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Number 54

Management of Allergic and Nonallergic Rhinitis

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Prepared by:
New England Medical Center Evidence-based Practice Center
Aidan Long, M.D., Primary Technical Expert
Caroline McFadden, M.D., Assistant Project Director
Deirdre DeVine, M. Litt., Project Manager
Priscilla Chew, M.P.H., Research Associate
Bruce Kupelnick, B.A., Research Associate
Joseph Lau, M.D., EPC Project Director
Investigators

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-Based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review prior to their release.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

We welcome written comments on this evidence report. They may be sent to: Director, Center for Practice and Technology Assessment, Agency for Healthcare Research and Quality, 6010 Executive Blvd., Suite 300, Rockville, MD 20852.

Carolyn M. Clancy, M.D.
Acting Director
Agency for Healthcare Research and Quality

Robert Graham, M.D., Director
Center for Practice and Technology Assessment
Agency for Healthcare Research and Quality

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Structured Abstract

Objectives. This report synthesizes the available evidence on the diagnosis of allergic and nonallergic rhinitis, the question of whether differentiating allergic from nonallergic rhinitis is important, the efficacy of treatments in nonallergic and allergic rhinitis, and how treatment of allergic rhinitis impacts the development of asthma or acute rhinosinusitis.

Search Strategy. Primary research articles and meta-analyses evaluated for this report were identified through a Medline search of English language literature published between 1966 and October 2000.

Selection Criteria. We included cross-sectional and prospective studies evaluating diagnostic methods in allergic and nonallergic rhinitis. We used randomized controlled trials to evaluate the efficacy of treatments. We looked for prospective studies that evaluated the relationship between allergic rhinitis and later development of asthma or acute rhinosinusitis.

Data Collection and Analysis. We reviewed 3,354 Medline titles, retrieved 228 articles, and included 88 randomized controlled trials and two prospective cohort studies in our report. Evidence tables of study features and results were produced for various treatment comparisons. Summary tables reported appraisal of the methodological quality of the studies, and summaries of their results.

Main Results. No prospective study explicitly attempted to differentiate allergic from nonallergic rhinitis. The minimum level of testing necessary to confirm or exclude a diagnosis of allergic rhinitis has not been established in the literature.

Pharmaceutical companies supported the majority of the treatment trials. Thirteen randomized controlled trials assessed the efficacy of medications for treatment of nonallergic rhinitis symptoms. Only one study examined the role of antihistamines and three studies examined the efficacy of nasal corticosteroids. Oral decongestants are effective in controlling the symptom of nasal congestion and ipratropium bromide is beneficial in the management of rhinorrhea. There is little published evidence for use of antihistamines or nasal corticosteroids for the management of nonallergic rhinitis. Overall, these treatment modalities were well tolerated and devoid of major side effects.

There were 73 randomized controlled trials on the treatment of allergic rhinitis. The majority of studies show a clear benefit on the use of intranasal corticosteroids over either sedating or nonsedating antihistamines for relief of symptoms of nasal allergy. With respect to symptom alleviation in seasonal and perennial allergic rhinitis, study results indicate no consistent differences between sedating and nonsedating antihistamines, though the side-effect profile favors nonsedating antihistamines. No randomized controlled trials were identified that compared immunotherapy with antihistamines or with nasal corticosteroids in the treatment of seasonal and/or perennial allergic rhinitis. Studies provide strong support for the beneficial effect of cromoglycate in the management of both seasonal and perennial allergic rhinitis. A majority of studies reported no serious adverse events associated with the use of antihistamines, cromolyn, or intranasal corticosteroids.

Two prospective cohort studies demonstrate an increased likelihood of developing asthma over time in patients with allergic rhinitis, though no study was identified which addressed the

question of whether treatment of allergic rhinitis can actually prevent the development of asthma. In addition, though the link between allergic rhinitis and rhinosinusitis is known, we identified no prospective studies on the outcomes of treated and untreated allergic rhinitis.

Conclusions. Beyond skin testing and diagnosis by exclusion, there is no literature on differentiating allergic from nonallergic rhinitis. The data concerning treatment of nonallergic rhinitis is scant and no single agent is identified as being uniformly effective in controlling all the symptoms associated with this condition. In allergic rhinitis treatment, nasal corticosteroids are superior to antihistamines and there is no consistent difference between sedating antihistamines and nonsedating antihistamines for the relief of nasal symptoms. The majority of studies reported no major adverse events associated with current treatments. There is insufficient evidence to address the relationship between allergic rhinitis and the development of asthma or rhinosinusitis.

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Summary

Introduction

Twenty to 40 million Americans are affected by allergic rhinitis, making it the sixth most prevalent chronic illness. The peak prevalence of allergic rhinitis is observed in children and young adults. Prevalence estimates range from 10 to 30 percent of adults and up to 40 percent of children, making allergic rhinitis currently the most common chronic condition found in children. Furthermore, in the past 30 years, there has been a dramatic increase in the prevalence of allergic rhinitis in "Westernized" societies; and studies from England, Sweden, and Australia have reported a doubling of prevalence over this time.

Allergic rhinitis is responsible for at least $1.8 billion annually for the direct cost of physician visits and medication expenses, or nearly 2.5 percent of the $47 billion annual direct cost for respiratory treatment in the United States. Moreover, the estimated value of lost productivity to employers and society resulting from allergic rhinitis approaches nearly $3.8 billion annually. In the mid-1990s the resulting total annual cost for allergic rhinitis amounted to $5.6 billion.

Rhinitis, in which the classification by etiology may be allergic or nonallergic, is a disorder characterized by inflammation of the mucous membranes lining the nasal passages. The symptoms of allergic rhinitis, which can be difficult to accurately distinguish from those of vasomotor rhinitis, typically include sneezing, nasal itch, rhinorrhea, nasal obstruction, post-nasal drip and occasionally nasal pain. Based on timing or periodicity of symptoms, allergic rhinitis may be classified as either seasonal or perennial.

The symptoms of allergic rhinitis result from exposure to allergens in a susceptible (sensitized) individual. Allergens include pollen, grass, weed, and house-dust mite etc., and symptoms are triggered by the interaction of an allergen with immunoglobulin E (IgE) molecules which bind through the high affinity IgE receptor to the surface of mast cells in the nasal mucosa or to circulating basophils. Recognition of the allergen by the IgE antibody leads to activation of the mast cell or basophil, causing the release of a variety of mediators, including histamine and leukotrienes, which in turn attract inflammatory cells from the peripheral circulation. This orchestrated chain of events results in the characteristic clinical features of allergic rhinitis.

Nonallergic rhinitis is characterized by sporadic or persistent perennial nasal symptoms that do not result from IgE-mediated immunopathologic events. The symptoms can be similar to allergic rhinitis, but with a less prominent nasal itch and conjunctival irritation. The distinction between allergic and nonallergic rhinitis can be difficult to distinguish clinically, but the distinction may be important for prognosis and treatment decisions.

Methods

The evidence report on the management of allergic rhinitis from which this summary is taken is based on a systematic review of the literature. The American Academy of Family Physicians served as the science partner on this report. The American College of Allergy, Asthma and Immunology and the American Academy of Allergy, Asthma and

Immunology also provided technical experts to work with the staff of the New England Medical Center Evidence-based Practice Center (EPC). Through a series of teleconferences, this panel of experts worked to identify specific issues and refine key questions central to this report, and they nominated peer reviewers who were not involved in the synthesis of evidence or in the writing of this report. The EPC then conducted a comprehensive search of the medical literature to identify studies addressing the key questions specified by the panel on the management of allergic rhinitis and nonallergic rhinitis.

With input from the science partners, the following questions were formulated:

Question 1. How does one diagnose allergic and nonallergic rhinitis (especially vasomotor)?

1.1 What differentiates allergic from nonallergic rhinitis with respect to symptoms, signs, physical examination, and diagnostic testing?

1.2 What is the minimum level of testing necessary to differentiate allergic from nonallergic rhinitis?

Question 2. Is differentiating allergic from nonallergic rhinitis important?

2.1 Are treatments different?

2.2 Are outcomes different?

Question 3. How does one treat nonallergic and allergic rhinitis?

3.1 For nonallergic rhinitis:

a) What is the efficacy of antihistamines (all classes), nasal corticosteroids, sympathomimetics, leukotriene modifiers, anticholinergics, or cromoglycate compared with placebo?

b) What are the side effects due to antihistamines, nasal corticosteroids, sympathomimetics, leukotriene modifiers, anticholinergics, or cromoglycate?

3.2 For allergic rhinitis:

a) What is the efficacy of antihistamines versus nasal corticosteroids, antihistamines versus immunotherapy (desensitization), nasal corticosteroids versus immunotherapy, sedating versus nonsedating antihistamines, other agents (cromolyn, leukotriene modifiers, sympathomimetics, ipratropium).

b) What are the side effects/adverse events due to antihistamines, nasal corticosteroids, sympathomimetics, or leukotriene modifiers?

3.3 Do efficacy and side effects of treatment vary by severity of rhinitis or patient characteristics?

Question 4. How does treatment of allergic rhinitis impact on the development of asthma?

4.1 What is the likelihood of developing asthma with untreated allergic rhinitis (natural history)?

4.2 How does treatment of allergic rhinitis affect the likelihood of developing asthma?

4.3 How does treatment of allergic rhinitis affect the likelihood of developing bacterial sinusitis?

Studies for the literature review were identified primarily through a MEDLINE® search of English language literature published between 1966 and October 2000. The investigators also consulted technical experts and examined references of published meta-analyses and selected review articles to identify additional studies. Articles that met the inclusion criteria were incorporated in the evidence report.

For this evidence report, the EPC compiled evidence tables of study features and results, appraised the study methods, and summarized results. If published meta-analyses were available on specific treatment topics, the effects of treatments evaluated in these reports were assessed.

Inclusion Criteria

The MEDLINE® search yielded 3,354 titles. The titles and abstracts of these citations were screened and 228 full-length articles were retrieved for further examination. Reports published only as abstracts in proceedings were rejected from further consideration. Specific inclusion criteria were developed for each of the key questions. Included for questions 1 and 2 were all cross-sectional and prospective studies evaluating diagnostic methods in allergic and nonallergic rhinitis including, but not limited to, allergen skin testing, serum IgE measurements, nasal provocation challenge, nasal rhinomanometry and nasal biopsy. Included for question 3 were randomized controlled trials of the following interventions in allergic rhinitis: antihistamines versus nasal corticosteroids, antihistamines versus immunotherapy, nasal corticosteroids versus immunotherapy, sedating versus nonsedating antihistamines, cromolyn sodium, anticholinergic agents, leukotriene modifers and sympathomimetics. Included in the treatment of nonallergic rhinitis were randomized controlled trials of antihistamines, nasal corticosteroids, sympathomimetic agents, leukotriene modifers, anticholinergics and cromoglycate. Included for question 4 were prospective studies evaluating the relationship between

allergic rhinitis and subsequent development of asthma or bacterial sinusitis.

Grading and Summarizing of the Evidence

The evidence-grading scheme used assessed four dimensions that are important for the interpretation of the evidence:

- Study size
- Applicability
- Summary of efficacy and safety outcomes
- Methodological quality

Reporting the Evidence

The evidence found for the management of allergic and nonallergic rhinitis is summarized in two complementary forms in the full evidence report: first, the evidence tables provide detailed information on key features of study design and results of all the studies reviewed; second, a narrative and tabular summary of the strength and quality of the evidence of each study is provided for each comparison.

Results

General Observations

In addition to the conclusions described in this summary, the investigators believe that the data support the following observations:

- Most of the clinical trials were supported by pharmaceutical companies.
- There were no studies that addressed the specific question of practical clinical interest: Is differentiating allergic rhinitis from nonallergic rhinitis important? Are treatments or outcomes different? Differentiation of allergic from nonallergic rhinitis is important if treatments are significantly different and if the outcomes of treatment including prevention of complications differ in response to those treatments. However, similar treatments are frequently employed in the two conditions.
- There were few trials in nonallergic rhinitis and their size was generally small. Thirteen trials conducted between 1982 and 1999 enrolled about 450 patients. In several comparisons of interest, there were only 20 to 30 patients in the trials. There were no studies that examined the efficacy of leukotriene modifiers. There were only two randomized controlled trials, with a total of 90 patients, that examined the role of oral decongestants in the relief of symptoms of nasal congestion.
- The trials were heterogeneous with respect to inclusion criteria, dosage regimens, study duration and reporting of results.
- The lack of reporting of data on variability of the outcome estimates made it difficult, if not impossible, to perform meta-analysis.
- Although almost all the studies analyzed were randomized controlled trials, many did not meet high standards for methodological quality.
- There were no specific studies of the pediatric population. Even though some studies may have enrolled patients in pediatric ranges, separate data were not reported for this subgroup. Therefore, no specific conclusions could be drawn for the pediatric population.

Specific Results

- No studies were found that specifically sought to differentiate between allergic and nonallergic rhinitis on the basis of clinical symptoms, signs on physical examination, or the presence or absence of comorbid conditions.
- The minimum level of testing necessary to confirm or exclude a diagnosis of allergic rhinitis has not been established in the literature. There were no studies addressing the question of minimum level of diagnostic testing necessary to differentiate between allergic and nonallergic rhinitis that met the inclusion criteria.
- No diagnostic test has been specifically developed to diagnose nonallergic rhinitis.
- Given the absence of studies to differentiate nonallergic rhinitis, diagnostic testing rather than symptoms or signs is necessary to differentiate isolated vasomotor or nonallergic rhinitis from allergic rhinitis. Only one small recent study suggests that total serum IgE may be as useful as specific allergy skin prick tests which, in turn, are more useful than radioallergosorbent testing (RAST) in confirming a diagnosis of allergic rhinitis.

Nonallergic Rhinitis: Efficacy of Treatment

- **Antihistamines (all classes) versus placebo:** Only one study which examined the role of antihistamines in the treatment of nonallergic rhinitis met the inclusion criteria. However, because the antihistamine used an ingredient in an antihistamine-decongestant combination product, the outcomes related to the

antihistamine component of this drug cannot be separately identified. The Food and Drug Administration (FDA) recently approved a nasal topical product – azelastine (an H1 antihistamine) – for the treatment of vasomotor rhinitis.

- **Nasal corticosteroids:** Two of three identified studies employed budesonide and the other used beclomethasone. One study indicated that the symptoms of nasal congestion were improved by budesonide without alteration in other symptoms of nonallergic rhinitis. In the other two studies, comparison was made between the nasal corticosteroid and nasal ipratropium bromide. One study favored the nasal corticosteroid but the other failed to differentiate between the two interventions on the basis of symptom relief. Intranasal corticosteroids have been recommended for long-term therapy in nonallergic rhinitis and the two are approved by the FDA.
- **Sympathomimetics versus placebo:** Only two randomized controlled studies were identified which examined the role of oral decongestants (phenylpropolamine) in treatment of nonallergic rhinitis. In both studies emphasis was placed on relief of symptoms of nasal congestion. However, the FDA has urged companies marketing phenylpropanolamine to voluntarily withdraw the drug from the market while the FDA initiated regulatory actions to mandate such withdrawals. The only currently available orally active decongestant, pseudoephedrine, was not identified in any clinical trial concerning management of nonallergic rhinitis.
- **Leukotriene modifiers versus placebo:** No studies were identified looking at the efficacy of leukotriene modifiers in the treatment of nonallergic rhinitis.
- **Anticholinergics versus placebo:** Each of these five trials studied intranasal ipratropium bromide and each study demonstrated the efficacy of ipratropium in reducing nose blowing frequency and rhinorrhea.
- **Cromoglycate versus placebo:** Two randomized controlled trials identified as looking at the effects of cromoglycate in nonallergic rhinitis recorded improvement in symptoms of rhinitis with active treatment compared to placebo.
- **Side effects/adverse effects:** There were no side effects or adverse events reported in the studies of antihistamines or nasal corticosteroids. There is a report on the suppressive effect of belcomethasone nasal spray on bone growth in children and all nasal steroid preparations in the United States now warn of this adverse event. In the two studies comparing cromoglycate, there were no significant adverse effects associated with its use. In only one of the two studies involving sympathomimetics were adverse events such as drowsiness, nausea and headache described. Significant side effects of nasal dryness and nasal irritation were recorded in three of the five studies looking at ipratropium.

Allergic Rhinitis: Efficacy of Treatment

- **Antihistamines vs. nasal corticosteroids:** One published systematic review reported that for six individual nasal symptoms studied, as well as for overall nasal symptoms, nasal corticosteroids produced significantly greater relief than did oral antihistamines. The search identified eight new studies that were not included in this meta-analysis. Seven of the studies favored intranasal corticosteroids over antihistamines both in respect to improvement in global nasal symptoms as well as in most individual nasal symptoms. One study showed better symptom improvement with cetirizine alone over fluticasone alone. Thus, the overwhelming majority of studies clearly favor the use of intranasal corticosteroids over either sedating or nonsedating antihistamines for relief of symptoms of nasal allergy. These results are true for both seasonal allergic rhinitis and perennial allergic rhinitis.
- **Antihistamines vs. immunotherapy:** No randomized controlled trials were identified directly comparing immunotherapy with antihistamines in the treatment of seasonal and/or perennial allergic rhinitis. Immunotherapy is generally considered as a long-term disease-modifying treatment measure requiring months to years of treatment, whereas antihistamines are most often used for immediate symptom relief. Therefore, direct comparisons with respect to effectiveness/efficacy are not likely to be undertaken.
- **Nasal corticosteroids versus immunotherapy:** No randomized controlled trials were identified which directly compared immunotherapy with intranasal corticosteroids in the treatment of seasonal and/or perennial allergic rhinitis.
- **Sedating versus nonsedating antihistamines:** With respect to symptom alleviation in seasonal and perennial allergic rhinitis, study results indicate no consistent benefit of sedating antihistamines over nonsedating antihistamines. However, the side-effect profile favors use of nonsedating antihistamines.
- **Other agents (cromolyn, leukotriene modifiers, sympathomimetics, ipratropium):** Studies provide strong support for the beneficial effect of cromoglycate in the management of both seasonal and perennial allergic

rhinitis. Two clinical trials were identified which looked at the effects of decongestant drugs in allergic rhinitis and suggest some benefit in relief of nasal congestion but not other symptoms. The trial of ipratropium showed no significant differences between dosages of ipratropium but there was significant reduction in rhinorrhea and postnasal drip.

- **Side effects/adverse events:** A majority of the studies reported no major adverse events associated with the use of antihistamines. In those studies where major adverse events were reported, somnolence, dry mouth, dizziness and headache were identified most frequently. These symptoms were seen almost exclusively with the sedating antihistamines. Epistaxis, headache and pharyngitis were the most frequently reported side effects of nasal corticosteroids. None of the studies reported systemic side effects from intranasal corticosteroids in the short-term treatment studies. There is a report on the suppressive effect of belcomethasone nasal spray on bone growth in children and all nasal steroid preparations in the United States now warn of this adverse event. No major adverse events were reported in studies of cromolyn; among the minor reported side effects were high frequency of nasal irritation, headache and nasal congestion.

Effect of Selected Variables on Efficacy and Side Effects

No data to address this question were found. There were no studies that categorized patients by disease severity or concurrent disease while addressing either efficacy or safety.

Likelihood of Developing Asthma With Untreated Allergic Rhinitis

Studies addressing the temporal relationship between onset of rhinitis symptoms and onset of asthma symptoms have revealed that a significant proportion of patients experience rhinitis symptoms in advance of the development of clinical symptoms of asthma. Two prospective cohort studies have been published which show an increased likelihood of patients with allergic rhinitis developing asthma over time.

Effect of Treatment of Allergic Rhinitis on the Likelihood of Developing Asthma

No study was identified which addressed the question of whether treatment of allergic rhinitis can actually prevent the development of asthma. The data, however, suggest a mechanistic linkage between these two diseases and the ability of nasal corticosteroids in treating allergic rhinitis to impact certain characteristics of asthma (e.g. seasonal increase in bronchial hyper-responsiveness).

Effect of Treatment of Allergic Rhinitis on the Likelihood of Developing Bacterial Sinusitis

The link between allergic rhinitis and rhinosinusitis is known. Cross-sectional studies have shown an increased prevalence of acute and chronic bacterial sinusitis among allergic rhinitis patients. Similarly, there is an increased prevalence of atopy and allergic rhinitis among patients with chronic bacterial sinusitis. However, in order to determine the effect of treatment of allergic rhinitis on the development of bacterial sinusitis, data from prospective studies on the outcomes of treated and untreated allergic rhinitis are needed. No such studies meeting these criteria were identified.

Future Research

More research on key clinical questions in allergic and nonallergic rhinitis should be funded by nonproprietorial sources. Almost every trial that reported funding sources was funded by a pharmaceutical company. These trials usually address issues of the drug of one company versus the drug of another company. Thus, important questions about optimal clinical management of patients are often not addressed or relevant clinical information is unavailable.

Better assessment of allergic and nonallergic rhinitis is required. The minimum amount of diagnostic testing required to differentiate between these two conditions remains uncertain. Research should be conducted to determine the type and panel size of inhalant aeroallergen skin testing and on RAST. Research on whether recommendation/implementation of standard measures to minimize exposure to indoor aeroallergens, such as house-dust mites, pet allergens and cockroaches, might be cost effective in the management of chronic rhinitis. Further research should be conducted to determine the effects of minimizing exposure to allergens, even in the absence of differentiation between allergic and nonallergic rhinitis and even without determining a patient's precise allergic sensitivities.

Additional studies are needed to address other specific questions:

- The role of antihistamines for symptom relief in nonallergic rhinitis.
- The role of nasal corticosteroids in nonallergic rhinitis. If it can be rigorously documented that nasal corticosteroids are helpful to treat nonallergic rhinitis, the need to differentiate from nonallergic rhinitis may be lessened.
- The role of antihistamines in nonallergic rhinitis with eosinophilia syndrome (NARES).
- The role of cromoglycate use in nonallergic rhinitis.

- The role of allergen avoidance in patients with allergic rhinitis. Would this approach obviate the need for diagnostic testing in a substantial proportion of patients?
- The efficacy of a myriad of complementary therapies now being employed in the treatment of nonallergic rhinitis.
- Whether interventions for allergic rhinitis have preventive effects on asthma.

Higher quality studies and more studies for multiple but standardized research variables are needed. Standards for clinical trials in allergic and nonallergic rhinitis must adhere to those for clinical trials in general. After the FDA approval of a drug, additional high-quality trials of rhinitis relief are still needed to understand the optimal use of the drug in specific populations and settings. The trials should enroll greater numbers of patients for longer intervals than has generally been true in the past; apply blinding and "active" placebos when appropriate or uniform control treatments otherwise; and employ adequate between-arm washout intervals, and assess side effects.

A major limitation of the data identified in this analysis is the heterogeneity of inclusion and exclusion criteria, diagnostic tests, outcome measures, and circumstances of testing found in the randomized controlled trials. This situation makes synthesizing the research results confusing and difficult. Reducing this heterogeneity by implementing a set of standard research variables would greatly assist when comparing studies. The characteristics of patients enrolled in studies also need to be clearly defined. This is critical to ensure internal validity and to allow for study comparisons, data analyses, and in the application of the results to clinical practice. Standardization of research variables would also aid in identifying the best strategies for identifying patients with allergic or nonallergic rhinitis.

Ordering Information

The full evidence report from which this summary is taken was prepared for AHRQ by the New England Medical Center Evidence-based Practice Center, Boston, MA, under contract No. 290-97-0019. It is expected to be available in late spring 2002. At that time, printed copies may be obtained free of charge from the AHRQ Publications Clearinghouse by calling 800-358-9295. Requesters should ask for Evidence Report/Technology Assessment No. 54, *Management of Allergic and Nonallergic Rhinitis*. Internet users will be able to access the report online through AHRQ's Web site at www.ahrq.gov.

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Evidence Report

Chapter 1. Introduction

Goal of the Report

This report summarizes the scientific evidence for diagnosing and treating allergic and nonallergic rhinitis. This topic was selected by the Agency for Healthcare Research and Quality in response to a request from the American Academy of Family Physicians. The report provides summaries of evidence for use by different groups, including primary care practitioners, specialists, researchers, policy decision makers, and health care financiers. Recognizing the different interests and approaches of these groups, this report focuses on the diagnosis and treatment of allergic and nonallergic rhinitis in the primary care, clinical practice setting. We sought evidence on diagnostic methods that can help differentiate between allergic from nonallergic rhinitis. We summarize the evidence on the efficacy of treatments for these conditions.

Scope of the Problem

Prevalence of Allergic Rhinitis

Twenty to forty million Americans are affected by allergic rhinitis (Dykewicz, Fineman, Skoner, et al., 1998) making it the sixth most prevalent chronic illness (Collins, 1997). The peak prevalence of allergic rhinitis is observed in children and young adults. Estimates range from 10 to 30 percent of adults and up to 40 percent of children suffer with this condition, making allergic rhinitis currently the most common chronic condition found in children (Fireman, 2000). In the past 30 years there has been a dramatic increase in the prevalence of allergic rhinitis in "Westernized" societies, and studies from England, Sweden, and Australia have confirmed a doubling of prevalence over this time (Aberg, 1989; Aberg, Hesselmar, Aberg, et al., 1995; Hopper, Jenkins, Carlin, et al., 1995).

Despite the high prevalence of the disease, there is still insufficient epidemiologic data. Population surveys frequently have relied on physician-diagnosed rhinitis for primary data, which might underestimate the true prevalence of rhinitis (Aberg, 1989; Aberg, Hesselmar, Aberg, et al., 1995; Fleming and Crombie, 1987; Hopper, Jenkins, Carlin, et al., 1995). While population studies have been regularly performed by directly administered questionnaires, followed by telephone contact, which probably provide more accurate information, this approach probably still underrates the true prevalence of disease (Dykewicz, Fineman, Skoner, et al., 1998). In addition, most epidemiological studies have been directed towards estimating the prevalence of seasonal rhinitis because perennial allergies are more difficult to identify since its symptom complex overlaps with chronic sinusitis, recurrent upper respiratory infections, and vasomotor rhinitis (Dykewicz, Fineman, Skoner, et al., 1998).

Biology of Disease, Natural History

Rhinitis encompasses a group of disorders affecting the mucous membranes lining the nasal passages. Typical symptoms of rhinitis include sneezing episodes, nasal itching, rhinorrhea, nasal obstruction, postnasal dripping and occasionally nasal pain. Based on timing or periodicity of symptoms, allergic rhinitis may be classified as either seasonal or perennial. Rhinitis is also classified under etiology as either allergic or nonallergic (Ng, Warlow, Chrishanthan, et al., 2000).

The symptoms of allergic rhinitis result from exposure to allergens in a susceptible (sensitized) individual (Kay, 2001). Allergens include pollen, grass, tree, weed, house-dust mite etc., and symptoms are triggered by the interaction of an allergen with IgE molecules bound, through the high affinity IgE receptor, to the surface of mast cells in the nasal mucosa or circulating basophils. Recognition of the allergen by the IgE antibody leads to activation of the mast cell or basophil causing the release of preformed granule-associated mediators (including histamine), membrane derived lipid mediators (including leukotrienes), as well as cytokines and chemokines which are responsible for attracting inflammatory cells from the peripheral circulation to the site of degranulation. This orchestrated chain of events results in the characteristic clinical features of allergic rhinitis (Fireman, 2000; Kay, 2001). Clinically, allergic rhinitis may be associated with "early phase" symptoms occurring within minutes of allergen exposure (due to the release of preformed mediators) and "late phase" symptoms, seen at 4-8 hours after exposure due to synthesis of newly formed mediators and infiltration of inflammatory white blood cells from the circulation (Bellanti and Wallerstedt, 2000; Skoner, 2001). Nasal itching is a prominent symptom during the early phase; sneezing, congestion and rhinorrhea are seen in both early and late phases, but nasal congestion dominates the late phase reaction.

Genetic factors probably play an important role in the development of allergic rhinitis (Fireman, 2000). It has been suggested that if both parents are atopic, chances of allergic disease risk in the offspring are 50 percent or higher, a number that increases to 72 percent if parents are afflicted with the same atopic disease (Fireman, 2000). While the precise details of the determinants of allergic sensitization and subsequent development of clinical symptoms remain poorly understood, the paradigm in modern allergy teaching is that the tendency to develop atopic disease is a heritable one but that the specific allergic sensitivities exhibited by an individual relate to specific allergen exposures.

Nonallergic rhinitis is characterized by sporadic or persistent perennial nasal symptoms that do not result from IgE-mediated immunopathologic events (Dykewicz, Fineman, Skoner, et al., 1998). The diagnosis of non-allergic rhinitis is frequently a diagnosis of exclusion when an allergic etiology can be substantiated by diagnostic testing. There is no universally accepted classification of non-allergic rhinitis. The symptoms can be similar to allergic rhinitis, but with a decrease in the amount of nasal itch and in the number of sneezing episodes and conjunctival complaints (Jones, 1988; Settipane and Lieberman, 2001). Examples of nonallergic rhinitis include infectious rhinitis, vasomotor rhinitis (noninfectious) and nonallergic rhinitis with eosinophilia syndrome (NARES), overuse of topical-adrenergic agonists/nasal decongestants (rhinitis medicamentosa) and structural or anatomic abnormalities in the nose (including septal deviation or nasal polyposis). Other less common causes of this problem include: endocrine changes of hypothyroid and hyperthyroid disease, pregnancy or damage to sympathetic nerves (Dykewicz, Fineman, Skoner, et al., 1998). Nonallergic rhinitis with eosinophilia is characterized by the presence of nasal eosinophilia without evidence of allergic sensitization. Typical symptoms include perennial symptoms of sneezing, nasal itching, rhinorhoea, nasal obstruction and occasionally loss of sense of smell. It has been associated with non-specifc bronchial hyper-reactivity (Teodoro, Pelucchi, Mastropasqua et al.). It has been suggested that NARES may be linked to aspirin sensitivity (Moneret-Vautrin, Hsieh, Wayoff et al.). The distinction between allergic and nonallergic rhinitis can be difficult clinically. The presence of concurrent symptoms in the eyes or upper respiratory tract such as ocular itching, scratchiness, tearing or redness, palatal itching, or asthma symptoms such as coughing, chest tightness, wheezing and shortness of breath are more likely to suggest allergic rhinitis. The presence of comorbid conditions, such as allergic eczema or asthma, also point toward a diagnosis

of allergic rhinitis. Recognition by the patient of trigger factors for symptoms, such as exposure to dusty environments, exposure to cats, dogs or other domestic animals, association of the symptoms with specific seasons, especially spring (tree and grass pollens) or fall (ragweed pollens), all point towards an allergic etiology. In contrast, the symptoms of vasomotor rhinitis are often exacerbated by exposure to nonspecific irritants (non-allergens) such as strong odors, fragrances, perfumes or other volatile chemicals such as exhaust fumes, cigarette smoke or solvents, or by exposure to changes in air temperature or humidity. Additionally, symptoms such as fever, sore throat, generalized malaise or achiness, might point to infectious causes of the rhinitic symptoms (Jones, 1988; Settipane and Lieberman, 2001). While no formal diagnostic criteria have been formulated for distinguishing allergic from vasomotor rhinitis, detailed history taking plays a crucial role in diagnosis.

The exact prevalence of nonallergic rhinitis is not known but estimates indicate that up to 50 percent of patients with rhinitis actually have nonallergic causes (Jones, 1988). Vasomotor rhinitis is more likely to affect adults, and it is more prevalent in women (Settipane and Lieberman, 2001).

Burden of Illness

In addition to the physical symptoms of allergic rhinitis, such as sneezing, rhinorrhea, nasal pruritus, sufferers from allergic rhinitis also experience symptoms such as significant fatigue, headache, and cognitive impairment. These symptoms in turn are often associated with psychosocial problems, ranging from public embarrassment and diminished physical and emotional well being due to lack of sleep and diminished participation in recreational activities. All told, this can have negative effects on their physical, psychological, and social aspects of their lives significantly because of continued symptoms of allergic rhinitis (Thompson, Juniper, and Meltzer, 2000). Accordingly, the human cost of rhinitis (allergic and nonallergic) is assessed in terms of symptoms, medication needs, interference with sleep, and activities of daily living, work impairment, absences from work and school, impaired learning efficiency, and interference with social commerce.

In a recent pooled analysis of two parallel health outcomes (Tanner, Reilly, Meltzer, et al., 1999) 70 percent of 1,948 patients with moderate-to-severe allergic rhinitis reported embarrassment and/or frustration with allergy symptoms. More that 90 percent believed that their ability to perform daily activities was impaired by allergies, and also reported that their work or classroom performance was negatively affected.

The comorbidities that complicate undertreated allergic rhinitis, typically including asthma, sinusitis and otitis media, add further to the economic and psychosocial burden of disease (Spector, 1997).

Estimated Costs of Health Care: Individual and Societal

Allergic rhinitis is responsible for at least $1.8 billion annually for the direct cost of physician visits and medication expenses (McMenamin, 1994), or nearly 2.5 percent of the $47 billion annual direct cost for respiratory treatment in the United States (Levit, Lazenby, Cowan, et al., 1991; McMenamin, 1994; Rice, Hodgson, and Kopstein, 1985). Furthermore, nearly $3.8 billion was the estimated value of lost productivity to employers and society resulting from allergic rhinitis (Ross, 1996). In the mid-1990s the resulting total annual cost for allergic rhinitis amounted to $5.6 billion.

Retail sales of over-the-counter allergy relief products exceed $140 billion per year, yet only about 12 percent of those affected seek treatment from a doctor, implying that all the other allergic

rhinitis sufferers probably self-treat. Because of the significant cost of treatment, it is important that a good method exists for determining resource allocation.

Defining Allergic Rhinitis

Allergic rhinitis is defined as the clinical expression of tissue changes in the upper airway and adjacent structures following interactions of IgE and specific allergens, characterized by the symptoms of nasal congestion, rhinorrhea, postnasal drainage, sneezing, nasal itching, and occasionally impaired sense of smell (and taste). Allergic rhinitis can be seasonal, usually indicative of pollen-allergen sensitivity, or it can be year-round, frequently related to sensitivity to perennial, indoor aeroallergens. Nonallergic rhinitis is characterized by chronic nasal symptoms, often identical to those of allergic rhinitis but without allergic causation. Nonallergic rhinitis is distinguished by the lack of identifiable triggers in the patient's history, making detailed history taking essential.

Diagnosing Patients with Allergic Rhinitis

The typical findings on physical examination in the patient with allergic rhinitis include pallor of the nasal mucous membranes, which are often engorged. In addition, they often have a bluish tint and frequently exhibit clear watery secretions. There is often enlargement of the inferior turbinates visible by anterior rhinoscopy. The identification of venous engorgement in the infraorbital tissues (allergic shiners), erythema of the conjunctivae, scleral injection, especially when bilateral, adds further evidence to suggest an allergic etiology for the nasal findings.

Absences of fever, oropharyngeal erythema or exudate, or lymphadenopathy in the cervical or submental areas also imply a diagnosis of allergic rhinitis. A history of allergy or atopy in first-degree relatives is also likely to be helpful in forming an opinion as to whether allergic rhinitis is the etiology of the nasal symptoms.

Documenting the presence of IgE antibodies against known aeroallergens substantiates the diagnosis of allergic rhinitis. This can be accomplished either by allergy skin testing with representative aeroallergens or by radioallergosorbent testing (RAST). Skin testing identifies the presence of allergen specific IgE antibodies on tissue bound mast cells in the skin, whereas RAST measures these same antibodies circulating in peripheral blood. In clinical practice, skin testing is generally preferred over RAST testing. Several methods of skin testing are available. Prick - puncture skin tests are considered the most reliable as they show a high degree of correlation with clinical symptoms and provocative allergen challenges. Scratch tests have been shown to be associated with poor reproducibility and possible systemic reactions. They are infrequently used. Intradermal tests, which employ a weak allergen solution, are more sensitive than prick-puncture tests. They can induce false positive reactions (Reid, Lockey, Turkeltaub, et al., 1993) and overall tend to correlate less well with symptoms (Dreborg, Backman, Basomba, et al., 1989). It has been suggested that the availability of standardized extracts may obviate the necessity for intradermal tests (Demoly and Bousquet, 1998; Nelson, Oppenheimer, Buchmeier, et al., 1996; Wood, Phipatanakul, Hamilton, et al., 1999). RAST testing in general correlates closely with the results of skin testing but has a higher cost than does skin testing. RAST tests can yield quantitative results but the titre of specifc IgE measured is frequently not correlated to clinical symptoms.

Because nasal symptoms that occur in nonallergic rhinitis are often indistinguishable from perennial allergic rhinitis, nonallergic rhinitis is often diagnosed by excluding allergic disease by an absence of positive allergy skin tests or negative results by RAST. The use of nasal cytology to evaluate mucosal cellular patterns has the potential to distinguish inflammatory from non-inflammatory nasal conditions, following the course of disease and response to treatment. There is evidence that nasal biopsy is superior to nasal smear for finding eosinophils (Ingels, Durdurez, Cuvelier, et al., 1997)

Rationale for Differentiating Allergic from Nonallergic Rhinitis

Antihistamines are an integral component in the treatment of allergic rhinitis, but they are unlikely to be effective in nonallergic rhinitis. In addition, there is increasing support for the position that the primary therapy in confirmed allergic rhinitis should be anti-inflammatory rather than symptomatic. Treating the allergic inflammation has been shown to significantly decrease all the symptoms of allergic rhinitis, not just those mediated by histamine, and also to significantly diminish the complications such as sinusitis and otitis media that frequently occur in patients with allergic rhinitis (Dykewicz and Fineman, 1998).

In contrast, anti-inflammatory therapies such as intranasally applied corticosteroids are often not helpful in other forms of chronic rhinitis such as vasomotor rhinitis where treatment often ends being merely symptomatic in nature. For example, when the dominant symptom is nasal congestion, oral decongestants are recommended, and when the dominant symptom is rhinorrhea, drying agents such as topical ipratropium bromide are more useful. Thus, from a theoretical standpoint, there would indeed appear to be important, therapeutic benefit in distinguishing allergic from nonallergic rhinitis.

Issues in Management of Allergic Rhinitis

Current Therapies in Allergic Rhinitis

Evaluation of the therapies used in allergic rhinitis and nonallergic rhinitis might reasonably include assessments of symptom relief, use of as-needed medications, numbers of days lost from work and school, and estimates of "quality of life." Recent examples of Health-Related Quality of Life questionnaires (HRQOL) used in studies of rhinitis are the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ), the Rhinitis Outcomes Monitoring System (ROMS), and the Work Productivity and Activity Impairment (WPAI) survey (Meltzer, 2001).

Environmental control measures to decrease exposure to inciting factors, e.g. allergens, irritants and irritant medications, are considered fundamental to the management of rhinitis (Dykewicz, Fineman, Skoner, et al., 1998). While the established treatment modalities of allergic rhinitis consist of allergen avoidance, anti-allergic medication and immunotherapy (desensitization) for specific allergens, avoidance of exposure to identified aeroallergens is the primary long-term therapeutic modality (Corren, 2000). There now exists sufficient clinical and experimental evidence that such measures are effective and result not only in the diminution of symptoms, but also significantly lessen medication needs as well as decrease associated morbidity from the complications of allergic rhinitis (Woodcock and Custovic, 2000). Allergen avoidance measures, such as removal of feather pillows and down comforters, and encasing mattresses in dust-proof covers to decrease dust-mite exposures as well as elimination of carpeting in favor of tile or hardwood floors and high-flow air filtration units like a HEPA cleaner are all recommended strategies for those with perennial symptoms due to indoor allergens (Arlian and Platts-Mills, 2001;

Corren, 2000; Woodcock and Custovic, 2000). Similarly, decreasing exposure in sensitized individuals to domestic animals, especially cats and dogs, has demonstrated efficacy (Chapman and Wood, 2001).

In contrast, outdoor allergens are somewhat more difficult to avoid completely, and recommended measures are to stay indoors and keep windows closed, particularly during periods of the day when certain airborne allergens are at their highest concentration (Corren, 2000).

Current pharmacological treatments for allergic rhinitis include antihistamines (oral and more recently intranasal antihistamines), decongestants (oral and to a lesser extent intra-nasal), and intra-nasally applied anticholinergic agents, all of which are used for symptom relief in rhinitis. Topical nasal corticosteroids and immunotherapy are also useful in suppressing allergic inflammation (Thompson, Juniper, and Meltzer, 2000).

Antihistamines, the most frequently prescribed medication for allergic rhinitis, are usually administered on an intermittent basis for patients with the mildest symptoms. They reduce symptoms of itching, sneezing, and rhinorrhea. Oral antihistamines, which act by competitively inhibiting the binding of histamine to H1 receptors, have arbitrarily been subdivided into first and second-generation categories. Second generation H1 receptor antagonists, such as loratadine, fexofenadine and cetirizine, are less sedating and more pharmacologically selective than earlier antihistamines. In addition, some H1 receptor antagonists have also been reported to inhibit allergen-induced infiltration of tissue by eosinophils, or to actually inhibit release of the mediators, histamine or prostaglandins. These effects are as yet of undetermined clinical relevance and apparently independent of their effects on histamine receptors (Corren, 2000; Kay, 2001; Meltzer, 1995; Nightingale, 1996).

Decongestants, which are sold in either oral or topical form, are often used in combination with antihistamines (Corren, 2000; Meltzer, 1995) and the ineffectiveness of oral antihistamines in relieving nasal obstruction has prompted the subsequent manufacture of agents combining antihistamines and decongestants. By themselves, decongestants help to reduce nasal congestion by their vasoconstrictor properties. Topically applied vasoconstrictor sympathomimetic agents, such as phenylephrine, or imidazoline derivatives, such as oxymetazoline, are effective in inducing nasal capacitance vessel vascular constriction through activation of alpha-adrenergic receptors. Vasoconstriction (nasal decongestion) occurs within five to 10 minutes and may last for six to eight hours with oxymetazoline. These agents are effective for short term use (for example, to assist in physical examination, or to use before air travel, or during the early stages of nasal infections or perhaps during the initiation of treatment with nasal corticosteroids (Beckman and Grammer, 1999; Dykewicz, Fineman, Skoner, et al., 1998; Howarth, 1989; Lund, 1996; Meltzer, 1995).

Oral decongestants (also vasoconstricting agents) include phenylephrine and pseudoephedrine and phenylpropanolamine (The FDA has urged companies marketing phenylpropanolamine to voluntarily withdraw the drug from the market while it initiated regulatory actions to mandate such withdrawals). They cause vasoconstriction by activation of alpha-adrenergic receptors and by indirectly stimulating release of norepinephrine from its storage sites. Although these agents decrease nasal resistance to a lesser degree than do topical agents, their long-term use is somewhat safer because they lack the "rebound" vasodilatation that has been associated with the topical vasoconstrictors. Nasal decongestion occurs within 30 minutes and persists for six to eight hours with oral pseudoephedrine at a dose of 60 mg. Decongestion may last for eight to 12 hours with extended release preparations (Beckman and Grammer, 1999; Dykewicz, Fineman, Skoner, et al., 1998; Howarth, 1989; Lund, 1996; Meltzer, 1995).

Increased cholinergic activity from parasympathetic stimulation is documented in allergic and nonallergic (including infectious) rhinitis (Druce, Wright, Kossoff, et al., 1985; Raphael, Baraniuk, and Kaliner, 1991; White, 1995) resulting in increased nasal secretions and congestion. Anticholinergic medications can cause a reduction in the volume of nasal secretions and some degree of vasoconstriction. Ipratroprium bromide, available as a nasal spray, is a quaternary derivative of isopropyl noratropine and is poorly absorbed by the nasal mucosa and does not cross the blood brain barrier. It has been demonstrated to be effective in reducing rhinorrhea in adults and children with both allergic and nonallergic rhinitis (Bronsky, Druce, Findlay, et al., 1995; Druce, Spector, Fireman, et al., 1992; Georgitis, Banov, Boggs, et al., 1994; Grossman, Banov, Boggs, et al., 1995; Meltzer, 1995; Meltzer, Orgel, Bronsky, et al., 1992).

Intranasal corticosteroids, and to a significantly lesser degree, cromolyn sodium, are anti-inflammatory medications that have been proven effective in treating patients with more pronounced or protracted allergic rhinitis (Weiner, Abramson, and Puy, 1998). The corticosteroids inhibit many of the steps in the cascade of allergic inflammation in allergic rhinitis and are documented to provide excellent symptom relief for all the symptoms of allergic rhinitis, including nasal congestion and blockage (Mygind, Nielsen, Hoffmann, et al., 2001). This has resulted in superior efficacy assessments for intranasal corticosteroids when compared to oral antihistamines in the treatment of allergic rhinitis (Weiner, Abramson, and Puy, 1998). Many formulations of intranasal corticosteroids are currently available. Examples include Nasonex (mometasone furoate), Flonase (fluticasone propionate), Rhinocort (budesonide), Beconase and Vancenase (beclomethasone diproprionate), Nasacort (triamcinolone acetonide), Nasarel and Nasalide (fluniolide) (Allen, 2000; Corren, 1999). The onset of action varies but it is believed that all require three to seven days for optimal effect. There are differences in estimated potency and systemic bioavailablity between the different agents, which might alter the long-term safety profile, but clear differences in clinical efficacy have not been established (Allen, 2000; Corren, 1999). Prophylactic use with initiation of use two weeks in advance of seasonal pollen symptoms has been proposed for maximal symptom reduction. The corticosteroids can inhibit inflammatory responses whether the inciting agent is allergic, chemical or infectious, and there is documented clinical efficacy of these agents in both allergic rhinitis and nonallergic rhinitis (Dykewicz, Fineman, Skoner, et al., 1998).

Cromolyn sodium requires frequent dosing (four times a day) for efficacy, and is also best used prophylactically since its postulated mechanism of action is to prevent mast cell degranulation rather to treat the symptoms of an established allergic reaction in the nose. It may require up to two weeks of continuous usage for maximal clinical effect. Its efficacy in treatment of allergic rhinitis is generally considered to be somewhat less than the antihistamines and significantly less than the intranasal corticosteroids (Brogden, Speight, and Avery, 1974; Dykewicz, Fineman, Skoner, et al., 1998; Meltzer, 1995).

Oral corticosteroids are used for treatment of very severe or intractable nasal symptoms or to treat significant nasal polyposis (Dykewicz, Fineman, Skoner, et al., 1998). They are not recommended for the routine treatment of allergic rhinitis or nonallergic rhinitis

Allergen desensitization immunotherapy is utilized for patients with more severe allergic rhinitis requiring significant amounts of medication or for those who exhibit poor tolerance or non-responsiveness to pharmacological treatment (Kay, 2001). Specific immunotherapy consists of administering increasing concentrations of extracts of allergen over a long period. A typical course of therapy consists of three or more years of subcutaneous injections of the highest or maintenance level of extract at intervals of two to six weeks. Initial therapy requires a series of weekly

injections at escalating doses over a period of four to six months in order to induce clinical tolerance to the effective (maintenance) dose (Adkinson, Jr., 1999). Immunotherapy for allergic rhinitis has been reported to be effective and has significant advantages over anti-allergic drugs in that: a) it remains effective for several years after treatment is discontinued (Durham, Walker, Varga, et al., 1999; Mosbech and Osterballe, 1988; Naclerio, Proud, Moylan, et al., 1997) and b) has the potential for decreasing the frequency or intensity of complications or comorbities of allergic rhinitis (Kay, 2001). Due to the increasing costs associated with pharmacotherapy of allergic rhinitis, allergen immunotherapy has been proposed as a cost-effective alternate treatment for allergic rhinitis (Dykewicz, Fineman, Skoner, et al., 1998).

Pharmacotherapy for nonallergic rhinitis therapy can be prescribed either on an as needed basis or as a long-term course of treatment. Until the pathophysiology of non-allergic rhinitis is more clearly delineated, it is unlikely that specific treatments will be identified. To date, most available pharmacotherapeutic approaches are predominantly aimed at symptom relief and can be prescribed either on an as-needed basis or as a long-term course of treatment. Oral decongestants and/or anticholinergics are generally more efficacious than oral antihistamines. However, clinical trials have shown that Azelastine nasal spray (a topical antihistamine) is effective for "total symptom complex" with no discrimination to type of nasal symptom in the treatment of vasomotor rhinitis (Banov, Lieberman, and Vasomotor Rhinitis Study Groups, 2001; Settipane and Lieberman, 2001). Intranasal corticosteroids have also been recommended for long term therapy in nonallergic rhinitis (Jones, 1988; Settipane and Lieberman, 2001). Since the mechanism of vasomotor rhinitis is poorly understood specific therapies are not available and treatments aimed at symptom relief in this syndrome are often not very satisfactory.

Therapies for Seasonal vs. Perennial Allergic Rhinitis

Pharmacologic therapies for seasonal and perennial allergic rhinitis do not differ substantively. However, antihistamines for symptom relief are probably more useful in treating seasonal allergic rhinitis (Howarth, 1989; Meltzer, 1995; Scadding, Richards, and Price, 2000), while immunotherapy is more effective in treating seasonal, rather than perennial allergic rhinitis (Adkinson, Jr., 1999). Immunotherapy is effective for perennial allergic rhinitis, but to a lesser extent (Bousquet, Lockey, and Malling, 1998; Kay, 2001). It is unclear whether the difference in efficacy observed with immunotherapy relates more to the constant nature of the allergen exposure in perennial versus seasonal allergic rhinitis or to the nature of the allergens. It should be noted that in the climates of certain geographic locales, perennial symptoms could be pollen-related. On the other hand, intranasal corticosteroids show a significant benefit in treatment for both seasonal and perennial allergic rhinitis (Corren, 1999; Corren, 2000; Howarth, 1989; Weiner, Abramson, and Puy, 1998), but trials have been unable to identify a meaningful difference in efficacy between the different intranasal corticosteroids for seasonal versus perennial allergies (Corren, 1999; Corren, 2000; Dykewicz, Fineman, Skoner, et al., 1998; Howarth, 1989; Weiner, Abramson, and Puy, 1998).

Therapy Questions Which Remain

Antihistamines, decongestants, and anticholinergics, which are used primarily for symptom relief in allergic and nonallergic rhinitis, are usually taken on an as-needed basis. In contrast, intranasal corticosteroids are recommended for use on a continuous basis (weeks to months at a time). Because of issues of patient non-compliance with these recommendations, studies are currently underway to determine whether that usage of intranasal corticosteroids on an as-needed

basis will prove as effective as regular dosing. One recent study suggests that this might indeed be the case (Jen, Baroody, de Tineo, et al., 2000). As our understanding increases concerning differences in systemic bioavailability of the different preparations of intranasal corticosteroids, further efficacy and relative safety profiles will be warranted (Allen, 2000).

The role of leukotriene modifying drugs in the management of rhinitis (possibly including nonallergic rhinitis), initially developed for use in asthma, is under active investigation. Indeed there are plans to formulate a combination product containing both a second-generation antihistamine and a leukotriene modifying agent (Howarth, 2000; Meltzer, 2000; Mygind, Dahl, and Bisgaard, 2000).

Given the benefits of intranasally applied Azelastine in nonallergic rhinitis (Banov, Lieberman, and Vasomotor Rhinitis Study Groups, 2001), further study of this modality of therapy is warranted. It is unclear whether the benefit in nonallergic rhinitis relates to the antihistaminic activity or associated vasoconstrictor properties of the intranasally applied preparation.

Alternative agents may herald a new era of treatments in rhinitis. As the pathophysiology of allergic rhinitis is becoming elucidated (Kay, 2001), newer biological modifiers are being identified as therapeutic agents or as potential targets of therapy (Kay, 2000). Several of these agents including a soluble recombinant humanized IL4 receptor called altrakincept, anti-IL5, and anti-IL-12 have already undergone clinical study in asthma (Borish, Nelson, Corren, et al., 2001; Bryan, O'Connor, Matti, et al., 2000; Leckie, ten Brinke, Khan, et al., 2000) and studies are planned or underway in allergic rhinitis, nonallergic rhinitis and nasal polyposis. Further evaluation of the promising role of anti-IgE monoclonal antibodies (i.e. omalizumab) in treatment of seasonal and perennial allergic rhinitis (Adelroth, Rak, Haahtela, et al., 2000) are already underway. Strategies directed against adhesion molecules have been considered but it might prove difficult to find targets specific for allergic inflammation that are not intimately involved in other aspects of normal immune functioning (Gundel, Wegner, and Letts, 1993; Wegner, Gundel, Reilly, et al., 1990). The recent discovery of soluble chemo-attractant proteins (chemokines) has provided a molecular basis for many of the observations concerning cellular infiltration in inflammatory processes. The development of antagonists to chemokine receptors offers another strategy for prevention and treatment of inflammation in allergic and possibly nonallergic rhinitis (Frew and Plummeridge, 2001).

Side-effects/Adverse Events

The main drawback of antihistamines is their sedative effect, which negatively affects quality of life (Nolen, 1997). Older antihistamines readily cross the blood-brain barrier and bind not only to H1 receptors, but in many cases, also to dopaminergic, serotinergic, and cholinergic receptors (Corren, 2000), which helps account for a host of adverse central nervous system effects (e.g. sedation, fatigue, dizziness, impairment of cognition and performance (Kay, 2000) and anticholinergic effects (e.g. dryness of the mouth and eyes, constipation, inhibition of micturition etc). The newer or second-generation antihistamines such as loratadine, cetirizine and fexofenadine are more pharmacologically selective than earlier antihistamines and are significantly less able to cross the blood brain barrier. Administration of recommended doses of some second-generation antihistamines (fexofenadine and loratadine) results in no greater incidence of sedation than seen with placebo. The reduced incidence of these side effects in second generation antihistamines has greatly improved the usefulness of this category of drug (Kay, 2000). Notably, however, in second-generation antihistamines, reports of sedation and performance impairment increase with upward titration of dosage (Bradley and Nicholson, 1987; Falliers, Brandon, Buchman, et al., 1991;

Hindmarch and Shamsi, 1999). Furthermore, some older, nonsedating second-generation antihistamines, such as astemizole and terfenadine may have adverse cardiac effects due to pharmacologic effects on repolarization in cardiac tissue (These 2 agents are no longer available in the United States).

Oral decongestants often produce stimulatory side effects in the central nervous system, causing insomnia, tremor, dizziness, loss of appetite or excessive nervousness, and in the cardiovascular system, resulting in tachycardia, palpitations and hypertension (Dykewicz, Fineman, Skoner, et al., 1998; Meltzer, 1995). These agents should be avoided or used with caution in patients with coronary artery disease, hypertension, hyperthyroidism and elderly patients (Corren, 2000).

The foremost problem with using topical decongestants is its rebound effect. If used longer than three to five days, patients might experience rebound congestion with withdrawal of drug. Continual use over months might even cause development of a form of rhinitis, rhinitis medicamentosa, characterized by persistent nasal congestion which will be difficult to treat effectively (Corren, 2000; Meltzer, 1995).

Intranasal corticosteroid sprays or aqueous forms occasionally have local side effects such as nasal irritation and bleeding. However, these events can be kept to a minimum if the patient is carefully instructed as to the use of the drug. Additionally, there is some concern that systemic corticosteroids might have negative side effects on children including growth retardation, hypothalamic-pituitary-adrenal suppression, and behavioral disturbances (Fireman, 2000; Pedersen, 2001). A recent study (Skoner, Rachelefsky, Meltzer et al, 2000) reported on the suppressive effect of belcomethasone nasal spray on bone growth in children and all nasal steroid preparations in the United States now warn of this adverse event. Agents with less systemic bio-availability may be devoid of these risks (Allen, 2000).

Immunotherapy can cause potentially fatal anaphylaxis, with risks being higher during initial dose escalation phase. Therefore, immunotherapy should only be prescribed after careful specialist evaluation and should only be administered under specialist guidance. While systemic reactions are uncommon, physicians administering allergen immunotherapy should be well acquainted with the procedure, and have facilities to administer treatment for acute allergic reactions if they occur. The risk of systemic reactions represents a general limitation in the use of immunotherapy. Risk factors for systemic allergic reactions in allergen immunotherapy have been identified and in addition to dosage escalation, include symptomatic rhinitis and asthma (Fireman, 2000; Lockey, 1995).

Chapter 2. Methods

This evidence report on the management of allergic rhinitis is based on a systematic review of the literature. Meetings and teleconferences of the EPC staff with technical experts were held to identify specific issues central to this report. A comprehensive search of the medical literature was conducted to identify studies addressing several key questions on the management of allergic rhinitis and nonallergic rhinitis. We compiled evidence tables of study features and results, appraised the methodological quality of the studies, and summarized their results. We identified published meta-analyses on specific treatment topics and evaluated and reported the findings of these reports.

The American Academy of Family Physicians originally proposed this topic and served as the primary science partner of this report. The American College of Allergy, Asthma and Immunology and the American Academy of Allergy, Asthma and Immunology also provided technical experts to work with the EPC staff to refine key questions, identify important issues, and nominate peer reviewers. The science partners were not involved in the synthesis of evidence or in the writing of this report.

Key Questions Addressed in the Evidence Report

The purpose of an evidence report is to summarize information from relevant studies addressing specific key questions. It is beyond the scope of an evidence report to cover all possible related issues for a topic. The aim of this evidence report is to determine how one diagnoses allergic and nonallergic rhinitis and to determine the minimum level of testing that is needed to differentiate allergic from nonallergic rhinitis; whether differentiating allergic from nonallergic rhinitis is important; the effectiveness of treatments in nonallergic and allergic rhinitis; and how treatment of allergic rhinitis impacts the development of asthma. With input from the science partners of this report, the following key questions (and sub-questions) were formulated. Patient population for this evidence report will include male and female children and adults, minorities, low-income, and elderly patients.

Question 1. How does one diagnose allergic and nonallergic rhinitis (especially vasomotor)?

What differentiates allergic from nonallergic rhinitis with respect to symptoms, signs, physical examination and diagnostic testing?
What is the minimum level of testing necessary to differentiate allergic from nonallergic rhinitis?

Question 2. Is differentiating allergic from nonallergic rhinitis important?

Are treatments different?
Are outcomes different?

Question 3. How does one treat nonallergic and allergic rhinitis?

For nonallergic rhinitis:

a) What is the efficacy of antihistamines (all classes), nasal corticosteroids,

sympathomimetics, or leukotriene modifiers compared with placebo?

b) What are the side effects due to antihistamines, nasal corticosteroids, immunotherapy, sympathomimetics, cromolyn, and leukotriene modifiers?

For allergic rhinitis:

a) What is the efficacy of antihistamines versus nasal corticosteroids, antihistamines versus immunotherapy (desensitization), nasal corticosteroids versus immunotherapy, sedating versus nonsedating antihistamines, other agents (cromolyn, leukotriene modifiers, sympathomimetics, ipratropium).

b) What are the side effects/adverse events due to: antihistamines, nasal corticosteroids, sympathomimetics, leukotriene modifiers?

Do efficacy and side effects of treatment vary by severity of rhinitis or patient characteristics?

Question 4. How does treatment of allergic rhinitis impact on the development of asthma?

What is the likelihood of developing asthma with untreated allergic rhinitis (natural history)?
How does treatment of allergic rhinitis affect the likelihood of developing asthma?
How does treatment of allergic rhinitis affect the likelihood of developing bacterial sinusitis?

Literature Search

Studies for the review of the primary literature were identified primarily through a Medline search of English language literature conducted between 1966 and October 2000. We also consulted technical experts and examined references of published meta-analyses and selected review articles to identify additional studies. Articles that met the inclusion criteria were incorporated in our evidence report.

Search Terms and Strategies

The literature search was conducted to identify clinical studies that reported primary data and published between 1966 through October 2000. The Medline search strategy is listed in Table 1. Separate searches were conducted to identify meta-analyses of nasal corticosteroids, immunotherapy and sedating and nonsedating antihistamines. The text words or medical subject headings for all treatments included 'rhinitis, perennial and allergic,' 'histamine antagonists,' 'nasal decongestants,' 'ipratropium,' 'cromolyn sodium,' 'leukotriene antagonists,' and 'anti-inflammatory agents.' The search was limited to human studies and published in English.

Medline search results were screened and potential studies were identified for retrieval based on setting, study question, population, and disease. Articles involving minority populations and gender issues were especially searched for (although none were found). Studies with no specific reference to allergic or nonallergic rhinitis were excluded. After retrieval, each paper was screened to verify that the condition and treatments under investigation were appropriate to each study question.

Study Selection

The Medline search yielded 3,381 citations. We screened the titles and abstracts of these

citations and retrieved 228 full-length articles for further examination. Reports published only as abstracts in proceedings were rejected from further consideration. Specific inclusion criteria were developed for each of the key questions and these are discussed below.

Question 1: Diagnosis of Allergic and Nonallergic Rhinitis

We included cross-sectional and prospective studies evaluating diagnostic methods in allergic and nonallergic rhinitis including, but not limited to, allergen skin testing, serum IgE measurements, nasal provocation challenge, nasal rhinomanometry and nasal biopsy.

Question 2: Differentiation of Allergic from Nonallergic Rhinitis

We included cross-sectional and prospective studies addressing diagnostic methods of differentiation of allergic from nonallergic rhinitis.

Question 3: Treatment of Allergic and Nonallergic Rhinitis

We included randomized controlled trials (RCTs) of the following interventions in allergic rhinitis: antihistamines versus nasal corticosteroids, antihistamines versus immunotherapy, nasal corticosteroids versus immunotherapy, sedating versus nonsedating antihistamines, cromolyn sodium, anticholinergic agents, leukotriene inhibitors, and sympthomimetics. In the treatment of nonallergic rhinitis we included randomized controlled trials of antihistamines, nasal corticosteroids, anticholinergics, and sympathomimetic agents. We excluded uncontrolled trials, case reports, and case series.

Question 4: Impact of Treated and Untreated Allergic Rhinitis on Development of Asthma and Bacterial Sinusitis

We included prospective studies evaluating the relationship between allergic rhinitis and later development of asthma or bacterial sinusitis. Cross-sectional studies, case reports, and case series were excluded.

We placed no restrictions on the patients' gender or ethnicity. Specifically, AAFP was interested in studies about minorities, low-income, and elderly patients. However, we found no study that addressed these populations in its entirety or as subgroups.

Data Abstraction

After categorizing all retrieved studies according to the above criteria a total of 88 studies qualified for data abstraction. Data for evidence tables were abstracted using the forms shown in the appendix. Information abstracted included the study population characteristics, inclusion and exclusion criteria, the descriptions and the diagnostic criteria, potential verification bias as well as the main results and the conclusions of the study. In addition, data for quality assessment of individual studies were systematically abstracted. Data were abstracted by one member and then verified by a second member. If two abstractors disagreed, a third party methodological expert resolved the dispute.

Reporting the Results

The evidence we found is summarized in three complementary forms. The evidence tables provide detailed information about key features of study design and results of all the studies reviewed. A narrative and tabular summary of the strength and quality of the evidence of each study are provided for each drug class.

Evidence Tables

For each of the study questions, separate evidence tables were constructed for the allergic and nonallergic populations. These tables are presented under the Evidence Tables section of this evidence report. The evidence tables list the clinical studies found for each of the drug class comparisons and that met the inclusion criteria. The specific information included in the evidence tables is described above.

Summarizing the Evidence of Individual Studies

Grading of the evidence can be useful by indicating the overall "quality." A simple evidence grading system using a single scale may be desirable, however, the "quality" of evidence is multi-dimensional, and a single metric cannot fully capture information needed to interpret a clinical study (Lowell and Franklin, 1965; Settipane, 1986; Silberg, Lundberg, and Musacchio, 1997; Varley, 1964). We believe that information on individual components of a study contribute more to the evaluation of evidence by deliberating bodies than a single summary score. The evidence-grading scheme we used here assesses four dimensions that are important for the proper interpretation of the evidence:

- study size
- applicability
- summary of efficacy and safety outcomes
- methodological quality

Study Size

The study (sample) size is used as a measure of the weight of the evidence. A large study provides a more precise estimation of the treatment effect but does not automatically confer broad applicability unless the study included a broad spectrum of patients. Very small studies, taken individually, cannot achieve broad applicability. But several small studies that enrolled diverse populations, taken together, may have broad applicability. The study size is included as a separate dimension used to assist the assessment of applicability. For summarizing all studies, this would be the number of studies and the total number of patients in these studies.

Applicability

Applicability, also known as generalizability or external validity, addresses the issue of whether the study population is sufficiently broad to be generalizable to the population at large. Individual studies are often unable to achieve broad applicability due to restricted study population characteristics and a small number of study subjects (Lau, Ioannidis, and Schmid, 1997). We define the applicability grade as below:

I. Patients enrolled in the trial represent a broad spectrum of the population (high degree of

applicability). Typically this would be a large study, although a large study in itself does not guarantee a high degree of generalizability.

II. The study included only a narrow/restricted study population, but the result is relevant to similar types of patient population (restricted applicability). Typically this would be a small study, but may also be a large study of a very homogeneous population.

III. Narrow sample, not well generalizable to other groups, or studied outlier population that is not immediately relevant to the study question (very limited direct applicability or not applicable), or where the study reported only limited information.

N.D. No data or insufficient information reported to assess the applicability.

Methodological Quality

Methodological quality or internal validity addresses the design, conduct, and reporting of the clinical trial. Some of the items belonging to this entity are widely used in various "quality" scales and usually include items such as concealment of random allocation, treatment blinding, and handling of dropouts. Most of the studies included in this evidence report are randomized controlled trials, we define a three categories scale to report the methodological quality: A (least bias), B (susceptible to some bias), or C (likely to have large bias).

A. Double-blinded, well-concealed randomization, few drop outs, and no (or only minor) reporting problem of the trial that is likely to cause significant bias.

B. Single-blinded only, unclear concealment of randomization, or has some inconsistency in the reporting of the trial but is unlikely to result in major bias.

C. Unblinded study, inadequate concealment of random allocation, high drop-out rate, or has substantial inconsistencies in the reporting of the trial such that it may result in large bias.

Summary of Efficacy and Side-effect Outcomes

Outcomes studied included the effect of nasal corticosteroids vs. antihistamines, sedating vs. nonsedating antihistamines, cromolyn sodium, anticholinergic agents, leukotriene inhibitors, and sympathomimetics in both allergic and nonallergic rhinitis. In addition, we examined the evidence for a causal link between allergic rhinitis and development of asthma or bacterial sinusitis.

The efficacy outcomes reported by most studies addressing the same question in this evidence report were often heterogeneous and not readily amenable to meta-analysis. Different studies often used different combinations of outcomes such as watery eyes, itchy eyes, rhinorrhea, sneezing, itchy nose, and nasal congestion. Outcomes were typically assessed using categorical scales but the range of scales varied across studies.

Summarizing side effects is also problematic due to non-standard reporting of these outcomes by individual studies. Studies frequently do not define side effects, do not report the same side effects or do not use the same metric to report the same side effect, and many studies do not report side effects.

The evidence tables report detailed information about the outcomes. The summary tables in the result section report primarily the nasal symptoms. Consistency of effect across most studies addressing the same question is used as an indication of efficacy for the treatment being evaluated.

Table 1. MEDLINE Search Strategy

1. rhin$.tw.
2. exp rhinitis, allergic, perennial/
3. exp rhinitis/
4. 1 or 2 or 3
5. limit 4 to human
6. limit 5 to english language
7. exp histamine antagonists/ or exp histamine h1 antagonists/
8. exp nasal decongestants/
9. exp ephedrine/ or exp phenylpropanolamine/
10. exp phenylephrine/
11. exp cromolyn sodium/
12. (ipratropium bromide or oxitropium bromide).mp.
13. exp ipratropium/
14. exp scopolamine derivatives/
15. exp anti-inflammatory agents/
16. exp leukotriene antagonists/ or exp leukotrienes/
17. exp drugs, chinese, herbal/
18. 6 and (6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17)
19. exp clinical trials/
20. exp randomized controlled trials/
21. (random$ or rct).tw.
22. 6 and (19 or 20 or 21)
23. 6 and (19 or 20 or 21)
24. limit 6 to (clinical trial or clinical trial, phase i, or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial)
25. 23 or 24
26. prevalen$.af.
27. prevalen$.af.
28. inciden$.af.
29. inciden$.af.
30. exp rhinitis, allergic, perennial/ep
31. 6 and (27 or 28 or 30)
32. exp "sensitivity and specificity"/
33. exp diagnosis/
34. exp reproducibility of results/
35. exp false negative reactions/ or false positive reactions/
36. exp logistic models/
37. exp regression analysis/
38. predictive value.tw.
39. diagnos$.tw.
40. diagnos$.tw.
41. (sensitivity and specificity).tw.
42. accuracy.tw.
43. logistic regression.tw.
44. screening.tw.

45. roc.tw.
46. reproducibility.tw.
47. (false positive or false negative).tw.
48. likelihood ratio.tw.
49. 32 or 33 or 34 or 35 or 36 or 36 or 37 or 38 or 39 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48
50. 6 and 49
51. 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or48.mp. [mp=title, abstract, registry number word, mesh subject heading]
52. 6 and 51
53. limit 52 to (clinical trial or clinical trial, phase i, or clinical trial, phase ii or clinical trial, phase iii or clinical
trial, phase iv or controlled clinical trial or randomized controlled trial)
54. exp rhinitis, allergic, perennial/di
55. limit 54 to (clinical trial or clinical trial, phase i, or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial)
56. 53 or 55
57. 25 or 31 or 56
58. limit 57 to (addresses or bibliography or biography or comment or dictionary or directory or editorial or festschchrift or interview or legal cases or letter or periodical index or review of reported cases) [Limit not valid in: MEDLINE; records were retained]
59. 57 not 58

Chapter 3. Results

General Observations

The MEDLINE® search identified 3,354 citations. We retrieved 228 articles for evaluation and included 88 into the evidence report. Among these 88 studies, 86 were RCTs and two were prospective cohort studies. Of the 86 randomized trials, 77 were double-blinded, six were single-blinded and in three studies the type of blinding was unstated. Forty-four of the 86 randomized trials reported the source of funding. Ninety-one percent of these 44 trials reported funding by pharmaceutical companies. There were only four trials supported by government funding.

There were no specific studies of the pediatric population. Even though some studies may have enrolled patients in pediatric ranges, separate data was not reported for this subgroup. Therefore, no specific conclusions could be drawn for the pediatric population.

Results for Specific Questions

Question 1. How does one diagnose allergic and nonallergic rhinitis (especially vasomotor)?

What differentiates allergic from nonallergic rhinitis with respect to symptoms, signs, physical examination, and diagnostic testing? *(Question 1.1)*

Summary of the evidence on what differentiates allergic from nonallergic rhinitis. No studies addressing these questions met the criteria described in the methods section of this report. Specifically, no studies were identified which sought to differentiate between allergic and nonallergic rhinitis on the basis of clinical symptoms or signs on physical examination. We found no study that evaluated a test specifically to diagnose nonallergic rhinitis.

One study was identified which sought to develop criteria for the definition of allergic rhinitis through a systematic evaluation of the relative importance of symptoms, signs and investigative tests (Ng, Warlow, Chrishanthan, et al., 2000). This study compared patients with diagnosed allergic rhinitis to normal individuals. It did not attempt to differentiate symptoms and signs between allergic and nonallergic rhinitis. It was suggested in that study that in establishing a diagnosis of allergic rhinitis the relative importance of skin prick testing is equal to a history of allergen-induced nasal and ocular symptoms. However, most authorities recommend confirmatory testing (Dykewicz, Fineman, Skoner, et al., 1998). Discordance between history and skin tests (or other diagnostic tests) is observed.

Due to the lack of studies that directly address this question, we therefore undertook an analysis of the inclusion criteria employed in those randomized controlled clinical trials addressing treatment issues in vasomotor rhinitis. In the majority of cases (7 out of 10 evaluable studies: Broms and Malm, 1982; Graf, Enerdal, and Hallen, 1999; Jokinen and Sipila, 1983; Kirkegaard, Mygind, Molgaard, et al., 1987; Kirkegaard, Mygind, Molgaard, et al., 1988; Nelson and Jacobs, 1982; Sjogren, Jonsson, Koling, et al., 1988) exclusion of allergic disease by an absence of positive allergy skin tests or negative results by RAST is the usual prerequisite criterion for diagnosing vasomotor rhinitis. The term vasomotor rhinitis will be used preferentially, since in all the studies we analyzed every otherwise identifiable form of rhinitis was excluded.

Vasomotor rhinitis can occur as an isolated condition, characterized by an increase in nasal symptoms attributable to exposures to nonspecific irritants such as strong odors, fragrances or perfumes, or indeed to changes in air pressure and temperature. Importantly, however, it can also occur in conjunction with (possibly as a complication of) allergic rhinitis.

Given the absence of well-designed studies addressing these questions, we can only report that, based on current clinical practices and the analysis of the inclusion criteria employed in studies of vasomotor rhinitis, diagnostic testing rather than signs and symptoms is necessary to differentiate isolated vasomotor rhinitis from allergic rhinitis.

What is the *minimum* level of testing necessary to differentiate allergic from nonallergic rhinitis? *(Question 1.2)*

The minimum level of testing necessary to confirm or exclude a diagnosis of allergic rhinitis has not been established. The small study by Ng, Warlow, Chrishanthan, et al. (2000) suggests that total serum IgE may be as useful as specific allergy skin prick tests which in turn are more useful than RAST-type testing in confirming a diagnosis of allergic rhinitis.

Henderson, Swedlund, and Van Delen (1971) conducted a prospective study in an adult allergy clinic and observed elevated serum IgE in 10% of patients with non-allergic rhinitis and in 62% of allergic rhinitis patients. A larger study by Wittig, Belloit and De Fillippi (1980) employed different cutoff levels of serum IgE to look at diagnostic sensitivity and specificity in rhinitic individuals and reported 98% specificty with the highest cutoff level but with a sensitivity of only 30%. Reduction of the cutoff level allowed an increase in sensitivity to 60% but a drop in the sensitivity to 80%. These studies suggest limited value for serum IgE in screening for allergic rhinitis.

Question 2. Is differentiating allergic from nonallergic rhinitis important?

Differentiation of allergic from nonallergic rhinitis is important if treatments are significantly different and if the outcomes of treatment including prevention of complications differ in response to those treatments. As seen in the evidence tables, similar treatments are frequently employed in the two conditions. However, what has been studied in the literature does not imply that differentiation might be important. It is generally believed that environmental control and immunotherapy have relevance only for treatment of allergic rhinitis. Therefore, differentiation is important for these two interventions.

Are treatments different? *(Question 2.1)*

Similar treatment modalities have been employed in RCTs in both conditions and include antihistamines, decongestants, nasal corticosteroids, cromoglycate, ipratropium bromide and other agents.

Are outcomes different? *(Question 2.2)*

The evidence tables and the details elaborated below indicate the difference in success rates of the various treatment modalities.

Question 3. How does one treat nonallergic and allergic rhinitis?

Nonallergic

What is the efficacy of antihistamines (all classes) vs. placebo, nasal corticosteroids vs. placebo, sympathomimetics vs. placebo, leukotriene modifiers, and other agents (anticholinergics, cromoglycate and sympathomimetics)?

(Question 3.1a)

[See Evidence Table 1]

Studies examining the efficacy and safety of the above treatments are summarized in Evidence Table 1. There were a total of 13 RCTs; one studied antihistamines, three nasal corticosteroids, three sympathomimetic agents, five anticholinergic agents, and two cromoglycate (one study examined both antihistamines and sympathomimetic agents). Twelve studies were conducted in Europe and one in the U.S. A total of 338 patients were enrolled and 333 evaluated in 10 evaluable studies. Study participants ranged in age from 14 to 87. Seven of ten evaluable studies required negative skin test results as an entrance criterion.

Summary of the evidence from RCTs comparing antihistamines (all classes) versus placebo. Studies looking at the various treatments employed in the treatment of nonallergic rhinitis are summarized in the evidence tables. Only one study (Broms and Malm, 1982) meeting the criteria for inclusion looked at the role of antihistamines in the treatment of nonallergic rhinitis. In this study, the antihistamine was used as part of antihistamines-decongestants combination product and accordingly, outcomes related to the antihistamine component of this drug cannot be separately identified. The FDA has approved a nasal topical product – azelastine (an H1 antihistamine) for treatment of vasomotor rhinitis.

Table 2. Summary of randomized trials: antihistamines (all classes) versus placebo

Author Year UI	Study size	Applica-bility	Outcome efficacy	Outcome safety	Methodo-logical Quality
Broms 1982 83046227	20	II	PPA reduced symptoms of rhinorrhea and sneezing. No comment on significance.	Headache in all groups. Difficulty in micturition 2 patients in brompheniramine group.	B

Summary of the evidence from RCTs of nasal corticosteroids. A small number of studies have looked at the benefit of nasal corticosteroids in this condition. In a double-blind placebo controlled trial, Wight, Jones, Beckingham, et al. (1992) showed a significant improvement in the symptom of nasal obstruction with each of two doses of budesonide. No other symptoms were altered, no difference was seen between the two doses and no significant side-effects were recorded. Comparisons of nasal corticosteroids and ipratropium in nonallergic rhinitis (NAR) yield conflicting results. Bende and Rundcrantz (1985) compared budesonide with ipratropium and showed a superior effect for budesonide with respect to symptoms of nasal secretion and sneezing. Jessen and Bylander (1990) report a double blind RCT comparing ipratropium and beclomethasone in 24 patients with NAR characterized by hypersecretion. No difference was identifiable between the efficacy of the two medications.

Summary of the evidence from RCTs comparing sympathomimetics versus placebo. Two randomized controlled studies were identified which looked at the role of oral decongestants (phenylpropanolamine) in treatment of nonallergic rhinitis. In both studies emphasis was placed on

relief of symptoms of nasal congestion. One study additionally focused on nasal sneezing while the other study focused additionally on rhinorrhea. The first study (Broms and Malm, 1982) contained data which were difficult to abstract, but did suggest a decrease in symptoms of nasal congestion by phenylpropanolamine. The second study (Renvall and Lindqvist, 1979) indicated that phenylpropanolamine was not superior to placebo in terms of relief of nasal congestion at a dosage of 50 mg per day with approximately 50 percent of patients reporting no improvement or worsening at this dosage. At a dosage of 100 mg per day there was a statistically significant improvement in symptoms of nasal obstruction with respect to placebo and also with respect to phenylpropanolamine 50 mg. The lower dosage was also poorly effective in alleviating symptoms of increased nasal secretion, whereas the 100 mg per day dosage was significantly more effective in relieving this symptom than the lower dose. The FDA has urged companies marketing that decongestant, phenylpropolamine, to voluntarily withdraw the drug from the marketplace, while it initiated regulatory actions to mandate such withdrawals.

Table 3. Summary of randomized trials: sympathomimetics versus placebo

Author Year UI	Study Size	Applica-bility	Outcome Efficacy	Outcome Safety	Method-ological quality
Renvall 1979 79214155	70	II	100 mg doses significantly reduced congestion and rhinorrhea. 100 mg PPA significantly more efficacious than 50 mg.	No major adverse effects. Minor effects: Drowsiness, flushing, nausea, increased alertness.	B

Summary of the evidence from RCTs of leukotriene modifiers versus placebo. No studies were identified looking at the efficacy of leukotreine modifiers in the treatment of nonallergic rhinitis.

Summary of the evidence from RCTs comparing anticholinergic agents versus placebo. Five randomized controlled clinical trials were identified addressing the efficacy of anticholinergic agents in the treatment of nonallergic rhinitis. All of the studies are rated B for methodological quality and the median grade for applicability is rated II. Each of these five trials studied intranasal ipratropium bromide, and each of the five studies documented efficacy for ipratropium in reducing nose blowing frequency and rhinorrhea. The first study (Kirkegaard, Mygind, Molgaard, et al., 1988) (n=38) documented a significant reduction in mean daily episodes of nose blowing by treatment with 80 micrograms q.i.d. of ipratropium. The second study (Sjogren, Jonsson, Koling, et al., 1988) (n=24) documented a dose-dependent decrease in methacholine induced nasal secretions by treatment for one day with doses of ipratropium of 40 micrograms, 100 micrograms and 200 micrograms. The third (Jokinen and Sipila, 1983) documented a physician rated significant reduction in the symptoms on rhinorrhea with ipratropium but no effect on the symptoms of nasal congestion, sneezing or nasal itching. The fourth study (Kirkegaard, Mygind, Molgaard, et al., 1987) compared two doses of ipratropium (80 micrograms q.i.d. versus 400 micrograms q.i.d.) to placebo. Both doses resulted in a significantly decreased mean daily number of nose blowing episodes compared to placebo, but 400 micrograms q.i.d. being significantly more effective than 80 micrograms q.i.d. No effect was observed on symptoms of nasal congestion or sneezing. The final study (Malmberg, Grahne, Holopainen, et al., 1983) also documented a

significant reduction in the number of nose blowing episodes as well as a significant reduction in the symptom of rhinorrhea with ipratropium compared to placebo. No effect was seen on nasal congestion.

Table 4. Summary of individual RCTs comparing anticholinergics versus placebo

Author Unique Identifier	Study Size	Applic-ability	Outcome Efficacy	Outcome Safety	Method-ological quality
Jokinen 1983 84120896	30	II	Significant reduction in nasal hypersecretion with ipratropium, but no effect on nasal blockage, sneezing, or tickling.	11 pts with mild side-effects on active treatment 7 with placebo: nasal irritation, nasal dryness, mild throat irritation.	B
Malmberg 1983 84082739	34	III	Active treatment reduced nasal discharge and nasal secretion.	18 active patients complained of nasal irritation, 9 placebo. 15 active complained of excessive drying of mucosa, 8 placebo.	B
Kirkegaard 1987 87167181	36	II	Number of nose-blowings 47% lower during active treatment than placebo, some slight reduction with high dose treatment but not statistical significant. Active treatment had no effect on number of sneezes or nasal blockage index.	Side-effects slight w/low dose treatment, but high dose caused unpleasant nasal dryness.	B
Kirkegard 1988 89074206	38	II	Ipratropium significantly reduced mean daily number of nose-blowing episodes compared with placebo.	Nasal dryness noted in both groups.	B
Sjogren 1988 89086030	24	II	All doses of ipratropium reduced volume of methacholine-induced nasal secretions vs placebo nasal symptoms. No significant difference between doses.	No major adverse effects. Sweating with high-dose ipratropium.	B

Summary of the evidence from RCTs comparing cromoglycate versus placebo. Two RCTs were identified looking at the effects of cromoglycate in nonallergic rhinitis. Both studies recorded improvement in symptoms of rhinitis with active treatment compared to placebo. In the first study (Balle and Illum, 1977) cromoglycate resulted in a significant decrease in sneezing and congestion

scores. In the second (Nelson and Jacobs, 1982) cromoglycate was documented to produce a significant decrease in nasal itching but no change in the other three symptoms evaluated.

Table 5. Summary of randomized trials: cromoglycate versus placebo

Author Year UI	Study size	Applic-ability	Outcome Efficacy	Outcome Safety	Method-ological quality
Balle 1977 78016773	25	II	Cromoglycate significantly reduced mean monthly scores for sneezing and nasal congestion.	No adverse events.	B

What are the side-effects/adverse events due to: antihistamines, nasal corticosteroids, sympathomimetics, leukotriene modifiers, anticholinergics and cromoglycate? *(Question 3.1b)*

[See Evidence Table 1]

Adverse events of antihistamines described included drowsiness, nausea, and headache. This study (Broms and Malm, 1982) involving a combination product (antihistamine plus decongestants) also had patients who described micturition difficulties. This is presumed to be related to the anticholinergic activity of the antihistamine component.

In three of the five studies looking at ipratropium in treatment of nonallergic rhinitis, significant side-effects of nasal dryness and nasal irritation were recorded (Jokinen and Sipila, 1983; Kirkegaard, Mygind, Molgaard, et al., 1988; Malmberg, Grahne, Holopainen, et al., 1983).

In the two studies looking at cromoglycate in nonallergic rhinitis no significant adverse effects were associated with use of this medication (Balle and Illum, 1977; Nelson and Jacobs, 1982).

[See Evidence Table 1]

Allergic: Seasonal

What is the efficacy of antihistamines (all classes) vs. nasal corticosteroids, antihistamines vs. immunotherapy (desensitization, NOT sublingual), nasal corticosteroids vs. immunotherapy (NOT sublingual), sedating vs. nonsedating antihistamines, other agents (cromolyn, leukotriene modifiers, sympathomimetics, ipratropium) *(Question 3.2a)*

[See Evidence Tables 2-5]

Summary of the evidence from RCTs comparing antihistamines versus nasal steriods. Studies examining the efficacy and safety of the above treatments are summarized in evidence table 2. There were a total of 18 RCTs. Eight studies were conducted in Europe, 1 in Canada and 9 in the U.S. A total of 3,557 patients were enrolled and 3,333 evaluated. Study participants ranged in age from under 12 to 90 years old, with 12 of 18 studies enrolling both adult and pediatric patients. Thirteen of 18 studies required positive allergen skin test results as an entrance criterion. The median grade for methodological quality of these studies is rated B and the median grade for applicability is rated II.

A recent meta-analysis of 17 RCTs published up to 1997 compared intranasal corticosteroids with antihistamines in the treatment of seasonal and/or perennial allergic rhinitis (Weiner, Abramson, and Puy, 1998). The analysis included several different nasal corticosteroid preparations and several different antihistamines including both nonsedating and sedating

antihistamines. The analysis reported that for the six nasal symptoms studied as well as for overall nasal symptoms score nasal corticosteroids produced significantly greater relief than did oral antihistamines. The specific symptoms that were improved included nasal blockage, nasal discharge, sneezing, or nasal itching and postnasal drainage. There were no significant differences identified between treatments for nasal discomfort, nasal resistance or eye symptoms. Three of the 17 RCTs address the issue cost effectiveness of intranasal corticosteroids versus oral nonsedating antihistamines with results favoring use of nasal corticosteroids in each case.

Our search identified eight additional studies that were not included in the meta-analysis undertaken by (Weiner, Abramson, and Puy, 1998). Seven of the studies favored intranasal corticosteroids over antihistamines both with respect to improvement in global nasal symptoms as well as most individual nasal symptoms. One study (D'Ambrosio, Gangemi, Merendino, et al., 1998) showed better symptom improvement with cetirizine alone over fluticasone alone. Thus, the overwhelming majority of studies show very clear benefits for the use of intranasal corticosteroids over either sedating or nonsedating antihistamines for relief of symptoms of nasal allergy. These results are similar for seasonal allergic rhinitis and perennial allergic rhinitis.

Table 6. Summary of randomized trials: antihistamines versus nasal corticosteroids

Author Year UI	Study size	Applic-ability	Outcome-efficacy	Outcome-safety	Method-ological quality
Munch 1983 84050113 SAR	61	II	Budesonide significantly improved rhinorrhea, nasal congestion and sneezing scores compared to dexchlorpheniramine.	No major adverse effects. Minor adverse effects-sedation.	B
Backhouse 1986 86165329 SAR	99	II	Terfenadine + flunisolide significantly improved sneezing, nasal blowing, nasal congestion and ocular symptoms scores compared to flunisolide alone.	No major adverse effects: Minor adverse effects: nasal irritation, drowsiness, and nausea.	B
Wood 1986 86245576 SAR	74	I	No significant difference between astemizole and beclomethasone for all nasal symptoms.	No major adverse effects Minor adverse effects: Drowsiness.	C
Juniper 1989 89175902 SAR	90	II	Both beclomethasone and beclomethasone + astemizole significantly improved sneezing, nasal congestion and rhinorrhea symptom scores compared to astemizole.	No major adverse effects. Minor adverse effects: nasal bleeding, headache, thirst, skin rash and nausea.	B

Author Year UI	Study size	Applic-ability	Outcome-efficacy	Outcome-safety	Method-ological quality
Robinson 1989 90002391 PAR	20	III	Beclomethasone significantly reduced rhinorrhea, sneezing, and nasal inflammation scores compared to terfenadine. Significant patient preference for beclomethasone.	No major adverse effects. Minor adverse effects: Nausea, sedation and epistaxis.	B
Darnell 1994 95196117 SAR	214	II	Fluticasone significantly improved nasal symptoms compared to terfenadine for sneezing, rhinorrhea, and nasal congestion.	No major adverse effects. Minor adverse effects: Fatigue, epistaxis, oral burning, asthma, headache, and breathlessness.	B
Van Bavel 1994 95085365 SAR	232	II	Fluticasone significantly Improved rhinorrhea, nasal congestion, sneezing, nasal itch, and total nasal symptom scores compared with terfenadine.	No major adverse effects. Minor adverse effects: asthma and headache	B
Hilberg 1995 96098156 SAR	18	II	Budesonide significantly increased nasal cross-sectional areas and nasal secretion volume. Budesonide significantly improved nasal congestion.	No adverse effects noted.	B
Schoenwetter 1995 96070357 SAR	298	I	Triamcinolone significantly improved sneezing, nasal congestion, nasal itch, postnasal drip, rhinorrhea, and ocular symptom scores compared to loratadine.	No major adverse effects. Minor adverse effects: Epistaxis, headache and rhinitis.	A

Author Year UI	Study size	Applic-ability	Outcome-efficacy	Outcome-safety	Method-ological quality
Bernstein 1996 96213647 SAR	239	II	Triamcinolone significantly improved nasal itch, nasal congestion, postnasal drip, rhinorrhea, sneezing and total nasal symptom scores compared with astemizole.	No major adverse effects Minor adverse effects: pharyngitis, headache, and weight gain	B
Bronsky 1996 96194242 SAR	348	I	Fluticasone significantly improved sneezing, rhinorrhea, nasal obstruction, nasal itch and total nasal symptom scores when compared with terfenadine.	No major adverse effects Minor adverse effects: headache	A
Jordana 1996 96191239 SAR	242	II	Fluticasone significantly improved nasal congestion, sneezing, nasal itch, and rhinorrhea scores compared to loratadine.	No major adverse effects Minor adverse effects: headache and pharyngitis	B
Gehanno 1997 97332767 SAR	114	II	Fluticasone significantly improved rhinorrhea, nasal congestion, sneezing and nasal itch. Scores compared with loratadine.	Major adverse effects Convulsions Minor adverse effects: nausea, asthma attack, dizziness, sweating, and weakness	A
Juniper 1997 97286890 SAR	61	I	Fluticasone significantly improved all nasal symptoms compared to terfenadine.	Major adverse effects: nausea. No minor adverse effects.	B
D'Ambrosio 1998 99133169 SAR	60	II	Cetirizine and cetirizine + fluticasone significantly improved sneezing, rhinorrhea, nasal itch and total nasal scores compared to fluticasone alone.	No major adverse effects. Minor adverse effects: Burning throat & nose, dizziness, gastric disorders, and visual disturbances.	B

Author Year UI	Study size	Applic-ability	Outcome-efficacy	Outcome-safety	Method-ological quality
Ratner 1998 98390023 SAR	600	I	Fluticasone and fluticasone + loratadine significantly improved rhinorrhea, nasal congestion, sneezing, and nasal itch scores compared to loratadine.	No major adverse effects. Minor adverse effects: blood in nasal mucosa, epistaxis, and xerostomia.	B
Ortolani 1999 20068053 SAR	288	II	Fluticasone significantly improved rhinorrhea, nasal congestion, sneezing, and nasal itch scores compared to levocabastine.	No major adverse effects. Minor adverse effects: respiratory symptoms, and exacerbations of nasal symptoms.	B
Condemi 2000 20289854 SAR	351	I	Triamcinolone significantly improved rhinorrhea, sneezing, and nasal congestion scores compared with loratadine.	Major adverse effects: Chest pain. Minor adverse effects: Headache.	B

Summary of the evidence from RCTs comparing antihistamines versus immunotherapy. No RCTs were identified directly comparing immunotherapy with antihistamines in the treatment of seasonal and/or perennial allergic rhinitis. Immunotherapy is generally considered a long-term disease modifying treatment measure requiring months to years of treatment whereas antihistamines are often used for immediate symptom relief. Therefore direct comparisons with respect to efficacy are not likely to be undertaken.

Summary of the evidence from RCTs comparing nasal corticosteroids versus immunotherapy. No RCTs were identified directly comparing immunotherapy with intranasal corticosteroids in the treatment of seasonal and/or perennial allergic rhinitis.

Summary of the evidence of effectiveness of immunotherapy. The efficacy of subcutaneous specific allergen immunotherapy has been documented in more than 40 placebo-controlled trials in allergic rhinitis. These studies frequently employ immunotherapy as an add-on treatment and do not compare it to other active treatment. Efficacy has been demonstrated in allergic rhinitis for many different inhalant allergens including tree pollens, grass pollens, ragweed pollens, other pollens, dust mite, cat and the mold alternaria (Bousquet, Lockey, and Malling, 1998; Bousquet 2001).

Summary of the evidence from RCTs comparing sedating versus nonsedating antihistamines. Studies examining the efficacy and safety of the above treatments are summarized in Evidence Table 3. There were a total of 12 RCTs, 10 in seasonal allergic rhinitis patients and two in perennial allergic rhinitis patients. The median grade for methodological quality is rated B and the median grade for applicability is rated II. Seven studies were conducted in Europe, one in Canada and four in the U.S. A total of 1,693 patients were enrolled and 1,562 evaluated. Study participants ranged in age from under 12 to 92 years old, with eight of 12 studies focusing on the

15-66 age group. Seven of 10 seasonal allergic rhinitis studies required a positive allergen skin test result as an entrance criterion.

Eight randomized controlled clinical trials were identified in which a direct comparison between nonsedating and sedating antihistamines in the treatment of seasonal allergic rhinitis were undertaken. Three of these studies (including approximately 589 patients) implicated superior relief of nasal symptoms by the sedating antihistamines (Gutkowski, Del Carpio, Gelinas, et al., 1985; Johansen, Bjerrum, and Illum, 1987; Thoden, Druce, Furey, et al., 1998). One other study (including approximately 138 patients) indicated superior relief of nasal symptoms by the nonsedating antihistamine (Backhouse and Rosenberg, 1987). The remaining four studies (including approximately 507 patients) showed no difference with respect to nasal symptoms between the two treatment arms (Buckley, Buchman, Falliers, et al., 1988; Hugonot, Hugonot, and Beaumont, 1986; Malmberg, Grahne, Holopainen, et al., 1983; Pastorello, Ortolani, Gerosa, et al., 1987). These results are interpreted as indicating no consistent benefit of sedating antihistamines over nonsedating antihistamines with respect to symptom alleviation in allergic (seasonal) rhinitis. In most of these studies an array of symptoms was evaluated (including nasal itching, sneezing, rhinorrhea, nasal congestion, post nasal drainage), and in most cases changes in symptoms tended to correlate with one another with respect to favoring either sedating or nonsedating antihistamines. Accordingly, emphasis is placed upon the global evaluation of symptom change for the purpose of this reporting. Changes in ocular symptoms were not included in this data analysis.

Two additional studies did not give outcomes in terms of improvement of nasal symptoms. Gastpar and Dieterich (1982) studied changes in IgE values, and Weiler, Bloomfield, Woodworth, et al. (2000) studied side-effects.

An additional two RCTs were identified in which a direct comparison between nonsedating and sedating antihistamines in the treatment of perennial allergic rhinitis were undertaken. One of these studies (Brostoff and Lockhart, 1982) showed no statistical difference between the groups with respect to treatment of nasal symptoms with both treatments being assessed as extremely effective. The other study (Druce, Thoden, Mure, et al., 1998) showed significant benefits in favor of the sedating antihistamine brompheniramine over loratadine with respect to each nasal symptoms evaluated. These results are interpreted as indicating no consistent benefit of nonsedating antihistamines over nonsedating in perennial allergic rhinitis.

Table 7. Summary of randomized trials: sedating versus nonsedating antihistamines

Author Year UI	Study size	Applic-ability	Outcome-efficacy	Outcome-safety	Method-ological quality
Brostoff 1982 83014720 PAR	60	III	No statistical difference between chlorpheniramine and terfenadine. Both antihistamines not extremely effective in perennial rhinitis treatment.	Major adverse effects: Upset stomach, headache, and fatigue. Minor adverse effects: sedation.	B
Gastpar 1982 83100633 SAR	20	III	Significant decrease in IgE values with terfenadine compared to clemastine.	No major adverse effects. Minor adverse effects: sedation, and conjunctivitis.	B

Author Year UI	Study size	Applic-ability	Outcome-efficacy	Outcome-safety	Method-ological quality
Malmberg 1983 83253693 SAR	51	II	No significant difference between chlorpheniramine and astemizole in all nasal symptoms studied.	No major adverse effects. Minor adverse effects: Fatigue, palpitations, headache, GI upset.	B
Gutkowski 1985 86030956 SAR	177	II	Dexchlorpheniramine significantly improved rhinorrhea, nasal congestion, sneezing, itchy nose and total nasal symptom scores compared to terfenadine.	No major adverse effects. Minor adverse effects: Dizziness, somnolence, headache, and dry mouth.	B
Hugonot 1986 86248368 SAR	147	II	No significant differences between terfenadine and mequitazine in all nasal symptoms studied.	No major adverse effects. Minor adverse effects: Headache, blurred vision, somnolence, dizziness, and nausea.	B
Backhouse 1987 89062246 SAR	138	II	Terfenadine significantly improved sneezing, rhinorrhea, nasal blowing and nasal congestion scores compared to chlorpheniramine.	No major adverse effects.	B
Johansen 1987 87205847 SAR	42	II	Dexchlorpheniramine significantly improved sneezing, nasal congestion, and nasal itch scores compared to terfenadine.	No adverse effects noted.	B
Pastorello 1987 88016480 SAR	65	II	No significant difference between terfenadine and dexchlorpheniramine in effect on sneezing, rhinorrhea, congestion, itchy throat and ocular symptom scores.	No major adverse effects. Minor side-effects unspecified.	C
Buckley 1988 88131974 SAR	244	II	No significant difference between terfenadine and chlorpheniramine on all nasal symptoms studied.	No major adverse effects. Minor adverse effects: Headache, sedation, nausea, dryness of mouth, nose and throat	B

Author Year UI	Study size	Applic-ability	Outcome-efficacy	Outcome-safety	Method-ological quality
Druce 1998 98250349 PAR	338	II	Brompheniramine significantly improved rhinorrhea, nasal congestion, sneezing, nasal itch, itchy throat and ocular symptoms scores compared to loratadine.	Major adverse effects: Hypertension. Minor adverse effects: somnolence and dizziness.	A
Thoden 1998 98413360 SAR	370	II	Brompheniramine significantly improved sneezing, nasal congestion, rhinorrhea, and nasal itch scores compared to terfenadine.	No major adverse effects. Minor adverse effects: somnolence.	B
Weiler 2000 20143057 SAR	41	I	Mean coherence value 0.88 with diphenhydramine, 0.915 with fexofenadine, 0.92 with alcohol, and 0.9 with placebo.	No adverse effects.	A

Summary of the evidence from RCTs comparing other agents (cromolyn, leukotriene modifiers, sympathomimetics, ipratropium). Studies examining the efficacy and safety of cromoglycate and other agents are summarized in Evidence Table 4. There were two studies examining sympathomimetic agents, one study of an anticholinergic agent, and 32 studies of cromoglycate. Twenty-one randomized controlled studies were in seasonal allergic rhinitis patients and 14 in perennial allergic rhinitis patients. Twenty-four studies were conducted in Europe, one in Canada, one in South Africa, one in New Zealand, two in Australia, one in India, and five in the U.S. A total of 1,320 patients were enrolled and 1,212 evaluated. Study participants ranged in age from 12 to 76 years old. Fourteen of 21 seasonal allergic rhinitis studies required positive allergen skin test result as an entrance criterion.

In all studies except for two, significant improvements in symptoms of allergic rhinitis were reported in those patients treated with cromoglycate compared to those patients treated with placebo.

In 16 of the studies, three or more of the five common symptoms associated with allergic rhinitis (nasal itch, sneezing, rhinorrhea, nasal congestion, or postnasal drainage) were significantly improved by treatment with cromoglycate compared to placebo. No consistent pattern of nonresponsiveness to cromoglycate with respect to a given symptom was identifiable across the studies. In five of the 13 studies that indicated failure of some symptoms to respond to treatment with cromoglycate, congestion was identified as one of the nonresponsive symptoms.

Eighteen studies (14/18 studies of seasonal allergic rhinitis and 4/11 studies of perennial allergic rhinitis) included documentation of patient preference or patient willingness to use the drug in the future. In 17 studies there was a clear-cut preference for the active ingredient

(cromoglycate). One study of cromoglycate in perennial allergic rhinitis fails to document a significant improvement in symptoms or a patient preference for future usage.

Overall, cromoglycate is an effective treatment for reducing symptoms associated with allergic rhinitis (30 of 32 studies). It seems to have higher efficacy in seasonal allergic rhinitis than it does in perennial allergic rhinitis. In those studies that looked at different dosing regimens, higher doses (including higher frequency of dosing) were more effective.

A single study was identified in seasonal allergic rhinitis looking at the efficacy of nedocromil compared with placebo in reducing symptoms of allergic rhinitis. It showed a significant reduction in daily nasal itch and rescue antihistamine usage. It showed no benefits for symptoms of sneezing, rhinorrhea, and nasal congestion even though 63 percent preferred this medication and 30 percent preferred placebo.

Oral alpha-adrenergic agents, such as pseudoephedrine, phenylephrine and phenylpropanolamine cause nasal vasoconstriction. Two clinical trials were identified looking at the effects of decongestant drugs in allergic rhinitis and suggest some benefit in relief of nasal congestion but not other symptoms.

Table 8. Summary of randomized trials: Other agents (cromolyn, leukotriene modifiers, sympathomimetics, ipratropium)

Author Year UI	Study size	Applic-ability	Outcome-efficacy	Outcome-safety	Method-ological quality
Green 1966 67044478 PAR	33	III	Significantly longer duration of decongestion with oxymetazoline than with phenylephrine.	No major adverse effects. Minor adverse effects- local nasal burning.	C
Coffman 1971 72025239 SAR	35	III	56% successful patient responses with cromoglycate vs 33% successful patient responses with placebo.	No major adverse effects. Minimal minor adverse effects.	B
Engstrom 1971 72012845 SAR	39	II	Cromoglycate significantly improved all nasal symptom scores. No significant difference for ocular symptoms.	ND	B
Holopainen 1971 71066421 SAR	27	II	Cromoglycate significantly reduced sneezing, nasal itch, nasal congestion, and rhinorrhea scores compared with placebo.	No major adverse effects. Minor adverse effects: itchy throat.	B
Anderson 1972 73004602 SAR	18	II	Cromoglycate significantly reduced rhinorrhea, sneezing, and ocular symptoms compared with placebo.	No major adverse effects Minor adverse effects: Nasal irritation, nasal congestion, nausea, and headache.	B

Author Year UI	Study size	Applic-ability	Outcome-efficacy	Outcome-safety	Method-ological quality
Hopper 1972 73166771 PAR	38	II	Cromoglycate significantly improved sneezing, rhinorrhea, and nasal congestion. Significantly higher number of successful treatments with cromoglycate compared to placebo.	Major and minor adverse effects not indicated.	C
Shore 1972 72159215 SAR	41	III	Cromoglycate significantly reduced total nasal symptom score compared to placebo.	No major adverse effects. Minor adverse effects: nausea, sneezing, cough, and rash.	C
Thorne 1972 73089706 PAR	40	II	Cromoglycate significantly reduced sneezing, rhinorrhea, and sense of smell. No significant difference in treatment of nasal congestion and nasal peak flow. Total symptom score of 2608 with cromoglycate vs. score of 3053 with placebo.	No major adverse effects. Minor adverse effects: sneezing and nasal soreness.	C
Blair 1973 74098976 SAR	40	II	Cromoglycate significantly improved rhinorrhea, congestion, itching and sneezing compared with placebo.	No major adverse effects. Minor adverse effects: Nasal irritation, sore throat, headache, and unpleasant taste.	B
Hetherington 1973 73166772 SAR	40	II	Cromoglycate significantly improved total nasal symptom score compared to placebo.	No major adverse effects. Minor adverse effects: nasal irritation.	B
Illum 1973 74133656 SAR	37	II	No significant difference between cromoglycate and placebo for sneezing, rhinorrhea, nasal congestion and nasal itch scores.	No adverse effects.	C

Author Year UI	Study size	Applic-ability	Outcome-efficacy	Outcome-safety	Method-ological quality
Jenssen 1973 74098975 SAR	10	III	Cromoglycate significantly improved nasal resistance.	ND	C
Manners 1973 74098980 SAR	50	II	Cromoglycate significantly reduced sneezing, rhinorrhoea, nasal congestion, nasal itch, and ocular symptom score.	ND	B
Sunderman 1973 73237443 PAR	74	II	Cromoglycate significantly improved rhinorrhea, sneezing, and nasal congestion. Significant preference for cromoglycate compared to placebo: 53 patients preferred cromoglycate, None preferred placebo, and 15 had no preference.	No major adverse effects. Minor adverse effects: sneezing.	C
Brain 1974 76192641 PAR	34	III	Cromoglycate significantly reduced sneezing, rhinorrhea, congestion and nasal itch scores. Significant patient preference for cromoglycate.	No major adverse events. Minor adverse effects: headache, dry/ sore throat, dizziness, and nasal irritation.	C
Blair 1975 75185857 PAR	20	II	Cromoglycate significantly improved sneezing, nasal congestion, and nasal itch compared to placebo. No significance in treatment of rhinorrhea. 14 patients preferred cromoglycate, 3 patients preferred placebo, and 1 patient had no preference.	No major adverse effects. Minor adverse effects: nasal irritation and sore throat.	C

Author Year UI	Study size	Applic-ability	Outcome-efficacy	Outcome-safety	Method-ological quality
Fagerberg 1975 75221540 PAR	23	II	Cromoglycate significantly improved sneezing and rhinorrhea. No significant difference for treatment of congestion and nasal itch. Significantly more preferences for Cromoglycate: 14 patients preferred cromoglycate vs. 5 patients preferred placebo.	No major adverse effects. Minor adverse effects: nasal itch/ irritation, and sneezing.	B
Girard 1975 76042257 PAR	30	II	Cromoglycate significantly reduced sneezing, nasal congestion, nasal itch, eosinophilia count, and nasal outflow resistance. No significant difference in treatment of rhinorrhea. Significant clinician-rated and patient-rated preference for cromoglycate.	No major adverse effects. Minor adverse effects: nasal irritation and headache.	B
Holopainen 1975 76084510 PAR	49	II	Cromoglycate significantly improved nasal congestion, nasal itch, and nasal patency. According to patient diaries only, not clinician evaluation, cromoglycate significantly reduced sneezing and rhinorrhea. Not significant for eosinophilia count or antihistamine use.	No major adverse effects. Minor adverse effects: nasal irritation, headache, eczema, and tiredness.	C
Leiferman 1975 SAR	26	II	Cromolyn sodium significantly reduced sneezing, coughing, nasal congestion, and rhinorrhea scores compared with placebo.	No major adverse effects. Minor adverse effects: nasal irritation.	C

Author Year UI	Study size	Applic-ability	Outcome-efficacy	Outcome-safety	Method-ological quality
Wilson 1975 76101270 SAR	39	II	No significant difference between cromoglycate groups and placebo. 53% preferred cromoglycate vs 21% preferred placebo.	No major adverse effects. Minor adverse effects: nausea, headache, sneezing, nasal dryness and irritation, and epistaxis.	B
Hasegawa 1976 77001950 SAR	38	II	Cromoglycate significantly improved nasal airway resistance and total nasal symptom score compared to placebo.	ND	C
Knight 1976 76238158 SAR	77	II	Significant improvement in total nasal score with cromoglycate vs. placebo.	No major adverse effects Minor adverse effects: sneezing, coughing, and headache.	C
Backman 1977 78120309 PAR	91	II	Higher preference for cromoglycate powder and solution compared to placebo. 23 patients preferred cromoglycate solution vs 10 patients preferred placebo. 31 patients preferred cromoglycate powder vs 3 patients preferred placebo.	No major adverse effects. Minor adverse effects: nasal irritation, headache, eczema, and tiredness.	C
Frostad 1977 78062986 SAR	44	II	Cromoglycate significantly reduced sneezing, rhinorrhea, nasal congestion and total nasal symptom scores compared with placebo.	No major adverse effects. Minor adverse effects: Nasal irritation.	C
Handelman 1977 77119242 SAR	104	II	Cromolyn sodium significantly reduced sneezing and rhinorrhea scores compared with placebo.	No major adverse effects Minor adverse effects- nasal irritation and sneezing.	B

Author Year UI	Study size	Applic-ability	Outcome-efficacy	Outcome-safety	Method-ological quality
Lofkvist 1977 77131029 PAR	49	II	No significant difference between cromoglycate and placebo for symptom-free condition, patient preference, or diary card data.	No major adverse effects. Minor adverse effects: dryness and irritation in nose and throat	B
McDowell 1977 77264819 SAR	17	II	Cromoglycate reduced sneezing and rhinorrhea symptom scores compared with placebo; non-significant difference.	No major adverse effects. Minor adverse effects: Transient burning and stinging, rash, pruritus, nausea, dizziness, epistaxis and headache.	B
Posey 1977 78063003 SAR	34	II	Cromolyn sodium significantly reduced rhinorrhea, nasal congestion, sneezing, nasal itch, itchy throat, mouth breathing, post-nasal drip, nose blowing, and eye irritation compared to placebo.	Major adverse effects: severe chemical rhinitis. Minor adverse effects: Nasal irritation, rhinorrhea, and sneezing.	B
Van der Bijl 1977 78033928 SAR	40	II	Cromoglycate significantly reduced rhinorrhea, nasal congestion, sneezing, nasal itch, and itchy eyes compared to placebo.	No major adverse effects. Minor adverse effects: nasal irritation, dizziness, and sneezing.	B
Warland 1977 77262676 PAR	21	II	No significant difference between two treatments. 6 out of 17 patients preferred cromoglycate vs. 2 preferred placebo. 9 had no preference.	No major adverse effects. Minor adverse effects: Nasal irritation, headache, nausea, and others.	C
Sorri 1979 79205990 SAR	38	II	Cromoglycate significantly improved rhinorrhea score only vs. placebo. Significant patient preference for cromoglycate.	ND	B

Author Year UI	Study size	Applic-ability	Outcome-efficacy	Outcome-safety	Method-ological quality
Sipila 1987 88110026 SAR	59	II	Nedocromil sodium significantly reduced nasal itch and rescue antihistamine usage compared to placebo.	No major adverse effects Minor adverse effects: sneezing, unpleasant taste, nasal and throat irritation, and dizziness.	B
Shaikh 1995 96080200 PAR	118	II	Ephedrine significantly improved sneezing, rhinorrhea, nasal blockage, and postnasal drip. Overall symptom score of 3.5 with ephedrine vs. score of 0.8 with placebo.	Major adverse effects: palpitations. Minor adverse effects: heaviness of head, nasal burning sensation, and swallowing of negligible amounts of fluids	B
Georgitis 1998 98372425 PAR	45	I	No significant differences between dosages of ipratropium. Both significantly reduced rhinorrhea and postnasal drip.	No major adverse effects. Minor adverse effects: pharyngitis, taste perversion, epistaxis, dizziness, dry mouth, chest pain, fever, headache, paresthesia, pruritus, dry skin, anxiety, asthma, bronchitis, dyspepsia, insomnia, pain, emotional upset, and tachycardia.	A

What are the side-effects/adverse events due to: antihistamines, nasal corticosteroids, sympathomimetics, leukotriene modifiers? *(Question 3.2b)*

[See Evidence Tables 2-3]

A majority of the studies reported no major adverse events associated with the use of antihistamines. In those studies where major adverse events were reported, somnolence, dry mouth, dizziness and headache were identified most frequently. These symptoms were seen almost exclusively with the sedating antihistamines.

Epistaxis, headache and pharyngitis were the most frequently reported side-effects of nasal corticosteroids. None of the studies reported systemic side effects from intranasal steriods, in the short-term treatment studies analyzed. However, a recent study (Skoner, Rachelefsky, Meltzer et al, 2000) reported on the suppressive effect of belcomethasone nasal spray on bone growth in children and all nasal steroid preparations in the United States now warn of this adverse event. Agents with less systemic bio-availability may be devoid of these risks (Allen, 2000).

No major adverse events were reported in studies of cromolyn. Minor reported side-effects included a high frequency of nasal irritation (18/29 studies), headache, and nasal congestion.

How do efficacy and side-effects of treatments vary by severity of rhinitis or patient characteristics? *(Question 3.3)*

We found no data to address this question. None of the studies categorized patients by disease severity or concurrent disease when addressing either efficacy or safety.

Meta-analyses

Identify and review relevant published meta-analyses in the following treatment areas:

Antihistamines vs. placebo in allergic rhinitis. No meta-analyses were identified.

Immunotherapy versus placebo in allergic rhinitis. Ross, Nelson, and Finegold (2000) report a meta-ananlysis of the efficacy of specific immunotherapy in the treatment of allergic rhinitis. Inclusion criteria required of the published studies were prospective nature, double blinding, placebo control and citation in MEDLINE® between 1966 and 1996. Data from sixteen studies (including 759 patients) were combined. Fifteen of 16 studies concluded that specific immunotherapy was effective and the analysis showed a significant effect in improvement in both symptom control and symptom medication scores in allergic rhinitis.

Nasal corticosteroids versus placebo in allergic rhinitis. No meta-analysis addressed the specific comparison posed in this question. However a meta-analysis looking at studies which compared nasal corticosteroids to oral antihistamines by Weiner, Abramson, and Puy (1998) is identified and has been discussed above.

The efficacy of treatment in seasonal versus perennial allergic rhinitis. No meta-analyses were identified addressing this question.

Question 4. How does treatment of allergic rhinitis impact on the development of asthma?

What is the likelihood of developing asthma with untreated allergic rhinitis? *(Question 4.1)*

It has long been recognized that there is an association between allergic rhinitis and asthma. A large number of cross-sectional studies have shown the prevalence of allergic rhinitis in asthmatic patients to be between 28 and 78 percent, compared with approximately 20 percent in the general population. In addition, prevalence of asthmatic symptoms amongst allergic rhinitis patients is reportedly between 19 and 39 percent of patients, again significantly higher than the 5 percent rate in the general population (Blair, 1977; Pedersen and Weeke, 1983; Settipane, 1986; Smith, 1983). Other cross-sectional studies have attempted to elucidate the temporal relationship between allergic rhinitis and asthma. In one study of 7662 subjects, 49 percent of patients with both asthma and allergic rhinitis reported onset of rhinitis symptoms prior to asthma symptoms, and 25 percent of patients experienced the onset of asthma within one year of developing allergic rhinitis (Pedersen and Weeke, 1983). Other studies demonstrated a similar temporal relationship. In addition, it is known that patients with allergic rhinitis commonly exhibit bronchial hyperreactivity. However, in order to illustrate a causal relationship between allergic rhinitis and asthma, well-conducted prospective cohort studies are necessary. We identified two such studies in our literature search. The first study (Settipane, Hagy, and Settipane, 1994) followed a group of college students for 23 years and found that those students with allergic rhinitis at the beginning of the study were three times more likely to develop asthma during followup than non-atopic controls. A similar study by Anderson, Pottier, and Strachan (1992) followed 7,225 children from birth to age 23 and found that children with allergic rhinitis were 2.7 to 3.0 times more likely to develop asthma during followup.

How does treatment of allergic rhinitis affect the likelihood of developing asthma? *(Question 4.2)*

No study was identified which addressed the question of whether treatment of allergic rhinitis can actually prevent the development of asthma. The data, however, suggest a mechanistic link between these two diseases and an ability to impact certain characteristics of asthma by use of nasal corticosteroids in treatment of allergic rhinitis. Conventional doses of cetirizine, loratadine and oral decongestants have been reported to improve asthma symptoms and pulmonary function in patients with allergic rhinitis (Corren, Harris, Aaronson, et al., 1997; Grant, Nicodemus, Findlay, et al., 1995).

How does treatment of allergic rhinitis affect the likelihood of developing bacterial sinusitis? *(Question 4.3)*

It is known that there is a link between allergic rhinitis and rhinosinusitis. Cross-sectional studies have shown an increased prevalence of acute and chronic bacterial sinusitis amongst allergic rhinitis patients. Similarly there is an increased prevalence of atopy and allergic rhinitis amongst patients with chronic bacterial sinusitis. However, in order to determine the effect of treatment of allergic rhinitis on the development of bacterial sinusitis, data from prospective studies on the outcomes of treated and untreated allergic rhinitis are required. We identified no studies meeting these criteria in our literature search.

Chapter 4. Conclusions

Overview

This report summarizes the scientific evidence on four specific questions and associated subquestions in the diagnosis and treatment of allergic and nonallergic rhinitis. The results presented in Chapter 3 are based on the screening of 3,354 MEDLINE titles and 228 full articles, 86 of which were the RCTs and the two prospective cohort studies analyzed in this report. The analysis also describes the limitations of the existing evidence base related to the questions of interest.

General Observations on the Studies Analyzed

In addition to the conclusions described in this chapter, we believe that the data support the following observations:

- Most of the clinical trials were supported by pharmaceutical companies.
- There are no studies that addressed the specific question of practical clinical interest: Is differentiating allergic rhinitis from nonallergic rhinitis important? Are treatments or outcomes different? Differentiation of allergic from nonallergic rhinitis is important if treatments are significantly different and if the outcomes of treatment including prevention of complications differ in response to those treatments. However, similar treatments are frequently employed in the two conditions.
- The number and size of trials in nonallergic rhinitis were small overall. There were 13 trials, from the period 1982 through 1999, which enrolled some 450 patients. In several comparisons of interest, trials were very small - 20 to 30 patients. There were no studies examining the efficacy of leukotriene modifiers. There were only two randomized controlled studies, with 90 enrolled patients, which examined the role of and oral decongestants for the relief of symptoms of nasal congestion. The FDA has urged companies marketing that decongestant, phenylpropolamine, to voluntarily withdraw the drug from the marketplace, while it initiated regulatory actions to mandate such withdrawals.
- Almost all the studies analyzed were RCTs, though most of the evidence for efficacy is based on studies that were given a 'B' or 'C' methodological quality rating, indicating the failure to meet high standards for methodological quality.
- There were no specific studies of the pediatric population. Even though some studies may have enrolled patients in pediatric ranges, separate data was not reported for this subgroup. Therefore, no specific conclusions could be drawn for the pediatric population.

Conclusions about Specific Questions

1. How does one diagnose allergic and nonallergic rhinitis (especially vasomotor rhinitis)?

In this analysis, there were no studies identified hat specifically sought to differentiate between allergic and nonallergic rhinitis on the basis of clinical symptoms, or signs on physical

examination, or the presence or absence of comorbid conditions. More importantly, no studies addressing the question of what minimum level of diagnostic testing is necessary to differentiate between allergic and nonallergic rhinitis met the criteria described in the methods section of this report. No diagnostic test has been specifically developed to diagnose nonallergic rhinitis.

Given the absence of studies addressing this question, we can only report that, based on current clinical practices and the analysis of the inclusion criteria employed in studies of nonallergic rhinitis, diagnostic testing rather than symptoms or signs is generally recommended to differentiate isolated vasomotor rhinitis from allergic rhinitis. Diagnostic tests employed fall into two categories: allergy skin testing and RAST.

What is the *minimum* level of testing necessary to differentiate allergic from nonallergic rhinitis?

The minimum level of testing necessary to confirm or exclude a diagnosis of allergic rhinitis has not been established in the literature. The study by Ng, Warlow, Chrishanthan, et al. (2000) suggests that total serum IgE may be as useful as specific allergy skin prick tests, which, in turn, are more useful than RAST-type testing in confirming a diagnosis of allergic rhinitis.

2. Is differentiating allergic from nonallergic rhinitis important? Are treatments different? Are outcomes different?

While the importance of distinguishing between allergic and nonallergic rhinitis has not been addressed directly and specifically by the published literature, the results suggest that this distinction is important. Different modalities of pharmacologic therapy for each diagnosis are supported by the literature and, perhaps more importantly, complications or comorbid conditions such as asthma and sinusitis can be impacted by the choice of pharmacotherapy for the underlying rhinitis. One of the potential benefits of differentiating allergic from nonallergic rhinitis would be that only allergic rhinitis can benefit from environmental control measures and immunotherapy.

Certain treatment modalities are well-established in the management of allergic rhinitis (for example, intranasal corticosteroids and oral antihistamines). A small number of studies (3, with a total of 97 patients) have looked at the benefit of nasal steroids in the treatment of nonallergic rhinitis, one with conficting results. However, intranasal corticosteroids are recommended for long-term therapy in nonallergic rhinitis. The FDA has approved two nasal corticosteroids for treatment of nonallergic rhinitis and has also approved one nasal topical product – azelastine (an H1 anithistamine) for treatment of vasomotor rhinitis.

There is some evidence for linkage between allergic rhinitis and asthma and there is also a small body of evidence indicating that appropriate treatment of allergic rhinitis by intranasal corticosteroids may have salutary effects on the features of asthma. Sinusitis is also a well-described secondary complication of allergic rhinitis. Therefore, it is possible that inappropriate diagnosis and treatment of allergic rhinitis may increase the pharmacoeconomic and socioeconomic burden of sinusitis.

3. How does one treat nonallergic and allergic rhinitis?

Nonallergic Rhinitis - Efficacy of Treatments

Antihistamines (all classes) versus placebo. Only one published study meeting the criteria for inclusion examined the role of antihistamines in the treatment of nonallergic rhinitis. Because the antihistamine was used as part of an antihistamine-decongestant combination product, outcomes related to the antihistamine component of this drug cannot be separately identified. Two additional

studies published after the completion of the literature search (Banov and Lieberman, 2001, Gehanno, Deschamps, Garay et al., 2001) demonstrated the efficacy of azelastine nasal spray for the treatment of vasomotor rhintis.

Effect of nasal corticosteroids. Though it is commonly assumed that many physicians recommend a therapeutic trial with nasal corticosteroids in the management of nonallergic rhinitis, there were only three studies identified which examined the efficacy of nasal corticosteroids in the treatment of nonallergic rhinitis. Two of the three studies employed budesonide and the other used beclomethasone. One study indicated that the symptoms of nasal congestion could be improved by budesonide without alteration in other symptoms of nonallergic rhinitis. In the other two studies, comparison was made between the nasal corticosteroid and nasal ipratropium bromide. One study favored the nasal corticosteroid and the other study failed to differentiate between the two on the basis of symptom relief. Intranasal corticosteroids have been recommended for long term therapy for nonallergic rhinitis (Settipane and Lieberman, 2001) and two nasal corticosteriods have FDA approval.

Sympathomimetics versus placebo. Only two randomized controlled studies were identified which looked at the role of oral decongestants (phenylpropanolamine) in treatment of nonallergic rhinitis. In both studies emphasis was placed on relief of symptoms of nasal congestion. Phenylpropanolamine was demonstrated in both trials to be helpful in the management of nasal congestion when used at sufficient dosages (e.g. 100 mg per day dosage). No major impact on the other associated symptoms experienced by patients with nonallergic rhinitis was observed in these studies.

While small in number, these studies do suggest a role for decongestants in treatment of nonallergic rhinitis with specific emphasis on the symptoms of nasal congestion. However, the FDA has urged companies marketing phenylpropanolamine to voluntarily withdraw the drug from the market while the FDA initiated regulatory actions to mandate such withdrawals. The only currently available orally active decongestant, pseudoephedrine, was not identified in any of the clinical trials concerning management of nonallergic rhinitis.

Leukotriene modifiers. No studies were identified looking at the efficacy of leukotriene modifiers in the treatment of nonallergic rhinitis.

Anticholinergics. Each of five studies identified in the analysis indicated a significant benefit from use of nasal ipratropium bromide (a topically applied anticholinergic agent) in the treatment of the symptom of rhinorrhea (increased nasal secretions) associated with nonallergic or vasomotor rhinitis. Relief of the symptom is dose-dependent - dosing often up to four times a day was required to achieve a significant clinical benefit. Other symptoms such as nasal congestion, nasal itching and sneezing do not appear to be benefited by ipratropium bromide.

Cromoglycate. Both of the two RCTs that examined the effects of cromoglycate in nonallergic rhinitis recorded improvement in symptoms of rhinitis with active treatment compared to placebo. Not all symptoms were improved by cromoglycate in either study and the specific symptoms which benefited most differed between these two studies. However, although small in quantity, the data appear to indicate that sodium cromoglycate may have a role in the management of nonallergic rhinitis.

Side-effects/adverse events. There were no side-effects or adverse events reported in the studies of antihistamines or nasal corticosteroids. However, a recent study (Skoner, Rachelefsky, Meltzer et al, 2000) reported on the suppressive effect of belcomethasone nasal spray on bone growth in children and all nasal steroid preparations in the United States now warn of this adverse event. Agents with less systemic bio-availability may be devoid of these risks (Allen, 2000).

In the two studies examining cromoglycate, no significant adverse events were associated with use. In only one of the two studies involving sympathomimetics were adverse events such as drowsiness, nausea and headache described. This study (Broms and Malm, 1982), involving a combination product (antihistamine plus decongestants) also had patients who described micturition difficulties, which were presumed to be related to the anticholinergic activity of the antihistamine component. Significant side-effects of nasal dryness and nasal irritation were recorded in three of the five studies looking at ipratropium in the treatment of nonallergic rhinitis. Overall, these treatment modalities are very well tolerated and devoid of major side-effects.

In conclusion, the literature concerning treatment of nonallergic rhinitis is scant and no single agent is identified as being uniformly effective in controlling all the symptoms associated with this condition. All treatments appear relatively free of major side-effects. Oral decongestants are effective in controlling the symptom of nasal congestion and ipratropium bromide is beneficial in the management of rhinorrhea. With the exception of azelastine for treatment of vasomotor rhinitis, there is little published evidence for use of antihistamines or nasal corticosteroids for the management of nonallergic rhinitis.

Allergic Rhinitis - Efficacy of treatments

Antihistamines versus nasal corticosteroids. There is strong evidence for the beneficial effects of nasal corticosteroids in the management of allergic rhinitis, and these agents are significantly superior to antihistamines.

The recent meta-analysis by Weiner (Weiner, Abramson, and Puy, 1998) of 17 RCTs published up to 1997 compared intranasal corticosteroids with antihistamines in the treatment of seasonal and/or perennial allergic rhinitis. The analysis included several different nasal corticosteroid preparations and several different antihistamines including both nonsedating and sedating antihistamines. For the six nasal symptoms studied as well as for overall nasal symptoms score, nasal corticosteroids produced significantly greater relief than did oral antihistamines. The specific symptoms that were improved included nasal blockage, nasal discharge, sneezing, nasal itching, and postnasal drainage. There were no significant differences identified between treatments for nasal discomfort, nasal resistance, or eye symptoms.

Our search identified eight additional studies that were not included in the Weiner meta-analysis. Seven of the studies favored intranasal corticosteroids over antihistamines both with respect to improvement in global nasal symptoms as well as most individual nasal symptoms. One study showed better symptom improvement with cetirizine alone over fluticasone alone. Thus, the overwhelming majority of studies show very clear benefits for the use of intranasal corticosteroids over either sedating or nonsedating antihistamines for relief of symptoms of nasal allergy. These results are similar for seasonal allergic rhinitis and perennial allergic rhinitis.

Antihistamines versus immunotherapy. No RCTs were identified directly comparing immunotherapy with antihistamines in the treatment of seasonal and/or perennial allergic rhinitis. Immunotherapy is generally considered a long-term disease modifying treatment measure requiring months to years of treatment whereas antihistamines are often used for immediate symptom relief. Therefore direct comparisons with respect to effectiveness/efficacy are not likely to be undertaken.

Nasal corticosteroids versus immunotherapy. For reasons similar to those above, no RCTs were identified which directly compared immunotherapy with intranasal corticosteroids in the treatment of seasonal and/or perennial allergic rhinitis.

Sedating versus nonsedating antihistamines. With respect to symptom alleviation in allergic (seasonal) rhinitis, study results indicate no consistent benefit of sedating antihistamines over

nonsedating antihistamines. In the eight randomized controlled clinical trials comparing sedating and nonsedating antihistamines in the treatment of seasonal allergic rhinitis, approximately equivalent numbers of patients seemed to benefit in terms of symptom relief from nonsedating antihistamines as from sedating antihistamines, though the side effect profile favors nonsedating antihistamines. Similar observations were seen with perennial allergic rhinitis except perhaps for a tendency to favor sedating antihistamines. The benefits were seen across a range of symptoms with no specific symptom appearing to be better improved by one class of treatment or the other.

Other agents (cromolyn, leukotriene modifiers sympathomimetics, ipratropium). Studies provide strong support for the beneficial effect of cromoglycate in the management of both seasonal and perennial allergic rhinitis. Eighteen studies (14/18 studies of seasonal allergic rhinitis and 4/11 studies of perennial allergic rhinitis) included documentation of patient preference or patient willingness to use the drug in the future. In 17 studies there was a clear-cut preference for the active ingredient (cromoglycate). Cromoglycate seems to have higher efficacy in seasonal allergic rhinitis than it does in perennial allergic rhinitis. In those studies that looked at different dosing regimens, higher doses (including higher frequency of dosing) were more effective.

Two clinical trials were identified looking at the effects of decongestant drugs in allergic rhinitis and suggest some benefit in relief of nasal congestion but not other symptoms. The trial of ipratropium documented no significant differences between dosages of ipratropium but significant reduction in rhinorrhea and postnasal drip.

Side-effects/adverse events. A majority of the studies reported no major adverse events associated with the use of antihistamines. In those studies where major adverse events were reported, somnolence, dry mouth, dizziness, and headache were identified most frequently. These symptoms were seen almost exclusively with the sedating antihistamines.

Epistaxis, headache, and pharyngitis were the most frequently reported side-effects of nasal corticosteroids. None of the studies reported systemic side-effects from intranasal corticosteroids in the short-term treatment studies analyzed. However, a recent study (Skoner, Rachelefsky, Meltzer et al, 2000) reported on the suppressive effect of belcomethasone nasal spray on bone growth in children and all nasal steroid preparations in the United States now warn of this adverse event. Agents with less systemic bio-availability may be devoid of these risks (Allen, 2000).

No major adverse events were reported in studies of cromolyn; minor reported side-effects included a high frequency of nasal irritation, headache, and nasal congestion.

Effect of Selected Variables on Effectiveness/efficacy and Side-effects

We found no data to address this question. None of the studies categorized patients by disease severity or concurrent disease when addressing either efficacy or safety.

Review of Relevant Published Meta-analyses

Two relevant meta-analyses were identified in the published literature. The meta-analysis of randomized controlled clinical trials comparing the use of nasal corticosteroids and antihistamines in the management of allergic rhinitis has been described above (Weiner, Abramson, and Puy, 1998). It shows a strong tendency to significantly greater improvement in all symptoms of allergic rhinitis by use of nasal corticosteroids when compared to either sedating or nonsedating antihistamines.

In a recent meta-analysis of specific allergen immunotherapy in the management of allergic rhinitis, Ross, Nelson, and Finegold (2000) document significant benefit for this therapy in the

management of allergic rhinitis. Benefit is seen both with respect to symptom control and symptom medication usage. No other meta-analysis of interest was identified in this analysis.

4. How does treatment of allergic rhinitis impact on the development of asthma?

Likelihood of Developing Asthma with Untreated Allergic Rhinitis

As our understanding of allergic rhinitis and asthma is increasing, it is becoming clear that the pathophysiology of the two diseases is very similar. The inflammation seen in the tissues is of similar type in both conditions and many of the inflammatory mediators appear to be similar. Furthermore, in addition to the high frequency of concurrence of these diseases in individual patients, there is now evidence of measurable abnormalities in the airways of patients without clinical manifestations of asthma who suffer with allergic rhinitis. Thus, subclinical asthma appears to be identifiable in patients with allergic rhinitis.

Studies addressing the temporal relationship between onset of rhinitis symptoms and onset of asthma symptoms have revealed that a significant proportion of patients experience rhinitis symptoms in advance of the development of clinical symptoms of asthma. A small number of prospective cohort studies (Anderson, Pottier, and Strachan, 1992; Settipane, Hagy, and Settipane, 1994) have been performed and demonstrate an increased likelihood of developing asthma over time in patients with allergic rhinitis.

Effect of Treatment of Allergic Rhinitis on the Likelihood of Developing Asthma

No study was identified which addressed the question of whether treatment of allergic rhinitis can actually prevent the development of asthma. The data, however, suggest a mechanistic link between these two diseases and an ability to impact certain characteristics of asthma by use of nasal corticosteroids in treatment of allergic rhinitis. Conventional doses of cetirizine, loratadine and oral decongestants have been reported to improve asthma symptoms and pulmonary function in patients with allergic rhinitis.

Effect of Treatment of Allergic Rhinitis on the Likelihood of Developing Bacterial Sinusitis

The link between allergic rhinitis and rhinosinusitis is known. Cross-sectional studies have shown an increased prevalence of acute and chronic bacterial sinusitis amongst allergic rhinitis patients. Similarly, there is an increased prevalence of atopy and allergic rhinitis amongst patients with chronic bacterial sinusitis. However, in order to determine the effect of treatment of allergic rhinitis on the development of bacterial sinusitis, data from prospective studies on the outcomes of treated and untreated allergic rhinitis is required. We identified no studies meeting these criteria in our literature search.

Chapter 5. Future Research

A paucity of rigorous data was identified within the existing published literature on allergic rhinitis. The lack of relevant high-quality evidence required that nearly every key question be answered on the basis of suboptimal or incomplete data.

Better Assessment of Allergic Rhinitis is Required

Studies that have focused on nonallergic rhinitis have arrived at this diagnosis by exclusion of allergic diseases (conventional allergy skin testing and/or RAST). There is no specific diagnostic test for nonallergic rhinitis. Until the mechanisms underlying vasomotor rhinitis have been studied further, it is unlikely that a diagnostic test will be developed. The minimum amount of testing required to differentiate between these two conditions remains to be determined. Important questions needing to be addressed include: Does one need a full panel of inhalant aeroallergen skin testing? If so, how big does this panel need to be, and should it vary by geographic region? Might it be feasible to combine groups of similar allergens as a screening panel? For example, a grouping covering the important indoor allergens such as house dust mites, cockroach, cat allergens, and dog allergens; a grouping covering the dominant springtime outdoor aeroallergens (representative local tree and grass pollen species); a grouping covering the dominant outdoor fall aeroallergens (ragweed and other weed pollens); and a grouping covering a mixture of mold spores might prove informative and useful as a screening panel. A similar approach might be applicable to RAST, thus decreasing the number of individual tests (and therefore costs) required. It would be valuable to investigate whether simpler laboratory tests such as measurement of total serum IgE or total eosinophil count might be useful in diagnosing or excluding allergic rhinitis.

One of the major advantages of determining whether allergens are responsible for the patient's condition relates to the benefit that would accrue to the patient from specific allergen avoidance through environmental modification. It would be useful to investigate whether recommendation or implementation of standard measures to minimize exposure to indoor aeroallergens such as house dust mites, pet allergens, and cockroach might be cost effective in the management of chronic rhinitis even in the absence of differentiation between allergic and nonallergic rhinitis and even without determining a patients precise allergic sensitivities.

Additional Studies are Needed to Address Specific Questions

It is not infrequent to encounter patients who claim to derive relief of symptoms of nonallergic rhinitis from use of antihistamines, and azelastine (an H1 antihistamine) is effective for treatment in vasomotor rhinitis. Since there is no evidence that histamine release is involved in the symptoms of nonallergic rhinitis, it is possible that the antihistamines are helping by improvement of rhinorrhea due to their anticholinergic effects, or by some other, as yet unidentified mechanism. This potential benefit is clearly worthy of further study. It is also possible, since many over-the-counter antihistamine preparations in fact are combined preparations that include nasoactive oral agents, that nasal decongestion provided by this agent is the basis of the symptom relief reported by the patients. These possibilities should be teased out by performing specific studies looking at the role of antihistamines in the management of nonallergic rhinitis. If antihistamines are indeed useful

in treatment of nonallergic rhinitis then the need to differentiate between allergic and nonallergic rhinitis would be lessened.

Many of the newer or second-generation antihistamines have insignificant anticholinergic properties. Studies of these agents may help differentiate any benefit from true antihistaminic activity from the benefit associated with the drying provided by anticholinergic mechanisms. Additionally, a new class of antihistamine agents known as H3 receptor antagonists has the potential to offer significant decongestant effects by inhibiting presynaptic mediator release in the nasal tissues, when used in association with an H1 receptor antagonist. Such an agent may offer the benefit of decongestion without the undesirable side-effects such as hypertension and agitation often associated with the vasoactive decongestants (McLeod, Mingo, Herczku, et al., 1999).

Further studies of the role of nasal corticosteroids in nonallergic rhinitis are necessary. Many physicians probably use nasal corticosteroids as a therapeutic trial in the management of nonallergic rhinitis but few studies exist in the published literature documenting that this is a helpful strategy. For reasons similar to those stated for antihistamines, if nasal corticosteroids can be documented to be helpful in nonallergic rhinitis, the need to differentiate allergic from nonallergic rhinitis may be lessened. It might be worth determining how widespread the use of nasal corticosteroids is in patients with nonallergic rhinitis amongst practitioners and to evaluate whether there is any downside to their use.

The potential benefit of cromoglycate in nonallergic rhinitis warrants further study. It is now an over-the-counter preparation with minimal side-effects and two studies have shown benefit for cromoglycate in nonallergic rhinitis. The mechanism of action of this medication is poorly understood as are the mechanisms underlying a majority of cases of nonallergic rhinitis. Accordingly, this may prove a fruitful line of investigation both with respect to disease mechanisms and development of new therapeutics.

Allergen avoidance, after specific diagnostic testing to identify the specific allergic sensitivities is a well-founded treatment recommendation, routinely employed as the first step in the management of allergic rhinitis. Comparative prospective studies would be useful to determine whether, at least in the first instance, empiric prescription with antihistamines or nasal corticosteroids is of value in allergic rhinitis and whether only the more "severe" cases need more specific evaluation as to which allergic sensitivities are present so that allergen avoidance strategies can be recommended. Alternatively, since recommended allergen avoidance measures frequently revolve around modification of the indoor living environment to decrease exposure to house dust mites, cat and dog allergens, and possibly molds, should these recommendations be automatic in patients with allergic rhinitis? Might that approach obviate the need for diagnostic testing in a substantial proportion of patients?

The increasing recognition of the close relationship between the pathophysiology of allergic rhinitis and epidemiological data is very important. Studies to accurately determine whether interventions for allergic rhinitis can have preventive effects for asthma are urgently needed. Such studies will, of necessity, have to be prospective, large in number, and long-term. Since mortality and morbidity from asthma are increasing (especially in urban populations) despite newer pharmacologic treatment agents - such an approach assumes strong imperative.

Our evidence review indicates that many drug interventions are effective in decreasing symptoms, yet data on individual variation in preferences for, responses to, and costs of different therapies are limited. Drug interactions require clarification. A host of complementary therapies are now employed in the treatment of nonallergic rhinitis, but with little rigorous testing of their efficacy.

The low numbers (or absence) of studies that address a variety of clinically meaningful questions may reflect that to date, many drug trials are efficacy trials conducted for purposes of FDA approval of a new pharmaceutical product or post marketing comparisons with competitive products. Postmarketing trials may enroll the minimum number of subjects to establish efficacy, for example, by showing equivalence between a new preparation and an established, approved one. If a product has no commercial potential (e.g., because it is no longer patented) funding to support its investigation will likely suffer.

The challenge for the healthcare research community transcends the biomedical dimension of allergic rhinitis management to encompass its societal and human aspects. Research studies must address prospectively and in increasing depth issues of importance to patients and clinicians (patient preferences, satisfaction with care, the proportion who improve with care, treatment side-effects), providers and payers (costs), and researchers (optimal trial design and reporting). Patients and their families must be invited to help formulate research priorities and to advise in the design of trials themselves, such as suggesting outcomes of interest and novel ways to assess them, e.g., via the Internet (Silberg, Lundberg, and Musacchio, 1997).

The Need for Higher Quality Studies and for Multiple but Standardized Research Variables

Standards for allergic and nonallergic rhinitis treatment trials must adhere to those for clinical trials in general. After the FDA approval of a drug, additional high-quality trials of rhinitis relief are still needed to understand the optimal use of the drug in specific populations and settings. The trials should enroll greater numbers of patients for longer intervals than has generally been true in the past; apply blinding and "active" placebos when appropriate or uniform control treatments otherwise; and employ adequate between-arm washout intervals, and assess side-effects.

A major limitation of the data identified in this analysis is the heterogeneity of inclusion and exclusion criteria, tests, outcome measures, and circumstances of testing found in the RCTs. This situation makes synthesizing the research results difficult. Reducing this heterogeneity by implementing a set of standardized research variables would greatly assist in comparing studies.

The characteristics of patients enrolled in studies need to be clearly defined. This is critical to ensure internal validity and to allow for study comparisons, data analyses, and in applying the results to clinical practice. Standardization of research variables would also aid in identifying the best strategies for detection of patients with allergic or nonallergic rhinitis.

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Evidence Table 1. Randomized controlled studies evaluating treatment of nonallergic rhinitis
Part I.

Author Year UI	Intervention	Duration	Demographics	Inclusion criteria	Exclusion criteria
Balle 1977 78016773	Disodium cromoglycate 21 mg daily vs. placebo double-blind crossover	4 weeks	Location: Denmark Mean age: ND Age range: 16 –53 % Male ND Race: ND Enrolled: 25 Evaluated: 24 Number of sites: 1	2 year history of vasomotor rhinitis requiring treatment	Asthma requiring treatment active sinusitis nasal polyposis
Renvall 1979 79214155	Oral PPA 100 mg vs. oral PPA 50mg vs. placebo RCT-Parallel	1 week	Location: Sweden Mean age: 42 Age range: 15-78 % Male: 32/70= 45.7% Race: ND Enrolled: 70 Evaluated: 70 Number of sites: 1	Rhinitis symptoms for a “long time / many years”	Usage of decongestant drugs History suggestive of allergy
Broms 1982 83046227	PPA 100mg vs. PPA 50mg vs. antihistamine	10 days	Location: Sweden Mean age: ND Age range: 18-65 % Male: ND Race: ND Enrolled: 20 Evaluated: 20 Number of sites: 1	Symptomatic nonallergic rhinitis	ND

Evidence Table 1. Randomized controlled studies evaluating treatment of nonallergic rhinitis
Part I. (continued)

Author Year UI	Intervention	Duration	Demographics	Inclusion criteria	Exclusion criteria
Nelson 1982 82240276	Cromolyn sodium 4% solution (6 sprays/d) vs. placebo RCT- Parallel	8 weeks	Location: US Mean age: 41 Age range: 18-60 % Male: 8/23 Race: ND Enrolled: 23 Evaluated: 23 - 12 (cromolyn) and 11 (placebo) Number of sites: 1	Negative skin prick test or ID skin test	ND
Jokinen 1983 84120896	Ipratropium 40μg vs. placebo Double blind cross-over	8 weeks	Location: Finland Mean age: 30 Age range: 14-66 % Male: ND Race: ND Enrolled: 30 Evaluated: 30 Number of sites: 1	Symptoms of vasomotor rhinitis requiring treatment for at least 1 year Normal sinus X-ray Negative skin test No anatomic nasal abnormality	NR
Malmberg 1983 84082739	Ipratropium 320 μg/d vs. placebo RCT-crossover	6 weeks	Location: Finland Mean age: 69.6 Age range: 48-87 % Male: 13/34 = 38.2% Race: ND Enrolled: 34 Evaluated: 34 (later changed to 33 when 1 patient stopped drug) Number of sites: 1	Elderly History of dripping (watery) vasomotor rhinitis	ND

Evidence Table 1. Randomized controlled studies evaluating treatment of nonallergic rhinitis
Part I. (continued)

Author Year UI	Intervention	Duration	Demographics	Inclusion criteria	Exclusion criteria
Bende 1985 86093211	Ipratropium vs. budesonide 100 μg bid x iod Open comparison crossver	40 days	Location: Sweden Mean age: 48 Age range: 22-70 % Male: 10/14 Race: ND Enrolled: 14 Evaluated: 14 Number of sites: 1	Symptoms of excessive nasal secretion for many years Negative routine skin prick test Previous treatment with decongestant and antihistamines ineffective	ND
Kirkegaard 1987 87167181	Ipratropium 80 μg vs ipratropium 400 μg qid vs placebo RCT- Parallel	10 weeks: 2wk- run-in 6wk- two 3wk treatment periods 2wk- open assessment of high-dose therapy	Location: Scandinavia Mean age: 51 Age range: 19-84 % Male: 50% Race: ND Enrolled: 39 Evaluated: 36 Number of sites: 1	Consecutively referred patients Predominant symptoms of working rhinorrhea Non-seasonal symptoms for at least 1 year Negative skin test	Nasal septal deviation Nasal polyposis Pregnant Other medications
Kirkegaard 1988 89074206	Ipratropium 80 μg qid vs. placebo double-blind crossover	3 weeks	Location: Sweden Mean age: ND Age range: ND % Male ND Race: ND Enrolled: 38 Evaluated: 38 Number of sites: 1	Perennial symptoms Negative skin test	ND

Evidence Table 1. Randomized controlled studies evaluating treatment of nonallergic rhinitis
Part I. (continued)

Author Year UI	Intervention	Duration	Demographics	Inclusion criteria	Exclusion criteria
Sjogren 1988 89086030	Ipratropium 200 μg vs ipratropium 100 μg vs Ipratropium 40 μg vs placebo Dosing study, non randomized	1 day	Location: Sweden Mean age: 38.8 (women) and 55.6 (men) Age range: 21-77 % Male: 11/24= 45.8% Race: ND Enrolled: 24 Evaluated: 24 Number of sites: 1	Rhinorrhea Negative skin test	Asthma Sinusitis Nasal polyposis “airway infection” Pregnancy Anticholinergics, antihistamines, antidepressants, and neuroleptics and steroids
Jessen 1990 90350004	Ipratropium 160 μg vs. beclomethasone 400 μg Double-dummy double-blinded randomized crossover trial	7 weeks	Location: Sweden Mean age: 49 Age range: (20-77) % Male: 10/24 Race: ND Enrolled: 31 Evaluated: 24 Number of sites: 1	Negative skin prick test	Nasal polyps Chronic asthma Pregnancy
Wight 1992 92405460	Budesonide 400 μg vs budesonide 800 μg Placebo-controlled, double-blinded crossover RCT	12 weeks 2 3-week active treatment periods	Location: UK Mean age: 31 Age range: 16-62 % Male: 30/59 Race: 53 Caucasian, 3 Black, 3 Others Enrolled: 59 Evaluated: 59 Number of sites: 1	12 months of perennial rhinitis	Seasonal allergic rhinitis Recurrent chronic rhinosinusitis Nasal polyps Nasal structural abnormality

Evidence Table 1. Randomized controlled studies evaluating treatment of nonallergic rhinitis
Part I. (continued)

Author Year UI	Intervention	Duration	Demographics	Inclusion criteria	Exclusion criteria
Graf 1999	Oxymetazoline 0.5mg/mL + Benzalkonium 0.1mg/mL vs oxymetazoline (3 sprays/d) RCT-Parallel	10 days	Location: Sweden Mean age: 38 Age range: 15-69 % Male: 9/35 = 25.7% Race: ND Enrolled: 35 Evaluated: 35 Total: 18 (oxymetazoline w/ benzalkonium) and 17 (oxymetazoline w/o benzalkonium Number of sites: 1	Vasomotor rhinitis	No medications for nasal symptoms within 30 days Negative skin test for allergy

Evidence Table 1. Randomized controlled studies evaluating treatment of nonallergic rhinitis
Part II.

Author Year UI	**Treatment outcomes studied**	**Symptom scale**	**Outcomes-efficacy**
Balle 1977 78016773	Sneezing score Rhinorrhea score Nasal congestion score Rescue antihistamine usage	Diary cards: scale 0-3	Mean monthly diary scores for sneezing significantly reduced in active treatment group (20 vs. 28 p<0.05) Mean monthly diary scores for nasal congestion significantly reduced in active treatment group (24.7 vs. 27.4 p<0.05)
Renvall 1979 79214155	Mean Total Symptom Score: Nasal obstruction Nasal secretion	Symptom Scale: Patient symptom questionnaire with scoring system -interviewed by doctors on day 1 and day 4 symptom scale(1-4)	For nasal obstruction, significant (p< 0.05) differences between 100 mg PPA and placebo and between high dose and low dose (p< 0.05) For nasal secretion, significant difference (P<0.05) between high dose and low dose. No other significant differences found Minimal data presented
Broms 1982 83046227	Mean Total Symptom Score Nasal airway resistance Nasal secretion Sneezing	Symptom scale: Diary card (2/d) Symptom intensity - 4 point scale 0-3 Sneezing- similar scale, but recording number of sneeze attacks	Unable to extract data from graphs “symptoms of nasal secretion and sneezing were reduced by PPA” “PPA is not an ideal nose decongestant” “DHE in dose lower than those giving adrenoceptor blockage seemed to be suitable drug”

Evidence Table 1. Randomized controlled studies evaluating treatment of nonallergic rhinitis
Part II. (continued)

Author Year UI	Treatment outcomes studied	Symptom scale	Outcomes-efficacy
Nelson 1982 82240276	Total Mean Symptom Score Rhinorrhea Nasal congestion Sneezing Itchy nose Itchy eyes Itchy throat Post-nasal drip Mouth breathing Nose-blowing	Symptom scale Patients completed questionnaire 2x/ day Symptom severity- 0-5 scale 0=none to 5= extreme Sneezing or nose blowing- by # of sneezes/ nose blows	For specific symptom scores, drug was statistically significant for itchy nose, itchy eyes (both P<0.01), and amount of nose blowings (P<0.02), but NS w/respect to runny nose, stuffy nose, itchy throat, mouth breathing, postnasal drip, sneezing episodes.
Jokinen 1983 84120896	Total Mean symptom score Rhinorrhea Sneezing Itchy nose Nasal blockage	Symptom scale: Diary cards- 0-3 scale. Number of handkerchiefs, nasal smears, McNemar test	Ipratropium had marked effects on nasal discharge; p< 0.001; also in amount of handkerchiefs used. Tx had no effects on nasal blockage, sneezing and tickling: changes all NS.
Malmberg 1983 84082739	Total mean symptom score Rhinorrhea Nasal congestion Sneezing Itchy eyes Nose blowing	Symptom scale Patient diary: 0-3 scale with 0= no symptoms, to 3= severe symptoms Nasal blowing- by counting handkerchiefs (1:1)	For nose-blowing frequency: smaller frequency of nose blowing during treatment with ipratropium P < 0.001 For rhinorrhea: Symptom score of 1.21 with ipratropium vs score of 1.52 with placebo; P < 0.001 For nasal congestion and Itchy eyes P = NS for both

Evidence Table 1. Randomized controlled studies evaluating treatment of nonallergic rhinitis
Part II. (continued)

Author Year UI	**Treatment outcomes studied**	**Symptom scale**	**Outcomes-efficacy**
Bende 1985 86093211	Nasal symptom scores: Secretion Blockage Sneezing Itching Stinging Drying Bleeding	VAS	Budesonide had a significant effect on nasal secretion and sneezes ($p<0.01$) No numerical data provided. Results presented as a graph. 12/14 patients wanted to continue budesonide. 2/14 found neither drug of value.
Kirkegaard 1987 87167181	Total Mean Symptom Score Rhinorrhea Nasal Congestion Sneezing	Symptom Scale: Diary card- For nasal blockage- 0-3 (free/easy breathing-3= completely abolished) For other nasal symptoms -recorded number of sneezes and nose blowings	Number of nose blowings were 47% lower during active lowdose tx compared to placebo ($P<0.01$), other slight reduction w/high dose compared to placebo ($P<0.05$). Active tx, hi or low, had no effect on number of sneezes or nasal blockage index.
Kirkegaard 1988 89074206	Average daily nose-blowing episodes	Diary cards x2hrs self-assessed questionnaires bid	Mean daily number of nose-blowing episodes significantly reduced when compared with placebo (29 ± 7.3 vs 17.6 ± 4.2)
Sjogren 1988 89086030	Mean total symptom score: Rhinorrhea Sneezing Volume of nasal secretion	Symptom scale: Nasal secretion – measured vol. secretion after pre-tx w/different dosages of med. Other nasal symptoms- McNemar test	Doses of 40 and 100 tx reduced volume of secretion, greatest reduction was found w/200 mg when compared to placebo. Ipratropium reduced significantly hypersecretion induced by metacholine when compared to placebo. 15 sneezing episodes w/placebo compared to 7 w/tx, NS. No changes in other nasal symptoms (itching).

Evidence Table 1. Randomized controlled studies evaluating treatment of nonallergic rhinitis
Part II. (continued)

Author Year UI	**Treatment outcomes studied**	**Symptom scale**	**Outcomes-efficacy**
Jessen 1990 90350004	Nasal symptom scores: Secretion Sneezing Blockage	0-4 symptom scale	No significant difference between ipratropium and beclomethasone.
Wight 1992 92405460	Nasal resistance to airflow. Nasal secretic eosinophilic count. Patient subjective symptom score. Effect on local and stimulated plasma control.	0-3 subjective assessment scale.	Nasal obstruction was significantly improved with budesonide. There was no significant difference between doses.
Graf 1999	Total mean symptom score Nasal congestion	Symptom scale: Visual analog scale (0-100) Nasal mucosal swelling measured by rhinostereo-metry and acoustic rhinometry	Reduction in mucosal swelling after 10 days for O+B was statistically significant at all 3 histamine provocation levels (P<0.001); for O alone, NS Mean symptom score for nasal stuffiness For O+B, a score of 50 at baseline and 49 after treatment --for O alone, a score of 48 at baseline and 51 after treatment

Evidence Table 1. Randomized controlled studies evaluating treatment of nonallergic rhinitis
Part III.

Author Year UI	**Outcome-safety**	**Potential Bias**	**Funding**
Balle 1977 78016773	No adverse events noted	Pooled crossover data Analyzed 23 of 24 patients Reasons for withdrawals not given. Internal validity C	ND
Broms 1982 83046227	No major adverse effects: Minor adverse effects: Total adverse effects: reported by 17/19 patients -Headache- 10 patients- 7 patients in placebo group, 2 in PPA group and 1 in PPA + BDE group -Micturition difficulties- 2 patients taking PPA	Small sample No data on demographics No info on the missing person	Government
Nelson 1982 82240276	No major adverse effects: Minor adverse effects: Increased nasal symptoms for 4 cromolyn patients, 4 placebo patients Nasal symptoms include: lacrimation, eyelid puffiness, nasal stuffiness, nasal irritation, sneezing, headaches, sore throat, and sleepiness	Most patients continued to experience usual NARES syndrome symptoms throughout the rhinitis study No benefit of DSG in NARES 4 Non-drug related withdrawals during study 3 from placebo group, 1 from cromolyn group: 2 patients due to concurrent use of diuretic mediation, other 2 patients due to occupational duties (their data while enrolled was included)	ND

Evidence Table 1. Randomized controlled studies evaluating treatment of nonallergic rhinitis
Part III. (continued)

Author Year UI	**Outcome-safety**	**Potential Bias**	**Funding**
Jokinen 1983 84120896	No major adverse effects. Minor adverse effects: 3 ipratropium therapy interruptions- (1)nose bleeding, (2) headache, and (3) increase symptoms 2 placebo therapy interruptions- (1) increased symptoms, and (2) tour abroad Report of mild side-effects: 11 patients taking ipratropium treatment, 7 patients taking placebo treatment -Nasal irritation- 8 patients from ipratropium group and 5 patients from placebo group reported effect -Nasal dryness- 6 patients taking ipratropium and 3 patients taking placebo -Throat irritation- 2 patients taking ipratropium and 1 patient taking placebo		Pharmaceutical
Malmberg 1983 84082739	Major adverse effects: 3 withdrawals- 1 patient from placebo group (no reason given); 2 patients from ipratropium group due to drying of mucosa Minor adverse effects: -Nasal dryness- 15 from ipratropium group and 9 from placebo group -Nasal irritation- 18 from ipratropium group and 8 from placebo group		ND
Bende 1985 86093211	“no serious adverse effects were noted”	Non-randomized open label study	ND

Evidence Table 1. Randomized controlled studies evaluating treatment of nonallergic rhinitis
Part III. (continued)

Author Year UI	**Outcome-safety**	**Potential Bias**	**Funding**
Kirkegaard 1987 87167181	Minor adverse effects: -Nasal dryness- 61% patients on ipratropium 80m; 72% patients on ipratropium 400 36% patients taking placebo. -Mouth dryness 42% patients on ipratropium 80 78% patients on ipratropium 400; 28% patients taking placebo; -Dysuria (Urinolic difficulties) 11% patients on ipratropium 80 28% patients on ipratropium 400 6% patients taking placebo; -Blurred vision 8% patients on ipratropium 80 14% patients on ipratropium 400 8% patients taking placebo	Other reasons for withdrawal: -1 pt- failed to fill score card -1pt- lost score card -1pt- did not follow last treatment protocol	ND
Kirkegaard 1988 89074206	Only adverse event noted was nose dryness in both active & placebo groups; no numbers given	Small sample size No data on adverse effect numbers Category C	ND
Sjogren 1988 89086030	No major adverse effects Minor adverse effects: Sweating- 1 patients after treatment with 400 μg ipratropium		Pharmaceutical
Jessen 1990 90350004	"side effects of treatment were negligible"		ND

Evidence Table 1. Randomized controlled studies evaluating treatment of nonallergic rhinitis
Part III. (continued)

Author Year UI	**Outcome-safety**	**Potential Bias**	**Funding**
Wight 1992 92405460	No increase in adverse effects occurred with higher dosage.		Astra Pharmaceutical
Graf 1999	ND		Pharmaceutical

Evidence Table 2. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Non-sedating antihistamines versus nasal corticosteroids
Part I.

Author Year UI	Intervention	Duration	Demographics	Inclusion criteria	Exclusion criteria
Munch 1983 84050113	**Seasonal Allergic Rhinitis** Dexchlor-pheniramine vs Budesonide RCT-Parallel After treatment, used intranasal allergen for post-challenge	21 days	Location: Denmark Mean age: 29 Age range: 18-65 % Male: 50% Race: ND Enrolled: 61 - 30 (dexchlorpheniramine) and 31 (budesonide) Evaluated: 60 - 29 (dexchlorpheniramine) and 31 (budesonide) Number of sites: 4	At least 15 years old Rhino-conjunctivitis for last 2 seasons Positive skin prick test to timothy grass	Asthma Sinusitis Nasal septal deviation Nasal polyposis Childbearing potential PAR SAR in pollen season Treated with other drugs or gluticocorticoids for last 2 weeks
Backhouse 1986 86165329	**Seasonal Allergic Rhinitis** Terfenadine vs Flunisolide RCT-Parallel	11 weeks	Location: UK Mean age: 35 Age range: 18-65 % Male: 52/99 Race: ND Enrolled:99 - 50 (terfenadine) and 49 (terfenadine and flunisolide) Evaluated: 82 - 33 (terfenadine) and 49 (terfenadine + flunisolide) Number of sites: 1	Moderate to severe symptoms of SAR for at least 2 years	Sinusitis Nasal septal deviation Nasal polyposis Pregnant/lactating Other RTI (respiratory tract infection) Systemic steroid use within 3 months Any allergy therapy within 2 weeks

Evidence Table 2. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Non-sedating antihistamines versus nasal corticosteroids
Part I. (continued)

Author Year UI	Intervention	Duration	Demographics	Inclusion criteria	Exclusion criteria
Wood 1986 86245576	**Seasonal Allergic Rhinitis** Astemizole vs Beclomethasone RCT- Parallel	13 weeks	Location: UK Mean age: 27.9 Age range: > 12 % Male: 35/73 Race: ND Enrolled: 74 Evaluated: 73 - 39 (astemizole) and 34 (beclomethasone) Number of sites: 1	"sound clinical history of hay fever"	Nasal polyposis "severe chronic rhinitis (vasomotor or intrinsic rhinitis)" Received systemic corticosteroid within 4 weeks Pregnant or lactating or likely to become pregnant
Juniper 1989 89175902	**Seasonal Allergic Rhinitis** Astemizole vs Beclomethasone [also tested Astemizole + Beclomethasone treatment] RCT-Parallel	42 days	Location: Canada Mean age: 39.8 Age range: 18-70 % Male: 53.3% Race: ND Enrolled: 90 Evaluated: 90: 30 each group Number of sites: 1	Rhinoconjunctivitis requiring treatment during 2 seasons Skin prick test	Pregnant/nursing mothers Perennial rhinitis No trial drug use within 6 weeks
Robinson 1989 90002391	**Perennial Allergic Rhinitis** Terfenadine vs Beclomethasone dipropionate (BDP) RCT- cross-over (unextractable)	4 weeks	Location: UK Mean age: 30.9 Age range: 18-65 %Male: 7/20 Race: ND Enrolled: 20 (10 each group) Evaluated: 13 - 5 (Group B-received terfenadine 1st), 8 (Group A- received beclomethasone 1st) [**see outcomes-efficacy section for clarification**] Number of sites: 1	With normal sinus X-ray and free from "serious" illness	With sinusitis, nasal septal deviation, and nasal polyposis. Pregnant women and those receiving or would require medicine affecting perennial rhinitis, such as antihistamines

Evidence Table 2. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Non-sedating antihistamines versus nasal corticosteroids
Part I. (continued)

Author Year UI	Intervention	Duration	Demographics	Inclusion criteria	Exclusion criteria
Darnell 1994 95196117	**Seasonal Allergic Rhinitis** Terfenadine vs. fluticasone RCT-Parallel	6 weeks	Location: Europe Mean age: 28 Age range: > 12 %Male: Race: ND Enrolled:214 : Evaluated: 173 Number of sites: 15	Positive skin-prick test to grass pollen Symptoms of seasonal allergic rhinitis for past two seasons	Sinusitis Corticosteroids or cromoglycate within one month Antihistamines within 6 weeks Immunotherapy within one year Perennial rhinitis Pregnancy
Van Bavel 1994 95085365	**Seasonal Allergic Rhinitis** Terfenadine vs. fluticasone [placebo also tested] RCT-Parallel	14 days	Location: USA Mean age: 39.2 Age range: > 12 % Male: 49% Race: ND Enrolled: 232 Evaluated: 232 - 78 (fluticasone), 77(terfenadine), and 77 (placebo) Number of sites: 5?	Symptomatic at entry with symptom score of 200/400 on 4/ 7 days preceding treatment Moderate to severe seasonal allergic rhinitis diagnosed as below 1yr history Nasal mucosal appearance consistent with allergic rhinitis Positive skin test to mountain cedar w/in 12 months Normal HPA axis by morning cortisol	No oral antihistamines or cromolyn for at last 2 weeks prior to screening No astemizole or inhaled intranasal or systemic steroids for 1 month prior to screening

Evidence Table 2. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Non-sedating antihistamines versus nasal corticosteroids
Part I. (continued)

Author Year UI	Intervention	Duration	Demographics	Inclusion criteria	Exclusion criteria
Hilberg 1995 96098156	**Seasonal Allergic Rhinitis** Terfenadine vs Budesonide [Placebo also tested] RCT- cross-over (extractable)	42 days- 14 days for each of 3 treatments	Location: Denmark Mean age: 25.4 Age range: 23-33 % Male: 14/17= 82% Race: Caucasian Enrolled: 18 Evaluated: 17 Number of sites: 1	Non-smoking volunteers "typical hay fever symptoms in the season" Positive prick test RAST against timothy of at least class 3	Asthma Prior nasal surgery "gross nasal pathology" Smoking
Schoenwetter 1995 96070357	**Seasonal Allergic Rhinitis** Loratidine vs Triamcinolone RCT-Parallel	28 days	Location: US Mean age: 31.2 Age range: 12-70 % Male: 43% Race: ND Enrolled: 298 - 149 each group Evaluated: 274 - 140 for loratadine, and 134 for triamcinolone Number of sites: ND	2 seasons of SAR symptoms	Sinusitis Nasal septal deviation Nasal polyposis Decongestants/antihistamine use within 42 days Oral/ nasal steroid use in 3 months Pregnant/lactating
Bernstein 1996 96213647	**Seasonal Allergic Rhinitis** astemizole vs. Triamcinolone RCT parallel	4 weeks	Location: US Mean age: 35.7 Age range: ND % Male: 46% Race: ND Enrolled: 239 - 120 (Triamcinolone) and 119 (Astemizole) Evaluated: 209 - 104 (Triamcinolone), and 105 (Astemizole) Number of sites:9	2 year history of symptoms Positive skin test Qualifying symptom score	Recent steroid use Recent cromolyn Recent immunotherapy Sinusitis Nasal polyposis Septal deviation Rhinitis Medicamentosa

Evidence Table 2. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Non-sedating antihistamines versus nasal corticosteroids
Part I. (continued)

Author Year UI	Intervention	Duration	Demographics	Inclusion criteria	Exclusion criteria
Bronsky 1996 UI	**Seasonal Allergic Rhinitis** Terfenadine vs. fluticasone RCT Parallel	4 weeks	Location: US Mean age: 35.7 Age range: ND % Male Race: ND Enrolled: 239 Evaluated: 209 Number of sites:9	>12years old Positive skin test Nasal mucosal appearance consistent with SAR 1 year history of symptoms	Antihistamines within 2 weeks Cromolyn sodium within 2 weeks Steroids (all Types) within 4 weeks Astemizole within 4 weeks
Bronsky 1996 96194242	**Seasonal Allergic Rhinitis** Terfenadine vs. fluticasone [Placebo also tested] RCT-Parallel	28 days	Location: US Mean age: 30 Age range: > 12 % Male: 58% Race: ND Enrolled: 348 - 117 (fluticasone), 116 (terfenadine) and 115 (placebo) Evaluated: 319 - 111 (fluticasone), 103 (terfenadine) and 105 (placebo) Number of sites: 10	Moderate to severe seasonal allergic rhinitis diagnosed by 1)positive skin test to at least one spring allergen 2)nasal mucosa appearance consistent with diagnosis of SAR 3)at least 1 year history of symptoms 4)moderate-severe symptoms by diary 5)morning plasma cortisol $\geq 7\mu g/dL$ 6)nasal symptom score $\geq$ 200/400 on 4/7 days immediately preceding enrollment	Oral antihistamine or cromolyn sodium within 2 weeks Astemizole or inhaled/systemic corticosteroids within 1 month

Evidence Table 2. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Non-sedating antihistamines versus nasal corticosteroids
Part I. (continued)

Author Year UI	Intervention	Duration	Demographics	Inclusion criteria	Exclusion criteria
Jordana 1996 96191239	**Seasonal Allergic Rhinitis** Loratadine vs. fluticasone RCT Parallel	4 weeks	Location: US Mean age: 12±17 Age range: ND % Male Race: ND Enrolled: 242 Evaluated: 240 - 121 (Fluticasone) and 119 (Loratadine) Number of sites: 5	Moderate to severe allergic rhinitis symptoms	Viral rhinitis Perennial rhinitis Steroids within 1 month Cromoglycate within 1 month Loratidine within 1 week Sinusitis Nasal surgery Structural nasal abnormalities
Gehanno 1997 97332767	**Seasonal Allergic Rhinitis** Loratidine vs. fluticasone RCT- Parallel	4 weeks	Location: France Mean age: 37.0 (fluticasone), and 41 (loratadine) Age range: > 12 % Male: 47% (fluticasone) and 42% (loratadine) Race: ND Enrolled: 114 Evaluated: 114 - 57 each group Number of sites: “multi-center”	Positive skin test to seasonal allergens	Women of childbearing potential Patient received oral, inhaled or intranasal corticosteroids within 1 month Intranasal cromolyn within 15 days prior to study
Juniper 1997 UI	**Seasonal Allergic Rhinitis** Terfenadine vs. Fluticasone RCT	6 weeks	Location: US Mean age: 41 Age range: ND % Male Race: ND Enrolled: 240 Evaluated: 240 Number of sites: 5	Diagnosis of SAR Symptomatic in previous season Positive ragweed skin test	Sinusitis Nasal polyposis Perennial rhinitis Immunotherapy within 12 months Antihistamine therapy All steroid therapy

Evidence Table 2. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Non-sedating antihistamines versus nasal corticosteroids
Part I. (continued)

Author Year UI	Intervention	Duration	Demographics	Inclusion criteria	Exclusion criteria
Juniper 1997 97286890	**Seasonal Allergic Rhinitis** Terfenadine vs. fluticasone RCT Parallel	6 weeks	Location: Canada Mean age: ND Age range: 17-66 % Male: 48% (fluticasone) and 53% (terfenadine) Race: ND Enrolled: 61 Evaluated: 60 Number of sites: 1	Diagnosis seasonal allergic rhinoconjunctivitis Nasal symptoms requiring treatment during previous ragweed season Positive skin test for ragweed	Sinusitis Nasal polyposis Perennial rhinoconjunctivitis Chronic nasal obstruction, polyposis or sinusitis Allergen injection of treatment within past 12 months Pregnant/nursing mothers Other diseases requiring antihistamine or oral steroid
D'Ambrosio 1998 99133169	**Seasonal Allergic Rhinitis** Cetirizine vs fluticasone [also one group treated with both cetirizine and fluticasone] RCT-Parallel	60 days	Location: Italy Mean age: 28.1 Age range: > 14 % Male: 9/18 Race: ND Enrolled: 60 Evaluated: 54 18(cetirizine), 19 (fluticasone), and 17 (cetirizine and fluticasone) Number of sites: 1	Clinical history of SAR Positive skin test	Use of drugs that may interfere with results of study

Evidence Table 2. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Non-sedating antihistamines versus nasal corticosteroids
Part I. (continued)

Author Year UI	Intervention	Duration	Demographics	Inclusion criteria	Exclusion criteria
Ratner 1998 98390023	**Seasonal Allergic Rhinitis** Loratadine vs. fluticasone [also studies combination of Loratadine + Fluticasone; placebo also tested] RCT- Parallel	14 days	Location: US Mean age: 40.1 Age range: >12 % Male: 46% Race: ND Enrolled:600 Evaluated: 569 142 (Loratadine), 142 (Fluticasone), 145 (Loratadine +Fluticasone), and 140 (Placebo) Number of sites: 5	Positive Skin prick to allergen	Nasal septal deviation Nasal polyposis Any treatment with trial drugs within 6 weeks Decongestants or steroids within 4 weeks “Candidal infection” Pregnant or lactating
Ortolani 1999 20068053	**Seasonal Allergic Rhinitis** Levocabastine vs fluticasone vs. placebo RCT-Parallel	6 weeks	Location: Italy Mean age: 29 Age range: 13-64 % Male: 169/288 Race: ND Enrolled:288 Evaluated: 288 Number of sites: 16	Clinical history of SAR for at least 2 years Positive skin prick test to seasonal pollens	Sinusitis Nasal septal deviation Nasal polyposis Long-acting Antihistamines Nasal systemic steroids(x 4 weeks) Pregnant/lactating PAR Paranasal sinuses/ respiratory tract infection Nasal surgery within past year

Evidence Table 2. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Non-sedating antihistamines versus nasal corticosteroids
Part I. (continued)

Author Year UI	Intervention	Duration	Demographics	Inclusion criteria	Exclusion criteria
Condemi 2000 20289854	**Seasonal Allergic Rhinitis** Loratidine vs. Triamcinolone RCT-Parallel	28 days	Location: US Mean age: 32 Age range: 12 - 69 % Male: 45% Race: 90% Caucasian Enrolled: 351 - 175 (triamcinolone) and 176 (loratadine) Evaluated: 317 - 160 (triamcinolone) and 157 (loratadine) Number of sites: 11	2 year consecutive history Positive skin prick test to grass pollen Combined symptom score of at least 24 on 4 of 5 baseline days (4 point scale, max 60)	Sinusitis Nasal septal deviation Rhinitis medicamentosa Nasal candidiasis Pregnant, lactating, childbearing women Recent use of treatment: corticosteroids, intranasal cromolyn, topical decongestants, systemic steroids, long-acting antihistamines

Evidence Table 2. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Non-sedating antihistamines versus nasal corticosteroids
Part II.

Author Year UI	**Treatment outcomes studied**	**Symptom scale**	**Outcomes-efficacy**
Munch 1983 84050113	Mean total symptom score Rhinorrhoea Nasal congestion Sneezing Itchy eyes Itchy throat	Sneezing (morning and evening): 0= no symptoms, 1= slight, 2= moderate, 3= severe Rhinorrhea and Blockage- rating scale Total Nasal symptom score- combination of sneezing, rhinorrhoea, and blockage scores	Global patient assessment: score of 82 for budesonide and 62 for dexchlorpheniramine P= 0.06 Total Nasal Symptom score: More improvement of symptoms for patients taking budesonide compared dexchlorpheniramine with p< 0.05 for budesonide vs dexchlorpheniramine Sneezing + Nose blowings: Dexchlorpheniramine group- not much diurnal variation during therapy Budesonide- symptom reduction for morning and evening symptoms Nasal blockage More improvement for morning and evening symptoms in patients taking budesonide compared to dexchlorpheniramine with p< 0.05 for budesonide vs dexchlorpheniramine Nasal itching No significant differences between groups, but trend for favoring budesonide over dexchlorpheniramine

Evidence Table 2. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Non-sedating antihistamines versus nasal corticosteroids
Part II. (continued)

Author Year UI	**Treatment outcomes studied**	**Symptom scale**	**Outcomes-efficacy**
Backhouse 1986 86165329	Total mean symptom score Rhinorrhoea Nasal congestion Sneezing Nose blowing Eye symptoms	Symptom scale Sneezing/nose-blowing 1= never/seldom 2= infrequent 3=frequent 4=very frequent Runny nose, stuffy nose, and ocular symptoms 1=none 2=mild 3=moderate 4=severe overall assessment (done at end of every visit) – excellent, good, poor, none or worse symptoms	All values taken from Week 7- when pollen level was highest Global Physician Assessment: Good/excellent response achieved by 62% of subjects in terfenadine group and 96% in terfenadine+flunisolide group, with p< 0.001 for terfenadine + flunisolide group vs terfenadine group Sneezing Symptom score of 1.9 with terfenadine, vs 1.4 with terfenadine+flunisolide, with p = 0.02 Nasal Blowing Symptom score of 2.3 with terfenadine vs 1.5 with terfenadine+flunisolide with p= 0.001 Nasal Congestion Symptom score of 2.2 with terfenadine vs 1.5 with terfenadine+flunisolide with p=0.008
Wood 1986 86245576	Total Mean Symptom Score Sneezing Rhinorrhoea Blocked nose Itchy eyes	Symptom scale Diary card that included five 10 cm visual analogue scale	Results presented as graphs mostly “No statistically significant difference between the scores for the astemizole and the beclomethasone from using an ANOVA for overall severity of symptom or for blocked nose, sneezing or runny nose Both medications decrease the VAS (0-100 scale) symptom scores at baseline to around 10-20 for individual symptoms of sneezing, rhinitis and rhinorrhoea

Evidence Table 2. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Non-sedating antihistamines versus nasal corticosteroids
Part II. (continued)

Author Year UI	**Treatment outcomes studied**	**Symptom scale**	**Outcomes-efficacy**
Juniper 1989 89175902	Total mean symptom score Nasal Congestion Sneezing Watery eyes Asthma	Symptom scale: Diary entries: Symptom severity: 0-3 scale: 0= absent 1=mild 2=moderate 3=severe Symptom duration: 0-3 scale: 0=absent 1=few short episodes 2= many episodes 3= continuous symptoms also evaluated after wk1,3,and 6 by clinician	Overall efficacy evaluation (from mean daily scores) Beclomethasone showed better improvement than astemizole for sneezing, stuffy nose, and runny nose Beclomethasone + Astemizole showed better improvement than astemizole for nasal symptoms, but little difference compared to beclomethasone Sneezing: Mean daily score of 0.395 for astemizole, score of 0.193 for beclomethasone, and score of 0.155 for astemizole + beclomethasone Rhinorrhoea: Mean daily score of 0.406 for astemizole, score of 0.152 for beclomethasone, and score of 0.192 for astemizole + beclomethasone Nasal Congestion: Mean daily score of 0.594 for astemizole, score of 0.319 for beclomethasone, and score of 0.322 for astemizole + beclomethasone

Evidence Table 2. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Non-sedating antihistamines versus nasal corticosteroids
Part II. (continued)

Author Year UI	**Treatment outcomes studied**	**Symptom scale**	**Outcomes-efficacy**
Robinson 1989	Mean total symptom score Rhinorrhoea Sneezing Nasal Congestion Watery Eyes Itchy Nose Itchy eyes Post nasal drip (PND) Nasal irritation	Symptom scale for patients with daily record card- 5 pt scale 0= no symptoms 1= mild 2= moderate 3= severe 4= very severe	**Treatment groups: Group A – Sequence #1 : Beclomethasone 1st period, then Terfenadine 2nd period Group B – Sequence #2 : Terfenadine 1st period, then Beclomethasone 2nd period Patient Preference: 9 preferred Beclomethasone, 2 preferred Terfenadine, and 2 had no preference Sneezing For group A, symptom score of 1.0 with terfenadine vs symptom score of 0.48 with beclomethasone; P = 0.04 for symptom category in general For group B, symptom score of 0.49 with terfenadine vs symptom sore of 0.25 with beclomethasone Rhinorrhoea For group A, symptom score of 1.29 with terfenadine vs symptom score of 0.69 with beclomethasone; P= 0.0006 for symptom category in general For group B, symptom score of 0.94 with terfenadine vs symptom score of 0.08 with beclomethasone Nasal Congestion For group A, symptom score of 0.92 with terfenadine vs symptom score of 0. 76 with beclomethasone; P= N/S for symptom For group B, symptom score of 0.85 with terfenadine vs symptom score of 0.84 with beclomethasone Nasal Itch For group A, symptom score of 0.62 with terfenadine vs symptom score of 0.39 with beclomethasone; P= N/S for symptom For group B, symptom score of 0.36 with terfenadine vs symptom score of 0.1 with beclomethasone

Evidence Table 2. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Non-sedating antihistamines versus nasal corticosteroids
Part II. (continued)

Author Year UI	**Treatment outcomes studied**	**Symptom scale**	**Outcomes-efficacy**
Darnell 1994 95196117	Mean total Symptom Score Sneezing Nasal Congestion Rhinorrhoea Itchy nose	**Overall assessment**- vertical line made by patients on 10 cm visual analogue scale Left=no symptoms, Right= worst symptoms **Individual Symptom** scale- 4 pt scale for each symptom [0-3, 0=best,3=worst] **Blockage-** 0= breathing freely easily, 1= slightly difficult, 2= moderately difficult, 3= difficult-impossible **Sneezing** 0=absent, 1= occasionally present, 2= troublesome episodes, 3= frequent troublesome episodes **nasal itching/rhinorrhoea** 0=absent,1=mostly unaware, 2= not a persistent distraction, 3= persistent distraction **drowsiness** 0=absent, 1= mild, 2= moderate, 3= severe	Nasal blockage P= 0.009 for fluticasone vs terfenadine, and p= 0.02 for fluticasone vs terfenadine Sneezing Days free of symptoms: 25 days with terfenadine, 40 days with fluticasone, and 20 days with placebo; P<0.001 for fluticasone vs placebo, and p= 0.057 for fluticasone vs terfenadine Rhinorrhoea Days free of symptoms: 45 days with terfenadine, 55 days with fluticasone, and 35 days with placebo; p<0.001 for fluticasone vs placebo, and p= 0.021 for fluticasone vs terfenadine Nasal congestion Days free symptoms on waking: 5 days with terfenadine, 35 days with fluticasone, and 6 days with placebo; p<0.017 for fluticasone vs placebo, and p<0.012 for fluticasone vs terfenadine Days free of symptoms during the day: 15 days with terfenadine, 45 days with fluticasone, and 10 days with placebo; p < 0.028 for fluticasone vs placebo, and p<0.01 for fluticasone vs terfenadine

Evidence Table 2. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Non-sedating antihistamines versus nasal corticosteroids
Part II. (continued)

Author Year UI	**Treatment outcomes studied**	**Symptom scale**	**Outcomes-efficacy**

Van Bavel 1994 95085365	Total Mean Symptom Score
	Rhinorrhoea
	Nasal Congestion
	Sneezing
	Itchy nose
	Nasal eosinophils
		Symptom Scale
		Diary cards- visual analog scale ranging from 0 (absent) to 100 (severe)
		- all symptoms evaluated in evening except nasal obstruction, which was also evaluated on awakening
		Rhinoprobe measurements (days 1and 15)- rated # inflammatory cells w/ 5 pt scale:
		0= none, 1= few, scattered; 2= moderate number, small clumps; 3= large clumps, not covering entire field; and 4= clumps covering entire field
		Overall physician assessment: following categories: significant improvement, mild improvement, no change, mildly worse, moderately worse, or significantly worse
			Overall clinician assessment:
			Significant/ Moderate Improvement: 64% in fluticasone group with $p < 0.01$ for drug vs placebo; 49% in terfenadine group with $p< 0.01$ for fluticasone vs terfenadine; and 44% in placebo group
			Mild Improvement: No change, or Mildly Worse: 33% in fluticasone group, 49% in terfenadine group, and 52% in placebo group
			Moderately or significantly worse: 2% in fluticasone group, 1% in terfenadine group, and 4% in placebo group
			
			Sneezing:
			Fluticasone did significantly better than placebo or terfenadine with $p< 0.05$.
			Terfenadine did significantly worse than fluticasone with $p< 0.05$
			
			Rhinorrhoea:
			Fluticasone did significantly better than placebo and terfenadine with $p< 0.05$. Terfenadine did significantly worse than fluticasone with $p < 0.05$
			
			Congestion:
			Fluticasone did significantly better than placebo or terfenadine with $p< 0.05$.
			Terfenadine did significantly worse than fluticasone with $p < 0.05$
			
			No mean symptom scores given for individual symptoms or magnitude of change- better work at 14 days only.

Evidence Table 2. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Non-sedating antihistamines versus nasal corticosteroids
Part II. (continued)

Author Year UI	**Treatment outcomes studied**	**Symptom scale**	**Outcomes-efficacy**
Hilberg 1995 96098156	Total Mean Symptom Score Nasal Congestion Nasal Itch Sneezing Nasal secretion	Symptom Scale Questionnaire- Visual 100 mm Linear Analog Scale- no symptoms to intolerable symptoms	Overall effect Minimum cross-sectional area (cm^2) (*Minimum cross-sectional area was tested to evaluate correlation with olfactory function) Area of 1.03 with terfenadine with $p < 0.01$ for terfenadine vs placebo; area of 1.11 with budesonide with $p < 0.005$ for budesonide vs placebo; area of 0.99 with placebo Nasal Volume (cm^3) Volume of 16.45 with terfenadine with $p< 0.1$= NS for terfenadine vs placebo; volume of 16.98 with budesonide with $p < 0.01$ for budesonide vs placebo; volume of 15.74 with placebo Budesonide also significantly improved nasal congestion Olfactory threshold- no results Surrogate end- points of uncertain clinical value
Schoenwetter 1995 96070357	Total Mean symptom score Rhinorrhoea Nasal congestion Sneezing Itchy Eyes Itchy nose Postnasal drip (PND)	Symptom Scale 4-pt scale: 0= no symptoms 1= mild symptoms 2= moderate symptoms 3=severe symptoms	Overall assessment: % symptom change of 31% with loratadine and 51% with triamcinolone with $p \leq 0.001$ for triamcinolone vs loratadine Sneezing % symptom change of 35% with loratadine and 58% with triamcinolone with $p\leq 0.001$ for triamcinolone vs loratadine Nasal Congestion % symptom change of 21% with loratadine and 42% with triamcinolone with $p\leq 0.001$ for triamcinolone vs loratadine Nasal Itch % Symptom change of 39% with loratadine and 55% with triamcinolone with $p\leq 0.001$ for triamcinolone vs loratadine

Evidence Table 2. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Non-sedating antihistamines versus nasal corticosteroids
Part II. (continued)

Author Year UI	**Treatment outcomes studied**	**Symptom scale**	**Outcomes-efficacy**
Bernstein 1996 96213647	Mean total nasal symptom score Nasal itch Nasal congestion Postnasal drip Rhinorrhoea Sneezing Ocular symptoms	SYMPTOM SCALE: Diary cards: 0-3 scale was used during run-in period to evaluate patient symptom severity	Triamcinolone produced moderate to complete relief in 77% of patients vs. 63% of placebo patients. P<0.01 Total nasal score reduced by 50% with triamcinolone vs. 37% with astemizole. p<0.01 Nasal itch reduced by 54% with triamcinolone vs. 42% with astemizole p<0.05 Nasal congestion reduced by 43% with triamcinolone vs. 27% with astemizole p<0.05 Sneezing reduced by 56% with triamcinolone vs. 42% with astemizole p<0.05
Bronksy 1996	Global assessment-MD Global assessment patient Sneezing Rhinorrhoea Nasal congestion on awakening Nasal itch Nasal outflow Nasal cytology score	SYMPTOM SCALE: Diary cards: 0-3 scale	

Evidence Table 2. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Non-sedating antihistamines versus nasal corticosteroids
Part II. (continued)

Author Year UI	**Treatment outcomes studied**	**Symptom scale**	**Outcomes-efficacy**
Bronsky 1996 96194242	Total Mean Symptom Scale Rhinorrhoea Nasal Congestion Sneezing Itchy nose	Symptom scale-Visual Analogue scale From 0(absent) to 100 (severe)	**Global patient assessment:** Total nasal symptom score of 113 with fluticasone with p< 0.05 for fluticasone vs placebo; score of 171 with terfenadine with p< 0.05 for fluticasone vs terfenadine (no p value for terfenadine vs placebo); score of 191 with placebo **Overall nasal symptom percent change from baseline** : Change of -57% with fluticasone with p< 0.001 for fluticasone vs placebo; percent change of –38% with terfenadine and p< 0.001 for fluticasone vs terfenadine; percent change of –32% with placebo **Global clinician assessment:** Total nasal symptom score of 115 with fluticasone and p< 0.05 for fluticasone vs placebo; score of 163 with terfenadine and p < 0.05 for fluticasone vs terfenadine; score of 174 with placebo Percent change from baseline of –52% with fluticasone and p< 0.001 for fluticasone vs placebo; percent change of –33% with terfenadine and p< 0.001 for fluticasone vs terfenadine; score of –22% with placebo **Sneezing** Clinician assessment: score of 21 with fluticasone and p< 0.05 for fluticasone vs placebo; score of 33 with terfenadine and no p-value for fluticasone vs terfenadine; score of 36 with placebo Patient Assessment: Score of 23 with fluticasone and p< 0.05 for fluticasone vs placebo; score of 39 with terfenadine and p< 0.05 for fluticasone vs terfenadine; score of 45 with placebo **Rhinorrhoea** Clinician assessment: score of 31 with fluticasone and p< 0.05 for fluticasone vs placebo; score of 40 with terfenadine and p< 0.05 for fluticasone vs terfenadine; score of 43 with placebo Patient assessment: score of 29 with fluticasone and p< 0.05 for fluticasone vs placebo; score of 42 with terfenadine and p< 0.05 for fluticasone vs terfenadine; score of 47 with placebo **Nasal obstruction during day** Clinician assessment: score of 39 with fluticasone and p< 0.05 for fluticasone vs placebo; score of 54 for terfenadine and p < 0.05 for fluticasone vs terfenadine; score of 53 with placebo.

Evidence Table 2. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Non-sedating antihistamines versus nasal corticosteroids
Part II. (continued)

Author Year UI	**Treatment outcomes studied**	**Symptom scale**	**Outcomes-efficacy**
Bronsky 1996 96194242 (cont.)			Patient assessment: score of 35 with fluticasone and p< 0.05 for fluticasone vs placebo; score of 50 with terfenadine and p < 0.05 for fluticasone vs terfenadine; score of 51 with placebo. **Nasal obstruction on awakening** Patient assessment: score of 41 with fluticasone and p< 0.05 for fluticasone vs placebo; score of 57 with terfenadine and p< 0.05 for fluticasone vs terfenadine; score of 56 with placebo **Nasal Itch** Clinician assessment: score of 25 with fluticasone and p< 0.05 for fluticasone vs placebo; score of 37 with terfenadine and p< 0.05 for terfenadine vs placebo; score of 42 with placebo Patient assessment: score of 26 with fluticasone and p< 0.05 for fluticasone vs placebo; score of 40 with terfenadine, and p < 0.05 for fluticasone vs terfenadine; score of 48 with placebo
Jordana 1996 96191239	Nasal congestion (day) Nasal congestion (night) Sneezing Nasal itching Rhinorrhoea Ocular irritation Peak inspiratory nasal flow	Symptom scale: 4 point scale: 0-3	Day and night nasal congestion significantly reduced by fluticasone p<0.0001 Sneezing reduced by fluticasone p<0.001 Nasal itching reduced by fluticasone p<0.003 Measurement included symptom-free days: fluticasone group had statistically significantly lower median symptom scores than loratadine for nasal blockage during the day Nasal blockage: (p= 0.0006) Sneezing: (p= 0.0054) Runny nose: (p < 0.0001) Nasal Itch: (p= 0.029)

Evidence Table 2. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Non-sedating antihistamines versus nasal corticosteroids
Part II. (continued)

Author Year UI	**Treatment outcomes studied**	**Symptom scale**	**Outcomes-efficacy**
Gehanno 1997 97332767	Total Mean Symptom Score Rhinorrhoea Nasal Congestion Sneezing Itchy nose Night/daytime obstruction-	Symptom scale: Severity nasal symptoms -4 pt scale: with 0= no symptoms to 3= very frequent symptoms Overall symptom severity- visual analog scale from 0 (no symptoms) to 100 (severe symptoms)	Global symptom assessment: Nasal symptom score: On day 14, 61% patient improvement in fluticasone group vs 43% patient improvement in loratadine group, p = 0.02 for fluticasone vs loratadine On day 28, 72% patient improvement in fluticasone group vs 49% patient improvement in loratadine group, p= 0.009 for fluticasone vs loratadine Overall symptom score: On day 28, 80% success rate in fluticasone group vs 70% success rate in loratadine group. Values interpolated from figure. Success defined as “very effective” or “effective” out of 4 point scale Global clinician assessment: Nasal symptom score: On day 14, 62% patient improvement in fluticasone group vs 48% patient improvement in loratadine group, p= 0.008 for fluticasone vs loratadine On day 28, 73% patient improvement in fluticasone group vs 56% patient improvement in loratadine group, p= 0.002 for fluticasone vs loratadine Overall symptom score: On day 28, 80% success rate in fluticasone group vs 63% success rate in loratadine group. Values interpolated from figure. Success defined as “very effective” or “effective” out of 4 point scale
Juniper 1997	Rhinoconjunctivitis HRQL score Rescue terfenadine usage		Health-related quality of life score higher in fluticasone group p<0.052

Evidence Table 2. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Non-sedating antihistamines versus nasal corticosteroids
Part II. (continued)

Author Year UI	**Treatment outcomes studied**	**Symptom scale**	**Outcomes-efficacy**
Juniper 1997 97286890	Total Mean symptom score Nasal symptoms Eye-symptoms Non-nasal symptoms Sleep impairment Practical problems Activity limitations Emotional function	Symptom scale At each visit, patients required to complete Rhinoconjunctivitis Quality of Life Questionnaire Symptom severity score: 7 point scale with 0= no bothered, to 6= extremely bothered	⊕ symptom score difference indicates Fluticasone better than Terfenadine-differences based on HRQL scores Overall global assessment: At height of ragweed season: symptom score difference of 0.11 between fluticasone and terfenadine. P= 0.052 At end of season, score difference of 0.14 between drugs Sneezing At height of ragweed season, symptom score difference of 0.21 between fluticasone and terfenadine At end of season, score difference of 0.31 between drugs P=0.005
D'Ambrosio 1998 99133169	Total Mean Symptom Score Rhinorrhoea Nasal Congestion Sneezing Itchy eyes	Symptom Scale 0= no symptoms 1=slight symptoms not interfering with the patient's daily activity and/or sleep 2= moderate symptoms, occasionally interfering with daily activity and sleep 3=grave symptoms, seriously interfering with activity and sleep	Overall Clinician assessment: Symptom score of 2.9 with cetirizine with p< 0.05 for initial vs final; score of 4.8 with fluticasone with p < 0.05 for initial vs final; and score of 2.2 with treatment of cetirizine and fluticasone, with p< 0.05 for initial vs final P< 0.05 for cetirizine vs fluticasone; p< 0.05 for fluticasone vs treatment of both cetirizine and fluticasone; and p= NS (> 0.05) for cetirizine vs treatment of both cetirizine of fluticasone Nasal Sneezing Symptom score of 0.4 with cetirizine, score of 1.8 with fluticasone, and score of 0.6 with both cetirizine and fluticasone Rhinorrhoea Symptom score of 0.6 with cetirizine, score of 1.3 with fluticasone, and score of 0.4 with both cetirizine and fluticasone Nasal Congestion Symptom score of 1.5 with cetirizine; score of 0.4 with fluticasone, and score of 0.7 with both cetirizine and fluticasone Nasal Itch Symptom score of 0.4 with cetirizine, score of 1.3 with fluticasone, and score of 0.5 with both cetirizine and fluticasone

Evidence Table 2. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Non-sedating antihistamines versus nasal corticosteroids
Part II. (continued)

Author Year UI	**Treatment outcomes studied**	**Symptom scale**	**Outcomes-efficacy**
Ratner 1998 98390023	Total Mean Symptom Score Rhinorrhoea Nasal Congestion Sneezing Itchy nose Nasal mucosa consistent with rhinitis	Symptom scale Diary Cards: Visual analog scale 0- 100 with 0= absent, and 100= severe -symptoms evaluated in evening	**Global patient evaluation:** Overall treatment: 62/142 patients indicated symptom *improvement with Loratadine and p< 0.001 for drug vs placebo; 90/142 patients indicated improvement with Fluticasone and p < 0.001 for drug vs placebo; 96/145 indicated improvement with Loratadine + Fluticasone with p < 0.001 for drug combination vs placebo and p< 0.001 for drug combo vs loratadine; and 61/140 indicated improvement with placebo (*improvement= significant, moderate + mild improvement) Total Nasal Symptoms Score: Score of 220 with Loratadine with p< 0.001 for loratadine vs placebo; score of 140 with fluticasone with p< 0.001 for fluticasone vs placebo and p< 0.001 for fluticasone vs loratadine; score of 110 with Loratadine +Fluticasone with p< 0.05 for drug combo vs fluticasone for mean change from baseline, p < 0.001 for drug combo vs loratadine, plus p < 0.001 for drug combo vs placebo; and score of 230 with placebo **Global clinician evaluation:** Total Symptoms: Score of –102.0 for Loratadine; score of –187.0 for fluticasone with p < 0.05 for fluticasone vs placebo, and p < 0.05 for fluticasone vs loratadine; score of 186.0 for Loratadine + Fluticasone with p < 0.05 for drug combo vs placebo, and p < 0.05 for drug combo vs loratadine; score of –102.0 for placebo Total Nasal Symptom Score: Score of 210 with Loratadine with p < 0.001 for loratadine vs placebo; score of 110 with fluticasone with p < 0.001 for fluticasone vs placebo and p < 0.001 for fluticasone vs loratadine; score of 110 with Loratadine + Fluticasone with p < 0.001 for drug combo vs placebo and p < 0.001 for drug combo vs loratadine; and score of 220 with placebo Following scores are from evaluations after 2 weeks **Sneezing:** Score of –26.3 for Loratadine; score of –48.4 for fluticasone with p < 0.05 for fluticasone vs placebo, and p < 0.05 for fluticasone vs loratadine; score of – 45.7 for Loratadine + Fluticasone with p < 0.05 for drug combo vs placebo, and p < 0.05 for drug combo vs loratadine; score of –26.6 for placebo loratadine; score of –27.1 for placebo

Evidence Table 2. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Non-sedating antihistamines versus nasal corticosteroids
Part II. (continued)

Author Year UI	Treatment outcomes studied	Symptom scale	Outcomes-efficacy
Ratner 1998 98390023 (cont.)			**Rhinorrhoea:** Score of –26.9 for Loratadine; score of –46.3 for fluticasone with $p < 0.05$ for fluticasone vs placebo, and $p < 0.05$ for fluticasone vs loratadine; score of –49.6 for Loratadine + Fluticasone with $p < 0.05$ for drug combo vs placebo, and $p < 0.05$ for drug combo vs **Nasal Congestion:** Score of –20.0 for Loratadine; score of –42.5 for fluticasone with $p < 0.05$ for fluticasone vs placebo, and $p < 0.05$ for fluticasone vs loratadine; score of –42.6 for Loratadine + Fluticasone with $p < 0.05$ for drug combo vs placebo, and $p < 0.05$ for drug combo vs loratadine; score of –20.0 for placebo **Nasal Itch:** Score of –29.3 for Loratadine; score of –50.0 for fluticasone with $p < 0.05$ for fluticasone vs placebo, and $p < 0.05$ for fluticasone vs loratadine; score of –48.2 for Loratadine + Fluticasone with $p < 0.05$ for drug combo vs placebo, and $p < 0.05$ for drug combo vs loratadine; score of –28.4 for placebo
Ortolani 1999 20068053	Total Mean Symptom Score Rhinorrhoea Nasal congestion Sneezing Watery eyes Itchy nose Itchy eyes	Patients- record symptoms on diary card (nasal and ocular symptoms) Nasal obstruction symptom scale 0= not present 1= slightly difficult to breathe through nose 2= moderately difficult 3= very difficult/ impossible All other symptom scales 0= none 1= mild (occasionally present) 2= moderate (rather frequent) 3= severe (persistent)	Higher % symptom-free days in patients in fluticasone group compared to those given placebo for symptoms of obstruction, rhinorrhea, sneezing, and itching Higher % of symptom-free days without obstruction and rhinorrhea and better frequency distribution of nasal scores for each symptom for patients in fluticasone group compared to those in levocabastine group *****Data: Median number of symptom-free days and Frequency distribution of median score given! *****No actual numerical data. All info in bar graphs.

Evidence Table 2. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Non-sedating antihistamines versus nasal corticosteroids
Part II. (continued)

Author Year UI	**Treatment outcomes studied**	**Symptom scale**	**Outcomes-efficacy**
Condemi 2000 20289854	Total Mean Symptom Score Rhinorrhoea Sneezing Nasal Congestion Watery eyes Itchy nose Itchy eyes Itchy throat	Symptom scale: Patient diary cards- 4 pt scale 0= none; symptoms absent 1= mild, symptoms present, but not annoying 2= moderate, symptoms present and annoying 3= severe, symptoms interfere with daily activities or sleep Daily pollen counts, clinical laboratory tests, and physical examinations were also done Patients also completed RQLQ at visits 2,3, and 4	Global patient assessment: (at 4 weeks) Rhinoconjunctivitis Quality of Life Questionnaire: overall score of 1.48 with triamcinolone vs score of 1.82 with loratadine; $p < 0.05$ Global physician assessment: Improvement with triamcinolone: total 136 patients (78%) showed improvement 54 patients (31%) showed moderate improvement 64 patients (37%) showed marked improvement 18 patients (10%) showed complete improvement p= NS Improvement with loratadine: total 116 patients (67%) showed improvement 51 patients (29%) showed moderate improvement 60 patients (35%) showed marked improvement 5 patients (3%) showed complete improvement p= NS Following scores taken at 4 weeks • Total Nasal score Mean weekly score of 3.8 with triamcinolone vs score of 5.0 with loratadine $P < 0.5$ • Sneezing Mean weekly score of 1.0 with triamcinolone vs score of 1.3 with loratadine $P< 0.05$ • Rhinorrhoea Mean weekly score of 1.25 with triamcinolone vs score of 1.5 with loratadine $P < 0.05$ • Nasal Congestion Mean weekly score of 1.3 with triamcinolone vs score of 1.5 with loratadine $P < 0.5$

Evidence Table 2. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Non-sedating antihistamines versus nasal corticosteroids
Part II. (continued)

Author Year UI	**Treatment outcomes studied**	**Symptom scale**	**Outcomes-efficacy**
Condemi 2000 20289854 (continued)			• Nasal Itch Mean weekly score of 1.1 with triamcinolone vs score of 1.4 with lortadine P= NS, but statistically significant at week 2 and week 3 Overall percent improvement from 48% to 58% in triamcinolone group Overall percent improvement from 36% to 46% in loratadine group

Evidence Table 2. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Non-sedating antihistamines versus nasal corticosteroids
Part III.

Author Year UI	**Outcome-safety**	**Potential Bias**	**Funding**
Munch 1983 84050113	No major adverse effects. Minor adverse effects: 1 withdrawal in dexchlorpheniramine group due to sedation effects Sedation during the day in 1st week- $p < 0.01$ for dexchlorpheniramine vs budesonide Sedation in the morning in 1st week- $p< 0.01$ for dexchlorpheniramine vs budesonide		ND

Evidence Table 2. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Non-sedating antihistamines versus nasal corticosteroids
Part III. (continued)

Author Year UI	**Outcome-safety**	**Potential Bias**	**Funding**
Backhouse 1986 86165329	No major adverse effects. Minor adverse effects: 17 withdrawals from terfenadine group- 12 due to medical reasons (10pts- poor symptom control, 1pt- headache, and 1pt- glandular fever) 5 withdrawals from terfenadine and flunisolide group- 2 due to medical reasons (2pts- poor symptom control) p< 0.005 between group withdrawals Total # reports of side effects: 28 from terfenadine group and 35 from terfenadine +flunisolide group -Nasal Irritation- 8 reports form terfenadine group and 10 reports from terfenadine +flunisolide group -Drowsiness- 9 reports from terfenadine group and 6 reports from terfenadine+ flunisolide group -Nausea- 5 reports from terfenadine group and 1 report from terfenadine + flunisolide group	Other reasons for withdrawal: 1pt-pregnant, , 2 patients- lack of symptoms, 3pt- personal reasons, 1 pt- lost to followup, and 1pt- leaving country	ND

Evidence Table 2. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Non-sedating antihistamines versus nasal corticosteroids
Part III. (continued)

Author Year UI	**Outcome-safety**	**Potential Bias**	**Funding**
Wood 1986 86245576	No major adverse effects. Minor adverse effects: “adverse effect did not appear to be a problem with either group” -Tiredness, drowsiness, sleepiness- 4 from astemizole group and 2 from beclomethasone group -stomach pains- 4 from beclomethasone group, none from astemizole group	Author is the investigator, care giver, and outcome assessor It is difficult to figure out how he could have ensure concealed randomization and double blinding, etc Mostly graph results	Pharmaceutical

Evidence Table 2. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Non-sedating antihistamines versus nasal corticosteroids
Part III. (continued)

Author Year UI	**Outcome-safety**	**Potential Bias**	**Funding**
Juniper 1989 89175902	No major adverse effects Minor adverse effects: -Drowsiness- 9 patients taking astemizole, 4 patients taking beclomethasone, and 4 patients taking astemizole + beclomethasone -Hunger- 3 patients taking astemizole, 3 patients taking beclomethasone, and 4 patients taking astemizole+beclomethasone -Dry nose/ lips etc.- 0 patients taking astemizole, 2 patients taking beclomethasone, and 3 patients taking astemizole + beclomethasone -Nasal bleeding- 0 patients taking astemizole, 2 patients taking beclomethasone, and 3 patients taking astemizole+ beclomethasone -Headache- 1 patient taking astemizole, 1 patient taking beclomethasone, and 3 patients taking astemizole+beclomethasone -Thirst- 0 patients taking astemizole, 2 patients taking beclomethasone, and 1 patient taking astemizole+beclomethasone -Skin rash- 0 patients taking astemizole, 2 patients taking beclomethasone, and 1 patient taking astemizole +beclomethasone -Nausea- 0 patients taking astemizole, 0 patients taking beclomthasone, and 2 patients taking astemizole+beclomethasone	Allowance of standardized concomitant medication prevented dropouts Other reasons for withdrawal: 1 patient- forgot to take medication	Pharmaceutical

Evidence Table 2. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Non-sedating antihistamines versus nasal corticosteroids
Part III. (continued)

Author Year UI	**Outcome-safety**	**Potential Bias**	**Funding**
Robinson 1989	No major adverse effects. Minor adverse effects 5 withdrawals- (2 after terfenadine treatment, 3 after beclomethasone treatment) -Drug-related adverse effect- 2 patients taking terfenadine causing nose-bleed, and frequent falling asleep; and 1 patient taking beclomethasone causing upset stomach/pain, are drug-related -Adverse effects- 2 patients taking terfenadine, and 5 patients taking beclomethasone reported adverse effects	Poorly described Small population	Pharmaceutical
Darnell 1994 95196117	No major adverse effects. Minor adverse effects 11 patients withdrew due to adverse effects: 5 from terfenadine group(1 pt- fatigue, 1pt-nasal itching+epistaxis,1pt-oral burning sensation,1pt-asthma, 1- acute asthma attack) 1 from fluticasone group(headache and breathlessness), 5 from placebo (1pt-nasal burning sensation, 1pt-developed erythematous rash,1pt-became pregnant, 1pt-developed Hepatitis A, 1pt-developed asthma) -Headache- 30 patients reported effect -Exacerbations of SAR- 18 patients Overall report of adverse effects- 56% from terfenadine group, 57% from fluticasone group, and 61% from placebo group	Poor enumeration of results Numeric data not given- data extracted by estimation of bar graph Other reasons for withdrawal: Non-compliance with protocol- 34 patients Usage of dis-allowed drugs- 11 patients	Pharmaceutical

Evidence Table 2. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Non-sedating antihistamines versus nasal corticosteroids
Part III. (continued)

Author Year UI	**Outcome-safety**	**Potential Bias**	**Funding**
Van Bavel 1994 95085365	No major adverse effects. Minor adverse effects: 15 withdrawals: 4 patients withdrew due to adverse effects: 1 from fluticasone group due to asthma (drug unrelated);1 due to secondary effects of allergic asthma and bronchitis (drug unrelated); 1 from fluticasone due to headache (drug related); and 1 from terfenadine group due to trauma (drug unrelated) 7 patients due to lack of efficacy Asthma- 2 patients in fluticasone group Headache- 4 patients in fluticasone group, 7 patients in terfenadine group, and 3 patients in placebo group Overall adverse effects: 24 patients in fluticasone group, 23 patients in terfenadine group, and 15 patients in placebo group reported adverse effects	Didn't provide mean baseline and mean p values for treatment symptoms scores Other reasons for withdrawal: 3 patients due to protocol violations (1 from each group) 1 patient did not return for followup visit	ND
Hilberg 1995 96098156	No side effects listed	Tiny study Challenge Mode Surrogate endpoint of uncertain clinical value Budesonide superior to terfenadine in treatment of nasal congestion in hay fever, especially in postchallenge reaction Other reasons for withdrawal: One patient left study for personal reasons (17/18 completed study)	Pharmaceutical

Evidence Table 2. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Non-sedating antihistamines versus nasal corticosteroids
Part III. (continued)

Author Year UI	**Outcome-safety**	**Potential Bias**	**Funding**
Schoenwetter 1995 96070357	No major adverse effects. Minor adverse effects 2 withdrawals form triamcinolone group (possible reason- patient 1- paresthesia, dizziness, nausea, and dyspepsia; patient 2- headache and myalgia(10 withdrawals form loratadine group due to adverse effects (1pt- epistaxis possibly due to drug, reasons for other 9 withdrawals not known) -Headache- 35% of patients from loratadine group and 43% of patients form triamcinolone group -Rhinitis- 10% from loratadine group and 4% from triamcinolone group	Triamcinolone significantly better for all endpoints than loratadine	Pharmaceutical
Bernstein 1996 96213647	No major adverse effects in either group. Minor adverse effects 4 withdrawals in each group for URI AE Pharyngitis NS Headache NS Weight gain 11% of astemizole group vs. 2% of triamcinolone group, $p<0.05$	No placebo group Analysis not intention to treat for efficacy data	Pharmaceutical
Bronsky 1996	No major adverse effects. No statistically significant incidence between groups Most common minor adverse event was headache.		

Evidence Table 2. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Non-sedating antihistamines versus nasal corticosteroids
Part III. (continued)

Author Year UI	**Outcome-safety**	**Potential Bias**	**Funding**
Bronsky 1996 96194242	No major adverse effects. Minor adverse effects: 6 patients withdrew due to adverse events : 1 patient from fluticasone group ("potentially related to study medication"), 2 from terfenadine group (1pt potentially from medication, 2nd patient from treatment), and 3 patients from placebo group (perhaps from secondary effects of treatment) 6 patients withdrew due to lack of efficacy: 3 from terfenadine and 3 from placebo groups Headaches: 3 from fluticasone group reported effect, 3 from terfenadine group, and 5 from placebo group [unclear if resulted from drug treatment]	Drop-out rate lower for fluticasone group Highly selected sample consistent with typical patients seen in office Other reasons for withdrawal 17 patients: 5 from fluticasone group, 8 from terfenadine group, and 4 from placebo group due to noncompliance, protocol violation, or withdrew consent not clear if drop-outs excluded from analysis or if included until time of drop-out	Pharmaceutical (Glaxo)
Jordana 1996 96191239	Commonest adverse events were headache and pharyngitis Significant increase in headache in fluticasone group		ND

Evidence Table 2. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Non-sedating antihistamines versus nasal corticosteroids
Part III. (continued)

Author Year UI	**Outcome-safety**	**Potential Bias**	**Funding**
Gehanno 1997 97332767	Major adverse effects: -1 withdrawal in loratadine group for adverse effects: 1 patient had history of epilepsy and developed convulsions requiring hospitalization. Minor adverse effects: ~2 withdrawals in fluticasone group due to lack of efficacy ~5 withdrawals in loratadine group due to: -4 withdrawals for lack of efficacy -1 patient had severe dizziness, sweating and weakness -Nausea- 1 patient in fluticasone group -Asthma attack- 1 patient in fluticasone group -Respiratory disorder- 1 patient in loratadine group and 1 patient in fluticasone group -Convulsions, dizziness, sweating, and weakness- each adverse effect reported by 1 patient in loratadine group	Other reasons for withdrawals (from 9 withdrawals in loratadine group: 2 patients failed to return, and 1 patient due to noncompliance	Pharmaceutical
Juniper 1997	No information on safety	No placebo group	No data on funding
Juniper 1997 97286890	No major adverse effects. Minor adverse effects 1 withdrawal from fluticasone group due to nausea (asked to be transferred to beclomethasone, but failed to keep last appointment)	Designed to replicate “real life” by allowing cross-over and PRNs Open (unblinded)	Pharmaceutical (Glaxo)

Evidence Table 2. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Non-sedating antihistamines versus nasal corticosteroids
Part III. (continued)

Author Year UI	**Outcome-safety**	**Potential Bias**	**Funding**
D'Ambrosio 1998 99133169	No major adverse effects. Minor adverse effects: Burning throat/ nose: 2 patients in fluticasone group and 3 patients in cetirizine+fluticasone group Dizziness- 4 patients in cetirizine group and 3 patients from cetirizine+fluticasone group Gastric disorders- 1 patient in cetirizine group Visual trouble- 1 patient in cetirizine group	Other reasons for withdrawal- 6 patients left for personal reasons	ND
Ratner 1998 98390023	No Major adverse effects: Minor adverse effects: -Blood in nasal mucous- 5-10 patients in active treatment group and 5 patients in placebo -Epitaxis- less than 6 patients for all treatments -Xerostomia- less than 12 patients for all treatments	Other reasons for withdrawal: 8 withdrawals due to allergic rhinitis 13 withdrawals due to lack of efficacy 7 withdrawals due to other reasons	Pharmaceutical

Evidence Table 2. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Non-sedating antihistamines versus nasal corticosteroids
Part III. (continued)

Author Year UI	**Outcome-safety**	**Potential Bias**	**Funding**
Ortolani 1999 20068053	No major adverse events. Minor adverse effects: 32 patients withdrew: 11 patients in levocabastine group, 9 patients in fluticasone group, and 12 patients in placebo group -Respiratory symptoms- 5 patients from levocabastine group, 5 from fluticasone group, and 8 patients from the placebo group -Exacerbations of nasal symptoms- 2 patients from levocabastine group, 0 patients from fluticasone group, and 1 from placebo group Adverse effects: 0 patients in levocabastine group, 3 in fluticasone group, and 1 in placebo group Lack efficacy: 5 patients in levocabastine group, 1 patient in fluticasone group, and 4 patients in placebo group	Good study Other reasons for withdrawal: 16 patients excluded (insufficient data): 6 from levocabastine group, 4 from fluticasone group, and 6 from placebo group	Pharmaceutical
Condemi 2000 20289854	Major adverse effects: 4 dropouts from the triamcinolone group due to headache, rhinitis , and chest pain 3 dropouts due to loratadine Headache: 25 patients total from triamcinolone group and 27 patients from loratadine group reported effect Minor adverse effects: None indicated	Other reasons for withdrawal: 15 patients due to protocol deviation 9 patients due to treatment failure 3 patients due to lost to followup	Pharmaceutical

Evidence Table 3. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Sedating versus nonsedating antihistamines
Part I.

Author Year UI	Intervention	Duration	Demographics	Inclusion criteria	Exclusion criteria
Brostoff 1982 83014720	**Perennial Allergic Rhinitis** Chlorpheniramine vs. terfenadine vs. placebo RCT- Parallel	2 weeks	Location: UK Mean age: none Age range: 18-65 %Male: ND Race: ND Enrolled: 60 Evaluated: 60 Number of sites: 1	Moderate to severe perennial allergic rhinitis symptoms.	ND
Gastpar 1982 83100633	**Seasonal Allergic Rhinitis** Clemastine vs. terfenadine RCT –Parallel	12 weeks	Location: Germany Mean age: ND Age range: 16-37 % Male: 50% Race: ND Enrolled:20 Evaluated: 20 Number of sites: 1	History of seasonal allergic rhinitis Positive skin test	Asthma Cromoglycate within 24 hours Corticosteroids within 1 week Depot corticosteroids within 8 weeks Malignant/chronic disease Pregnancy/lactation Drug abuse/ alcoholism
Malmberg 1983 83253693	**Seasonal Allergic Rhinitis** Chlorpheniramine vs. astemizole vs. placebo RCT-Parallel	36 days	Location: Finland Mean age ND Age range: 16-53 % Male: 43.1% Race: ND Enrolled: 51 Evaluated: 51 Number of sites: 1	Seasonal birch pollen symptoms for 8 years Positive birch pollen skin test or birch RAST Positive nasal provocation with birch pollen	Other nasal disease

Evidence Table 3. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Sedating versus nonsedating antihistamines
Part I. (continued)

Author Year UI	Intervention	Duration	Demographics	Inclusion criteria	Exclusion criteria
Gutkowski 1985 86030956	**Seasonal Allergic Rhinitis** Dexchlorpheniramine vs. terfenadine RCT- Parallel	14 days	Location: Canada Mean age: ND Age range: 12-60 % Male: ND Race: ND Enrolled: 177 Evaluated: 174 Number of sites: 4	Positive skin test for ragweed History of ragweed allergy	Corticosteroid within 2 weeks Pregnant/ lactating
Hugonot 1986 86248368	**Seasonal Allergic Rhinitis** Mequitazine vs. terfenadine RCT- Parallel	1 week	Location: France Mean age: 29.7 Age range: 18-65 % Male: 49.6% Race: ND Enrolled: 147 Evaluated: 141 Number of sites: 1	Seasonal allergic rhinitis symptoms	None listed
Backhouse 1987 89062246	**Seasonal Allergic Rhinitis** Chlorpheniramine vs terfenadine RCT-Parallel	6 days	Location: UK Mean age: ND Age range: 18-65 % Male: 47% Race: ND Enrolled: 138 Evaluated: 121 Number of sites: 1	Positive skin test and documented allergy to grass pollen within past two years.	Pregnancy or lactation, any "major systemic illness", antihistamines within 4 weeks
Johansen 1987 87205847	**Seasonal Allergic Rhinitis** Dexchlorpheniramine vs. terfenadine RCT-Parallel	3 weeks	Location: Denmark Mean age: 31 Age range: 18-63 % Male: ND Race: ND Enrolled:42 Evaluated: 38 Number of sites: 1	Symptoms of seasonal allergic rhinitis for at least 2 years Positive skin prick test	Antihistamines within 3 days, cromoglycate within 3 days, oral corticosteroid use within 2 weeks, depot corticosteroid use within 8 weeks, hyposensitization therapy during previous 12 months, pregnant/lactating

Evidence Table 3. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Sedating versus nonsedating antihistamines
Part I. (continued)

Author Year UI	Intervention	Duration	Demographics	Inclusion criteria	Exclusion criteria
Pastorello 1987 88016480	**Seasonal Allergic Rhinitis** Dexchlorpheniramine vs. terfenadine RCT- Parallel	7 days	Location: Italy Mean age: ND Age range: 13-63 % Male: ND Race: ND Enrolled: 65 Evaluated: 62 Number of sites: 2	History of seasonal allergic rhinitis Diagnosis by history, RAST, positive skin test	Oral steroids within 1 week, nasal decongestants within 1 week, other antihistamines, sedatives or tranquilizers within 3 days
Buckley 1988 88131974	**Seasonal Allergic Rhinitis** Chlorpheniramine vs. terfenadine vs. placebo RCT-Parallel	7 days	Location: US Mean age: ND Age range: 12-66 % Male: 53% Race: ND Enrolled:244 Evaluated: 215 Number of sites: 6	Reversible seasonal hay fever symptoms >12 years old Late summer or fall allergic rhinitis and conjunctivitis Positive skin test	Asthma, sinusitis, nasal polyposis, pregnant/lactating, upper respiratory infection, history of steroid use during past 2 years, antibiotics or cromoglycate within 7 days,antihistamine or decongestant within 2 years
Druce 1998 98250349	**Perennial Allergic Rhinitis** Brompheniramine vs loratadine vs. placebo RCT- Parallel	7 days	Location: US Mean age: 33 Age range: 18-56 %Male: 46.4% Race: ND Enrolled: 338 Evaluated: 297 Number of sites: 5	History of allergic rhinitis Active symptoms Evidence of nasal mucosal changes with antigen exposure	Astemizole within 30 days Cold/allergy medication within 72 hours; Antihistamine within 24 hours Pregnancy/lactation
Thoden 1998 98413360	**Seasonal Allergic Rhinitis** Brompheniramine vs. terfenadine vs. placebo RCT- Parallel	14 days	Location: US Mean age: ND Age range: 15- 92 % Male: ND Race: ND Enrolled:370 Evaluated: 343 Number of sites: 3	Symptoms of allergic rhinitis	Astemizole within 30 days, other allergy medication within 72 days, pregnancy or lactating, contra-indication to antihistamine usage

Evidence Table 3. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Sedating versus nonsedating antihistamines
Part I. (continued)

Author Year UI	Intervention	Duration	Demographics	Inclusion criteria	Exclusion criteria
Weiler 2000 20143057	**Seasonal Allergic Rhinitis** Diphenhydramine vs fexofenadine	5 weeks	Location: US Mean age: 31 Age range: 25-44 % Male: 37.5% Race: ND Enrolled:41 Evaluated: 40 Number of sites: 1	History of alcohol use Seasonal allergic rhinitis symptoms Previous successful use of antihistamine Licensed driver	Pregnancy, excessive alcohol use, tobacco use in past year, excessive caffeine intake

Evidence Table 3. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Sedating versus nonsedating antihistamines
Part II.

Author Year UI	**Treatment outcomes studied**	**Symptom scale**	**Outcomes-efficacy**
Brostoff 1982	Mean total symptom score- Rhinorrhoea Sneezing Itchy eyes Nasal Congestion Watery Eyes Itchy throat Itchy nose	0-3 symptom scale, and (9 symptoms scored) 3-severe; 2- moderate; 1- mild; 0- absent	Mean score improvement from 7.6 to 5.1 with terfenadine Mean score improvement from 8.0 to 4.6 with chlorpheniramine Mean score improvement from 7.8 to 5.8 with placebo
Gastpar 1982 83100633	Total Mean symptom score Not indicated	Symptom Scale Not indicated But lab tests (blood chemistry, hematology, and urinalysis) plus IgE antibodies and ophthalmological examinations were conducted	No clinical data reported 15 patients treated with terfenadine showed significant decrease in IgE values ($p < 0.001$) vs 5 patients in clemastine group who showed only slight reduction Terfenadine tablets did not cause abnormal changes in laboratory values (blood chem, hematology, and urinalysis) and did not alter physiological body functions(heart rate, respiratory rate, body temp and blood pressure) after oral administration of (120mg/day)
Malmberg 1983 83253693	Total Mean Symptom Score Running nose Nasal blockage Sneezing Itchy nose Itchy eyes Red eyes Eye Swelling	Symptom scale: 4 pt scale (0-3) recorded on diary cards	Overall patient assessment: both antihistamines were better than placebo Overall physician assessment: both antihistamines were better than placebo

Evidence Table 3. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Sedating versus nonsedating antihistamines
Part II. (continued)

Author Year UI	**Treatment outcomes studied**	**Symptom scale**	**Outcomes-efficacy**
Gutkowski 1985 86030956	Total Mean symptom score Rhinorrhoea Nasal Congestion Sneezing Watery eyes Itchy nose Itchy eyes	Symptom Scale Symptom severity- 0-3 scale, with 0= none to 3= severe Overall treatment response assessment scale: 1= excellent- 75% improvement or more 2= good-between 75% and 50% improvement 3= fair-between 50% and 25% improvement 4= poor-less than 25% improvement 5= treatment failure	Global patient assessment: Mean score of 2.5 with dexchlorpheniramine and score of 3.2 with terfenadine. P < 0.001 Global physician assessment Mean score of 2.4 with dexchlorpheniramine and score of 3.2 with terfenadine. P< 0.001 64% of dexchlorpheniramine group had good/excellent response vs 40% of terfenadine group had good/excellent response Total signs and symptoms: Mean symptoms score of 5.9 with dexchlorpheniramine, and score of 8.8 with terfenadine. P< 0.001 Total Nasal Symptoms: Mean symptom score of 3.9 with dexchlorpheniramine and score of 5.9 with terfenadine. P< 0.001

Evidence Table 3. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Sedating versus nonsedating antihistamines
Part II. (continued)

Author Year UI	**Treatment outcomes studied**	**Symptom scale**	**Outcomes-efficacy**
Hugonot 1986 86248368	Total Mean Symptom Score Rhinorrhoea Nasal congestion Sneezing Itchy nose Itchy eyes	Symptom scale Patient diary card- with 0 to 3 scale for nasal itching, sneezing, runny nose, blocked nose, irritated eyes, and presence and intensity of somnolence On day 0 and day 7, patient judged degree of discomfort on visual analogue scale Physician assessment: on days 0 and 7, physician evaluated associated symptoms (lacrimation, irritated throat, and cough) and judged efficacy on day 7	Global patient assessment: Daily symptom score- no difference between treatment groups Global physician assessment: Not much difference in global efficacy between treatment groups All p values= N/S
Backhouse 1987 89062246	Total Mean Symptom Score Sneezing itchy or watery eyes Running or blocked nose	Symptom Scale 4 point scale 0= absent 1= slight 2= moderate 3= severe	Sneezing Overall symptoms core of 83 with chlorpheniramine and score of 78 with terfenadine Rhinorrhoea Overall score of 82 with chlorpheniramine and score of 79 with terfenadine Nasal Congestion Overall symptom score of 85 with chlorpheniramine and score of 81 with terfenadine All scores compiled from patient diary scores. No p values given

Evidence Table 3. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Sedating versus nonsedating antihistamines
Part II. (continued)

Author Year UI	**Treatment outcomes studied**	**Symptom scale**	**Outcomes-efficacy**
Johansen 1987 87205847	Total mean symptom score Sneezing Nasal congestion Runny nose Itchy nose Eye symptoms Tiredness	Symptom scale 4-point scale 0= no symptoms 1= mild symptoms 2= moderate symptoms 3= severe symptoms	Sneezing Symptom score of 0.58 with dexchlorpheniramine vs score of 0.65 with terfenadine Nasal Congestion Symptom score of 0.55 with dexchlorpheniramine vs score of 0.63 with terfenadine Nasal itch Symptom score of 0.37 with dexchlorpheniramine vs score of 0.53 with terfenadine Dexchlorpheniramine revealed significant ($p<0.05$) improvement in symptoms for nasal itching and tiredness (improved on treatment) Compared to dexchlorpheniramine, terfenadine did poorly

Evidence Table 3. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Sedating versus nonsedating antihistamines
Part II. (continued)

Author Year UI	**Treatment outcomes studied**	**Symptom scale**	**Outcomes-efficacy**
Pastorello 1987 88016480	Total Mean Symptom Score Rhinorrhoea Nasal Congestion Sneezing Watery eyes Itchy nose Itchy throat Itchy eyes Red Eyes	Symptom Scale Symptom severity- 5 point scale: 0= absent 1= poor 2= mild 3= severe 4= very severe Physician evaluation – based on skin test (+ to ++++), rhinomanometry and symptom evaluation done on "every entry" and after 7 days	Global patient assessment: 25/32 patients in terfenadine group rated treatment good/excellent; 7/32 patients in terfenadine group rated treatment poor/nil 22/30 patients in dexchlorpheniramine group rated treatment good/excellent; 8/ 30 patients in dexchlorpheniramine group rated treatment poor/nil Difference between drug effects not significant (p> 0.05) Global physician assessment: Rhinomanometric data: reduction in total nasal resistance after treatment, but not significant from baseline, and no significant difference between two groups p> 0.05 between 2 groups [no absolute data] Nasal Sneezing: Mean pre-score of 2.2 and post-score of 0.93 with terfenadine; mean pre-score of 2.1 and post-score of 0.82 with dexchlorpheniramine; p > 0.05 between two groups Rhinorrhoea Mean pre-score of 1.93 and post-score of 0.93 with terfenadine; mean pre-score of 1.85 and post-score of 1.15 with dexchlorpheniramine. P> 0.05 between two groups Nasal Congestion: Mean pre-score of 1.57 and post-score of 1.37 with terfenadine; mean pre-score of 1.64 and post score 1.28 with dexchlorpheniramine. P> 0.05 between two groups Both drug significantly reduce all symptoms except nasal obstruction for both groups, and cough/itchy throat for terfenadine group No significant difference between groups

Evidence Table 3. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Sedating versus nonsedating antihistamines
Part II. (continued)

Author Year UI	**Treatment outcomes studied**	**Symptom scale**	**Outcomes-efficacy**
Buckley 1988 88131974	Total Mean Symptom score Rhinorrhoea Nasal Congestion Sneezing Watery eyes Itchy nose Itchy eyes Itchy throat	Symptom scale Sneezing, rhinorrhea, nasal itch, ocular symptoms: 5 point scale (0= absent to 4= very severe) effectiveness of patient treatment (at final visit): 6-point scale (0= worse to 5= complete relief)	Global patient assessment: % patients would use treatment again: 60% in terfenadine group with p= 0.04 for terfenadine vs placebo; 66% in chlorpheniramine group with p= 0.006, and 45% in placebo group p= 0.006 for chlorpheniramine vs placebo and p= 0.01 for terfenadine vs placebo Global Physician assessment: P< 0.001 for chlorpheniramine vs placebo and p= 0.001 for terfenadine vs placebo Sneezing P< 0.05 for chlorpheniramine vs placebo and p< 0.05 for terfenadine vs placebo Rhinorrhoea P< 0.05 for chlorpheniramine vs placebo and p< 0.05 for terfenadine vs placebo Only p values stated, no raw data

Evidence Table 3. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Sedating versus nonsedating antihistamines
Part II. (continued)

Author Year UI	Treatment outcomes studied	Symptom scale	Outcomes-efficacy
Druce 1998 98250349	Mean total symptom score Rhinorrhoea Nasal Congestion Sneezing Watery Eyes Itchy Nose Itchy eyes Itchy throat Ocular Redness	0 – 4 scale for symptom severity 0= none 1= mild 2= moderate 3= severe 4= very severe 11pt scale for global evaluation 0= poor to 10= excellent	**Global Patient Assessment:** At day 3 (visit #2)- Symptom score of 5.8 with brompheniramine, p < .001 for brompheniramine compared to placebo; vs Symptom score of 4.1 with loratadine ,p< 0.001 for brompheniramine vs loratadine; Symptom score of 3.4 with placebo At day 7(visit#3)- Symptom score of 7.3 with brompheniramine, p< .05 for brompheniramine compared to placebo; vs symptom score of 9.7 with loratadine, p<.05 for brompheniramine vs loratadine; symptom score of 11.6 with placebo **Global Physician Assessment:** At day 3 (visit #2)- Symptom score of 5.9 with brompheniramine, p<0.001 for brompheniramine compared to placebo; vs symptom score of 4.6 with loratadine, p<0.001 for brompheniramine vs loratadine; symptom score of 4.0 with placebo At day 7(visit #3)- Symptom score of 6.7 with brompheniramine, p<0.05 for brompheniramine compared to placebo; vs symptom score of 8.7 with loratadine, p<0.05 for brompheniramine vs loratadine; symptom score of 10.8 with placebo When data from visit #2 and visit #3 were summarized: Loratadine > P, P < 0.05 Summed cluster symptoms (Rhinorrhoea, Sneezing, and Congestion) **Global Patient Assessment:** At day 3 (visit #2)- Symptom score of 3.5 with brompheniramine, p< 0.01 for brompheniramine vs placebo; Symptom score of 4.1 with loratadine, p<0.05 for loratadine vs placebo; P < 0.01 for brompheniramine vs loratadine; symptom score of 5.3 with placebo At day 7(visit #3)- Symptom score of 3.2 with brompheniramine, p<0.01 for brompheniramine vs placebo; symptom score of 4.3 with loratadine, p- NS for loratadine vs placebo; P< 0.01 for brompheniramine vs loratadine; symptom score of 4.8 with placebo **Global Physician Assessment:** At day 3 (visit #2)- Symptom score of 3.4 with brompheniramine, p<0.01 for brompheniramine vs placebo; symptom score of 4.3 with loratadine, p <0.05 for loratadine vs placebo; P<0.01 for brompheniramine vs loratadine;

Evidence Table 3. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Sedating versus nonsedating antihistamines
Part II. (continued)

Author Year UI	**Treatment outcomes studied**	**Symptom scale**	**Outcomes-efficacy**
Druce 1998 98250349 (continued)			symptom score of 5.0 with placebo At day 7(visit #3)- Symptom score of 3.0 with brompheniramine, p<0.01 for brompheniramine vs placebo; symptom score of 4.4 with loratadine, p<0.05 for loratadine vs placebo; P<0.01 for brompheniramine vs loratadine; symptom score of 4.8 with placebo
Thoden 1998 98413360	Mean total Symptom Score Rhinorrhoea Nasal congestion Sneezing Watery eyes Itchy nose Itchy eyes Itchy throat	Physician assessment- 5 pt symptom scale (0= none to 4= very severe) Patient/physician global overall effectiveness- 10 pt scale (0= poor to 10= excellent) [done 3 times- day3, d7 &d14)	Overall, brompheniramine did better than placebo and terfenadine in relieving symptoms Summed symptom score 1)"Severity rating": 10.1 for 12mg brompheniramine, 11.9 for terfenadine, and 12.9 for placebo; p < 0.05 for 12 mg brompheniramine vs placebo 2) "Total nasal symptom: 4.3 for 12mg brompheniramine, 5.1 for terfenadine, and 5.5 for placebo; p<0.05 for 12mg brompheniramine vs placebo Improvement in nasal symptoms, including nasal sneezing, congestion, and itching greater in 12mg brompheniramine than terfenadine ($p \leq 0.05$) Sneezing: p<0.05 for 8mg brompheniramine vs placebo, and p<0.05 for 12mg brompheniramine vs placebo Nasal congestion: p<0.05 for 12mg brompheniramine vs placebo; p<0.05 for 12mg brompheniramine vs terfenadine; and p<0.05 for 8mg bromphenriamine vs placebo in chart Nasal itching: p<0.05 for 8mg bromphenriamine vs terfenadine; p= 0.05 for 12mg brompheniramine vs terfenadine; p= 0.05 for 8mg brompheniramine vs placebo; and p= 0.05 for 12mh brompheniramine vs placebo

Evidence Table 3. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Sedating versus nonsedating antihistamines
Part II. (continued)

Author Year UI	**Treatment outcomes studied**	**Symptom scale**	**Outcomes-efficacy**
Weiler 2000 20143057	Driving skills	Symptom score – none Data analyzed with SAS software, versions 6.12 and 7.0	Overall assessment: Mean coherence value of 0.88 with diphenhydramine, value of 0.915 with fexofenadine, value of 0.92 with alcohol, and value of 0.9 with placebo Minimum following distance of 16.3m with diphenhydramine, distance of 17.1m with fexofenadine, distance of 15.1m with alcohol, and distance of 17.4m with placebo Steering instability of 0.527 with diphenhydramine, instability of 0.492 with fexofenadine, instability of 0.512 with alcohol, and instability of 0.495 with placebo Left-lane excursions of 3.15 with diphenhydramine, excursions of 1.17 with fexofenadine, excursions of 2.12 with alcohol, and excursions of 1.32 with placebo (based on distance crossed over center line when during left turns)

Evidence Table 3. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Sedating versus nonsedating antihistamines
Part III.

Author Year UI	**Outcome-safety**	**Potential Bias**	**Funding**
Brostoff 1982	No major adverse effects. Minor adverse effects: -Stomach Upset – 1 patient taking chlorpheniramine -Headache/Fatigue- 2 patients taking terfenadine 12 withdrawals- 5 due to placebo, 3 due to chlorpheniramine, and 4 due to terfenadine Minor adverse effects: -3 patients (20%) from placebo, 9 (53%(from chlorpheniramine, and 6(38%) from terfenadine -sedation	No utility of antihistamines in PAR (contrast to usual observations in SAR)	ND
Gastpar 1982 83100633	No major adverse effects Minor adverse effects -Sedation- 2 patients from clemastine group and 0 patients from terfenadine group reported effects -attacking allergic rhinitis and conjunctivitis- 2 patients from clemastine group and 1 patient from terfenadine group reported effect	Purpose of study was to evaluate tolerance of terfenadine	ND

Evidence Table 3. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Sedating versus nonsedating antihistamines
Part III. (continued)

Author Year UI	**Outcome-safety**	**Potential Bias**	**Funding**
Malmberg 1983 83253693	No major adverse effects. Minor adverse effects: 4 withdrawals- 3 patients from placebo group due to headaches or fatigue, and 1 patient from pheniramine group (unlisted reason) Tiredness- 8 patients in pheniramine group, 5 patients in astemizole group, and 5 patients in placebo group Palpitations- 1 patient in pheniramine group , and 1 patient in placebo group Headache- 6 patients in pheniramine group, 4 patients in astemizole group, and 3 patients in placebo group GI- symptoms- 1 patient in pheniramine group	Not possible to extract meaningful data	Government

Evidence Table 3. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Sedating versus nonsedating antihistamines
Part III. (continued)

Author Year UI	**Outcome-safety**	**Potential Bias**	**Funding**
Gutkowski 1985 86030956	No major adverse effects. Minor adverse effects: 45 withdrawals: 22 from dexchlorpheniramine and 23 from terfenadine 34 treatment failures: 14 from dexchlorpheniramine and 20 from terfenadine 5 discontinued due to adverse effects (4 from dexchlorpheniramine group and 1 patient from terfenadine) Any adverse effect- 49 patients in dexchlorpheniramine group, and 35 patients in terfenadine group; p< 0.05 Dizziness- 4 patients in dexchlorpheniramine group and 6 patients in terfenadine group Somnolence- 38 (43%) patients in dexchlorpheniramine group and 18 (21%) in terfenadine group. p< 0.002 Headaches- 3 in dexchlorpheniramine group and 4 in terfenadine group Dry-mouth- 4 in dexchlorpheniramine group and 6 in terfenadine group	Poor patient characterization Other reasons for withdrawal- 6 patients for miscellaneous reasons	ND
Hugonot 1986 86248368	No major adverse effects. Minor adverse effects: 4 patients withdrew from mequitazine treatment: 2 patients from lack of efficacy, 1 patient from severe headache, and 1 patient from blurred vision 2 patients withdrew from terfenadine treatment- 1 for inefficacy, and 1 for somnolence, dizziness, and nausea (most likely drug-unrelated because was taking terfenadine before study and when resumed again after reported effect, were no side-effects)	Other reasons for withdrawal: 4 patients excluded because of unallowed concomitant treatment 2 additional patient excluded due to procedural technicality (assigned 2 patients 1 number so unable to distinguish between their treatments)	Pharmaceutical funding

Evidence Table 3. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Sedating versus nonsedating antihistamines
Part III. (continued)

Author Year UI	**Outcome-safety**	**Potential Bias**	**Funding**
Backhouse 1987 89062246	No major adverse effects. Minor adverse effects: Withdrawal due to drowsiness: 4 patients from the chlorpheniramine group and 2 patients from the terfenadine group; p< 0.05 Withdrawal due to lack of efficacy: 2 patients from chlorpheniramine group and 1 patient from terfenadine group Overall adverse effects: 51% from, chlorpheniramine and 37 % from terfenadine. P= 0.03	Poorly defined study population Other withdrawals: 8 withdrawals due to failure to attend, or protocol deviation	Unfunded
Johansen 1987 87205847	No major adverse effects. Minor adverse effects: Severe tiredness- 6 from dexchlorpheniramine group (2 withdrew) ; 2 from terfenadine group	Small study Other reasons for withdrawal: 2 patients, one from each group, did not complete protocol	ND
Pastorello 1987 88016480	No major adverse effects. Minor adverse effects 3/33 in terfenadine group and 16/32 in dexchlorpheniramine group reported adverse effects Significantly greater number of side effects in dexchlorpheniramine group	No baseline characteristics given	ND

Evidence Table 3. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Sedating versus nonsedating antihistamines
Part III. (continued)

Author Year UI	**Outcome-safety**	**Potential Bias**	**Funding**
Buckley 1988 88131974	Major adverse effects No indicated withdrawals due to adverse effects Minor adverse effects -Headache- 3.8% of patients from chlorpheniramine group, 11.1% from terfenadine group, and 9.5% from placebo group reported headaches Sedation- 7.6% from chlorpheniramine, 2.5% from terfenadine and 2,4% from placebo group reported drowsiness Nausea- 3.7% from terfenadine group, 0% from chlorpheniramine group, and 1.2% from placebo group Dryness of mouth, nose, throat- 1.2% from terfenadine group, 1.3% from chlorpheniramine group, and 2.4% from placebo group	Only p values stated, no raw data -Study well-done but most data reported graphically -did not look at change in scores, only new scores -Did not directly compare p values between chlorpheniramine vs terfenadine Reasons for patient exclusion from efficacy analysis: Inter-current infection, non-compliant use of study medication, incomplete data, or use of interfering concomitant medication	ND

Evidence Table 3. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Sedating versus nonsedating antihistamines
Part III. (continued)

Author Year UI	**Outcome-safety**	**Potential Bias**	**Funding**
Druce 1998 98250349	No major adverse effects. Minor adverse effects: 10 withdrawals due to adverse effects: 2 in placebo group due to “cold” and “flu”, 7 in brompheniramine due to somnolence, 1 in brompheniramine due to hypertension Overall, 25 experienced adverse effects with brompheniramine, 14 with loratadine, 22 with placebo Any side effect: At visit 2: 53% taking brompheniramine, 33% taking loratadine, and 36% taking placebo reported adverse effects At visit 3: 34% taking brompheniramine, 20% taking loratadine, and 29% taking placebo reported adverse effects Somnolence At visit 2: 28% taking brompheniramine, 6%taking loratadine, and 9% taking placebo reported somnolence. P<0.001 At visit 3: 10% taking brompheniramine, 2%taking loratadine, and 3% taking placebo reported somnolence. P<0.01 Dizziness At visit 2: 6.3% taking brompheniramine, 2%taking loratadine, and 0%taking placebo experienced dizziness	Poorly defined population But well designed study	Pharmaceutical

Evidence Table 3. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Sedating versus nonsedating antihistamines
Part III. (continued)

Author Year UI	**Outcome-safety**	**Potential Bias**	**Funding**
Thoden 1998 98413360	No major adverse effects. Minor adverse effects: 12 subjects withdrew due to adverse effects (6 from, 12 mg brompheniramine 2 from 8mg brompheniramine, 3 from terfenadine, and 1 from placebo) -Somnolence- 37 patients(34.9%) taking 12mg brompheniramine, 25 patients (23.8%) taking 8mg brompheniramine, 12 patients (11.3%) taking terfenadine, and 6 (11.3%) patients taking placebo p<0.001 for 12mg brompheniramine vs 8mg brompheniramine, terfenadine and placebo; p<0.05 for one vs each other p< 0.05 for 8mg brompheniramine vs terfenadine and placebo p<0.05 for one vs each other -Adverse experiences- 155 (41.9%) total: 61 patients(57.5%) taking 12mg brompheniramine (with p< 0.05 for brompheniramine vs placebo), 40 patients(38.1%) taking 8mg brompheniramine, 33 patients(31%) taking terfenadine, and 21 patients(39.6%) taking placebo	Other reasons for withdrawal: 27 subjects did not adhere to protocol	Pharmaceutical
Weiler 2000 20143057	No major adverse effects 1 withdrawal (no reason given) No minor adverse effects	Unusual end points, but otherwise valid	Pharmaceutical (Hoechst Marion Roussel, Inc)

Evidence Table 4. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Cromoglycate or cromolyn versus placebo
Part I.

Author Year UI	Intervention	Duration	Demographics	Inclusion criteria	Exclusion criteria
Coffman 1971 72025239	**Seasonal Allergic Rhinitis** Disodium cromoglycate vs placebo RCT- parallel	14 days	Location: UK Mean age: ND Age range: 9-61 % Male: 20/33 Race: British and West Indian Enrolled: 35 - 16 (cromoglycate) and 17 (placebo) Evaluated: 33 - 16 (cromoglycate) and 15 (placebo) Number of sites: 1	Positive prick test to grass pollen History of seasonal allergic rhinitis for at least 2 years	None indicated
Engstrom 1971 72012845	**Seasonal Allergic Rhinitis** Cromoglycate 20mg capsules insufflated qid. vs. placebo	6 weeks	Location: Denmark Mean age: ND Age range: 7-17 % Male 79 Race: ND Enrolled: 39 Evaluated: 38 Number of sites:2	2 year history of allergic rhinitis symptoms during birch pollen season. Positive skin test to birch. Positive nasal provocation test to birch	None noted

Evidence Table 4. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Cromoglycate or cromolyn versus placebo
Part I. (continued)

Author Year UI	Intervention	Duration	Demographics	Inclusion criteria	Exclusion criteria
Holopainen 1971 71066421	**Seasonal Allergic Rhinitis** Cromoglycate vs Placebo RCT Parallel	28 days	Location: Sweden Mean age: ND Age range: 5- 43 % Male: ND Race: ND Enrolled: 29 Evaluated: 27 - 13 (cromoglycate) and 14 (placebo) Number of sites: 1	Known history of allergic rhinitis due to pollen Positive skin test Positive nasal provocation test	None indicated
Anderson 1972 73004602	**Seasonal Allergic Rhinitis** Disodium cromoglycate 10mg qid vs. placebo RCT parallel	2 weeks	Location: UK Mean age: 32 Age range: 10-63 % Male ND Race: ND Enrolled:18 Evaluated: 18 Number of sites:1	History of hay fever symptoms requiring repeat prescriptions At least two year history of hay fever	None
Hopper 1972 73166771	**Perennial Allergic Rhinitis** Cromoglycate versus Placebo RCT- Cross-over (extractable)	28 days	Location: UK Mean age: ND Age range: not given %Male: ND Race: ND Enrolled: ≥ 38 Evaluated: 38 (19 each group) Number of sites: 1	6 month history of perennial rhinitis symptoms Allergic appearance of nasal mucosa Eosinophilia ≥ 6% Positive skin test	None noted
Shore 1972 72159215	**Seasonal Allergic Rhinitis** Disodium cromoglycate 5mg qid vs. placebo RCT crossover	8 weeks	Location: S. Africa Mean age: ND Age range: <18 % Male ND Race: ND Enrolled:41 Evaluated: 41 Number of sites:1	Symptomatic seasonal allergic rhinitis	Adenoidal obstruction

Evidence Table 4. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Cromoglycate or cromolyn versus placebo
Part I. (continued)

Author Year UI	Intervention	Duration	Demographics	Inclusion criteria	Exclusion criteria
Thorne 1972 73089706	**Perennial Allergic Rhinitis** Cromoglycate vs Placebo RCT-cross-over (extractable)	8 weeks	Location: UK Mean age: N/A Age range: 10-65 %Male: ND Race: ND Enrolled: 40 Evaluated: 35 Number of sites: 1	With perennial rhinitis symptoms for at least 2 years With severe symptoms not responding to antihistamines Constant symptoms-perennial 10 years and younger	Those with viral rhinitis or nasal polyposis Those with seasonal symptoms of oral/ systemic steroids within 3 months Pregnant women
Blair 1973 74098976	**Seasonal Allergic Rhinitis** Sodium Cromoglycate versus Placebo RCT- Parallel	6 weeks	Location: UK Mean age: 29 Age range: 10-49 % Male: 17/40 Race: ND Enrolled: 40 Evaluated: 40 - 20 people each group Number of sites: 1	History of Seasonal allergic rhinitis Positive skin test	Viral rhinitis Nasal polyposis Those patients who had responded adequately to antihistamines Pregnant
Hetherington 1973 73166772	**Seasonal Allergic Rhinitis** Disodium cromoglycate 5mg capsule qid vs placebo RCT parallel	14 days	Location: Australia Mean age: ND Age range: ND Adult % Male ND Race: ND Enrolled:40 Evaluated: 35 Number of sites:1	Hay fever for past two seasons requiring treatment	Asthma Immunotherapy Nasal disease
Illum 1973 74133656	**Seasonal Allergic Rhinitis** Disodium cromoglycate vs. placebo RCT parallel	3 weeks	Location: Denmark Mean age: ND Age range: >18 % Male ND Race: ND Enrolled:37 Evaluated: 37 Number of sites: 1	2 year history of seasonal allergic rhinitis with grass pollen Positive skin test to grass pollen Positive nasal provocation test to grass pollen	Asthma Total nasal obstruction Pregnancy

Evidence Table 4. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Cromoglycate or cromolyn versus placebo
Part I. (continued)

Author Year UI	Intervention	Duration	Demographics	Inclusion criteria	Exclusion criteria
Jenssen 1973 74098975	**Seasonal Allergic Rhinitis** Sodium cromoglycate vs. placebo	N/A	Location: Norway Mean age: ND Adult Age range: >18 % Male ND Race: ND Enrolled:10 Evaluated: 10 Number of sites: 1	Seasonal allergic Rhinitis symptoms during grass pollen season	None noted
Manners 1973 74098980	**Seasonal Allergic Rhinitis** Sodium cromoglycate versus Placebo RCT- Parallel	28 days	Location: UK Mean age: 26 (cromoglycate) and 29 (placebo) Age range: 12-64 % Male: ND Race: ND Enrolled: 50 Evaluated: 46 - 23 People each group Number of sites: 1	At least 2 years of sneezing and nasal discharge during hay fever season Positive skin prick test to grass pollen Use of antihistamines for previous 2 summers	Immunotherapy Usage of "antispasmodics" or steroids
Sunderman 1973 73237443	**Perennial Allergic Rhinitis** Cromoglycate vs Placebo RCT- cross-over (extractable)	28 days	Location: Australia Mean age: 35 Age range: not given %Male: ND Race: ND Enrolled: 74 Evaluated: 68 Number of sites: 1	3 year history of chronic perennial rhinitis	Patients with nasal polyposis Patients responding to antihistamine Those with steroid therapy within 3 months Patients with nasal polyps or those with seasonal exacerbations

Evidence Table 4. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Cromoglycate or cromolyn versus placebo
Part I. (continued)

Author Year UI	Intervention	Duration	Demographics	Inclusion criteria	Exclusion criteria
Brain 1974 76192641	**Perennial Allergic Rhinitis** Cromoglycate Vs Placebo RCT-cross-over (extractable)	28 days	Location: UK Mean age: 26.5 Age range: 18-65 %Male: 15/29= 51.7% Race: ND Enrolled: 34 Evaluated: 29 Number of sites: 1	1 year history of perennial rhinitis not responding to antihistamines/ decongestants Capable of cooperation /completing diary card	Those with nasal polyposis, or steroid use within 3 months
Blair 1975 75185857	**Perennial Allergic Rhinitis** Cromoglycate Vs. Placebo RCT- cross-over(extractable)	8 weeks	Location: UK Mean age: none Age range: 7-54 %Male: 11/19 = 57.9% Race: ND Enrolled: 20 Evaluated: 19 Number of sites: 1	Perennial rhinitis	With viral rhinitis or nasal polyposis Patients with local nasal sepsis or previous immunotherapy within 2 years
Fagerberg 1975 75221540	**Perennial Allergic Rhinitis** Cromoglycate vs Placebo RCT- cross-over (extractable)	28 days	Location: Sweden Mean age: 30.6 Age range: 17-54 %Male: 12/23 Race: ND Enrolled: 23 Evaluated: 23 - 12 (Active-Placebo) and 11 (Placebo-Active) Number of sites: 1	1 year history of perennial rhinitis requiring treatment	With nasal polyposis
Girard 1975 76042257	**Perennial Allergic Rhinitis** Cromoglycate versus Placebo RCT- Parallel	4 weeks	Location: Switzerland Mean age: 30.4 Age range: 14-57 %Male: 16/30 Race: ND Enrolled: 30 Evaluated: 30 (15 for each group) Number of sites: 1	2 year history of perennial rhinitis Symptoms sufficiently severe as to require treatment	None listed

Evidence Table 4. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Cromoglycate or cromolyn versus placebo
Part I. (continued)

Author Year UI	Intervention	Duration	Demographics	Inclusion criteria	Exclusion criteria
Holopainen 1975 76084510	**Perennial Allergic Rhinitis** Cromoglycate versus Placebo RCT- cross-over (extractable)	28 days	Location: Finland Mean age: 35 Age range: 6-69 %Male: 15/40 Race: ND Enrolled: 49 Evaluated: 40 - 19 (active-placebo) and 21 (placebo- active) Number of sites: 1	2 year history of perennial rhinitis Sufficiently severe to require treatment Symptoms present year-round	Viral rhinitis Nasal polyposis Previous immunotherapy and were no longer symptomatic
Leiferman 1975	**Seasonal Allergic Rhinitis** Cromolyn sodium powder vs Placebo RCT-Parallel	49 days	Location: US Mean age: 34 Age range: 14-66 % Male: 65% Race: ND Enrolled:26 Evaluated: 24 (12 each group) Number of sites: 1	Symptoms of ragweed pollinosis for several years Positive ragweed skin test Elevated IgE to ragweed	Immunotherapy within 5 years
Wilson 1975 76101270	**Seasonal Allergic Rhinitis** Sodium cromoglycate vs placebo RCT-cross-over (extractable)	4 weeks	Location: NZ Mean age: 28 Age range: 6-76 % Male: 50% Race: ND Enrolled: 39 Evaluated: 38 Number of sites: 1	Severe and intractable chronic perennial rhinitis for at least 3 years	Responded to antihistamine Steroid treatment within 3 months Obstructive polyposis Seasonal exacerbations Pregnancy

Evidence Table 4. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Cromoglycate or cromolyn versus placebo
Part I. (continued)

Author Year UI	Intervention	Duration	Demographics	Inclusion criteria	Exclusion criteria
Hasegawa 1976 77001950	**Seasonal Allergic Rhinitis** Cromoglycate 10mg vs placebo RCT crossover	1 time dose	Location: UK Mean age: ND Age range: ND % Male ND Race: ND Enrolled: 38 Evaluated: 29 Number of sites:1	History of seasonal allergic rhinitis confirmed by history, physical and skin testing. Nasal airway resistance > 1.5 Symptomatic at time of study.	None noted
Knight 1976 76238158	**Seasonal Allergic Rhinitis** Disodium cromoglycate vs placebo RCT- cross-over (extractable)	28 days	Location: Canada (Toronto and Hamilton) Mean age: ND Age range: 10-59 % Male: 29/77 Race: ND Enrolled: 77 Evaluated: 77 - 36 (cromoglycate) and 41 (placebo) Number of sites: 2	Allergic to ragweed pollen by history and positive skin prick test	Large nasal polyps Chronic nasal/ sinus infection
Backman 1977 78120309	**Perennial Allergic Rhinitis** Cromoglycate vs Placebo RCT- cross-over (extractable)	28 days	Location: Sweden Mean age: none Age range: ND %Male: ND Race: ND Enrolled: 91 Evaluated: 91 - 51 (Cromoglycate powder) and 40 (Cromoglycate solution) Number of sites: 1	Perennial rhinitis or with history, clinical, nasal cytology	None noted

Evidence Table 4. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Cromoglycate or cromolyn versus placebo
Part I. (continued)

Author Year UI	Intervention	Duration	Demographics	Inclusion criteria	Exclusion criteria
Frostad 1977 78062986	**Seasonal Allergic Rhinitis** Cromoglycate vs Placebo RCT Parallel	3 months- May, June, and July	Location: Norway Mean age: 23.9 Age range: 15- 34 % Male: 21/44 Race: ND Enrolled: 44 Evaluated: 44 - 25 (cromoglycate) and 19 (placebo) Number of sites: 1	History of previous seasonal allergic rhinitis during grass pollen season Positive test to grass pollen Positive nasal provocation test to grass pollen Symptoms of allergic rhinitis during pollen season Residing in area during grass pollen season	Asthma Perennial rhinitis symptoms
Handelman 1977 77119242	**Seasonal Allergic Rhinitis** Cromolyn sodium Vs. placebo	6 weeks	Location: US Mean age: ND Age range: 5-51 % Male Race: ND Enrolled: 104 Evaluated: 88 Number of sites: 2	2 year history of ragweed allergy Positive skin test Ragweed IgE titer > 60mg/ml Reside within 25 miles	Asthma Perennial rhinitis Corticosteroids Cromolyn Bronchodilators Recent change in immunotherapy Regimen/new immunotherapy regimen
Lofkvist 1977 77131029	**Perennial Allergic Rhinitis** Intranasal Cromolyn Sodium Vs Placebo RCT- cross-over (extractable)	13 weeks	Location: Sweden Mean age: 34 Age range: 18-65 %Male: ND Race: ND Enrolled: 49 - 25 (placebo) and 24 (cromolyn sodium) Evaluated: 26 - 2 (placebo) and 24 (cromolyn sodium) Number of sites: 1	Included those with "vasomotor for many years", and those with negative allergic skin tests	Those with asthma, nasal septal deviation, and nasal polyposis were not included

Evidence Table 4. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Cromoglycate or cromolyn versus placebo
Part I. (continued)

Author Year UI	Intervention	Duration	Demographics	Inclusion criteria	Exclusion criteria
McDowell 1977 77264819	**Seasonal Allergic Rhinitis** Cromolyn 2% aqueous nasal spray vs placebo RCT- cross-over (un-extractable)	4 weeks	Location: US Mean age: ND Age range: 17-71 % Male: ND Race: ND Enrolled: 17 Evaluated: 13 Number of sites: 1	At least 3 years of perennial allergic rhinitis by history or physical examination Immediate symptoms requiring medication Positive skin test to dust or mold Otherwise good health	Asthma Nasal polyposis Chronic nasal disease (other than PAR) Cromolyn or systemic or topical steroids within 3 months
Posey 1977 78063003	**Seasonal Allergic Rhinitis** 4% cromolyn sodium vs placebo nasal spray [also compares use of drug administered before and during weed pollen season] RCT-Parallel	8 weeks	Location: US Mean age: 30 Age range: 12-54 % Male: 52.9% Race: ND Enrolled: 34 Evaluated: 34 Preseasonal Study-17 each group Coseasonal Study- 9 (cromolyn) and 13 (placebo) Number of sites: 1	Late summer allergic rhinitis symptoms 2-yr history of SAR positive skin test to ragweed, sage mix positive nasal allergen challenge	Sinusitis Nasal septal deviation Nasal polyposis Perennial rhinitis Topical steroids within 1 month
Van der Bijl 1977 78033928	**Seasonal Allergic Rhinitis** Cromoglycate Vs Placebo RCT-Parallel	4 weeks	Location: Netherlands Mean age: 28.4 Age range: 7-60 % Male: 19/32 Race: ND Enrolled:40 (20 each group) Evaluated: 32 18(cromoglycate) and 14 (placebo) Number of sites: 1	Diagnosis of seasonal allergic rhinitis, symptomatic	None noted

Evidence Table 4. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Cromoglycate or cromolyn versus placebo
Part I. (continued)

Author Year UI	Intervention	Duration	Demographics	Inclusion criteria	Exclusion criteria
Warland 1977 77262676	**Perennial Allergic Rhinitis** Cromoglycate versus Placebo RCT- cross-over (extractable)	28 days	Location: Norway Mean age: 25.4 Age range: 15-57 %Male: 9/17 Race: ND Enrolled: 17 Evaluated: 17 - 10 (active-placebo) and 7 (placebo-active) Number of sites: 1	History of perennial allergic rhinitis for at least 1 year	None noted
Sorri 1979 79205990	**Seasonal Allergic Rhinitis** Cromoglycate vs. placebo	4 weeks	Location: Finland Mean age: ND Age range: ND % Male ND Race: ND Enrolled: 38 Evaluated: 38 Number of sites: 1	1 year history of perennial rhinitis necessitating treatment	None noted
Sipila 1987 88110026	**Seasonal Allergic Rhinitis** Nedocromil sodium 1% 5.2mg daily vs. placebo RCT parallel	4 weeks	Location: Finland Mean age: ND Age range: >16 % Male ND Race: ND Enrolled:59 Evaluated: 54 Number of sites: 2	>16 years History of birch pollen rhinitis in previous 2 seasons Positive skin test to birch pollen	Viral rhinitis Nasal septal Deviation Steroid use Vasoconstrictor use Cromoglycate use Pregnancy

Evidence Table 4. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Cromoglycate or cromolyn versus placebo
Part II.

Author Year UI	**Treatment outcomes studied**	**Symptom scale**	**Outcomes-efficacy**
Coffman 1971 72025239	Total mean symptom score Sneezing Rhinorrhoea Nasal obstruction Nasal itch	Symptom score: Diary cards: 0-3 scale	Global clinician assessment: 9/16 successful patient response with cromoglycate vs 5/15 successful patient response with placebo
Engstrom 1971 72012845	Total nasal symptom score Total eye symptom score Global assessment by clinician Rescue antihistamine usage	Symptom scale used: Range 0-3 0=none 1=occasional 2=intermittent 3=constant	Global assessment by clinician as follows: 5 of 18 successes with placebo and 14 of 20 successes in active treatment group ($p<0.01$) Significantly improved total nasal score for weeks 3 and 5 and peak pollen season period only with active treatment.
Holopainen 1971 71066421	Mean sneezing score Mean rhinorrhoea score Mean nasal congestion score Mean nasal itch score	Symptom scale used: Range 0-3 0=absent 1=mild 2=moderat e 3=severe	Mean diary sneezing symptom score: 30.8 in placebo group, 23.5 in active treatment group $p>0.05$ Mean diary rhinorrhoea score: 59.5 in placebo group vs. 34.3 in active treatment group $p<0.025$ Mean diary nasal congestion score: 52.3 in placebo group vs. 12 in active treatment group $p<0.05$ Mean diary nasal itch score: 21.6 in placebo group vs. 13.5 in active treatment group $p<0.05$
Anderson 1972 73004602	Total Mean Symptom Score Rhinorrhoea Sneezing Sore, itching eyes	No symptom scale Diary cards and clinician assessment	8/9 successes and 1/9 failures with cromoglycate 1/9 successes and 8/9 failures with placebo

Evidence Table 4. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Cromoglycate or cromolyn versus placebo
Part II. (continued)

Author Year UI	**Treatment outcomes studied**	**Symptom scale**	**Outcomes-efficacy**
Hopper 1972 73166771	Mean total symptom score Rhinorrhoea Sneezing Nasal congestion	Symptom scale: 0= no symptoms 1= occasional symptoms 2= intermittent symptoms 3= constant symptoms	Global patient assessment: 16 success + 3 failures with cromoglycate vs 9 successes, 9 failures + 1 unsure with placebo; p< 0.05 for drug vs placebo Global clinician assessment: 14 successes + 5 failures with cromoglycate vs 8 successes + 11 failures with placebo; p< 0.05 for drug vs placebo Sneezing (% of scores that fell in 2-3 range on scale): 1% with cromoglycate vs 11% with placebo; p < 0.01 for drug vs placebo Rhinorrhoea (% of scores that fell in 2-3 range on scale): 12% with cromoglycate vs 32% with placebo; p< 0.01 for drug vs placebo Nasal Congestion (% of scores that fell in 2-3 range on scale): 14% with cromoglycate vs 30% with placebo; p < 0.01 for drug vs placebo Nasal itch NA
Shore 1972 72159215	Global assessment by patient Global assessment by clinician	No symptom scale specified.	Global assessment by patient 15 of 21 rated placebo success 16 of 20 rated active treatment successful p>0.05 Global assessment by clinician: In 7 of 21 rated placebo successful In 12 of 20 rated active treatment successful p<0.057

Evidence Table 4. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Cromoglycate or cromolyn versus placebo
Part II. (continued)

Author Year UI	**Treatment outcomes studied**	**Symptom scale**	**Outcomes-efficacy**
Thorne 1972	Mean Total Symptom Score Rhinorrhoea Nasal Congestion Sneezing	0-3 symptom scale 0= no symptoms 1= occasional symptoms 2= intermittent symptoms 3= constant symptoms	Global assessment done by patient in diary: Total symptom score of 2608 with cromoglycate vs score of 3053 with placebo, p= ND Patient Evaluation based on diary score Sneezing- Symptom score of 18.5 +/-13.7 with cromoglycate vs score of 24.5 +/- 14.1 with placebo; p<0.0005 for cromoglycate vs placebo Rhinorrhoea- Symptom score of 26.7 +/- 15.9 with cromoglycate vs score of 32.3 +/- 18.7 with placebo; p< 0.002 for cromoglycate vs placebo Nasal Congestion- Symptom score of 35.7 +/- 24.7 with cromoglycate vs score of 38.5 +/- 24.7 with placebo; p = NS In those patients receiving placebo, find all symptoms significantly lower (blockage, discharge, sneezing). In patients receiving cromoglycate, find only sneezing and discharge (rhinorrhoea) significantly reduced
Blair 1973 74098976	Global assessment by patient and clinician of total symptom score (rhinorrhoea, congestion, itching and sneezing) Patient wish to continue with treatment Whether symptoms improved over last season (patient rated)	N/A	Global assessment by patient 3 of 15 placebo successes vs 13/20 active treatment successes p<0.025 Global assessment by clinician 2 of 16 placebo rated successful; 11 of 20 on active treatment rated successful p<0.025 Symptoms improved over last year in 4 of 15 of placebo group and 8 of 19 of active treatment group NS

Evidence Table 4. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Cromoglycate or cromolyn versus placebo
Part II. (continued)

Author Year UI	**Treatment outcomes studied**	**Symptom scale**	**Outcomes-efficacy**
Hetherington 1973 73166772	Rhinorrhoea symptom score Nasal congestion symptom score Overall symptom severity as rated by patient.	Symptom scale: Severity of nose-running and nose-blocking: range= 0-6 General condition assessment: 3-point scale	• Rhinorrhoea symptom severity No significant difference between groups • Nasal congestion symptom severity No significant difference between groups • Overall symptom severity rating by patient Good to fair in 10 of 16 of placebo group, 19 of 19 of active treatment group p<0.05
Jenssen 1973 74098975	Total Mean Symptom Score Nasal resistance following nasal allergen challenge	N/A	Nasal resistance following allergen challenge Nasal resistance improved in 7 of 8 patients on active treatment
Illum 1973 74133656	Total Mean Symptom Score Sneezing score Rhinorrhoea score Nasal congestion score Nasal itch score	Symptom scale Range 0-3 0=no symptoms 3=severe symptoms	Global assessment by patient: No significant differences between groups. No significant difference between groups in sneezing, rhinorrhoea, nasal congestion sneezing and eye symptom scores.
Manners 1973 74098980	Global assessment by patient Global assessment by clinician Sneezing score Rhinorrhoea score Nasal congestion score Nasal itch score Eye symptoms Rescue antihistamine usage Nasal eosinophils on nasal smear	Symptom scale used Range 0-3 0=absent 1=mild 2=moderat e 3=severe	Global assessment by patient: In placebo group 13 of 23 rated successful vs. 15 if 23 if active treatment group p>0.05 Global assessment by clinician: 7 of 23 rated successes in placebo group vs. 10 of 23 in active treatment group p>0.05 Mean sneezing score week 2 and 3: 19.7 in placebo group vs. 19.2 in active treatment group p>0.8 Mean rhinorrhoea score weeks 2 and 3: 20.3 in placebo group vs. 14.7 in active treatment group p>0.05 Mean nasal congestion score weeks 3 and 4: 12.7 in placebo group vs. 12.4 in active treatment group p>0.9 Mean nasal itch score weeks 3 and 4: 15.3 in placebo group vs. 12.7 in active treatment group p>0.4

Evidence Table 4. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Cromoglycate or cromolyn versus placebo
Part II. (continued)

Author Year UI	**Treatment outcomes studied**	**Symptom scale**	**Outcomes-efficacy**
Sunderman 1973	Mean total symptom score Rhinorrhoea Nasal Congestion Sneezing	Symptom scale No scale given	Out of 68 patients, 53 patients preferred cromoglycate, 0 preferred placebo, and 15 had no preference; p < 0.05 for cromoglycate vs placebo Report stated that symptoms of rhinorrhoea, obstruction, and sneezing in cromoglycate group significantly improved p< 0.05 (absolute data not given)
Brain 1974 76192641	Mean total nasal symptom score Nasal sneezing Rhinorrhoea Nasal congestion Nasal itch	No symptom scale Mild/Moderate-Severe (0-3)	Global patient assessment: 20 preferred cromoglycate, 6 preferred placebo, and 3 indicated no preference P<.01 Nasal sneezing symptom score of 32.5 with placebo vs. 22.6 with cromoglycate, p<.025 Rhinorrhoea symptom score of 34 with placebo vs. 23.5 with cromoglycate, p<.02 Nasal congestion symptom score of 37.3 with placebo vs 26.2 with cromoglycate, p< .05 Nasal Itch symptom score of 24.8 with placebo vs 16.1 with cromoglycate, p< .012

Evidence Table 4. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Cromoglycate or cromolyn versus placebo
Part II. (continued)

Author Year UI	**Treatment outcomes studied**	**Symptom scale**	**Outcomes-efficacy**
Blair 1975	Mean total symptom score Nasal Sneezing Rhinorrhoea Nasal congestion Nasal Itch	Symptom severity score based on 0-3 scale	Overall patient assessment: 14 preferred cromoglycate, and 3 preferred placebo, 1 patient indicated no preference (out of 18 because one patient symptoms classified as intrinsic or nonallergic) Nasal sneezing symptom score (out of 15 people) of 20.5 with cromoglycate vs score of 28.2 with placebo; p> 0.1 for drug vs placebo [~change in score of -0.7 with cromoglycate vs +0.1 change in score with placebo; p< 0.01 for drug vs placebo] (*note* out of 15 people, instead of 19, because some failed to adequately record daily symptoms) Rhinorrhoea symptom score of 27.1 with cromoglycate vs 40.3 with placebo; p< 0.05 for drug vs placebo [~change in score of -0.7 with cromoglycate vs +0.1 change in score with placebo; p< 0.1 for drug vs placebo] Nasal congestion symptom score of 29.7 with cromoglycate vs 49.1 with placebo; p< 0.1 for drug vs placebo [~change in score of -0.1 with cromoglycate vs –0.1 change in score with placebo; p< 0.02 for drug vs placebo] Nasal Itch symptom score of 19.4 with cromoglycate vs 23.2 reduction with placebo; p> 0.1 for drug vs placebo [~change in score of -1.2 with cromoglycate; vs +0.2 change in score with placebo; p< 0.01 for drug vs placebo]

Evidence Table 4. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Cromoglycate or cromolyn versus placebo
Part II. (continued)

Author Year UI	**Treatment outcomes studied**	**Symptom scale**	**Outcomes-efficacy**
Fagerberg 1975	Mean Total Symptom Score Rhinorrhoea Nasal congestion Sneezing Itchy nose	Symptom scale 0-3: Mild-Moderate-Severe	Sneezing (n=23) In clinician evaluation, mean difference of –0.7 with cromoglycate vs difference of –0.3 with placebo; p> 0.1 for cromoglycate vs placebo In patient evaluation recorded in diary card, mean symptom score of 19.5 with cromoglycate vs mean score of 30.2 with placebo; p < 0.01 for cromoglycate vs placebo Rhinorrhoea (n=23) In clinician evaluation, mean difference of –0.8 with cromoglycate vs difference of –0.1 with placebo; p< 0.01 for cromoglycate vs placebo In patient evaluation recorded in diary card, mean symptom score of 37.9 with cromoglycate vs mean score of 47.2 with placebo; p < 0.05 for cromoglycate vs placebo Nasal congestion (n=23) In clinician evaluation, mean difference of –0.8 with cromoglycate vs difference of –0.3 with placebo; p< 0.02 for cromoglycate vs placebo In patient evaluation recorded in diary card, mean symptom score of 29.3 with cromoglycate vs score of 35.2 with placebo; p< 0.1 for cromoglycate vs placebo Nasal Itch (n= 21 included data- 2 cases of inconclusive data) In clinician evaluation, mean difference of –0.2 with cromoglycate vs difference of +0.1 with placebo; p>0.10 for cromoglycate vs placebo In patient evaluation recorded in diary card, mean symptom score of 8.7 with cromoglycate vs score of 15.5 with placebo; p> 0.05 for cromoglycate vs placebo

Evidence Table 4. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Cromoglycate or cromolyn versus placebo
Part II. (continued)

Author Year UI	**Treatment outcomes studied**	**Symptom scale**	**Outcomes-efficacy**
Girard 1975 76042257	Mean total symptom score Rhinorrhoea Sneezing Nasal congestion Nasal itch Eosinophilia Nasal outflow resistance	Symptom scale: Daily record cards- 0- 3 scale with 0= no symptoms to 3= severe symptoms	Global patient assessment: 12/15 patients rated cromoglycate successful in symptom treatment vs 6/ 15 in placebo group. P < 0.03 for drug vs placebo Global clinician assessment: 13/15 successful cases vs 5/15 successful cases. P< 0.008 for drug vs placebo Sneezing Mean difference of –0.6 with cromoglycate and difference of 0 with placebo; p < 0.02 for drug vs placebo Rhinorrhoea Mean difference of –0.1 with cromoglycate vs difference of –0.6 with placebo; p> 0.05 for drug vs placebo Nasal congestion Mean difference of –1.4 with cromoglycate vs difference of –0.3 with placebo; p< 0.02 for drug vs placebo Nasal itch Mean difference of –0.7 with cromoglycate vs difference of –0.2 with placebo; p< 0.05 for drug vs placebo

Evidence Table 4. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Cromoglycate or cromolyn versus placebo
Part II. (continued)

Author Year UI	**Treatment outcomes studied**	**Symptom scale**	**Outcomes-efficacy**
Holopainen 1975 76084510	Mean total symptom scale Rhinorrhoea Nasal congestion Sneezing Nasal Itch	Symptom scale Nasal Symptoms 0-3 scale: none, mild, moderate, and severe Nasal patency 0-2 scale: open, partially blocked, and completely blocked Overall examination of nose: 0-4 scale	Sneezing Clinician mean score: score of 0.7 for cromoglycate vs score of 1.0 for placebo; p> 0.10 for drug vs placebo Patient mean diary score: score of 17.4 for cromoglycate vs score of 22.5 for placebo; p<0. 05 for drug vs placebo Rhinorrhoea Clinician mean score: score of 1.1 for cromoglycate vs score of 1.4 for placebo; p>0.10 for drug vs placebo Patient mean diary score: score of 30.9 for cromoglycate vs score of 37.8 for placebo; p< 0.01 for drug vs placebo Nasal Congestion Clinician mean score: score of 1.2 for cromoglycate vs score of 1.7 for placebo; p < 0.01 for drug vs placebo Patient mean diary score: score of 32.1 for cromoglycate vs score of 39.1 for placebo; p< 0.01 for drug vs placebo Nasal itch Clinician mean score: score of 0.4 for cromoglycate vs score of 0.8 for placebo; p< 0.05 Patient mean diary score: score of 12.2 for cromoglycate vs score of 16.5 for placebo; p< 0.05 for drug vs placebo. Study combined groups from each arm of cross-over..

Evidence Table 4. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Cromoglycate or cromolyn versus placebo
Part II. (continued)

Author Year UI	**Treatment outcomes studied**	**Symptom scale**	**Outcomes-efficacy**
Leiferman 1975	Total mean symptom score Sneezing Coughing Stuffy, or runny nose Red, itchy eyes asthma	Symptom score (0-3) [score 2 times/day-midnight-noon, and noon-midnight]	Global patient assessment: All patients(12 pair of patients)- overall score of 9.5 with cromolyn vs score of 10.5 with placebo; p> 0.10 for drug vs placebo Group 1 (7pair patients– patients with pre-seasonal Radio-allergosorbent test(RAST) readings > 5%)- overall score of 7.5 with cromolyn vs score of 12 with placebo; p< 0.03 for drug vs placebo Group 2 (5 pair patients- those with RAST<5%)- overall score of 11 with cromolyn vs score of 8 with placebo; p> 0.10 for drug vs placebo [scores approximated from graph] End-study questionnaire on efficacy of treatment (10 subjects from each group): 40% of cromolyn group vs 10% of placebo group found treatment extremely beneficial 30% in both groups found treatment moderately beneficial 10% in both groups found treatment slightly beneficial 20% of cromolyn group vs 50% of placebo group found treatment not beneficial 80% of cromolyn group vs 50% of placebo group indicated would use treatment next year

Evidence Table 4. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Cromoglycate or cromolyn versus placebo
Part II. (continued)

Author Year UI	Treatment outcomes studied	Symptom scale	Outcomes-efficacy
Wilson 1975 76101270	Mean total symptom score Nasal blockage Nasal Discharge Nasal Sneezing	Symptom scale Daily diary cards No scale given	Global patient assessment: Patient preference: 20/38 preferred cromoglycate, and 8/38 preferred placebo Sneezing: Physician assessment: From baseline, change in score of – 0.5 with cromoglycate, and change of –0.4 with placebo; data missing on significance, but clearly NS Patient assessment (n= 37): total symptom score of 19.0 with cromoglycate and score of 20.2 with placebo, p= NS Rhinorrhoea (nasal “discharge”) Physician assessment: From baseline, change in score of –0.6 with cromoglycate and change of –0.6 with placebo; p= NS Patient assessment (n= 37): total symptom score of 32.3 with cromoglycate and score of 31.7 with placebo; p= NS Nasal Congestion Physician assessment: From baseline, change in score of –0.9 with cromoglycate and change of –0.6 with placebo; p= NS Patient assessment (n= 37): total symptom score of 33.7 with cromoglycate and score of 37.8 with placebo; p= NS No meaningful difference between those groups with placebo or cromolyn administered first
Hasegawa 1976 77001950	Total nasal symptom score comprising sneezing, rhinorrhoea, congestion and itchy nose. Nasal airways resistance		Total nasal symptom score improved in 1 of 16 in placebo group and 10 of 16 on active treatment. p<0.05 Nasal airway resistance improved to greater than 1.5 in 0 placebo patients and 11 active treatment patients p<0.05

Evidence Table 4. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Cromoglycate or cromolyn versus placebo
Part II. (continued)

Author Year UI	**Treatment outcomes studied**	**Symptom scale**	**Outcomes-efficacy**
Knight 1976 76238158	Total Mean symptom score Sneezing Nasal obstruction Rhinorrhoea Itchy eyes Itchy nose Sinus pain	Symptom scale: Personal/ telephone interviews: Degree- very good, good, or poor responders Anti-ragweed IgE antibody level (RAST level) ; scale 0-4 0= negative 1= borderline 2=clearly positive 3= strongly positive 4=highly positive	Overall patient evaluation: 25/34 successful patient responses with cromoglycate, and 12/41 successful responses with placebo Inconclusive results- there is a Toronto group of patients + Toronto group which are analyzed separately, never together
Backman 1977	Mean total Symptom Score N/A	Symptom Scale N/A	Patient Global Assessment: Cromoglycate 2% solution Vs placebo - Out of 40 patients 23 patients preferred cromoglycate vs 10 patients preferred placebo (significant p value not given Cromoglycate powder- 10mg/nostril, 4x daily Vs Placebo- Out of 51 patients 31 patients preferred SCG powder, 3 preferred placebo, 17 patients with no preference indicated Outcomes only reported for 33/ 40 patients. Information for 7 patients missing. Also, MD outcomes only given for 2 studies, so un- interpretable for this group

Evidence Table 4. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Cromoglycate or cromolyn versus placebo
Part II. (continued)

Author Year UI	**Treatment outcomes studied**	**Symptom scale**	**Outcomes-efficacy**
Frostad 1977 78062986	Patient global rating Clinician global rating 28-day sneezing score 28-day rhinorrhoea score 28 day nasal congestion score Total nasal symptom score	Diary card- Symptom scale: 0-3 scale Each patient also asked to record number of antihistamine tablets/ day	Global assessment by patient: 5 of 19 of placebo group rated treatment successful vs. 25 of 25 of active treatment group p<0.01 Global assessment by clinician: Rated 3 of 19 of placebo patients successfully treated vs. 25 of 25 of active treatment. No p value provided. 28-day sneezing score 45.6 in placebo group vs. 25.3 in active treatment group p<0.01 28-day rhinorrhoea score 39.9 in placebo group vs. 22.5 in active treatment group p<0.05 Nasal congestion 28-day score 38.1 in placebo group and 23.8 in active treatment group p<0.01 Total nasal symptom score 123.5 in placebo group vs. 71.6 in active treatment group p<0.01
Handelman 1977 77119242	Sneezing Rhinorrhoea Ocular irritation Nose-blowing episodes Chlorpheniramine usage IgE titer	0-3	Sneezing significantly reduced by cromolyn sodium vs. placebo p<0.013 Rhinorrhoea significantly reduced by cromolyn sodium p<0.001
Lofkvist 1977	Mean total symptom score Blocking Running Sneezing Itching	No symptom scale supplied	Shows an effect with DSCG No significance for symptom free condition, patient preference, or diary card scores. Saw “dramatic improvement in symptoms in some patients after treatment with SCG” (42) No significant difference detected between SCG and placebo treatment (42)

Evidence Table 4. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Cromoglycate or cromolyn versus placebo
Part II. (continued)

Author Year UI	**Treatment outcomes studied**	**Symptom scale**	**Outcomes-efficacy**
McDowell 1977 77264819	Total Mean Symptom Score Itchy nose Runny nose Stuffy nose Mouth breathing Postnasal drip Itchy eyes Itchy throat	Symptom Scale Symptom severity: 6 point scale- 0= no occurrence, 1= mild, and 5= extreme and causing considerable interference with sleep and/or life	Following values are averaged symptom scores for 4 weeks Sneezing: From baseline of 4.0, score of 3.0 with cromoglycate and score of 3.4 with placebo; p = ND Rhinorrhoea: From baseline 2.5, score of 1.9 with cromoglycate and score of 2.2 with placebo; p = ND
Posey 1977 78063003	Total Mean Symptom Score Rhinorrhoea Nasal Congestion Sneezing Itchy nose Itchy throat Mouth breathing Eye-irritation Post-nasal drip Nose-blowing	Symptom scale 5 point scale (0-4) with 0= no symptoms to 4= incapacitating symptoms	Pre-seasonal study: Overall patient assessment: 11/17 reported good/very good relief with cromoglycate; 7/15 patient reported good/very good relief with placebo $\chi 2$ (chi-squared) analysis indicates no significant difference between groups Overall physician assessment: found no significant differences between groups P< 0.025 Co-seasonal study Overall patient assessment- 4/9 patients treated with cromoglycate rated it good/very good; 8/ 13 patients treated with placebo rated it good/ very good $\chi 2$ analysis- revealed no significant difference between two groups; only 1 patient from placebo group reported very good relief p< 0.025 No raw data- all in graph form

Evidence Table 4. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Cromoglycate or cromolyn versus placebo
Part II. (continued)

Author Year UI	**Treatment outcomes studied**	**Symptom scale**	**Outcomes-efficacy**
Van der Bijl 1977 78033928	Total Mean Symptom score Rhinorrhoea Nasal Congestion Sneezing Itchy nose Itchy eyes	Symptom severity scale: 4 degrees- none, mild, moderate, severe	Global patient assessment: Overall success/ failure uncertain Sneezing: Clinician assessment: mean change of –0.7 with cromoglycate, and change of 0 with placebo. P< 0.5 for drug vs placebo Patient assessment: Mean diary card score of 28.8 with cromoglycate, and score of 35.9 with placebo. P> 0.05 for drug vs placebo Rhinorrhoea: Clinician assessment: Mean change of –1.0 with cromoglycate, and change of 0 with placebo. P< 0.1 for drug vs placebo Patient assessment:: Mean diary card score of 26.7 with cromoglycate and score of 35.4 with placebo. P> 0.05 for drug vs placebo Nasal Congestion: Clinician assessment: mean score of –0.5 with cromoglycate and score of –0.1 with placebo. P>0.05 for drug vs placebo Patient assessment: Mean diary card score of 28.1 with cromoglycate, and score of 26.5 with placebo. P> 0.05 Nasal Itch Clinician assessment: Mean change of –0.8 with cromoglycate and score of –0.1 with placebo. P< 0.05 for drug vs placebo Patient assessment: Men diary score of 23.6 with cromoglycate and score of 23.0 with placebo. P> 0.5 for drug vs placebo

Evidence Table 4. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Cromoglycate or cromolyn versus placebo
Part II. (continued)

Author Year UI	**Treatment outcomes studied**	**Symptom scale**	**Outcomes-efficacy**
Warland 1977 77262676	Mean total symptom score Rhinorrhoea Nasal congestion Sneezing Nasal itch	Symptom scale: Clinician and patient daily diary card scores : 0- 3 scale 0= no symptoms to 3= considerable symptoms	Patient overall preference (n= 17): 6 patients preferred cromoglycate vs 2 patients preferred placebo. 9 patients had no preference Sneezing Patient assessment (n= 14): Mean monthly score of 17.9 for cromoglycate vs score of 18.1 for placebo; p> 0.10 for drug vs placebo Clinician assessment (n= 16): Mean monthly score of 0.8 for cromoglycate vs score of 0.9 for placebo; p> 0.1 for drug vs placebo Rhinorrhoea Patient assessment (n= 14): Mean monthly score of 23.6 for cromoglycate vs score of 26.2 for placebo; p> 0.1 for drug vs placebo Clinician assessment (n= 17): Mean monthly score of 0.8 for cromoglycate vs score of 1.4 for placebo; p> 0.10 for drug vs placebo Nasal congestion Patient assessment: Mean monthly score of 27.4 for cromoglycate vs score of 28.4 for placebo; p > 0.1 for drug vs placebo- NS Clinician assessment: Mean monthly score of 1.11 for cromoglycate vs score of 1.3 for placebo; p > 0.1 for drug vs placebo; p> 0.1- NS Nasal Itch Clinician assessment- Mean monthly score of 0.5 for cromoglycate vs score of 0.8 for placebo; p> 0.1 for drug vs placebo
Sorri 1979 79205990	Patient preference Sneezing Rhinorrhoea Nasal itch Nasal congestion Antihistamine usage	0-3	Patient preference 22 preferred active treatment; 11 preferred placebo; 5 had no preference No comment on significance MD symptom assessment Significant improvement in rhinorrhoea only with active drug. No significant difference in sneezing, nasal congestion nasal itch or nasal patency

Evidence Table 4. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Cromoglycate or cromolyn versus placebo
Part II. (continued)

Author Year UI	**Treatment outcomes studied**	**Symptom scale**	**Outcomes-efficacy**
Sipila 1987 88110026	Sneezing score Rhinorrhoea score Nasal congestion score Nasal itch score Total symptom score Clinician overall rating Rescue antihistamine use Patient preference Nasal peak inspiratory flow	Symptom scale Range 0 – 4	Mean daily sneezing score 1.4 in placebo group vs. 1.17 with active treatment p=0.31 Mean daily rhinorrhoea score 1.4 in placebo group vs. 1.17 in active treatment group p=0.86 Mean daily nasal congestion score 1.34 in placebo group vs. 1.38 in active treatment group p=0.82 Mean daily nasal itch score 1.31 in placebo group vs. 0.91 in placebo group p<0.04 Total mean nasal symptom score 5.39 in placebo group vs. 4.7 in active treatment group p=0.34 Patient preference: 8 of 27 preferred placebo; 17 of 27 preferred active treatment p<0.03 Clinician rating: Rated 14 of 27 successes in active treatment group vs. 7 of 27 successes in placebo group P<0.05

Evidence Table 4. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Cromoglycate or cromolyn versus placebo
Part III.

Author Year UI	**Outcome-safety**	**Potential Bias**	**Funding**
Coffman 1971 UI 72025239	No major adverse effects. Minor adverse effects: "minimal" side effects- specifics not listed	No inclusion/exclusion criteria given Outcome measurement ambiguous Other reasons for withdrawal: 2 (from original group 35) withdrawals due to failure to comply to protocol, incomplete diaries or failure to report back to review	Pharmaceutical
Engstrom 1971 72012845	No safety data provided.	One patient omitted from analysis. No safety data. Applicability/Internal validity II/B	Pharmaceutical.
Holopainen 1971 71066421	No major adverse effects. 1 patient in placebo group experienced itching of throat. No minor adverse effects in active treatment group.	No baseline characteristics reported. 2 patients omitted from final analysis. Applicability II Internal validity B	ND
Anderson 1972 73004602	No major adverse effects. Minor adverse effects: Nasal irritation Nasal congestion Nausea Headache No significant difference between groups.	No baseline characteristics for Treatment groups. Applicability II Internal validity B	Pharmaceutical
Hopper 1972 73166771	No safety data provided	Generalizability- II / Internal Validity- C Reasons for patient exclusion: -2 due to existing colds -3 due to existing symptoms other than obstruction, rhinorrhoea, or sneezing -4 due to incomplete diaries	Pharmaceutical

Evidence Table 4. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Cromoglycate or cromolyn versus placebo
Part III. (continued)

Author Year UI	**Outcome-safety**	**Potential Bias**	**Funding**
Shore 1972 72159215	No major adverse effects. Minor adverse effects: Nausea, sneezing, cough, rash. No information on difference between active and placebo adverse effects.	No baseline characteristics provided. No information on difference in adverse effects between treatments. Applicability III Internal validity C	Government
Thorne 1972	No major adverse effects. Minor adverse effects -DSCG Insufflation followed by sneeze- 2 patients taking placebo and 1 patient taking cromoglycate reported effect -Soreness of nose- 1 patient taking placebo and 1 patient taking cromoglycate reported effect	Data combined from crossover areas Evaluated 35/40 Only 32 patients had complete diary data	Pharmaceutical
Blair 1973 74098976	No major adverse effects. Minor adverse effects: nasal irritation, sore throat in both groups; in addition, headache and unpleasant taste in active treatment group and itching of face in placebo group. No information on statistical significance of difference between groups.	Four patients omitted from final analysis as responded to rescue antihistamines – all in placebo group. No information on rescue antihistamine usage by group. Applicability II Internal validity B	ND
Hetherington 1973 73166772	No major adverse effects. Nasal irritation occurred in 1 patient in placebo group and 7 patients in cromoglycate group.	No baseline characteristics of groups. 35 of 40 patients evaluated Applicability II Internal validity B	Pharmaceutical
Illum 1973 74133656	No major adverse effects.	Global assessment by patient: No significant differences between groups. No significant difference between groups in sneezing, rhinorrhoea, nasal congestion sneezing and eye symptom scores.	

Evidence Table 4. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Cromoglycate or cromolyn versus placebo
Part III. (continued)

Author Year UI	**Outcome-safety**	**Potential Bias**	**Funding**
Jenssen 1973 74098975	Nasal resistance following allergen challenge Nasal resistance improved in 7 of 8 patients on active treatment No safety data	Small sample size Omitted 2 patients from analysis. No baseline characteristics of group provided. Applicability III Internal validity C	
Manners 1973 74098980	No safety data	Only analyzed individual symptom scores for weeks 3 and 4 of trial. Omitted 4 patients from final analysis as non-compliant with medication and diary keeping regimen.	ND
Sunderman 1973	No major adverse effects. 6 patients withdrew- no information Minor adverse effects -Sneezing- 1 patient taking placebo, and 0 patients taking cromoglycate reported effect	Pooled cross-over data No baseline characteristics Reasons for withdrawal not given	Pharmaceutical
Brain 1974 76192641	No major adverse effects in either group. 5 withdrawals –(1 due to severe nasopharyngitis, 1 due to severe nasal irritation development, 2 didn't complete visits, and 1 patient immunotherapy during study) Minor adverse effects- Headache Dry throat Sore throat Dizziness Nasal irritation	No baseline characteristics Analyzed 29/32 patients Cross-over trial pooled data No period 1 data	Pharmaceutical
Blair 1975	No major adverse effects. Minor adverse effects: No withdrawals for adverse effects (but one female patient after trials withdrew, finding the treatment "unpleasant and distasteful") -Nasal irritation and Sore throat (4 from placebo, and 3 from cromoglycate)	Pooled data from cross-over answers No baseline- find period data given Small sample size Analyzed 19/20	Pharmaceutical

Evidence Table 4. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Cromoglycate or cromolyn versus placebo
Part III. (continued)

Author Year UI	Outcome-safety	Potential Bias	Funding
Fagerberg 1975	No major adverse effects. Minor adverse effects -Itching/ nasal irritation- 3 patients taking placebo, and 4 patients taking cromoglycate -Sneezing- 3 patients taking placebo and 0 patients taking cromoglycate -Headache- 1 patient taking placebo, and 0 patients taking cromoglycate -"other" – 6 patients taking placebo, and 3 patients taking cromoglycate	Crossover pooled data	ND
Girard 1975 76042257	No major adverse effects. Minor adverse effects: Nasal irritation- 5 patients in cromoglycate group and 3 patients in placebo group Headache- 0 patients in cromoglycate group and 1 patients in placebo group	Small sample size No outcome data on rescue antihistamine use Analysis was intention to treat Randomization method / site not specified Generalizability- II/ Internal validity- B Other reasons for withdrawals: 3 withdrawals from active group- 2 due to treatment failure, and 1 due to partial success 8 withdrawals from placebo group- 6 due to no treatment benefit, and 2 due to induced nasal obstruction	Pharmaceutical
Holopainen 1975 76084510	No major adverse effects. Minor adverse effects: Nasal irritation- 8 reports due to cromoglycate and 9 reports due to placebo Headache- 1 report due to cromoglycate and 1 report due to placebo Eczema- 1 report due to cromoglycate, and no reports of effect due to placebo Tiredness- 1 report due to cromoglycate, and no reports of effect due to placebo	Analyzed 40/49 Mixed allergic and nonallergic perennial rhinitis Generalizability: II / Internal Validity: C Reasons for withdrawal: (9 total) 2 due to change in environment 2 were on another therapy 2 did not return after admission 2 did not return after treatment 1	Pharmaceutical

Evidence Table 4. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Cromoglycate or cromolyn versus placebo
Part III. (continued)

Author Year UI	**Outcome-safety**	**Potential Bias**	**Funding**
Leiferman 1975	Minor adverse effects 1 patient from placebo group withdrew due to nasal irritation (later also withdrew his treatment pair)	Unclear of what specific inclusion criteria Gave graph results of total score over whole time period only after saying that data from peak pollen period probably of greater value Did not give breakdown of scores by symptom Minimal data on SE 1-tailed p-values small N	Government and private foundation
Wilson 1975 76101270	No major adverse effects. Minor adverse effects: -Nausea: 1 patient from cromoglycate group -Headache: 1 patient from cromoglycate group -Sneezing- 3 patients from cromoglycate group and 1 patient from placebo group -Nasal dryness and Irritation- 1 patient from cromoglycate group and 6 patients from placebo group Epistaxis- 1 patient from cromoglycate group and 1 patient from placebo group Other adverse effects- 3 patients from cromoglycate group and 4 patients from placebo group (other effects include sore throat, itchy eyes, tiredness, aggravated symptoms, mucosa flakiness, dry mouth at night, and stinging	Small cross-over study, washout, unclear what scores mean	Pharmaceutical

Evidence Table 4. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Cromoglycate or cromolyn versus placebo
Part III. (continued)

Author Year UI	**Outcome-safety**	**Potential Bias**	**Funding**
Hasegawa 1976 77001950	No safety data	No baseline characteristics Pooled crossover data NO absolute values for individual or total nasal symptom scores. Applicability II Internal validity C	ND
Knight 1976 76238158	Sneezing, Coughing, and Headache- occurring in a few patients, but no numbers given -sneezing + coughing- seemed more prevalent in placebo group headaches- seemed more prevalent in the cromoglycate group	Inconclusive data Useless data Indeterminate number of subjects	Pharmaceutical
Backman 1977	No major adverse effects No withdrawals for adverse effects Minor adverse effects -Nasal Irritation- 9 taking placebo and 8 taking SCG reported effect -Headache- 1 taking placebo and 1 taking SCG reported -Eczema- 1 taking placebo and 0 taking SCG reported effect -Tiredness- 1 taking placebo, and 0 taking SCG reported effect	No withdrawals for adverse effects noted No data on 7 out of 40 patients- possible withdrawals, but not indicated as such No information given on possible withdrawals	ND
Frostad 1977 78062986	No major adverse effects noted Minor adverse effects as follows: Nasal irritation, no significant difference between groups. No withdrawals for adverse events.	Applicability II Internal validity B	ND

Evidence Table 4. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Cromoglycate or cromolyn versus placebo
Part III. (continued)

Author Year UI	**Outcome-safety**	**Potential Bias**	**Funding**
Handelman 1977 77119242	No data on withdrawals No major adverse events Minor adverse events: Nasal irritation Sneezing No significant difference between groups in incidence of these.	Only analyzed week 2-5 data of 6 weeks Analysis did not include all enrolled participants No information on reasons for study dropouts	ND
Lofkvist 1977	No major adverse effects. Minor adverse effects -Dryness and irritation in nose and throat (5 patients with SCG, and 4 patients with placebo)	Adequate duration study Shows an effect with DSCG	Pharmaceutical
McDowell 1977 77264819	No major adverse effects. Minor adverse effects: Transient burning and stinging- 10/17patient reports with cromoglycate and 13/17 patient reports with placebo Mild rash/pruritis- 2 patients in cromoglycate group and 3 patients in placebo group Nausea and dizziness- 1 patient in cromoglycate group and 1 patient in placebo group Nosebleed- 3 patients in cromoglycate group and 6 patients in placebo group Headache- 8 patients in cromoglycate group and 5 patients in placebo group Treatments had no effect on blood pressure, heart rate, respiratory rate, hematologic profiles, urinalysis or blood chemical parameters	Cross-over, washout period All data merged Nothing on order of drugs Reasons for withdrawals: 4 total: 3- poor compliance or incomplete data 1- severe nasal congestion, but not significant rhinorrhoea or sneezing	Pharmaceutical

Evidence Table 4. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Cromoglycate or cromolyn versus placebo
Part III. (continued)

Author Year UI	**Outcome-safety**	**Potential Bias**	**Funding**
Posey 1977 78063003	No major adverse effects. Minor adverse effects: 2 withdrawals: 1 patient due to severe symptoms not controlled by antihistamines; 1 patient from placebo group due to development of severe chemical rhinitis after 1 week Nasal irritation, rhinorrhea, and sneezing (no data given)	No raw data- all in graph form	ND
Van der Bijl 1977 78033928	No major adverse effects. Minor adverse effects: Nasal Irritation: 1 patient in placebo group Dizziness and Sneezing- 1 patient in cromoglycate group	Omitted 8 patients from final analysis (did not follow treatment protocol)	ND
Warland 1977 77262676	No major adverse effects. Minor adverse effects: Nasal irritation- 1 complaint due to cromoglycate and 3 complaints due to placebo Headache- 4 complaints due to cromoglycate and 2 complaints due to placebo Nausea- 1 complaint due to cromoglycate and 0 complaints due to placebo Other- 4 complaints due to cromoglycate and 3 complaints due to placebo	Combined data from cross-over trial Small sample size Not all patients enrolled were analyzed Generalizability- II / Internal Validity- C Other reasons for withdrawal 4 drop-outs total: 1 due to steroid use 3 due to lack of cooperation	ND
Sorri 1979 79205990			

Evidence Table 4. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Cromoglycate or cromolyn versus placebo
Part III. (continued)

Author Year UI	**Outcome-safety**	**Potential Bias**	**Funding**
Sipila 1987 88110026	No major adverse effects Minor side effects as follows: Sneezing 5 in active treatment Group Unpleasant taste 2 in placebo group Nasal irritation 2 in placebo group 2 in active treatment group Throat irritation 2 in active treatment group Dizziness 1 in placebo group	Considered data from peak pollen season only 5 patients omitted from analysis	ND

Evidence Table 5. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Sympathomimetic treatments

Part I.

Author Year UI	Intervention	Duration	Demographics	Inclusion criteria	Exclusion criteria
Green 1966 67044478	**Perennial Allergic Rhinitis** (1)oxymetazoline HCl vs (2) Phenylephrine HCl	1 day	Location: UK Mean age: 3-13 Age range: <18 %Male: 15/33=45.5% Race: ND Enrolled: 33 Evaluated:33 Number of sites:1	Children with allergic rhinitis	N/A
Svensson 1980 81129988	**Seasonal Allergic Rhinitis** KWD 2131 and Terbutaline Sulphate vs Placebo RCT- cross-over (extractable)	2 months in pollen-free season – January-March	Location: Sweden Mean age: 28 Age range: 17-38 % Male: 14/29 Race: ND Enrolled: 29 Evaluated: 29 - 16 (normal) and 13 (SAR patients) Number of sites:2	Normal patients- normal IgE/serum readings SAR patients- positive skin and provocation tests Suffered form hay fever for at least 2 seasons All patients-asymptomatic	Normal patients- Symptoms of SAR, dermatitis, urticaria or bronchial asthma Asthma No heredity for above disease

Evidence Table 5. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Sympathomimetic treatments
Part I. (continued)

Author Year UI	Intervention	Duration	Demographics	Inclusion criteria	Exclusion criteria
Svensson 1981 82087563	**Seasonal Allergic Rhinitis** KWD 2131 (β-adrenoceptor stimulants) vs Placebo RCT- cross-over (extractable)	3 months	Location: Sweden Mean age: 24.5 Age range: 17-34 % Male: 13/22 Race: ND Enrolled: 22 Normal and seasonal allergic rhinitis volunteers Evaluated: 22 - 11 (normal) and 11(seasonal allergic rhinitis) Number of sites: ND	Normal patients- No symptoms of allergic rhinitis Normal IgE/serum Seasonal allergic rhinitis patients- Asymptomatic during trial Positive skin test for grass pollen Hay fever for at least last 2 years	None indicated
Svensson 1982 83040698	**Seasonal Allergic Rhinitis** KWD 2131 (β-adrenoceptor stimulants) vs placebo RCT- cross-over (extractable)	28 days	Location: Sweden Mean age: 27 Age range: 14-52 % Male: 23/27 Race: ND Enrolled: 27 Evaluated: 27 - 14 (KWD 2131-plac) and 13 (placebo- KWD 2131) Number of sites:1	Sensitive to grass pollen Positive skin or positive provocation test Suffered form hay fever for at least last two seasons Prior insufficient treatment with antihistamines, cromoglycate, beclomethasone, or hyposensitization	Currently undergoing hyposensitization therapy

Evidence Table 5. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Sympathomimetic treatments
Part I. (continued)

Author Year UI	Intervention	Duration	Demographics	Inclusion criteria	Exclusion criteria
Borum 1987 87239270	**Seasonal Allergic Rhinitis** Fenoterol (β-2-adrenostimulant) vs Placebo RCT- cross-over	5 weeks- 2.5 weeks for each treatment	Location: Denmark Mean age: 24.5 Age range: 18-65 % Male: 24/33 Race: ND Enrolled: 35 Evaluated: 33 - 17 (fenoterol- placebo) and 16 (placebo- fenoterol) Number of sites:1	Positive skin prick test to grass pollen SAR	Asthma Perennial Allergic rhinitis Patients receiving immunotherapy No topical steroid treatment for at least 1 month prior to study All other drug usage discontinued for at least 1 week prior to study
Shaikh 1995 96080200	**Perennial Allergic Rhinitis** Ephedrine saline wash (10% solution) vs Placebo RCT- cross-over (extractable)	4 weeks	Location: India Mean age: 25.69 Age range: 15-49 %Male: 68/118 = 57.6% Race: ethnically restricted Enrolled: 137 - 69 (placebo) and 68 (ephedrine) Evaluated: 118 -63 (placebo) and 55 (ephedrine) Number of sites:1	With PAR, normal spirometry values, and positive skin prick test	With asthma, and other atopic disease such as urticaria and eczema Also excluded patients who had SAR
Svensson 1995 96357837	**Seasonal Allergic Rhinitis** Terbutaline (β-2-receptor agonist) vs Placebo RCT- cross-over (extractable)	30 s each	Location: Sweden Mean age: 29 Age range: 21-49 % Male: 5/12= 58.3% Race: ND Enrolled: 12 Evaluated: 12 Number of sites:1	History of pollen-induced AR Positive skin prick test to birch or timothy	No other organic manifestation of their allergic disease No drugs permitted during 3-week period prior to study

Evidence Table 5. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Sympathomimetic treatments
Part I. (continued)

Author Year UI	Intervention	Duration	Demographics	Inclusion criteria	Exclusion criteria
Georgitis 1998 98372425	**Perennial Allergic Rhinitis** Atropine SO4 Spray (50 μg) Vs Atropine Spray (75 μg) [Nasal placebo also tested] RCT Parallel	2 weeks	Location: US Mean age: 31.6 Age range: 18-59 %Male: 60 Race: ND Enrolled: 45 Evaluated: 45 (15 each group) Number of sites:1	Normal Vital signs and Physical Examination w/o severe rhinorrhoea – runny nose or PN Drainage Rhinorrhoea severity score 3 or 4 and PND in 2-week baseline period [pre-inclusion: systemic steroids * 4wks; non-maintenance immunotherapy x 4wks; topical steroids x 2wks; antihistamine x 2 weeks; sympathomimetics x 2wks	Those with nasal septal deviation or nasal polyposis Grossly overweight or underweight Serious systemic disorders Local nasal obstruction (polyps, deviated septum, structural defect)

Evidence Table 5. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Sympathomimetic treatments
Part II.

Author Year UI	**Treatment outcomes studied**	**Symptom scale**	**Outcomes-efficacy**
Green 1966	Mean total symptom score Mucosal turgescence	1+ - 3+ scale with 3+ = turbinates so boggy and edematous that they touch nasal septum. Heavy serous or mucoid discharge; hyperemia or greyish membrane present to 1+ = hyperemia and serous secretion but no enlargement of the turbinates	Overall assessment: oxymetazoline proved significantly superior to phenylphedrine in inducing long-lasting nasal decongestion: Oxymetazoline- decongestion in 16/22 cases, and 9 cases decongestion period ≥ 5.5 hours Phenylephrine- decongestion in 11/22 cases, and 3 cases decongestion period ≥ 5.5 hours ~ at 0.5 hr:14/22 mucosal turgescence cases symptoms reduced with oxymetazoline vs reduction of 13/22 cases with phenylephrine ~at 1.0 hr: 14/22 mucosal turgescence cases symptoms reduced with oxymetazoline vs 7/22 reduction with phenylephrine ~at 2.0 hr: 14/22 mucosal turgescence cases symptoms reduced with oxymetazoline vs 7/22 reduction with phenylephrine ~at 5.0 hr: 12/22 mucosal turgescence cases symptoms reduced with oxymetazoline vs 4/22 reduction with phenylephrine ~at 6.0 hr: 12/22 mucosal turgescence cases symptoms reduced with oxymetazoline vs 4/22 reduction with phenylephrine (*note* out of 22 because 3 groups of 11 each tested with different solutions- 2 groups with 1 solutions A or B, and 1 group with both solutions (cross-over group))

Evidence Table 5. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Sympathomimetic treatments
Part II. (continued)

Author Year UI	**Treatment outcomes studied**	**Symptom scale**	**Outcomes-efficacy**
Svensson 1980 81129988	Total Mean Symptom Score Nasal Airway resistance Nasal symptoms Nasal secretions	Symptom Scale Nasal symptoms 0-3 scale Oedema and secretion- 0-3 scale (before and after drug administration) 0= no symptoms 1= mild 2= moderate 3= severe Hand tremor (before and after drug administration)- 0-3 scale Nasal air-flow-rhinomanometry readings	Terbutaline and placebo both induced minor increase in airway resistance to same degree; p= NS Terbutaline (0.5 mg) and KWD 2131 (1.25 mg) produced almost same nasal airway changes as compared to placebo Terbutaline (5 mg) and KWD 2131 (5 mg) both produced marked increase in nasal airway resistance - small change, but still significant with p< 0.05 for both stimulants No nasal changes in normal and SAR patients with all treatments
Svensson 1981 82087563	Total Mean symptom score Nasal Congestion Itchy Nose Nasal secretion Sneezing Nasal air resistance	Symptom Scale Nasal symptom scale- 0-3 scale Also used rhinomanometry to analyze nasal resistance	Nasal airway resistance (after histamine application)- values were statistically significant- mean value somewhat higher for SAR patients vs normal, but only occasional significant differences between groups Sneezing, Nasal stuffiness, and Nasal itch (after histamine application)- similar in both groups normal and SAR patients; occasional significant differences between groups P< 0.05 Nasal stuffiness, secretion, nasal itch, number of sneezes- occasional significance revealed P< 0.05

Evidence Table 5. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Sympathomimetic treatments
Part II. (continued)

Author Year UI	**Treatment outcomes studied**	**Symptom scale**	**Outcomes-efficacy**
Svensson 1982 83040698	Total mean symptom score Rhinorrhoea Nasal congestion Itchy nose Itchy eyes Itchy throat	Symptom scale Diary cards- Nasal blockage, running, itchy nose and ocular symptoms 0-3 scale: 0= no symptoms 1= mild symptoms 2= moderate symptoms 3= severe symptoms Sneezing attacks- 0-3 scale: 0= no attacks 1= 1-5 attacks 2= 6-15 attacks 3= more than 15 attacks/ 24 hrs oedema/ secretion – 0-3 scale physician evaluation-hematological and urine analysis also conducted	Global patient evaluation: P= NS: study did not reveal any significance between treatment groups Diary card scores- did not reveal any difference in symptom –relieving capacity between groups Overall evaluation: No significant differences documented between treatment with KWD 2131 and placebo No actual data- just graphs

Evidence Table 5. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Sympathomimetic treatments
Part II. (continued)

Author Year UI	**Treatment outcomes studied**	**Symptom scale**	**Outcomes-efficacy**
Borum 1987 87239270	Total Mean Symptom Score Sneezing Nose-blowings Secretion Blockage Ocular symptoms	Symptom Scale Nasal symptoms, secretion, and ocular symptoms (estimated during evenings)- 0-3 scale 0= no symptoms 1= slight symptoms 2= moderate symptoms 3= severe symptoms Nose –blowings - 1 tissue/blow Pollen counts also continuously monitored	Global patient evaluation: 21 patients preferred fenoterol, 5 patients preferred placebo, and 7 had no preference p< 0.01 Following scores out of n= 25 (8 withdrawals due to side effects) Sneezing After first treatment: (Group1- fenoterol/ Group2-placebo): Difference between run-in baseline score and 1st treatment, difference of 0.67 for G1 (fenoterol) vs score difference of 6.04 for G2 (placebo) P< 0.01 After second treatment: (Group1- placebo/Group 2- fenoterol) Difference between 1st and 2nd treatment score, difference of 3.04 for G1 (placebo) vs score difference of 4.48 for G2 (fenoterol) P< 0.01 Nasal Secretion After first treatment: (Group1- fenoterol/ Group2-placebo): Difference between run-in baseline score and 1st treatment, difference of 0.30 for G1 (fenoterol) vs score difference of 0.65 for G2 (placebo) P= NS After second treatment: (Group1- placebo/Group 2- fenoterol) Difference between 1st and 2nd treatment score, difference of 0.16 for G1 (placebo) vs score difference of 0.49 for G2 (fenoterol) P= NS Insignificant reduction for nose-blowings and blockage
Shaikh 1995	Mean total symptom score- Sneezing, Rhinorrhoea Nasal Blockage Postnasal drip	0-4 scale, with 0= worsening of symptoms or no improvement to 4= excellent improvement	Ephedrine treatment showed global score improvement with symptom score of 3.5 with ephedrine vs 0.8 symptom score with placebo; p < .001 for drug vs placebo Peak in spirometry, nasal flow rate – symptom score of 2-5 with placebo, and symptom score of 140??? With ephedrine; p< .01

Evidence Table 5. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Sympathomimetic treatments
Part II. (continued)

Author Year UI	**Treatment outcomes studied**	**Symptom scale**	**Outcomes-efficacy**
Svensson 1995 96357837	Total Mean Symptom Score Nasal Congestion Sneezing Itchy nose	Symptom Scale Nasal Symptoms: 0-3 scale 0= no symptoms 1= mild 2= moderate 3= severe symptoms Number of sneezes- 0-3 scale 0= none 1= 1-4 sneezes 2= 5-9 sneezes 3= 10+ sneezes -total symptom score- sum of nasal symptoms -pulse rate registration also done immediately after nasal lavage	Global physician assessment: Nasal blockage: $p < 0.05$ for terbutaline vs placebo Corporate nasal symptom: $p < 0.01$ for terbutaline vs placebo Terbutaline seemed to reduce all of the allergen challenge- induced nasal symptoms

Evidence Table 5. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Sympathomimetic treatments
Part II. (continued)

Author Year UI	**Treatment outcomes studied**	**Symptom scale**	**Outcomes-efficacy**
Georgitis 1998	Mean total symptom score Nasal Rhinorrhoea	Patients daily log of rhinitis symptoms - 5 pt scale Patients used scale 0-4 to rate severity of symptoms ("higher numerical value to short duration of control similar to use of higher scores for severity reflecting worse symptoms" p3) Global evaluation done by patients and physicians based on 6 pt-scale Global evaluation done also at weekly physician visits with 5pt scale (0- worse, 1- no control, and 5- complete control and relief of symptoms	Overall symptom score of 3.0 with atropine SO_4 spray(50μg), p<.05 compared to placebo; Overall symptom score of 3.0 with atropine sprain(75μg), p< .05 compared to placebo; Overall symptom score of 2.0 with placebo Post-natal drainage symptom score of 1.75 with atropine SO_4 spray(50μg) and p= .002 for drug1 compared to placebo vs symptom score of 1.6 with atropine sprain(75μg) and p= .002 drug2 compared to placebo; symptom score of 3.25 with placebo [~from baseline, -1.0 change in score with atropine SO_4 spray(50μg), p< .001 for drug 1 compared to placebo; vs –0.8 change in score with atropine sprain(75μg), p< .001 for drug 2 compared to placebo; -0.1 score change with placebo] Rhinorrhoea symptom score of 1.25 with atropine SO_4 spray(50μg), p= .002 for drug 1 compared to placebo; vs symptom score of 1.5 with atropine sprain(75μg), p= .002 for drug 2 compared to placebo; symptom score of 3.0 with placebo [~from baseline, -0.9 change in score with atropine SO_4 (50μg), p<.001 for drug 1 compared to placebo; vs -0.8 change in score with atropine sprain (75μg), p<.001 for drug 2 compared to placebo; -0.1 score change with placebo]

Evidence Table 5. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Sympathomimetic treatments
Part III.

Author Year UI	**Outcome-safety**	**Potential Bias**	**Funding**
Green 1966	No major adverse effects. Minor adverse effects- Local nasal burning problem (1/22 for patients taking oxymetazoline, and 2/22 patients taking phenylephrine)	Oxymetazoline produced longer-lasting nasal decongestion than phenylphedrine	ND
Svensson 1980 81129988	Major adverse effects: Tremor- induced in all patients after high dosage of terbutaline No minor adverse effects:		ND
Svensson 1981 82087563	No side effects indicated	Limitation in randomization process	ND
Svensson 1982 83040698	Minor adverse effects: 3 withdrawals- one potentially drug-related- 1 patient taking KWD 2131 experienced tremor	Other reasons for withdrawal (out of 3 withdrawals): 1 patient due to insufficient effect of treatment 1 patient due to intervening illness	ND

Evidence Table 5. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Sympathomimetic treatments
Part III. (continued)

Author Year UI	**Outcome-safety**	**Potential Bias**	**Funding**
Borum 1987 87239270	Major adverse effects: Minor adverse effects: 2 Withdrawals before study (out of n= 35) 1 patient due to headache after taking placebo 1 patient due to severe symptoms in pretreatment and after taking fenoterol 8 withdrawals during study (out of n= 33) due to tremor and/or restlessness [note- patients without side effects (n= 25)- 13 preferred fenoterol, 5 preferred placebo, 7 without preference p< 0.05] -Trembling/Restlessness-higher degree of trembling and restlessness during absorption of treatment -Nasal irritation- 30% complained of nasal irritation with both placebo and fenoterol		ND
Shaikh 1995	Major adverse effects- 19 total withdrawals- 2 patients complained of palpitations Minor adverse effects- -Heaviness of head (6 patients) -Burning sensation in nose for few min. after administration (5 patient) -Swallowing negligible amounts of fluid during ESNW administration (4 patients)	Not conventional Rx as in US/UK Other reasons for withdrawal: 4/ 19 dropped out due to inability to master technique of ephedrine nasal wash administration	ND

Evidence Table 5. Randomized controlled studies evaluating treatment of seasonal and perennial allergic rhinitis
Sympathomimetic treatments
Part III. (continued)

Author Year UI	**Outcome-safety**	**Potential Bias**	**Funding**
Svensson 1995 96357837	No major adverse effects indicated. Minor adverse effect- Tremor- 9 patients taking terbutaline experienced tremor, while 0 patients experienced effect with placebo Pulse rate- significant increasing increments recorded after 2 doses terbutaline, vs no increase with placebo High doses of topical terbutaline will produce antiallergic effects in human airways		ND
Georgitis 1998	No major adverse effects. Minor side effects: Pharyngitis, Taste perversion, Epistaxis, Dizziness, Dry Mouth, Chest Pain, Fever, Headache, Paresthesia, Pruritis, Dry Skin, Anxiety, Asthma, Bronchitis, Dyspepsia, Insomnia, Pain, Emotional Upset, and Tachycardia		Pharmaceutical

Evidence Table 6. Studies evaluating risk of asthma with allergic rhinitis

Part I.

Author Year UI	Study Type	Duration	Demographics	Inclusion criteria	Exclusion criteria
Settipane 1994	Prospective cohort	23 year followup	Location: US Mean age: 40 Age range: ND % Male ND Race: ND Enrolled: 1836 Evaluated: 738 Number of sites: 1	College student cohort	None
Anderson 1992	Prospective cohort study	23 year followup of 1958 birth cohort	Location: UK Mean age: 23 Age range: N/A % Male ND Race: ND Enrolled: 16833 Evaluated: 12521 Number of sites: N/A	1958 birth cohort	None

Part II.

Author Year	Associations noted	Potential bias Funding
Settipane 1994	Incidence of asthma in subjects with prior allergic rhinitis was 10.5% vs. 3.6% in those without. Greater than 3-fold risk of asthma in patients with prior allergic rhinitis.	No data on funding
Anderson 1992	Subjects with a history of allergic rhinitis had a 1.7-2.0 greater chance developing asthma symptoms during followup.	No data on funding

Bibliography

Reference list is bibliography.

Appendix

Evidence Report Staff, Technical Expert Advisory Group, and Peer Reviewers

New England Medical Center EPC Project Staff

EPC/Project Director	Joseph Lau, MD
Assistant Project Director	Caroline McFadden, MD
Primary Technical Expert	Aidan Long, MD
Project Manager	Deirdre DeVine, M Litt
Statistician	Norma Terrin, PhD
Research Associate	Priscilla Chew, MPH

EPC Technical Expert Panel

Joseph Lau, MD	Project Director Division of Clinical Care Research New England Medical Center Boston, Massachusetts
Aidan Long, MD	Primary Technical Expert Director of Allergy Massachusetts General Hospital Boston, MA
Harry Handelsman, DO	Medical Officer Center for Practice and Technology Assessment Agency for Healthcare Research and Quality Rockville, MD
William Berger, MD, MBA	American College of Allergy, Asthma and Immunology Mission Viejo Medical Center Mission Viejo, CA
John W. Georgitis, MD, FAAAAI	American Academy of Allergy, Asthma and Immunology Wake Forest University School of Medicine Winston-Salem, NC
Barbara Yawn, MD, MSc	American Academy of Family Physicians Olmsted Medical Center Rochester, MN

Peer Reviewers

The American Academy of Family Physicians, partner organization for the evidence report, nominated individuals to participate in the peer review of the report, as did the other organizations of the EPC Technical Expert Panel, the American College of Allergy, Asthma and Immunology, and the American Academy of Allergy, Asthma and Immunology.

We are grateful to the peer reviewers for generously offering their time and knowledge.

External Reviewers

American Academy of Family Physicians	Doug Campos-Outcalt, MD Stuart Stoloff, MD
American College of Allergy, Asthma & Immunology	Daniel Ein, MD Richard G. Gower, MD
American Academy of Allergy, Asthma & Immunology	Harold S. Nelson, MD, FAAAAI Michael J. Schumacher, MD, FAAAAI