone propionate **Group 2:** Azelastine one spray per nostril twice daily for a daily dosage total of 548 μg of azelastine hydrochloride **Group 3:** Fluticasone, one spray per nostril twice daily for a daily dosage total of 200 μg of fluticasone propionate **Group 4:** Placebo nasal spray, one spray per nostril twice daily
Outcomes	**Primary Outcome:** change from baseline in 12-hr reflective total nasal symptom score (TNSS) **Secondary Outcomes:** (not included in analysis)• change from baseline in individual symptoms scores • onset of action • change from baseline in 12-hr Total Ocular Symptom Score (TOSS) • change from baseline in individual ocular symptom scores • change from baseline in the RQLQ
Notes	Standard deviation was not reported for any outcome data, therefore the RevMan calculator was used in the Total Nasal Symptom Score (TNSS) and Total Ocular Symptom Score (TOSS) outcome tables.

Risk of bias table

Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Computer generated randomization schedule (blocks of 4)
Allocation concealment (selection bias)	Low risk	Randomization data was kept confidential
Blinding of participants and personnel (performance bias)	Low risk	All treatments were administered in the same vehicle and in the same nasal spray delivery device; Blinding maintained for all researchers until all participants had completed the study and the database was locked
Blinding of outcome assessment (detection bias)	High risk	Participants reflexively self-recorded outcomes every 12 hours in a diary
Incomplete outcome data (attrition bias)	High risk	In supplemental study materials, the authors disclose the ITT population of $N = 776$ which does not reflect the number of randomized participants $N = 779$; low risk would have been attributed to this bias as the analysis population is very close to the ITT population; however, the authors did not meet needed sample size
Selective reporting (reporting bias)	Low risk	Expected outcomes reported
Other bias	Unclear risk	Study funded by a research grant from Meda Pharmaceuticals, Somerset, New Jersey Drs. Meltzer, La Force, Ratner, and Carr have consulted for and received research support from Meda Pharmaceuticals Inc., Dr. Price has consulted for Meda Pharma, Dr. Ginsberg is an employee of Meda Pharmaceuticals Inc.

Ratner, Hampel, Van Bavel, Amar, Daftary, Wheeler, Sacks[15]

Methods	Randomized, double-blind, placebo-controlled, parallel-group trial
Participants	**Setting:** 2 week, multicenter (5 study centers) trial conducted during the Texas mountain cedar season, December 27, 2005 - February 17, 2006 **Number randomized:** $N = 151$ Group 1: $n = 49$ Group 2: $n = 50$ Group 3: $n = 52$ **Completed study:** $N = 147$ Group 1: $n = 49$ Group 2: $n = 48$ Group 3: $n = 50$ **Age in years, mean (range):** **Group 1:** 38.4 (12-73) **Group 2:** 37.4 (12-72) **Group 3:** 36.0 (13-70) **Gender:** 56 Males, 95 Females (37% Male) **Inclusion Criteria:**• Minimum 2-year history of allergy to Texas mountain cedar pollen, confirmed by a positive allergy skin test within the past year. • Use of existing medications was discontinued at various times prior to the study based on elimination of the half-life of each drug before participants began the study. **Exclusion Criteria:** None noted **Power analysis:** the authors do not disclose how many participants were needed to detect significance
Interventions	**Group 1:** Azelastine nasal spray: Two sprays per nostril twice daily (1.1-mg azelastine), in the morning and evening with Placebo spray: once daily in the morning **Group 2:** Fluticasone nasal spray: Two sprays per nostril once daily (200-μg fluticasone), in the morning with placebo spray twice daily in the morning and evening **Group 3:** Azelastine nasal spray, 2 sprays per nostril twice daily (1.1-mg azelastine), in the morning and evening with Fluticasone nasal spray, 2 sprays per nostril once daily (200-μg fluticasone), in the morning
Outcomes	**Primary outcome:** • Total Nasal Symptom Score consisting of rhinorrhea, sneezing, itchy nose, and nasal congestion. Intention to treat (ITT) analyses performed on this outcome. • Adverse events **Secondary outcome: (not included in this analysis)** • Rhino conjunctivitis Quality of Life Questionnaire (RQLQ)
Notes	• Individual symptoms of the Total Nasal Symptom Score (TNSS) were scored on a 4-point scale, where 0 indicates no symptoms; 1, mild symptoms; 2, moderate symptoms; and 3, severe symptoms (such that the maximum combined morning and evening TNSS was 24).

Risk of bias table

Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Participants were randomized to treatment by a computer generated randomization schedule.
Allocation concealment (selection bias)	Low risk	Computer generated randomization schedule was accessible only to authorized persons who were not involved in the study
Blinding of participants and personnel (performance bias)	Low risk	The identity of the study medications were concealed through use of a device (Pharmask Inc, Medfield, Massachusetts) that prevented identification of the product but allowed for the proper administration of the nasal sprays.
Blinding of outcome assessment (detection bias)	High risk	Participants reflexively self-recorded outcomes every 12 hours in a diary
Incomplete outcome data (attrition bias)	High risk	In supplemental study materials, the authors disclose the ITT population of $N = 151$ which does not reflect the number of randomized participants $N = 147$; low risk would have been attributed to this bias as the analysis population is very close to the ITT population; however, the authors did not disclose the needed sample size therefore high risk was assigned.
Selective reporting (reporting bias)	Low risk	
Other bias	Unclear risk	Study funded by Med Pointe Pharmaceuticals

References

[1] Anolik R. Clinical benefits of combination treatment with mometasone furoate nasal spray and loratadine vs monotherapy with mometasone furoate in the treatment of seasonal allergic rhinitis. *Ann Allergy Asthma Immunol*. 2008;100(3):264–271.

[2] Barnes ML, Ward JH, Fardon TC, Lipworth BJ. Effects of levocetirizine as add-on therapy to fluticasone in seasonal allergic rhinitis. *Clin Exp Allergy*. 2006;36(5):676–684.

[3] Benincasa C, Lloyd RS. Evaluation of fluticasone propionate aqueous nasal spray taken alone and in combination with cetirizine in the prophylactic treatment of seasonal allergic rhinitis. *Drug Investigation*. 1994;8(4):225–233.

[4] Di Lorenzo G, Pacor ML, Pellitteri ME, et al. Randomized placebo-controlled trial comparing fluticasone aqueous nasal spray in mono-therapy, fluticasone plus cetirizine, fluticasone plus montelukast and cetirizine plus montelukast for seasonal allergic rhinitis. *Clin Exp Allergy*. 2004;34(2):259–267.

[5] Ratner PH, van Bavel JH, Martin BG, et al. A comparison of the efficacy of fluticasone propionate aqueous nasal spray and loratadine, alone and in combination, for the treatment of seasonal allergic rhinitis. *J Fam Pract*. 1998;47(2):118–125.

[6] Lu S, Malice MP, Dass SB, Reiss TF. Clinical studies of combination montelukast and loratadine in patients with seasonal allergic rhinitis. Study 1. *J Asthma*. 2009;46(9):878–883.

[7] Martin BG, Andrews CP, van Bavel JH, et al. Comparison of fluticasone propionate aqueous nasal spray and oral montelukast for the treatment of seasonal allergic rhinitis symptoms. *Ann Allergy Asthma Immunol*. 2006;96(6):851–857.

[8] Nathan RA, Yancey SW, Waitkus-Edwards K, et al. Fluticasone propionate nasal spray is superior to montelukast for allergic rhinitis while neither affects overall asthma control. *Chest*. 2005;128(4):1910–1920.

[9] Pullerits T, Praks L, Ristioja V, Lotvall J. Comparison of a nasal glucocorticoid, antileukotriene, and a combination of antileukotriene and antihistamine in the treatment of seasonal allergic rhinitis. *J Allergy Clin Immunol*. 2002;109(6):949–955.

[10] Ratner PH, Howland WC 3rd, Arastu R, et al. Fluticasone propionate aqueous nasal spray provided significantly greater improvement in daytime and nighttime nasal symptoms of seasonal allergic rhinitis compared with montelukast. *Ann Allergy Asthma Immunol*. 2003;90(5):536–542.

[11] Carr W, Bernstein J, Lieberman P, et al. A novel intranasal therapy of azelastine with fluticasone for the treatment of allergic rhinitis. Study MP4002. *J Allergy Clin Immunol*. 2012a;129(5):1282–1289.e1210.

[12] Carr W, Bernstein J, Lieberman P, et al. A novel intranasal therapy of azelastine with fluticasone for the treatment of allergic rhinitis. Study MP4006. *J Allergy Clin Immunol*. 2012b;129(5):1282–1289.e1210.

[13] Hampel FC, Ratner PH, Van Bavel J, et al. Double-blind, placebo-controlled study of azelastine and fluticasone in a single nasal spray delivery device. *Ann Allergy Asthma Immunol*. 2010;105(2):168–173.

[14] Meltzer EO, LaForce C, Ratner P, Price D, Ginsberg D, Carr W. MP29-02 (a novel intranasal formulation of azelastine hydrochloride and fluticasone propionate) in the treatment of seasonal allergic rhinitis: a randomized, double-blind, placebo-controlled trial of efficacy and safety. *Allergy Asthma Proc*. 2012;33(4):324–332.

[15] Ratner PH, Hampel F, Van Bavel J, et al. Combination therapy with azelastine hydrochloride nasal spray and fluticasone propionate nasal spray in the treatment of patients with seasonal allergic rhinitis. *Ann Allergy Asthma Immunol*. 2008;100(1):74–81.

[16] Schünemann H, Santesso N. *How to GRADE the Evidence*, http://training.cochrane.org/.

[17] Can D, Tanac R, Demir E, Gulen F, Veral A. Is the usage of intranasal glucocorticosteroids alone in allergic rhinitis sufficient? *Allergy Asthma Proc*. 2006;27(3):248–253.

[18] Modgill V, Badyal DK, Verghese A. Efficacy and safety of montelukast add-on therapy in allergic rhinitis. *Methods Find Exp Clin Pharmacol*. 2010;32(9):669–674.

[19] Brooks CD, Francom SF, Peel BG, Chene BL, Klott KA. Spectrum of sealsonal allergic rhinitis symptom relief with topical corticoid and oral antihistamine given singly or in combination. *American Journal of Rhinology*. 1996;10(3):193–199.

[20] Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines: 2. Framing the question and deciding on important outcomes. *J Clin Epidemiol*. 2011;64(4):395–400.

Appendix C

#	Query	Limiters/expanders	Last run via	Results
S9	S3 AND S6	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - Cochrane Central Register of Controlled Trials	2
S8	S3 AND S5	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - Cochrane Central Register of Controlled Trials	1
S7	S3 AND S4	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - Cochrane Central Register of Controlled Trials	0
S6	olopatadine or azelastine or intranasal antihistamine or nasal antihistamine	Limiters - Published Date: 20120701-20160631; MEDLINE Publication Type: Clinical Trial; Language: English Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - Cochrane Central Register of Controlled Trials	3
S5	leukotriene receptor antagonist or montelukast	Limiters - Published Date: 20120701-20160631; MEDLINE Publication Type: Clinical Trial; Language: English Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - Cochrane Central Register of Controlled Trials	7
S4	histamine antagonist or H1 histamine antagonist or antihistamine or nonsedating antihistamine or cetirizine or levocetirizine or loratadine or desloratadine or terfenadine or fexofenadine or brompheniramine or chlorpheniramine or carbinoxamine or dexchlorpheniramine or clemastine or diphenhydramine or doxylamine or triprolidine	Limiters - Published Date: 20120701-20160631; MEDLINE Publication Type: Clinical Trial; Language: English Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - Cochrane Central Register of Controlled Trials	26
S3	(intranasal steroid or intranasal corticosteroid or nasal steroid or nasal corticosteroid or budesonide or beclomethasone or ciclesonide or betamethasone or fluocinolone or flunisolide or fluticasone or mometasone or triamcinolone) AND (S1 AND S2)	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - Cochrane Central Register of Controlled Trials	18
S2	intranasal steroid or intranasal corticosteroid or nasal steroid or nasal corticosteroid or budesonide or beclomethasone or ciclesonide or betamethasone or fluocinolone or flunisolide or fluticasone or mometasone or triamcinolone	Limiters - Published Date: 20120701-20160631; MEDLINE Publication Type: Clinical Trial; Language: English Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - Cochrane Central Register of Controlled Trials	118
S1	allergic rhinitis or seasonal allergic rhinitis or perennial allergic rhinitis or hay fever	Limiters - Published Date: 20120701-20160631; MEDLINE Publication Type: Clinical Trial Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - Cochrane Central Register of Controlled Trials	66

Embase Session Results

No.	Query	Results
#11	**#5** AND **#8**	5
#10	**#5** AND **#7**	12
#9	**#5** AND **#6**	20
#8	**olopatadine** OR **azelastine** OR **intranasal** AND **antihistamine** OR **nasal** AND **antihistamine**	1,114
#7	**leukotriene** AND **receptor** AND **antagonist** OR **montelukast**	10,920
#6	**histamine** AND **antagonist** OR **h1** AND **histamine** AND **antagonist** OR **nonsedating** AND **antihistamine** OR **antihistamine** OR **cetirizine** OR **loratadine** OR **desloratadine** OR **terfenadine** OR **fexofenadine** OR **levocetirizine** OR **brompheniramine** OR **chlorpheniramine** OR **carbinoxamine** OR **dexchlorpheniramine** OR **clemastine** OR **diphenhydramine** OR **doxylamine** OR **triprolidine**	50,033
#5	**#3** AND **#4**	59
#4	**intranasal** AND **corticosteroid** OR **intranasal** AND **steroid** OR **nasal** AND **corticosteroid** OR **nasal** AND **steroid** OR **budesonide** OR **beclomethasone** OR **betamethasone** OR **ciclesonide** OR **fluocinolone** OR **flunisolide** OR **fluticasone** OR **mometasone** OR **triamcinolone**	77,830
#3	**#1** AND **'human'**/de AND (**'case control study'**/de OR **'cohort analysis'**/de OR **'controlled study'**/de OR **'cross-sectional study'**/de OR '**major clinical study**'/de OR '**meta analysis**'/de OR '**multicenter study**'/de OR '**phase 3 clinical trial (topic)**'/de OR '**prospective study**'/de OR **'randomized controlled trial'**/de OR **'randomized controlled trial (topic)'**/de)	482
#2	**#1** AND **'human'**/de	1,042
#1	**allergic** AND (**'rhinitis'**/exp OR **rhinitis**) OR **perennial** AND **allergic** AND (**'rhinitis'**/exp OR **rhinitis**) OR **seasonal** AND **allergic** AND ('**rhinitis**'/exp OR **rhinitis**) OR '**hay**'/exp OR **hay** AND (**'fever**'/exp OR **fever**) AND [2012-2016]/py	1,094

Appendix D. Quality Assessment of Bias of References for Questions 1, 2, and 3 (Updated February 5, 2017)

Study	Random Sequence Generation (Selection Bias)	Allocation Concealment (Selection Bias)	Blinding of Participants and Personnel (Performance Bias)	Blinding of Outcome Assessment (Detection Bias)	Incomplete Outcome Data (Attrition Bias)	Selection Reporting (Reporting Bias)	Other Bias
Anolik,[65] 2008	Low risk	Unclear risk, probably low A1	Low risk	Low risk	Low risk	Low risk	Unclear risk
Barnes et al,[66] 2006	Unclear risk BA1	Unclear risk BA2	Low risk	Unclear risk BA3	High risk BA4	Low risk	Unclear risk
Benincasa and Lloyd,[67] 1994	Low risk BE1	Low risk BE2	Low risk BE3	Low risk	Low risk BE4	Low risk	Unclear risk
Di Lorenzo et al,[68] 2004	Unclear risk D1	Unclear risk D2	Low risk	Low risk	Unclear risk D3	Low risk	Unclear risk
Ratner et al,[69] 1998	Unclear risk R1	Unclear risk R2	Unclear risk R3	Unclear risk R4	High risk R5	Low risk	Unclear risk
Overall	Unclear	Unclear risk	Low risk	Low	Unclear to moderate risk	Low risk	Unclear risk

Figure 1. Risk of Bias and Quality Assessment for Question 1 Studies[a,b].

[a]Conclusion: moderate risk of bias.

[b]A1, Separate randomization schedules were prepared for each center, and patients and investigators were masked to treatment identity. Letter sent to Dr Anolik, who responded that the data are not available; BA1, BA2, BA3, BA4, Letter send to Dr Barnes requesting additional information, but no reply was received; BE1, BE2, BE3, BE4, Dr Reginald Stuart Lloyd was contacted and responded to each question. His response to random sequence generation and to the process of allocation concealment assignment to treatment groups was as follows: The sequence has been generated using the StatDirect software. Randomization was performed in blocks of 5 by the pharmacist of Verona, who generates random assignment of treatment groups to randomization numbers. His response to blinding of participants and personnel was as follows: The pharmacist of University Hospital of Verona has prepared a specific set with the treatments in study. The investigators and patients were blinded to the contents of the sets. The pharmacist using commercially tablets of cetirizine (Zirtec, UCB, Milan, Italy) or tablets of montelukast (Singulair, Merck Sharp and Dome, Rome, Italy) or fluticasone propionate nasal aqueous spray (Flixonase, GlaxoSmithKline [GSK], Verona, Italy) or tablets of placebo or placebo of fluticasone propionate nasal aqueous spray prepared the sets. Regarding the placebo of fluticasone propionate nasal aqueous spray, the pharmacist used an empty bottle of fluticasone propionate prepared placebo of nasal spray using saline solution. In response to the issue of incomplete outcome data, Dr Lloyd provided detailed power size calculations with graphs for this process, using the method of Erdfelder E, Faul F, and Buchner A. GPOWER: a general power analysis program. *Behav Res Methods Instruments Computers.* 1996;28:1-11. The sample size calculated for each group to achieve a power of 1.0 was 20 subjects; D1, D2, D3, Letter sent to Dr Gabriele Di Lorenzo, who responded that all the data were with GSK and that he did not recall the details of the study. Given the fact that GSK had destroyed all the regulatory information for the Ratner 1998 study, it is highly unlikely that any regulatory information for the 1994 study exists at GSK; R1, R2, R3, R4, R5, Letter sent to Dr Ratner, who was able to contact GSK and trace down this study (protocol FLTA4006) but unfortunately the "regulatory binder box" had been destroyed.

Study	Random Sequence Generation (Selection Bias)	Allocation Concealment (Selection Bias)	Blinding of Participants and Personnel (Performance Bias)	Blinding of Outcome Assessment (Detection Bias)	Incomplete Outcome Data (Attrition Bias)	Selection Reporting (Reporting Bias)	Other Bias
Lu et al,[70] 2009	Low risk L1	Low risk L2	Low risk	Low risk	Low risk L3	Low risk	Unclear risk
Martin et al,[71] 2006	Unclear risk M1	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
Nathan et al,[72] 2005	Unclear risk N1	Unclear risk N1	Low risk	Low risk N2	Unclear risk N3	Low risk N4	Unclear risk
Pullerits et al,[73] 2002	Low risk	Low risk P1	Low risk	Low risk	Low risk P2	Low risk	Unclear risk
Ratner et al,[74] 2003	Low risk R1	Low risk R1	Low risk R1	Low risk	Low risk	Low risk	Unclear risk
Overall	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk

Figure 2. Risk of Bias for Question 2 Studies[a,b].

[a]Conclusion: low risk of bias.

[b]L1, Dr Lu was contacted and responded that random sequence generation was completed for study 1 and study 2. Eligible patients were randomly allocated in a double-blind, double-dummy manner to 1 of the 5 (study 1) or 4 (study 2) treatment groups according to a computer-generated, randomized, allocation schedule; L2, Dr Lu was contacted and responded that enrolled patients (and the investigator and study site staff) in both studies were not aware of the group to which the next enrolled patient would be allocated. Patients, caregivers, those recording outcomes, or data analysts were not aware of the arm to which patients were allocated; there was no adjudication of outcomes for either study; L3, Dr Lu was contacted and responded with the following detailed explanation: Study 1 was designed to have 150 patients in the montelukast plus loratadine group and 50 patients in the placebo group complete the study to have a 95% power to detect (α = .050, 2-sided test), a between-treatment difference of 0.27 score in the primary comparison of change from baseline in the primary end point of mean composite symptom score, assuming an SD of 0.45. The sample size for the primary comparison in study 1 was met: 168 patients in the montelukast plus loratadine group and 55 patients in the placebo group completed the study. In addition, the study was designed to have 100 patients complete the study in the loratadine and montelukast monotherapy groups and 150 patients in the beclomethasone group. For the secondary comparisons between montelukast plus loratadine and montelukast or loratadine monotherapy, this would allow the detection of a 0.17 score difference in change from baseline in composite symptom score with 80% power (SD, 0.45; α =0.050; 2-sided test). For the comparison between montelukast plus loratadine and beclomethasone, the length of the 95% confidence interval for the treatment difference was expected to be equal to 0.20 score. The sample size for the secondary comparisons in study 1 was met: 115 patients in the loratadine, 107 in the montelukast, and 172 patients in the beclomethasone groups completed the study. There was 1 subject (montelukast plus loratadine group) in study 1 who was lost to follow-up. Study 2 was designed to have 200 patients in the montelukast plus loratadine group and 150 patients in the loratadine group complete the study to have a 94% power to detect (α = 0.050, 2-sided test) a between-treatment difference of 0.20 score in the primary comparison of change from baseline in the primary end point of mean composite symptom score, assuming an SD of 0.52. The sample size for the primary comparison in study 2 was met: 207 patients in the montelukast plus loratadine group and 160 patients in the loratadine group completed the study. In addition, the study was designed to have 100 patients complete the study in the montelukast group and 50 patients in the placebo group. For the secondary comparisons between montelukast plus loratadine and montelukast monotherapy, this would allow the detection of a 0.20 difference in change from baseline in composite symptom score with 87% power. For the comparison between montelukast plus loratadine and placebo, this would allow the detection of a 0.30 difference in change from baseline in composite symptom score with 95% power (SD, 0.52). A total of 99 patients in the montelukast group and 52 patients in the placebo group completed the study. There was 1 subject (loratadine group) in study 2 who was lost to follow-up. The main efficacy analysis was based on the intention-to-treat (ITT) (all patients treated) principle. Because the primary end point of composite symptom score was analyzed based on change from baseline during the treatment period, patients were required to have a baseline and at least one postbaseline measurement. In addition, no missing values were imputed (eg, data points were not carried forward). Data collected during discontinuation visits (for patients discontinuing before study completion) and unscheduled visits during the treatment period were included in the analysis. In study 1, 1 patient in the loratadine group did not have any baseline data for the composite symptom score, and 2 patients (1 each in the montelukast and beclomethasone groups) did not have treatment period data; thus, these patients were not included in the ITT analysis in Table 2. The Joint Task Force on Practice Parameters (JTFPP) unanimously thought that there was a low risk for attrition bias; M1, Article indicated randomization but did not indicate the method. Dr Martin was contacted and responded that the authors did not have the data and did not recall the specifics of the study; N1, February 1, 2017, correspondence with Dr Oliver Keene (GlaxoSmithKline [GSK]) indicated that there was random sequence generation and allocation concealment: The report states that "Subjects were assigned to study treatment in accordance with the randomization schedule generated by GSK's Statistics and Programming group. Treatment kits were dispensed in sequential numerical order." Schedules from GSK's Statistics and Programming group are computer generated random sequences from a validated randomization system. Eligible subjects were randomized to receive one of the following double-blind treatments: (1) fluticasone propionate aqueous nasal spray, 200 μg/d plus placebo capsule daily; (2) montelukast, 10-mg capsule daily plus placebo aqueous nasal spray daily; and (3) placebo capsule daily plus placebo aqueous nasal spray daily. Matching placebo capsules were provided for montelukast capsules and matching placebo inhalers for fluticasone propionate aqueous nasal spray. Montelukast and matching placebo were supplied as hard gelatin capsules. The report also states the following: "Only in the case of an emergency, when knowledge of the investigational product was essential for the clinical management or welfare of the subject, did the investigator unblind a subject's treatment assignment. If the blind was broken for any reason, the investigator notified GSK immediately of the unblinding incident without revealing the subject's study treatment assignment. In addition, the investigator recorded the date and reason for revealing the blinded treatment assignment for that subject in the appropriate CRF"; N2, The methods rated the blinding of outcome assessment as high for asthma measurements but low for daytime total nasal symptom score (D-TNSS) in the quality assessment table; thus, for this rhinitis systematic review, this would be low risk. Furthermore, the scoring of D-TNSS and nighttime total nasal symptom score (N-TNSS) was well defined. D-TNSS was scored as 1 to 100 for each of the 4 symptoms for a total of 1 to 400. Overnight scores were different: 0 to 3 for overnight nasal symptoms related to stuffy nose, sleep difficulty attributable to nasal symptoms, and frequency of nighttime awakenings attributable to nasal symptoms for a N-TNSS from 0 to 9; N3, February 1, 2017, correspondence with Dr Oliver Keene (GSK) indicated that there was no attrition bias. The study report states that the ITT population included all subjects randomized to double-blind treatment and that analyses included all available data for these subjects. For the primary end point of mean change from baseline during weeks 1 and 2 (days 2 to 15) in subject-rated D-TNSS, a total of 9 of 863 patients (1%) had missing outcomes for this end point. By treatment group, this was 4 of 290 (1%) in the placebo group, 4 of 291 (1%) in the fluticasone group, and 1 of 282 (<1%) in the montelukast group. The published article also comments, "The most common reasons for study discontinuation were protocol violations and adverse events"; N4, The JTFPP unanimously agree that the US Food and Drug Administration accepted standard for evaluating efficacy is using the reflective TNSS or the reflective D-TNSS and that this would not constitute a high risk of bias. The methods

Study	Random Sequence Generation (Selection Bias)	Allocation Concealment (Selection Bias)	Blinding of Participants and Personnel (Performance Bias)	Blinding of Outcome Assessment (Detection Bias)	Incomplete Outcome Data (Attrition Bias)	Selection Reporting (Reporting Bias)	Other Bias
Carr et al,[78] 2012a	Low risk	Low risk	Low risk	Low risk C1	Low risk C2	Low risk	Unclear risk
Carr et al,[78] 2012b	Low risk	Low risk	Low risk	Low risk C3	Low risk C4	Low risk	Unclear risk
Hampel et al,[75] 2010	Low risk	Low risk H1	Unclear risk H2	Low risk H3	Low risk H4	Low risk	Unclear risk
Meltzer et al,[76] 2012	Low risk	Low risk	Low risk	Low risk M1	Low risk M2	Low risk	Unclear risk
Ratner et al,[77] 2008	Low risk	Low risk	Low risk	Low risk R1	Low risk R2	Low risk	Unclear risk
Overall	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk

Figure 3. Risk of Bias for Question 3 Studies[a,b].

[a]Conclusion: low risk of bias.

[b]C1, The blinding of outcome assessment is viewed to be low risk by the Joint Task Force on Practice Parameters (JTFPP) because the reflective total nasal symptom score (TNSS) is the US Food and Drug Administration preferred method of evaluating efficacy of rhinitis pharmaceutical products. The use of the reflective TNSS as the method of assessment should not be a factor that reduces the quality of an article; C2, The JTFPP does not consider there to be a significant risk of incomplete outcome data (attrition bias). The 2012a study by Carr et al[78] indicates that 832 participants were randomized and 831 completed the study; C3, same as C1; C4, the JTFPP does not consider there to be a significant risk of incomplete outcome data (attrition bias). The 2012b study by Carr et al[78] randomized 1801 individuals, but only 1791 completed the study. This is a 0.0055% dropout rate, which is excessively low; H1, Dr Hampel was contacted and indicated that a centralized research center was contacted each time a subject qualified for the study and this person was randomly assigned to one group; H2, Dr Hampel was contacted to provide more details on blinding because commercial products were used for this study. However, no further details were provided; H3, Same as C1; H4, The JTFPP does not consider there to be a significant risk for incomplete outcome data (attrition bias). The article by Hampel et al[75] indicates that 610 subjects were randomized, with the ITT being 607, indicating a very low dropout rate. Statistical significance was detected; M1, Same as C1; M2, The JTFPP does not consider there to be a significant risk for incomplete outcome data (attrition bias). In the study by Meltzer et al,[76] the authors stated before enrollment that the needed sample size per group was 195 subjects. Of the 4 arms, group 1 had 195; group 2, 194, group 3, 189; and group 4, 201. Thus, groups 2 and 3 failed to make the number. However, a total of 779 subjects were randomized, and the ITT (completed at least one baseline efficacy evaluation) was 776. This was a very low dropout rate, and statistical significance was detected. The heterogeneity and overall effect were favorable. Taking all these elements into account, there was not considered to be a high risk of bias; R1, Same as C1; R2, The JTFPP does not consider there to be a significant risk for incomplete outcome data (attrition bias). In the study by Ratner et al,[77] 151 subjects were randomized, 150 completed postbaseline diary data, and 147 completed the study. Reasons for withdrawal were clearly stated. Although the authors did not indicate within the article the needed sample size before subject enrollment, there was a low dropout rate, and statistical significance was reached.8

group thought that the reflective TNSS was not truly objective and considered it high risk of bias for selective reporting; P1, February 2, 2017, correspondence with Dr Pullerits indicated that there was allocation concealment; P2, February 2, 2017, correspondence with Dr Pullerits indicated that the attrition rate was 0. All patients enrolled completed the study; R1, February 2, 2017, correspondence with Oliver Keene (GSK) indicated that there was random sequence generation, allocation concealment, and blinding of participants and personnel. The study report states that "The treatment number was an identification number for the blinded study medication that came from a randomization schedule created by GSK." Schedules created by GSK are computer generated random sequences from a validated randomization system. Those enrolling patients were therefore not aware of the group to which the next enrolled patient would be allocated.7