Evidence Report/Technology Assessment
Number 67

Management of Allergic Rhinitis in the Working-Age Population

Agency for Healthcare Research and Quality

This report may be used, in whole or in part, as the basis for development of clinical practice guidelines and other quality enhancement tools, or as a basis for reimbursement and coverage policies. Endorsement by the Agency for Healthcare Research and Quality (AHRQ) or the U.S. Department of Health and Human Services (DHHS) of such derivative products may not be stated or implied.

AHRQ is the lead Federal agency charged with supporting research designed to improve the quality of health care, reduce its cost, address patient safety and medical errors, and broaden access to essential services. AHRQ sponsors and conducts research that provides evidence-based information on health care outcomes; quality; and cost, use, and access. The information helps heath care decisionmakers—patients and clinicians, health system leaders, and policymakers—make more informed decisions and improve the quality of health care services.

Evidence Report/Technology Assessment

Number 67

Management of Allergic Rhinitis in the Working-Age Population

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
http://www.ahrq.gov

Contract No. 290-97-0014

Prepared by:
Duke Evidence-based Practice Center

Douglas C. McCrory, MD, MHSc
John W. Williams, MD
Rowena J. Dolor, MD, MHS
Rebecca N. Gray, DPhil
Jane T. Kolimaga, MA
Shelby Reed, PhD
John Sundy, MD, PhD
David L. Witsell, MD
Investigators

AHRQ Publication No. 03-E015
March 2003

ISBN: 1-58763-077-X
ISSN: 1530-4396

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

Jean R. Slutsky, P.A., M.S.P.H.
Acting Director
Center for Practice and Technology Assessment
Agency for Healthcare Research and Quality

The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services of a particular drug, device, test, treatment, or other clinical service.

Structured Abstract

Objectives. This report assesses the evidence on how allergic rhinitis affects costs and work performance in working-age populations; the effectiveness of environmental measures, immunotherapy, and combination pharmacologic therapies; differences in treatment approaches and outcomes by clinician specialty; and variability in prevalence, treatment patterns, and outcomes by patient race and ethnicity.

Search Strategy. Nearly 1,600 English-language articles were identified principally from searches of MEDLINE, CINAHL, Cochrane Database of Systematic Reviews, DARE, International Pharmaceutical Abstracts, EconLit, and EMBASE.

Selection Criteria. Studies were included if the study population had allergic rhinitis, and if the study provided data on one of the key research questions and met minimal level-of-evidence criteria. We required patient-assessed symptom outcomes for efficacy questions.

Data Collection and Analysis. We summarized descriptive data in evidence tables and evaluated each study for methodological quality. Meta-analysis was considered when multiple studies on the same topic provided quantitative outcome data.

Main Results. Estimates of the effect of allergic rhinitis on *work performance* are variable. Patient-reported level of work impairment associated with allergic rhinitis ranged from 33 to 41 percent using a standardized validated instrument, with demonstrable improvement by seven to nine percentage points after treatment. Studies that directly measure work performance generally show lower degrees of impairment.

A few trials of *environmental control measures* in highly selected patients suggest that dust mite control measures decrease rhinitis symptoms. There is no strong evidence that air filtration systems decrease rhinitis symptoms.

Multiple trials of specific injection *immunotherapy* show improvement in symptoms compared with placebo. No serious adverse events were reported, and immunotherapy was well tolerated. Primary quality concerns are small trial size, lack of standardized clinical outcome assessments, and issues related to randomization procedures and concealment of allocation.

Combination symptomatic pharmacotherapy with antihistamines plus decongestants shows positive effects compared to monotherapy with either antihistamines or decongestants alone. Combination treatment with antihistamines plus nasal glucocorticoids shows positive effects compared to antihistamine alone, but no difference when compared to monotherapy with nasal glucocorticoids.

Little is described in the literature regarding patterns of allergic rhinitis care by *clinician specialty.* Several studies point to less-than-adequate knowledge regarding allergy treatment among patients in general medical practice. Two studies suggest that specialist clinician-delivered patient education results in improved allergic rhinitis symptoms.

Allergic rhinitis occurs in similar proportions across *racial and ethnic groups* in epidemiological studies, but there are essentially no data describing variation in treatment or outcomes by race or ethnicity.

Conclusions. Allergic rhinitis clearly has a negative impact on *work performance,* but the magnitude of this impact differs depending on the methodology used to measure it. Estimates of the effect of allergic rhinitis on *healthcare costs* appear to be unreliable. *Environmental measures* to reduce allergen exposure have not been definitively shown to be effective, with the possible exception of house dust mite controls. Specific *immunotherapy* is more effective than placebo, and *combination pharmacotherapy* is generally more effective than monotherapy for symptom control. There are insufficient data from which to draw conclusions about differences in treatment approaches between *generalist and specialist physicians* and in treatment patterns or outcomes by *patient race or ethnicity.*

Suggested Citation:
McCrory DC, Williams JW, Dolor RJ, et al. Management of Allergic Rhinitis in the Working-Age Population. Evidence Report/Technology Assessment Number 67. (Prepared by Duke Evidence-based Practice Center under Contract No. 290-97-0014.) AHRQ Publication No. 03-E015. Rockville, MD: Agency for Healthcare Research and Quality. March 2003.

Agency for Healthcare Research and Quality

Evidence Report/Technology Assessment

Number 67

Management of Allergic Rhinitis in the Working-Age Population

Summary

Overview

Allergic rhinitis affects as many as 35 million people in the United States annually; of these, an estimated 19 million are employed adults. Overall, 10 to 30 percent of adults and up to 40 percent of children are affected, making it the sixth most common chronic illness in the United States. Approximately one-third to one-half of sufferers have seasonal rhinitis, with the remainder experiencing perennial disease or both seasonal and perennial forms of the disease. Other atopic conditions, such as atopic eczema, allergic conjunctivitis, and asthma, often co-occur.

Estimates of the annual direct medical costs of allergic rhinitis in the US range from $1.16 billion to $4.5 billion, rising to $7.7 billion when indirect costs are included. These estimates, however, are based on information that predates the increased use of non-sedating antihistamines and nasal glucocorticoids. Recent prescription claims data show that approximately two-thirds of patients with allergic rhinitis receive treatment with one or more medications from these two drug classes, with expenditures exceeding $3.0 billion for prescription antihistamines alone.

Rhinitis is typically classified etiologically into allergic and non-allergic causes. Non-allergic rhinitis is characterized by chronic nasal symptoms and the lack of identifiable allergic triggers. This report focuses on individuals with allergic rhinitis, including both seasonal and perennial allergic rhinitis. Seasonal allergic rhinitis is associated with sensitization to fungal, tree, grass, and weed pollens, and with symptoms that vary seasonally. Perennial allergic rhinitis is associated with sensitization to indoor allergens such as fungi, cockroaches, dust mites, and animal proteins (e.g., cat dander), and with year-round symptoms, with or without seasonal exacerbations.

The physical symptoms of allergic rhinitis, such as sneezing, rhinorrhea, and nasal congestion, may interfere with one's ability to carry out daily activities. Rhinitis symptoms may be associated with headache, irritability, poor concentration, loss of sleep, and resulting fatigue. The functional impact of these symptoms ranges from mild to seriously debilitating effects on social, physical, and emotional functioning. Allergic rhinitis may interfere with cognitive tasks, may impair work performance, and may cause work absences.

Because allergic rhinitis is so common in the population and allergens are ubiquitous, allergic rhinitis creates a significant burden in the workplace in terms of effects on work performance and health care costs. Although some occupational exposures to airborne allergens present in the workplace can cause occupational rhinitis, non-occupational allergic rhinitis represents a vastly greater burden in workplace settings overall.

The topic of this report was selected by the Agency for Healthcare Research and Quality (AHRQ) in response to a nomination by the American Association of Health Plans. The Duke Evidence-based Practice Center (EPC) conducted the research and developed the final report for AHRQ. The emphasis on the working-age population raises unique issues, including the relationship between symptoms or functional status and work performance, the effects of allergic rhinitis and its treatments on costs and work performance, and variability in management approaches and patient outcomes among patients treated by generalist physicians, allergy specialists, and otolaryngologists.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES • Public Health Service

The general diagnostic and treatment issues relating to allergic rhinitis were summarized in an earlier evidence report, *Management of Allergic and Nonallergic Rhinitis*, prepared by the EPC at the New England Medical Center. However, the Duke evidence report prioritizes issues not addressed in the New England Medical Center report, including the effect of allergic rhinitis treatment on work performance and costs, and the effectiveness of combinations of pharmacological treatments, immunotherapy, and the use of strict environmental control measures. The Duke research team sought evidence on these issues, evidence that may be valuable not only to employers, policy decisionmakers, and guideline developers, but also to researchers who wish to identify and address gaps in evidence, and to clinicians who care for patients with allergic rhinitis.

Reporting the Evidence

The Duke EPC staff, in consultation with AHRQ and a multidisciplinary panel of experts, refined the key research questions addressed in this report:

1. How do currently available clinical treatments for allergic rhinitis affect costs and work performance?
2. What is the relationship between symptom outcomes or disease-specific quality-of-life measures and work performance among adults with allergic rhinitis? Can data on symptomatic outcome or quality of life be reliably translated into work performance measures?
3. How effective are (a) environmental measures, (b) immunotherapy, and (c) combined treatments, such as antihistamines and nasal steroids or antihistamines and oral decongestants, for relief of symptoms in adults with allergic rhinitis?
4. How do different types of health care providers (generalists, allergy specialists, and otolaryngologists) treat adults with allergic rhinitis, and how do treatment outcomes vary by provider?
5. In adult patients with symptoms of allergic rhinitis, does the prevalence, treatment patterns, or response to treatment vary according to a patient's race or ethnicity?

Methodology

The Duke EPC researchers systematically reviewed the literature for evidence addressing the above questions. They searched for English-language articles indexed in computerized bibliographic databases: MEDLINE®, CINAHL®, the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effectiveness, International Pharmaceutical Abstracts, EconLit, and EMBASE. Searches of these databases were supplemented by searching the reference lists of all included articles, especially review articles and meta-analyses, and by scanning current issues of relevant journals not yet indexed in the online databases.

The results of the literature searches were screened by two investigators according to inclusion and exclusion criteria. Empirical studies were included if: (a) the study population had allergic rhinitis; (b) the study provided data on at least one of the five key research questions; and (c) the study met minimal study design criteria for the question being addressed. Minimal study design criteria for the key questions follow:

- Question 1 and 2—Costs and work performance. Any empirical study involving more than 20 patients with allergic rhinitis. Includes randomized controlled trials (RCTs), case series, cohort studies, non-randomized comparison studies, surveys, and secondary data analyses.
- Question 3a—Environmental measures. RCTs and non-randomized prospective cohort comparisons.
- Quesitions 3b and 3c—Immunotherapy and combination drug therapy. RCTs and pseudo-randomized placebo-controlled trials.
- Questions 4 and 5—Clinician specialty differences and racial and ethnic variation. Any empirical study involving more than 20 patients with allergic rhinitis. Includes RCTs, case series, cohort studies, non-randomized comparison studies, surveys, and secondary data analyses.

The full text of each article included at the screening stage was independently reviewed by two investigators. Articles found to meet inclusion criteria were selected for data abstraction. The EPC required patient-assessed symptom outcomes for efficacy questions, and researchers also reported quality of life, functional status, adverse events, and patient global assessments for these questions. For all questions, they recorded work performance and cost outcomes.

The EPC's senior writer/editor began the data abstraction process with a partial abstraction, which included a description of the study design, intervention, number of subjects at the start of the study, and types of outcome data collected. One investigator then completed abstraction of details of the study population, results, and comments; a second investigator over-read the table for completeness and accuracy and performed quality scoring. They evaluated each article included in the evidence tables for methodological quality, grading the level of evidence and describing 13 factors affecting internal or external validity.

The EPC employed quality-monitoring checks at every phase of the literature search, review, and data abstraction process to reduce bias, enhance consistency, and check the accuracy of screening.

Findings

Costs and Work Performance

Few studies assess the impact of the treatment of allergic rhinitis on costs or work performance. The cost-effectiveness literature for allergic rhinitis is small in quantity and suffers from several methodological shortcomings, principally the lack

of a standardized measure of effectiveness, the lack of prospectively collected cost or resource utilization data, and extrapolation of effectiveness data based on short-term randomized trials to long-term economic analyses.

The effects of allergic rhinitis on productivity have been studied by two approaches: by querying workers for a subjective estimate of impairment and by direct objective measurements of worker output. According to one standardized and validated instrument, overall work impairment associated with allergic rhinitis measured subjectively in three studies ranged from approximately 33 to 41 percent. Conversely, two studies using direct measurement found productivity changes ranged from a 10 percent decrease to a 5 percent increase. The discrepancy between methods and studies suggests that the level of impairment due to allergic rhinitis reported by workers may overestimate objectively measured percent reduction in productivity. This finding calls into question the indirect cost estimates from the burden-of-illness studies of allergic rhinitis, all of which used impairment estimates of around 25 percent.

Few data are available on the association between allergic rhinitis symptoms and work performance. A single study reported a moderate correlation between symptom improvement and change in work performance (as measured by a subjective validated instrument). Thus, although it is reasonable to conclude that treatments that improve symptoms while minimizing side effects will likely improve work performance, the increment in productivity would be difficult to estimate from symptom change data.

Environmental Measures

Studies of air filtration systems do not show strong evidence for decreasing rhinitis symptoms; however, studies were likely underpowered to detect clinically relevant differences. A few trials in highly selected patients suggest that dust mite control measures such as an acaricide, impervious covers, and extra house cleaning may decrease rhinitis symptoms. Studies of mite-sensitive asthmatics do not demonstrate any overall clinical benefit of a variety of measures designed to reduce mite exposure.

Immunotherapy

Nearly all of 60 clinical trials of immunotherapy in allergic rhinitis reported symptom outcomes favoring injection immunotherapy over placebo. While this effect was more certain for seasonal allergic rhinitis treated with seasonal allergens, the response among the few studies of perennial rhinitis was similar. No serious adverse events were reported, and immunotherapy was generally well tolerated. Primary quality concerns related to small trial size, lack of standardized clinical outcome assessments, and trial design issues related to randomization procedures and concealment of allocation.

Combined Treatments

Combination symptomatic pharmacotherapy with antihistamines plus decongestants has been well studied and overall shows greater improvement in total and nasal symptoms than monotherapy with either antihistamines or decongestants alone. Combination treatment with antihistamines plus nasal glucocorticoids shows greater improvement in nasal symptoms than antihistamines alone, but no difference when compared to monotherapy with nasal glucocorticoids. Other combinations have been studied in a small number of trials and overall show that, compared with antihistamines alone, the addition of:
(a) ipratropium is beneficial for rhinorrhea symptoms;
(b) ophthalmic antihistamine reduces eye itching; and
(c) the mast cell stabilizer, nedocromil sodium, or a nonsteroidal anti-inflammatory drug improves overall rhinitis symptoms.

Clinician Specialty Differences

Although differences in care and outcomes have been demonstrated between generalist and specialist care in other conditions, including asthma, few data are available in allergic rhinitis. Two studies suggested that clinician-delivered patient education interventions coupled with medical treatment may improve allergic rhinitis symptoms more than medical treatment alone. Several studies point to less-than-adequate knowledge regarding allergy treatment among patients in general medical practice. Although survey data suggest that many patients are referred from generalist practices to specialist clinicians based on the severity of symptoms, there are no published empirical data to support the view that specialist clinicians see more severely affected patients.

Racial and Ethnic Variation

There are few studies addressing any aspect of racial variation in relation to prevalence, treatment patterns, or response to treatment for patients with allergic rhinitis. The largest and most representative study, The National Health and Nutrition Examination Survey, 1976-80, did not show a consistent relationship between allergic rhinitis prevalence and race. Among the randomized trials reviewed for other questions addressed in this literature synthesis, only 11 percent described the racial characteristics of the study population. The only data on variation in treatment patterns with respect to race or ethnicity suggested that in a pediatric population, whites were more likely to continue injection immunotherapy treatment than non-whites. No data exist describing variation in treatment outcomes by race.

Future Research

The EPC assessment of the current evidence suggests that the following issues should be addressed in future research.

Updated estimates of the cost of allergic rhinitis could become more accurate by:

- Estimating indirect costs using valid objective measures of productivity changes.
- Including over-the-counter medications in direct medical costs.
- Accounting for increased use of non-sedating antihistamines and nasal corticosteroids.
- Carefully defining allergic rhinitis, particularly when using administrative data sets.

Although environmental control measures are strongly endorsed by experts, studies of such interventions have been equivocal. More comprehensive environmental control measures, such as those recommended in the National Heart, Lung, and Blood Institute's *Practical Guide for the Diagnosis and Management of Asthma* should be tested in patients with allergic rhinitis and significant functional impairment. If comprehensive interventions prove effective, then future studies should identify critical components.

To better understand the role of immunotherapy in the treatment of allergic rhinitis, we need trials employing vaccines with most or all of the relevant allergens for each individual to assess immunotherapy as it is administered in most community settings. Additional future research objectives should focus on the following:

- Methods to identify patients likely to benefit from immunotherapy.
- Determination of whether immunotherapy alters the natural history of allergic rhinitis and reduces possible sequelae such as bacterial sinusitis and asthma.
- Comparisons of immunotherapy and the best available medical management and/or allergen avoidance.
- Clarifying the optimal duration of immunotherapy.

Certain combination pharmacologic treatments have been shown to be effective in relatively short-term trials, mostly in seasonal allergic rhinitis. Additional data are needed on:

- The effectiveness of combination treatment in perennial allergic rhinitis.
- Longer duration treatment in primary care populations with clinically diagnosed seasonal or perennial allergic rhinitis.
- Effectiveness trials that include outcomes such as health-related quality of life and cost-effectiveness.
- The effectiveness of combinations including mast cell stabilizers, ipratropium, and newer drugs such as leukotriene antagonists.

To understand the quality of current patient care by different clinical specialists, we need:

- Studies describing current practice patterns.
- Prospective studies that compare symptomatic treatment to allergen identification with specific treatment, two approaches commonly used in generalist and specialty practices.
- Observational studies that compare treatment patterns and outcomes across specialties that provide case-mix adjustment. (A standardized and validated severity-of-illness scale would facilitate this research.)

Finally, the research team did not identify any studies that described racial or ethnic differences in treatment patterns or treatment response, in part because study populations were often incompletely described. Future studies should provide more complete descriptions of patient populations, including racial and ethnic descriptors that might allow subgroup analyses to assess racial or ethnic differences in treatment or response.

Availability of Full Report

The full evidence report from which this summary was taken was prepared for AHRQ by the Duke Evidence-based Practice Center under contract number 290-97-0014. It is expected to be available in early 2003. At that time, printed copies may be obtained free of charge from the AHRQ Publications Clearinghouse by calling 800-358-9295. Requestors should ask for Evidence Report/Technology Assessment No. 67, *Management of Allergic Rhinitis in the Working-Age Population.* When available, Internet users will be able to access the report online through AHRQ's Web site at: www.ahrq.gov.

www.ahrq.gov
AHRQ Pub. No. 03-E013
January 2003
ISSN 1530-440X

Chapter 1. Introduction

This chapter describes the background, scope, purpose, target populations, practice settings, audience, and limitations of the evidence report. It also identifies the key research questions addressed, provides an overview of the epidemiology and disease biology of allergic rhinitis, and describes the burden of illness associated with this condition.

Background

Allergic rhinitis, also known as hay fever, is one of the most common allergic diseases in the United States. The National Institute of Allergy and Infectious Diseases currently estimates that allergic rhinitis affects as many as 35 million Americans and accounts for 16.7 million office visits to healthcare providers each year (National Institute of Allergy and Infectious Diseases, 2002; National Institutes of Health, 2002). A recent report from the American Academy of Allergy, Asthma & Immunology estimates that about 19 million employed adults suffer from allergic rhinitis, and that approximately $4.5 billion in direct costs and 3.8 million lost work and school days are attributable to this disease annually (American Academy of Allergy, Asthma & Immunology, 2000).

Allergic rhinitis usually begins in childhood, adolescence, or early adulthood, and often wanes, but may persist, with increasing age. Rhinitis is defined as inflammation of the membranes lining the nose. The symptoms of allergic rhinitis usually include sneezing, rhinorrhea, itching and watery eyes, nasal congestion, and, in severe cases, facial pressure or pain. These symptoms may be associated with headache, irritability, poor concentration, loss of sleep, and fatigue. The functional impact of allergic rhinitis ranges from mild to seriously debilitating effects on social, physical, and emotional functioning, which may interfere with cognitive tasks, impair work performance, and cause work absences.

Because allergic rhinitis is so common and allergens are ubiquitous, allergic rhinitis creates a significant burden in the workplace in terms of work performance and healthcare costs. Although exposures to airborne allergies present in the workplace can cause occupational rhinitis, non-occupational rhinitis represents a vastly greater burden in workplace settings overall.

An evidence report on the topic of allergies and their effect on working-age populations was proposed to the Agency for Healthcare Research and Quality (AHRQ) by the American Association of Health Plans (AAHP), who became the Duke Evidence-based Practice Center's partner in developing this report. The specific research questions were refined in consultation with AHRQ, AAHP, and an advisory panel of eight experts convened especially for this study. The key research questions addressed in this report are:

1) How do currently clinically available treatments for allergic rhinitis affect costs and work performance?

2) What is the relationship between symptom outcomes or disease-specific quality-of-life measures and work performance among adults with allergic rhinitis? Can data on symptomatic outcome or quality of life be reliably translated into work performance measures?

3) How effective are (a) environmental measures, (b) immunotherapy, and (c) combined treatments, such as with antihistamines and nasal steroids or antihistamines and oral decongestants, for relief of symptoms in adults with allergic rhinitis?

4) How do different types of healthcare providers (generalists, allergy specialists, and otolaryngologists) treat adults with allergic rhinitis, and how do treatment outcomes vary by provider?

5) In adult patients with symptoms of allergic rhinitis, does the prevalence, treatment patterns, or response to treatment vary according to a patient's race or ethnicity?

Scope and Purpose

The purpose of this evidence report is to review the published evidence on strategies for managing the treatment of patients with allergic rhinitis, particularly those of employment age (18 to 64 years old). The report covers both seasonal and perennial allergic rhinitis. Seasonal allergic rhinitis is associated with sensitization to fungal, tree, grass, and weed pollens, and with symptoms that vary seasonally. Perennial allergic rhinitis is associated with sensitization to indoor allergens such as fungi, cockroaches, dust mites, and animal proteins (e.g., cat dander), and with year-round symptoms, with or without seasonal exacerbations.

Treatment options considered in this report are environmental measures (allergen avoidance), immunotherapy, and combination therapies employing antihistamines and nasal steroids or antihistamines and oral decongestants.

Also considered in the present report are the unique issues raised by the emphasis on working-age populations, including the relationship between symptoms or functional status and work performance, and the effects of allergic rhinitis and its treatment on costs and work performance. In addition, the report reviews the evidence on variability in management approaches and patient outcomes by type of clinician (generalist physician vs. allergy specialist vs. otolaryngologist), as well as by patient race and ethnicity.

Our goals were primarily to identify, review, and evaluate the published literature on these topics and, secondarily, where relevant evidence could not be identified or had important limitations, to describe the type of data that would be needed to more fully address the research questions. Ultimately, we hope to provide clinicians, policymakers, and patients with the evidence they need to decide for themselves on the best treatment and management options from among those considered here.

Epidemiology of Allergic Rhinitis

Allergic rhinitis affects 20 to 40 million people in the United States annually, including 10 to 30 percent of adults and up to 40 percent of children (Joint Task Force on Practice Parameters in Allergy, Asthma and Immunology, 1998). Approximately one-third to one-half of these patients suffer from seasonal allergic rhinitis, with the remainder experiencing perennial disease or both seasonal and perennial forms of the disease (Joint Task Force on Practice Parameters in Allergy, Asthma and Immunology, 1998). Other atopic conditions, such as atopic eczema, allergic conjunctivitis, and asthma, often co-occur with allergic rhinitis.

Allergic rhinitis may begin at any age, with most individuals developing symptoms as children or young adults. Risk factors include a family history of atopy, higher socioeconomic class, and exposure to indoor allergens such as animals and dust mites (Joint Task Force on Practice Parameters in Allergy, Asthma and Immunology, 1998). The risk of allergic rhinitis is 30 percent if one parent is atopic, at least 50 percent if both parents are atopic, and greater than 70 percent if both parents have the same allergic disease (Nimmagadda and Evans, 1999).

The Centers for Disease Control and Prevention (CDC) report an overall population prevalence rate of 89.8/1,000 persons, representing 23,721,000 Americans, in 1996, the latest year for which data are available (Centers for Disease Control and Prevention, 1999). Table 1 shows US prevalence rates and numbers by age, sex, race, and family income. Generally, prevalence is higher in females and in the white population. In the working-age population, 18- to 44-year-olds represent approximately one-half of all persons with allergic rhinitis, and 45- to 64-year-olds represent approximately one-fourth of allergic rhinitis cases. In families with incomes of $10,000 or higher, the prevalence rate generally increases with increasing income; however, the lowest income families (< $10,000) have a prevalence rate approaching those found in families at higher income levels.

By geographic location, the CDC reports that persons in the Western part of the US have the highest prevalence of allergic rhinitis (36 percent of total US prevalence), while residents of the Northeast have the lowest (18 percent of total US prevalence); by place of residence, four times as many persons in Metropolitan Statistical Areas (MSAs) have allergic rhinitis than persons living in non-MSAs (Table 2) (Centers for Disease Control and Prevention, 1999).

Overview of Disease Biology

The symptoms of allergic rhinitis result from exposure to particulate allergens that are large enough to be filtered by the nose. In susceptible adults, allergen-specific T cell sensitization leads to B cell production of allergen-specific immunoglobulin E (IgE) antibodies after an initial allergen exposure (e.g., pollen) (American Academy of Allergy, Asthma & Immunology, 2000). Allergen-specific IgE then binds to the surface of mast cells in the nasal mucosa or to circulating basophils. With subsequent exposure, the allergen is recognized by its specific antibody, resulting in the activation of IgE-primed mast cells and basophils, with release of a variety of potent inflammatory mediators. These include granule-associated mediators (e.g., histamine), membrane-derived lipid mediators (e.g., leukotriene), as well as cytokines and chemokines that attract inflammatory cells from the peripheral circulation to the site of degranulation. These mediators cause immediate mucosal edema and vasodilation and the clinical features of allergic rhinitis. "Early-phase" symptoms occur within minutes of the allergen exposure and are due to release of preformed mediators; "late-phase" symptoms occur 4 to 12 hours after exposure and involve synthesis of newly formed mediators and infiltration of inflammatory white blood cells from the circulation (Bellanti and Wallerstedt, 2000; Parikh and Scadding, 1997; Skoner, 2001). The late phase has been observed with large exposure allergen challenges, but the clinical importance of this observation is uncertain. Symptoms affect about 30 to 40 percent of individuals during the "late-phase" time period. Nasal itching is prominent during the early phase. Sneezing, nasal congestion, and rhinorrhea are common to early and late phases, and nasal congestion dominates during the late-phase reaction.

Burden of Illness

The symptoms of allergic rhinitis, such as sneezing, rhinorrhea, and nasal congestion, may interfere with one's ability to carry out daily activities. Rhinitis symptoms may be associated with headache, irritability, poor concentration, loss of sleep, and resulting fatigue. The functional impact of these symptoms ranges from mild to seriously debilitating effects on social, physical, and emotional functioning (Blaiss, 1999; Thompson, Juniper, and Meltzer, 2000). In a study comparing 116 healthy subjects to 111 patients with moderate to severe perennial allergic rhinitis, patients with allergic rhinitis had significantly decreased functioning in eight domains; negative effects were particularly prominent for physical and emotional role limitations, social functioning, and general health perceptions (Bousquet, Bullinger, Fayol, et al., 1994). Allergic rhinitis may interfere with cognitive tasks, may impair work performance, and may cause work absences. In a pooled analysis of 1,948 patients with moderate to severe allergic rhinitis, over 90 percent reported that their classroom or work performance was affected negatively (Tanner, Reilly, Meltzer, et al., 1999).

In addition to direct symptom effects, allergic rhinitis may be related to the development of asthma, sinusitis, or otitis media (Bousquet, van Cauwenberge, Khaltaev, et al., 2001; Spector, 1997). Asthma symptoms occur in 17 to 19 percent of patients with allergic rhinitis, a prevalence that is significantly higher than the five percent prevalence observed in the general population (Blair, 1977; Moller, Dreborg, Ferdousi, et al., 2002; Pedersen and Weeke, 1983; Settipane, 1986). In a cohort of 7,225 children followed from birth to age 23, children with allergic rhinitis were 2.0 to 2.9 times more likely to develop asthma during followup (Anderson, Pottier, and Strachan, 1992). A similar cohort study of college students found that those with allergic rhinitis were three times more likely to develop asthma than non-atopic controls during the 23-year followup (Settipane, Hagy, and Settipane, 1994). In cross-sectional studies, allergic rhinitis is associated with acute and chronic bacterial sinusitis (Long, McFadden, DeVine, et al., 2002).

Adverse effects from therapies are an additional burden associated with this illness, since they may impact more significantly on functional status than the disease itself, especially for patients with very mild disease. For adults, the only life-threatening effect from commonly used treatments is anaphylaxis associated with immunotherapy, which occurs at a rate of about one fatality per two million doses (Cook and Farias, 1998). Non-fatal systemic reactions are more common; estimates of their frequency vary widely, from 0.3 percent to more than 30 percent (Cook and Farias, 1998). Minor adverse effects of somnolence, dry mouth, dizziness, and headache may occur in up to 50 percent of patients taking sedating antihistamines (Long, McFadden, DeVine, et al., 2002). Published experimental work suggests that adverse effects associated with some treatments, particularly sedating antihistamines, which cause somnolence and psychomotor impairment, have an adverse impact on driving performance and reaction time (Adelsberg, 1997; Weiler, Bloomfield, Woodworth, et al., 2000); these effects may also interfere with work productivity and increase on-the-job accidents. The most frequently reported adverse effects associated with nasal corticosteroids are epistaxis, headache, and pharyngitis; with cromolyn, nasal irritation and headache are the most commonly reported adverse effects.

Management Strategies and Treatment Options

Allergen avoidance, immunotherapy, and an array of pharmacotherapies are commonly used to treat allergic rhinitis. For clinicians, management begins with accurate diagnosis, distinguishing between allergic and non-allergic etiologies. The clinical evaluation may include radioallergosorbent testing (RAST) or allergy skin testing to confirm allergy sensitization. For patients with allergic rhinitis, relevant treatment issues are: the efficacy of individual treatments; monotherapy versus combinations of treatments; the most cost-effective sequencing of treatments; and the effectiveness of generalist versus specialist care. In working populations, relevant treatment outcomes are: symptom control; effects on health-related quality of life; cost-effectiveness; and effects on work performance.

The specific therapies covered in this evidence report are environmental measures, or allergen avoidance; immunotherapy; and combination therapies such as antihistamines and nasal steroids or antihistamines and oral decongestants. Given the variety of treatment options, the variability in acceptability and cost of treatments, and the lack of a previous focus on work-related outcomes, a systematic review that addresses these issues is timely.

Environmental Measures

Given the known biology of allergic rhinitis, environmental measures (allergen avoidance) represent a conceptually appealing treatment option. Such measures are recommended in the rhinitis clinical guidelines developed by the Joint Task Force on Practice Parameters in Allergy, Asthma, and Immunology (1998), and by the American Academy of Otolaryngic Allergy (Fornadley, Corey, Osguthorpe, et al., 1996); they have also been recognized by the American Academy of Allergy, Asthma & Immunology in its recent report (2000). Allergen avoidance measures range from relatively inexpensive measures, such as removing feather pillows and down comforters, to more intensive measures, such as high-flow air filtration units like a high efficiency particulate air (HEPA) cleaner, elimination of carpeting in favor of tile or hardwood floors, and acaricides or dust-proof covers for mattresses and bedding to control house dust mites. Allergen avoidance may be more difficult in the case of outdoor allergens and may have important life implications for individuals working outdoors or who experience occupational rhinitis.

Immunotherapy

Immunotherapy (allergen desensitization) is most often used by specialists for patients with more severe allergic rhinitis or for patients who do not tolerate or respond well to multiple medications. A program of immunotherapy requires once- or twice-weekly injections of escalating doses of allergen extracts over a period of months. This is followed by once- or twice-monthly maintenance injections, typically for a period of at least 2 to 3 years. Immunotherapy is costly and inconvenient to patients, but has the potential for continued efficacy after the treatment is discontinued (Durham, Walker, Varga, et al., 1999; Mosbech and Osterballe, 1988). Given the potential for long-term effectiveness, immunotherapy may be cost-effective compared to continuous treatment with medications for patients with more severe disease. In addition, immunotherapy has the potential to prevent the development of asthma (Ragusa, Passalacqua, Gambardella, et al., 1997).

Pharmacologic Therapy

Symptoms of allergic rhinitis may be treated with any of several different types of medication, including antihistamines, intranasal corticosteroids, decongestants, cromolyn sodium, and ipratropium. Each of these medications has a different mechanism of action and a different pattern of symptom relief. Clinically, these drugs are often used concurrently for improved symptom relief or for relief of multiple symptoms.

Antihistamines are the most commonly used medications for allergic rhinitis and are usually administered on an intermittent basis for patients with mild or seasonal symptoms. Oral antihistamines act in part by competitively inhibiting the binding of histamine to H1 receptors. Second generation oral antihistamines such as cetirizine, fexofenadine, loratadine, and desloratadine are more pharmacologically selective and less sedating than earlier antihistamines. A unique topical antihistamine, azelastine, is non-selective, but may be associated with less sedation and fewer other systemic adverse effects than oral non-selective antihistamines. Sedating and non-sedating antihistamines appear roughly equivalent for controlling symptoms of seasonal and perennial allergic rhinitis (Long, McFadden, DeVine, et al., 2002).

Intranasal corticosteroids are anti-inflammatory medications that require days to weeks for maximal symptom relief. Nasal steroids inhibit multiple steps in the inflammatory cascade of allergic rhinitis and provide excellent relief for numerous symptoms, including itching, sneezing, rhinorrhea, and nasal congestion. Multiple preparations are available: beclomethasone dipropionate (Beconase® and Vancenase®), budesonide (Rhinocort®), flunisolide (Nasarel® and Nasalide®), fluticasone propionate (Flonase®), mometasone (Nasonex®), and triamcinolone acetonide (Nasacort®). In head-to-head comparisons, nasal corticosteroids relieve allergic rhinitis symptoms more effectively than sedating or non-sedating antihistamines (Long, McFadden, DeVine, et al., 2002).

Nasal decongestants reduce nasal congestion through vasoconstriction. They are available in topical (phenylephrine, oxymetazoline) and oral (phenylephrine, pseudoephedrine) formulations. Oral agents are less likely to cause rebound vasodilation, accompanied by increased nasal congestion, than topical decongestants. Two studies have shown some benefit for nasal congestion but not for the other symptoms of allergic rhinitis (Long, McFadden, DeVine, et al., 2002).

Cromolyn sodium is postulated to prevent mast cell degranulation and is thus best used prophylactically. It requires four-times-per-day dosing and may require up to 2 weeks of continuous use for maximal benefit. In 32 randomized trials of cromolyn, all but two showed significant improvements in symptoms of allergic rhinitis. Cromolyn appeared to have higher efficacy for seasonal than perennial rhinitis. Dosing studies showed greater effect at higher doses (Long, McFadden, DeVine, et al., 2002). The anticholinergic ipratropium (Atrovent® nasal) decreases rhinorrhea for non-allergic rhinitis and has the potential for similar benefits in allergic rhinitis (Long, McFadden, DeVine, et al., 2002).

Although drug treatments for allergic rhinitis are often used clinically in regimens that combine more than one drug from different classes, most clinical trials have focused on proving individual drugs superior to placebo (Long, McFadden, DeVine, et al., 2002). Combined drug treatments, compared with single-agent treatments, may work synergistically to provide greater efficacy, may complement one another to relieve a broader array of symptoms, and may allow lower dosing and, hence, reduce adverse effects.

Costs and Work Performance

The American Academy of Allergy, Asthma & Immunology estimates that approximately 19 million employed adults are affected by allergic rhinitis, resulting in several million lost work days each year and annual direct healthcare costs of $4.5 billion (American Academy of Allergy, Asthma & Immunology, 2000). An evaluation of the evidence on costs and on work performance and symptoms requires the review of several types of literature. Determining the overall economic impact of allergic rhinitis requires a review of burden-of-illness studies. The effects of allergic rhinitis on work performance can be measured by studying employees' subjective estimates of their work performance and/or through the use of objective measurements of employee productivity. The impact of specific treatments can also be assessed by cost-effectiveness analysis, which estimates the costs associated with observed improvements in symptoms or quality of life, and by cost-benefit analysis, which considers the benefit of treatment in monetary terms, such as improvements in work productivity, balanced against the cost of treatment. There are few studies that directly associate allergic rhinitis symptoms and work performance, but studies of the treatment effects of various pharmacologic therapies, such as comparisons of sedating and non-sedating antihistamines, may be informative.

Treatment Outcomes by Clinician Specialty

The research question for this topic focuses on two issues: (a) whether different types of clinicians treat allergic rhinitis patients differently; and (b) whether treatment outcomes vary by type of clinician. Primary care clinicians are likely to be the first medical contact for someone with allergic rhinitis, and they have been shown to effectively treat a significant proportion of allergic rhinitis sufferers. On the other hand, allergy specialists and otolaryngologists tend to treat patients with more severe cases of allergic rhinitis (often referred by a primary care clinician), have more precise diagnostic tools available (e.g., nasal endoscopy), and are skilled in administering more specific and complex treatments (e.g., immunotherapy). Also at issue is whether there are variations in treatment and patient outcomes between specialists, i.e., between medically trained allergists and surgically trained otolaryngologists.

Prevalence and Patient Outcomes by Race and Ethnicity

There are some indications that susceptibility to allergic diseases may vary for reasons such as genetic predisposition and exposure to environmental factors. Prevalence of allergic rhinitis has been shown to vary by race, with whites having an overall higher prevalence rate than blacks. In the under-45 age group, the rates are 92.0/1,000 persons versus 66.2/1,000. The difference holds in the 45 to 64 age group, 110.0/1000 persons versus 64.6/1000 (Table 1). There have been few empirical research studies on variations in types of treatment or treatment outcomes by patient race or ethnicity.

Target Populations

We focused on patients with either seasonal or perennial allergic rhinitis. Given our focus on working populations, we prioritized studies in adults. Due to sparse data, we broadened the target population to include school-age children for questions with little relevant data in adults. Our rationale was that the clinical syndrome and underlying biology are similar in children and adults, and that effects on school performance may serve as a rough proxy for work productivity.

Subclinical or clinical asthma frequently co-exists with allergic rhinitis, and patients with co-occurring asthma were included in our review. Because data were extremely limited on the effects of environmental measures in adults with allergic rhinitis, we expanded our scope to patients with asthma. This decision is supported by the "unified airway" theory, according to which treatments for allergic rhinitis may affect asthma and, conversely, treatments for asthma may affect allergic rhinitis (Bousquet, van Cauwenberge, Khaltaev, et al., 2001).

We did not specifically target patients with occupational rhinitis. By definition a work-related illness, occupational rhinitis has allergic and non-allergic mediators, but its prevalence is far lower than non-occupational allergic rhinitis.

Target Practice Settings

Because of the broad scope of this report, multiple practice settings were relevant. We were interested in primary care and specialty settings, where pharmacological and immunotherapy treatments are often initiated. Environmental control measures are usually prescribed in medical settings, but are typically carried out in the home. In addition, interventions aimed at increasing worker productivity may be designed for, or delivered in, the work setting.

Target Audience

Our principal audience is groups developing guidelines or educational documents on allergic rhinitis for healthcare professionals. In addition, we expect healthcare professionals who provide care to patients with allergic rhinitis will have a particular interest in the report. These include family physicians, internal medicine physicians, allergy specialists, otolaryngologists, occupational medicine physicians, nurse practitioners, and physician assistants. Secondary target audiences include employers, policymakers involved in payment decisions, agencies involved in funding research, media involved in dissemination and education about health issues, and patients interested in state-of-the-art medical literature.

Limitations of the Report

This report reviews published evidence relevant to the five key research questions listed above. It does not cover topics addressed in the evidence report on "Management of Allergic and Nonallergic Rhinitis" recently completed by the Evidence-based Practice Center at the New England Medical Center (Long, McFadden, DeVine, et al., 2002). The latter report includes comprehensive assessments of the literature on diagnosis of allergic and non-allergic rhinitis, efficacy of single-agent treatments for both conditions, and co-morbidity with asthma and acute rhinosinusitis.

Occupational rhinitis is much less common than non-occupational rhinitis, and includes both allergic and non-allergic causes. Because of its relatively high prevalence, non-occupational allergic rhinitis creates a greater burden in the workplace in terms of work performance and healthcare costs than does occupational rhinitis. Although occupational allergic rhinitis falls within the scope of this report, few data on this condition focus on the key questions addressed here, and thus nearly all the data reviewed concern allergic rhinitis associated with the most common allergens rather than workplace-specific exposures.

Finally, several agents are currently being evaluated in clinical trials, but are not yet in common use, and are thus not reviewed in this report. These agents include leukotriene inhibitors, anti-immunoglobulin E (anti-IgE) therapy, and cytokine antagonists.

Table 1. 1996 US prevalence rates and numbers for hay fever/allergic rhinitis without asthma by age, sex, race, and family income

Prevalence rates	Age 18-44 (unless otherwise noted)	Age 45-64	Total population
Per 1,000 persons	109.4	104.8	89.8
By sex	Male, under 45: 86.3 Female, under 45: 92.1	Male: 85.6 Female: 122.8	Not available (NA)
By race	White, under 45: 92.0 Black, under 45: 66.2	White: 111.0 Black: 64.6	NA
By family income	< $10,000, under 45: 82.7 $10,000-19,999, under 45: 69.1 $20,000-34,999, under 45: 75.1 $35,000 or more, under 45: 108.9	< $10,000: 106.9 $10,000-19,999: 111.8 $20,000-34,999: 105.0 $35,000 or more: 109.2	NA

Prevalence numbers, in thousands	Age 18-44 (unless otherwise noted)	Age 45-64	Total population
Number	11,809	5,572	23,721
By sex	Male, under 45: 7,751 Female, under 45: 8,248	Male: 2,198 Female: 3,374	NA
By race	White, under 45: 13,404 Black, under 45: 1,665	White: 5,077 Black: 350	NA
By family income	< $10,000, under 45: 1,128 $10,000-19,999, under 45: 1,673 $20,000-34,999, under 45: 2,797 $35,000 or more, under 45: 8,406	< $10,000: 290 $10,000-19,999: 621 $20,000-34,999: 983 $35,000 or more: 2,866	NA

Source: Centers for Disease Control and Prevention, National Center for Health Statistics. Current estimates from the National Health Interview Survey, 1996. Vital and Health Statistics, Series 10, No. 200. DHHS Publication No. (PHS) 99-1528. Hyattsville, MD: US Department of Health and Human Services. October 1999.

Table 2. 1996 US prevalence rates and numbers for hay fever/allergic rhinitis without asthma, by geographic location and place of residence

Geographic location	Prevalence rates per 1,000 persons	Prevalence numbers, in thousands
US	89.8	23,721
Northeast	78.3	4,220
Midwest	85.5	5,424
South	94.9	8,593
West	97.3	5,484

Place of residence	Prevalence rates per 1,000 persons	Prevalence numbers, in thousands
All Metropolitan Statistical Areas (MSA)	90.6	18,887
Central city	86.3	6,742
Not central city	93.3	12,145
Not MSA	86.5	4,834

Source: Centers for Disease Control and Prevention, National Center for Health Statistics. Current estimates from the National Health Interview Survey, 1996. Vital and Health Statistics, Series 10, No. 200. DHHS Publication No. (PHS) 99-1528. Hyattsville, MD: US Department of Health and Human Services. October 1999.

Chapter 2. Methodology

The basis of this evidence report is a comprehensive, systematic review of the literature. This chapter describes the basic methodology for conducting the literature review, from the refinement of the key research questions through the literature search, screening, and data abstraction process. Included are descriptions of the literature search strategies and results, literature sources, screening and grading criteria, and quality control procedures.

Topic Assessment and Refinement

The American Association of Health Plans (AAHP) proposed the original topic for this report, "Seasonal Allergies, Effect on Working Populations." An eight-member national advisory panel of technical experts, which included a representative of AAHP, was convened to work with the Duke research team to refine the key research questions and to review literature search strategies, inclusion and exclusion criteria, the causal pathway or evidence model, quality scoring criteria, interventions to be assessed, and specific outcomes to be reported in the evidence tables. The panel also assisted in identifying key research issues, advised on the scope of the project and methods, nominated peer reviewers, and reviewed preliminary drafts of research findings. Specialties represented on the panel included allergy and immunology, family medicine, general internal medicine, occupational medicine, otolaryngology, and pharmacology. Two meetings of the full panel were conducted via conference calls.

During its first conference call, the panel was presented with the five key research questions specified in the task order:

1) What is the appropriate treatment protocol for diagnosing and managing seasonal allergic rhinitis in a timely and cost-effective manner?

2) What measures can healthcare providers take to help prevent complications or reduce the severity of complications associated with chronic allergic rhinitis?

3) What is the role of new therapies such as anti-immunoglobulin E (anti-IgE) therapy and cytokine antagonists?

4) Can early interventions by allergy specialists reduce the rate of complications associated with chronic allergic rhinitis and lower costs?

5) Do treatment outcomes vary according to a patient's race or ethnicity?

Based on Duke's preliminary assessment of the literature and individual and group discussion with the advisory panel and the task order officer at the Agency for Healthcare Research and Quality (AHRQ), all parties agreed to refine the questions as follows:

1) How do currently clinically available treatments for allergic rhinitis affect costs and work performance?

2) What is the relationship between symptom outcomes or disease-specific quality-of-life measures and work performance among adults with allergic rhinitis? Can data on symptomatic outcome or quality of life be reliably translated into work performance measures?

3) How effective are (a) environmental measures, (b) immunotherapy, and (c) combined treatments, such as with antihistamines and nasal steroids or antihistamines and oral decongestants, for relief of symptoms in adults with allergic rhinitis?

4) How do different types of healthcare providers (generalists, allergy specialists, and otolaryngologists) treat adults with allergic rhinitis, and how do treatment outcomes vary by provider?

5) In adult patients with symptoms of allergic rhinitis, does the prevalence, treatment patterns or response to treatment vary according to a patient's race or ethnicity?

Given the changes in the research questions, after the second conference call and with the panel's agreement, we requested that the title of the task order be changed to "Management of Allergic Rhinitis in the Working-Age Population" to more accurately reflect the contents of the evidence report. This request was approved by AHRQ.

Causal Pathway

Figure 1 represents the causal pathway underlying our analysis of the key research questions related to specific therapies. It illustrates the effects of specific treatments on cellular mechanisms, on symptoms, and ultimately on health status, costs, and work performance. This report focuses on the effects of treatments or combinations of treatments on symptoms, health status, costs, and work performance (outcomes represented on the right side of Figure 1). We do not describe evidence regarding the mechanisms by which the various treatments exert their clinical effects (outcomes represented on the left side of Figure 1).

Literature Search and Review

The comprehensive review of the literature, from identification of databases through abstraction of individual articles into evidence tables, was a multi-step, sequential process.

Literature Sources

The primary sources of literature are six of the most widely used computerized bibliographic databases: MEDLINE (1966-January 2002), CINAHL (1983-January 2002), the Cochrane Database of Systematic Reviews (CDSR) (Issue 4, 2001), the Database of Abstracts of Reviews of Effectiveness (DARE), International Pharmaceutical Abstracts, EconLit (1969-August 2002), and EMBASE (1980-February 2002). Searches of these databases were supplemented by searching the reference lists of review articles and meta-analyses, and by scanning current issues of journals not yet indexed in the computerized bibliographic databases. Specialty journals regularly scanned included Allergy; Annals of Allergy, Asthma & Immunology; Clinical & Experimental Allergy; and

the Journal of Allergy & Clinical Immunology. General interest journals regularly scanned included Annals of Internal Medicine, BMJ, JAMA, Lancet, and the New England Journal of Medicine.

Search Strategy

We developed the basic search strategy using the National Library of Medicine's MeSH key word nomenclature developed for MEDLINE. The same strategy was used to search the other databases listed above. A Duke University Medical Center librarian checked the strategies and assisted with their translation to the key word structure used by EMBASE.

The initial searches, conducted in October 2001, were performed in MEDLINE, updated in MEDLINE in January 2002, and duplicated in additional databases in January 2002. All years of each database were searched – the periods covered by the searches are given above. The searches were limited to the English language and to human subjects. For topics concerning treatment efficacy, search terms focused on identifying randomized controlled trials, except in the case of the environmental measures topic, where the search strategy used additional, less restrictive, search terms, including "controlled trials" and "clinical trials." Suggestions regarding search terms and specific articles were solicited from the advisory panel and resulted in additions to the literature database.

The basic search strategies used are reproduced in Tables 3 to 6.

Screening Criteria

Inclusion and exclusion criteria were developed for the literature searches so that the yield of articles would be appropriately focused. Citations were *excluded* based on the following criteria:

- Article was not original research;
- Article did not address allergic rhinitis or was not applicable to the key research questions;
- The study design was a single case report;
- The study design was a small case series with 20 or fewer subjects.

Empirical studies were *included* based on the following criteria:

- The study population must address allergic rhinitis;
- All original research or relevant reviews must relate to at least one of the five key research questions;
- Included study designs varied depending on the key research question being addressed (Table 7). Randomized controlled trials (RCTs) were included for all questions. For question 3a (environmental measures), we also included non-randomized prospective cohort comparisons. For questions 3b (immunotherapy) and 3c (combined treatments), we included RCTs and pseudo-randomized placebo-controlled trials. We defined "pseudo-randomized" to mean using some unbiased but non-random method of allocation, such as enrollment order, identification

number, or date of birth. For question 1 (costs and work performance), question 2 (relationship between symptom outcomes or disease-specific quality of life and work performance), question 4 (clinician specialty differences), and question 5 (racial and ethnic variation), we included RCTs, large case series (> 20 subjects), cohort studies, non-randomized comparison studies, and articles reporting data from surveys and secondary data analyses.

The final version of the abstract and full-text screening criteria is shown in Table 8.

Screening Results

The literature search yielded 1,593 articles. The titles and abstracts of these articles were reviewed against the inclusion/exclusion criteria by the investigators. Two investigators reviewed each abstract. When no abstract was available, the title, source, and keywords were screened. At this stage, articles were included if requested by one investigator. The full text of each article passing the title-and-abstract screen was retrieved from the library for further review.

At the full-text screening stage, each article was independently reviewed by two investigators, who forwarded their decisions to the task order manager for recording and comparison. If indicated, reviewers were asked to reconcile differences of opinion and return a reconciled final decision to the task order manager. Overall, the teams reconciled about 40 percent of their decisions. If team members had difficulty reaching agreement on decisions, or submitted indecisive codes, the principal investigator was the arbiter. This situation arose in about 10 percent of the reconciled decisions, largely when "include" or "exclude" decisions were at variance with the study design (e.g., an RCT coded as "exclude").

The records in the literature database were coded at each screening stage. A summary of the results of the title-and-abstract and full-text screenings is provided in Table 9. A more detailed accounting of the screening process is provided in Table 10.

Data Abstraction

Not all of the "included" articles mentioned above were abstracted into evidence tables. Some of these studies were included as background and supporting evidence and may be cited in the text, but were not abstracted into evidence tables (see bottom of Table 8 for categories of articles summarized in evidence tables).

We determined that the data from the included articles could be abstracted directly into an evidence table template, which served as a data abstraction "form." To facilitate the development of the evidence tables and to use everyone's particular skills and time to their best advantage, the senior writer/editor began the data abstraction process with a partial abstraction of each article. This partial abstraction included a description of the study design, description of the intervention, number of subjects at the start of the study, and types of outcomes data that were collected (see Table 11 for a sample). The partial evidence table was forwarded to an investigator for completion. It was pre-formatted so that the investigator could easily see which additional data needed to be inserted and where. The completed evidence table was returned to the writer/editor who checked it for completeness and consistency of information and then forwarded the table to another investigator for over-reading. The over-reader returned the table to the writer/editor for final review of the completeness of the content and for editing and formatting.

In the partial abstraction performed by the senior writer/editor, all outcomes reported were listed, and the outcomes meeting our criteria were selected for abstraction. We required patient-assessed symptom outcomes for efficacy questions; we also reported quality of life, functional status, adverse events, and patient global assessments for these questions. For all questions, we recorded work performance and cost outcomes. Specifically, outcomes abstracted for each key research question were as follows:

Question 1:
- Work performance
- Costs (direct medical or non-medical)
- Costs (indirect)

Question 2:
- Association between symptoms and work performance
- Association between quality-of-life and work performance

Question 3:
- Symptoms, assessed by patients
- Quality of life
- Functional status
- Global assessments by patients
- Adverse events

Question 4:
- Practice patterns by provider specialty (referral, drug and other treatment use, case mix)
- Drug and other treatment response by provider specialty

Question 5:
- Allergic rhinitis prevalence by racial/ethnic groups
- Severity of allergic rhinitis by racial/ethnic groups
- Provider consultation by racial/ethnic groups
- Drug and other treatment use by racial/ethnic groups
- Drug and other treatment response by racial/ethnic groups

Grading of Articles (Quality Scoring)

We evaluated each article included in the evidence tables for factors affecting internal and external validity. The quality scoring criteria are given below:

Internal validity:

1) What is the level of evidence (Oxford Centre for Evidence-based Medicine, 2001; see Table 12)?

2) Were the main outcomes of interest measured in a way that has been demonstrated empirically to be valid and reliable (e.g., using a standardized scale such as the

Rhinoconjunctivitis Quality of Life Questionnaire [RQLQ] or the Medical Outcome Study Short-Form Health Survey [SF-36])?

External validity:

3) Was the study population described and reasonably similar to an adult working US population? (Based mostly on age of study population.)

4) Were the intervention protocols referenced or described in sufficient detail to replicate?

5) Was the presence of comorbid asthma (or other upper respiratory conditions) described in the study population?

6) Was the diagnosis of allergic rhinitis based on physician diagnosis?

7) If physician-diagnosed, was the diagnosis supported by objective evidence of allergy (e.g. skin prick or serum IgE antibody testing)?

Additional quality criteria were applied to studies on environmental measures, immunotherapy, and combination therapy:

1) Was the study described as "randomized"?

2) If the method for concealing allocation from the investigators was described, was it adequate (table of random numbers, computer generated, coin toss, etc.) or inadequate (alternating, date of birth, hospital number, etc.)?

3) Was the study described as "double-blind"?

4) If the method of double-blinding was described, was it adequate (e.g., identical placebo, active placebo, injection vs. tablet with double dummy) or inadequate (e.g., tablet vs. injection with no double dummy)?

5) Did the study describe dropouts and withdrawals so that all patients entering the trial could be accounted for?

6) Was the analysis performed according to the intention-to-treat principle? (Did the analysis in some way consider all patients that were allocated to treatment, including dropouts and withdrawals?)

We did not aggregate these items into an overall quality score; rather, we considered and reported them individually. We favored this approach for several reasons:

- Previous work has shown that numeric grading systems may not discriminate well between "high" and "low" quality studies, even for randomized trials (Jüni, Witschi, Bloch, et al., 1999; Moher, Cook, Jadad, et al., 1996).

- Development and use of a new quality score would require additional work for validation, for which there is no time or budget allocation in the task order.

- Identification of specific weaknesses in each study will be helpful in identifying trends, which in turn will assist with our recommendations for future research.

- Describing key design components, rather than assigning a single aggregate score, is also consistent with recent recommendations from an expert panel on meta-analysis of observational studies (Stroup, Berlin, Morton, et al., 2000).

Summaries of each quality evaluation are provided in the far right column of the evidence tables. Grades were assigned by the primary abstractor and confirmed by the over-reader. When required, additional notes were made in the same column of the evidence table.

Quality Control Procedures

We employed quality-monitoring checks at every phase of the literature search, review, and data abstraction process to reduce bias, enhance consistency, and check the accuracy of screening. The quality checks included:

- Medical librarian review of the literature search strategy;

- Review of literature search strategies by advisory panel of technical experts;

- Check on completeness of the literature search results through reference list checks by the screener of each article;

- Reconciliation of all differences of opinion by reviewers on all full-text articles;

- Agreement of two reviewers for all eligible studies;

- Data abstractions completed by one investigator and reviewed (over-read) by another;

- Additional checks of evidence table entries for completeness and accuracy by a non-physician abstractor;

- Solicitation of advice at key decision points from the advisory panel of technical experts;

- Expert peer review of complete draft evidence report.

Figure 1. Causal Pathway

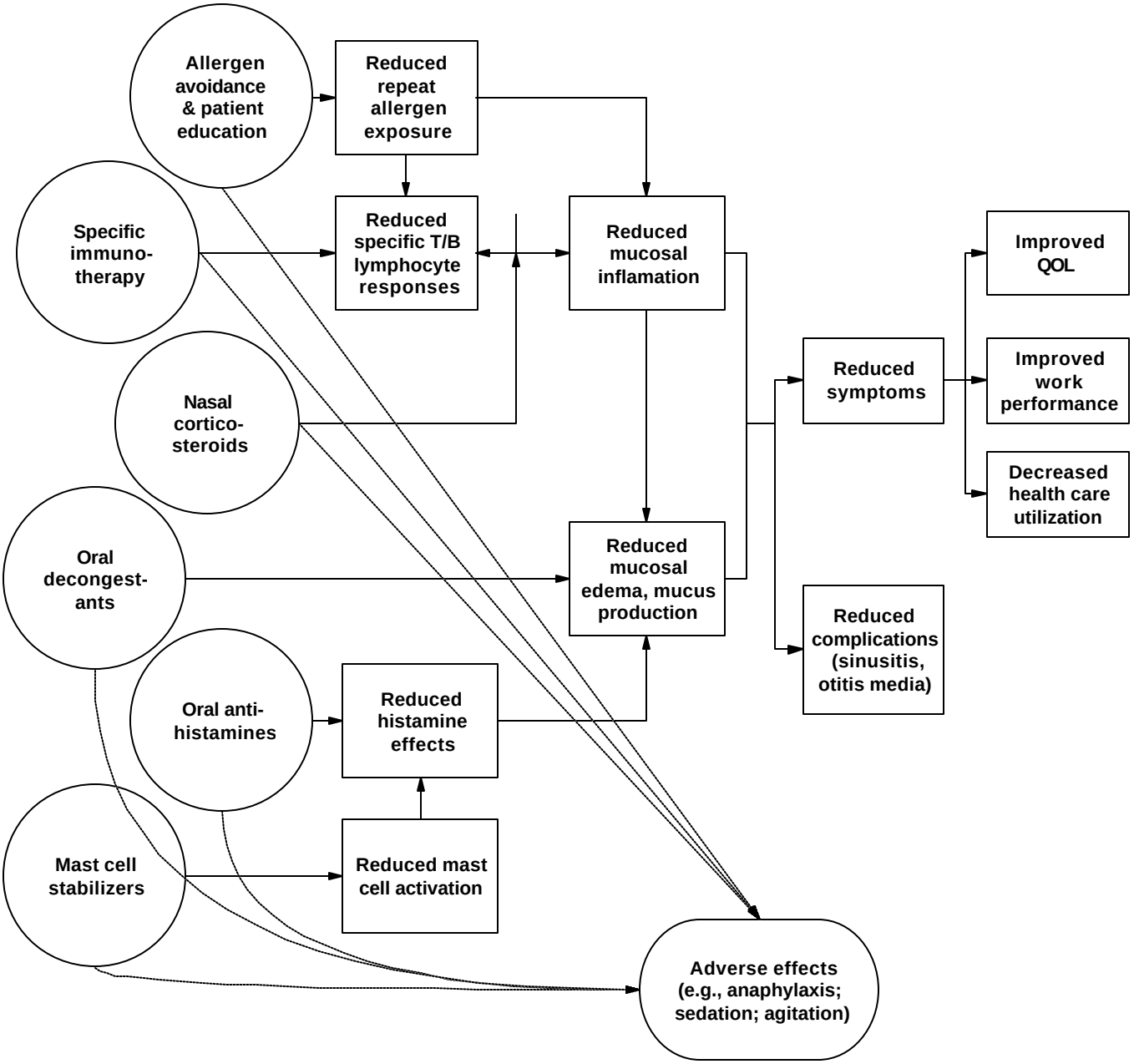

Table 3. Search strategy – preliminary general search, MEDLINE, 1966 through September 2001

Set	Search term	Results
1	exp rhinitis/	12649
2	pollinosis.tw.	842
3	hay fever.tw.	1215
4	rhinitis.tw.	8000
5	or/1-4	15475
6	desensitization, immunologic/	4765
7	immunotherapy.tw.	15633
8	desensitization.tw.	11430
9	or/6-8	29720
10	and/5,9	1679
11	limit 10 to human	1647
12	limit 11 to english language	1128
13	limit 12 to randomized controlled trial	159
14	exp filtration/	21390
15	air conditioning/	1546
16	air pollution, indoor/	2810
17	dust/	11250
18	"bedding and linens"/	2461
19	mites/	5942
20	environmental control.tw.	696
21	mite$.tw.	6141
22	or/14-21	45324
23	5 and 22	1312
24	limit 23 to human	1280
25	limit 24 to english language	930
26	limit 25 to randomized controlled trial	66
27	drug therapy, combination/	65666
28	5 and 27	142
29	limit 28 to human	138
30	limit 29 to english language	104
31	limit 30 to randomized controlled trial	54
32	exp psychology, industrial/	36848
33	exp "costs and cost analysis"/	110582
34	burden of illness.tw	188
35	or/32-34	144427
36	5 and 35	72
37	limit 36 to human	71
38	limit 37 to english language	68
39	leukotriene antagonists/tu	241
40	interleukin-4/tu	141
41	antibodies, anti-idiotypic/	9499
42	or/39-41	9879
43	5 and 42	106
44	limit 43 to human	103
45	limit 44 to english language	92
46	limit 45 to randomized controlled trial	17
47	quality of life/	28524
48	health status/	17994
49	karnofsky performance status/	404
50	activities of daily living/	21523
51	or/47-50	62587
52	5 and 51	117
53	limit 52 to human	117
54	limit 53 to english language	107
55	limit 54 to abstracts	94
56	exp anti-inflammatory agents, steroidal/tu	45608
57	5 and 56	619

(continued on next page)

Set	Search term	Results
58	limit 57 to human	614
59	limit 58 to english language	505
60	limit 59 to randomized controlled trial	190
61	cetirizine/tu	194
62	fexofenadine/tu	0
63	loratadine/tu	145
64	terfenadine/tu	168
65	or/61-64	441
66	exp histamine h1 antagonists/tu	7227
67	66 not 65	6786
68	5 and 65	225
69	limit 68 to human	223
70	limit 69 to english language	198
71	limit 70 to randomized controlled trial	127
72	limit 67 to human	6094
73	limit 72 to english language	4250
74	limit 73 to randomized controlled trial	787
75	71 or 74	914

Table 4. Search strategy – clinician specialty differences, MEDLINE, 1966 to October Week 3 2001

Set	Search term	Results
1	physicians,family/	8358
2	exp physician's practice patterns/	11285
3	family practice/	38292
4	internal medicine/	9345
5	"referral and consultation"/	29576
6	specialties, medical/	11701
7	specialties, surgical/	935
8	surgery/	17749
9	exp attitude of health personnel/	55556
10	exp "outcome and process assessment (health	151936
11	"allergy and immunology"/	2635
12	or/1-11	310954
13	exp rhinitis/	12676
14	pollinosis.tw.	843
15	hay fever.tw.	1217
16	rhinitis.tw.	8034
17	or/13-16	15518
18	and/12,17	450
19	from 18 keep 28,43-44,50,52,63,66,108,110,1	18
20	limit 18 to yr=1966-1998	289
21	limit 20 to yr=1966-1997	217
22	from 21 keep 30,33,40,43,88,99,107,156,205,	10

Table 5. Search strategy – environmental measures (1), MEDLINE, 1966 to October Week 1 2001

Set	Search term	Results
1	exp rhinitis/	12654
2	air pollutants, Environmental/ip	49
3	Allergens/ip	972
4	MITES/	5946
5	1 or 2 or 3 or 4	18967
6	Rhinitis/pc	64
7	air pollution/pc	2146
8	respiratory hypersensitivity/pc	206
9	dust/pc	288
10	Micropore Filters/	1779
11	FILTRATION/	11554
12	INSECTICIDES/	7545
13	Insect Control/	3225
14	air-cleaning.tw.	48
15	(air adj filter).tw.	96
16	(air adj cleaner$).tw.	48
17	acaricide.tw.	343
18	acardust.tw.	3
19	hepa.tw.	582
20	(allergen adj avoidance).mp. [mp=title, abstract, registry number word, mesh subject heading]	216
21	(allergen adj control).mp. [mp=title, abstract, registry number word, mesh subject heading]	27
22	(environmental adj control$).mp. [mp=title, abstract, registry number word, mesh subject heading]	811
23	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22	27516
24	5 and 23	543
25	randomized-controlled-trial (pt)	151353
26	meta-analysis (pt)	5987
27	controlled-clinical-trial (pt)	58987
28	clinical-trial (pt)	319348
29	random$.ti,ab,sh.	254436
30	(meta-anal$ or metaanaly$ or meta analy$).ti,ab,sh.	9346
31	((doubl$ or singl$) and blind$).ti,ab,sh.	67067
32	exp Clinical trials/	127044
33	crossover.ti,ab,sh.	18070
34	25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33	501236
35	24 and 34	89

Table 6. Search strategy – environmental measures (2), MEDLINE, 1966 to October Week 1 2001

Set	Search term	Results
1	exp rhinitis/	12654
2	air pollutants, Environmental/ip	49
3	Allergens/ip	972
4	MITES/	5946
5	1 or 2 or 3 or 4	18967
6	Rhinitis/pc	64
7	air pollution/pc	2146
8	respiratory hypersensitivity/pc	206
9	dust/pc	288
10	Micropore Filters/	1779
11	FILTRATION/	11554
12	INSECTICIDES/	7545
13	Insect Control/	3225
14	air-cleaning.tw.	48
15	(air adj filter).tw.	96
16	(air adj cleaner$).tw.	48
17	acaricide.tw.	343
18	acardust.tw.	3
19	hepa.tw.	582
20	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19	26537
21	Randomized Controlled Trials/	20303
22	5 and 20	421
23	21 and 22	1
24	pollinosis.tw.	842
25	hay fever.tw.	1216
26	rhinitis.tw.	8011
27	mite$.tw.	6147
28	5 or 24 or 25 or 26 or 27	23563
29	exp filtration/	21404
30	air conditioning/	1548
31	air pollution, indoor/	2815
32	dust/	11255
33	“bedding and linens”/	2463
34	20 or 29 or 30 or 31 or 32 or 33	51223
35	randomized-controlled-trial (pt)	151353
36	meta-analysis (pt)	5987
37	controlled-clinical-trial (pt)	58987
38	clinical-trial (pt)	319348
39	random$.ti,ab,sh.	254436
40	(meta-anal$ or metaanaly$ or meta analy$).ti,ab,sh.	9346
41	((doubl$ or singl$) and blind$).ti,ab,sh.	67067
42	exp Clinical trials/	127044
43	crossover.ti,ab,sh.	18070
44	35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43	501236
45	28 and 34	2799
46	44 and 45	291
47	limit 46 to (human and english language)	224

Table 7. Included study designs, by key research question

Question	Topic	Included study designs
1 2	Costs and work performance Relationship between symptom outcomes or disease-specific quality of life and work performance	Any empirical study involving more than 20 patients with allergic rhinitis. Includes randomized controlled trials (RCTs), case series, cohort studies, non-randomized comparison studies, surveys, and secondary data analyses.
3a	Environmental measures	RCTs, non-randomized prospective cohort comparisons
3b 3c	Immunotherapy Combination drug therapy	RCTs, pseudo-randomized placebo-controlled trials
4 5	Clinician specialty differences Racial and ethnic variation	Any empirical study involving more than 20 patients with allergic rhinitis. Includes RCTs, case series, cohort studies, non-randomized comparison studies, surveys, and secondary data analyses.

Table 8. Abstract and full-text screening criteria

Key research questions:

1. How do currently clinically available treatments for allergic rhinitis affect costs and work performance?
2. What is the relationship between symptom outcomes or disease-specific quality-of-life measures and work performance among adults with allergic rhinitis? Can data on symptomatic outcome or quality of life be reliably translated into work performance measures?
3. How effective are (a) environmental measures, (b) immunotherapy, and (c) combined treatments, such as with antihistamines and nasal steroids or antihistamines and oral decongestants, for relief of symptoms in adults with allergic rhinitis?
4. How do different types of healthcare providers (generalists, allergy specialists, and otolaryngologists) treat adults with allergic rhinitis, and how do treatment outcomes vary by provider?
5. In adult patients with symptoms of allergic rhinitis, does the prevalence, treatment patterns or response to treatment vary according to a patient's race or ethnicity?

Inclusion/exclusion criteria:

1	Not original research or relevant review
2	Not allergic rhinitis or allergic rhinitis not applicable to research questions
3	Case report
4	Small case series (≤ 20 patients, no controls)
5	Large case series (> 20 patients, no controls)
6	Non-randomized assignment to treatment (comparison group, but not randomly assigned)
7	Randomized controlled trial
8	Relevant review
9	Original research on other aspects (for use as background or in model, e.g., prevalence, natural history, diagnostic testing)
10	Basic science
11	Survey and secondary data

Inclusion rules:

Question 1:	codes 5-9,11:	Evidence tables for codes 5, 6 7, 11
Question 2:	codes 5-9,11:	Evidence tables for codes 5, 6, 7, 11
Question 3a:	codes 6-9,11:	Evidence tables for codes 6, 7
Question 3b:	codes 7-9,11:	Evidence tables for code 7
Question 3c:	codes 7-9,11:	Evidence tables for code 7
Question 4:	codes 5-9,11:	Evidence tables for codes 5, 6, 7, 11
Question 5:	codes 5-9,11:	Evidence tables for codes 5 ,6, 7,11

Table 9. Summary of results of abstract and full-text screening

Articles identified	1593
Abstracts:	
Included	546
Excluded	1089
Full-text articles:	
Included	258
Excluded	288

Table 10: Full-text screening results, by key research question and by inclusion/exclusion criteria

INCLUDED ARTICLES (ET = included in evidence tables)	
Question 1 (Note: one article screened for this question reported results of both an RCT and a large case series)	**54**
5-large case series (> 20 patients, no controls): ET	14
6-non-randomized controlled trials: ET	0
7-randomized controlled trial: ET	7
8-relevant review	11
9-original research on other aspects for use in background or model	13
11-survey or secondary data: ET	11
Question 2 (screened with Question 1 articles)	**6**
5-large case series (> 20 patients, no controls): ET	0
6-non-randomized controlled trials: ET	0
7-randomized controlled trial: ET	3
8-relevant review	2
9-original research on other aspects for use in background or model	0
11-survey or secondary data: ET	1
Question 3a (environmental measures)	**40**
6-non-randomized controlled trials: ET	1
7-randomized controlled trial: ET	26
8-relevant review	9
9-original research on other aspects for use in background or model	0
11-survey or secondary data	4
Question 3b (immunotherapy)	**80**
7-randomized controlled trial: ET	62
8-relevant review	11
9-original research on other aspects for use in background or model	4
11-survey or secondary data	3
Question 3c (combination treatments)	**32**
7-randomized controlled trial: ET	31
8-relevant review	0
9-original research on other aspects for use in background or model	1
Question 4	**26**
5-large case series (> 20 patients, no controls): ET	4
6-non-randomized controlled trials: ET	0
7-randomized controlled trial: ET	0
8-relevant review	12
9-original research on other aspects for use in background or model	6
11-survey or secondary data: ET	1
Question 5	**8**
5-large case series (> 20 patients, no controls)	1
6-non-randomized controlled trials	0
7-randomized controlled trial	0
8-relevant review	3
9-original research on other aspects for use in background or model	0
11-survey or secondary data	4

(continued on next page)

EXCLUDED ARTICLES

Question 1	**82**
1-not original research or relevant review	24
2-not allergic rhinitis or not applicable to study questions	48
3-case report	0
4-small case series (≤ 20 patients, no controls)	1
10-basic science	0
Excluded during data abstraction (e.g., no relevant data reported)	9
Question 2 (screened with Question 1 articles)	**15**
1-not original research or relevant review	6
2-not allergic rhinitis or not applicable to study questions	5
3-case report	0
4-small case series (≤ 20 patients, no controls)	0
5-large case series (> 20 patients, no controls)	0
10-basic science	1
Excluded during data abstraction (no relevant data)	3
Question 3a (environmental measures)	**41**
1-not original research or relevant review	10
2-not allergic rhinitis or not applicable to study questions	10
3-case report	0
4-small case series (≤ 20 patients, no controls)	0
5-large case series (> 20 patients, no controls)	3
6-non-randomized controlled trials	0
10-basic science	11
Excluded during data abstraction (e.g., no relevant data, insufficient data, no symptom outcomes or other relevant outcomes, only atopic dermatitis)	7
Question 3b (immunotherapy):	**87**
1-not original research or relevant review	5
2-not allergic rhinitis or not applicable to study questions	71
3-case report	0
4-small case series (≤ 20 patients, no controls)	0
5-large case series (> 20 patients, no controls)	1
6-non-randomized controlled trials	4
10-basic science	2
Excluded during data abstraction (e.g., no separate results for allergic rhinitis, asthma data only, no symptom outcomes)	4
Question 3c (combination treatments)	**25**
1-not original research or relevant review	5
2-not allergic rhinitis or not applicable to study questions	14
3-case report	0
4-small case series (≤ 20 patients, no controls)	0
10-basic science	0
Excluded during data abstraction (no relevant data)	6
Question 4	**30**
1-not original research or relevant review	6
2-not allergic rhinitis or not applicable to study questions	9
3-case report	0
4-small case series (≤ 20 patients, no controls)	1

(continued on next page)

10-basic science	1
Excluded during data abstraction (e.g., no relevant allergic rhinitis data; no data on provider differences)	13
Question 5	**21**
1-not original research	2
2-not allergic rhinitis or not applicable to study questions	18
3-case report	0
4-small case series (≤ 20 patients, no controls)	0
10-basic science	0
Excluded during data abstraction (e.g., no relevant data)	1

Table 11. Partial data abstraction – sample

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score/Notes
Andri, Senna, Betteli, et al., 1992 **#210**	Design: RCT, parallel-group, method of randomization not described Interventions: 1) Terfenadine 60 mg bid + nimesulide 100 mg bid (n = 15) 2) Terfenadine 60 mg bid + placebo (n = 15) Duration of study treatment: 30 days No other drugs "likely to affect hay fever" permitted No pre-trial washout period described Dates: **Location:** **Setting:** **Type(s) of providers:**	No. of subjects at start: 30 Dropouts/withdrawals: No. of subjects at end: Inclusion criteria: Exclusion criteria: Age: Sex: Race: [IF RESULTS ARE BROKEN DOWN BY RACE/ETHNICITY, PLEASE MAKE THIS CLEAR IN "RESULTS" COLUMN] Other:	1) Investigator-assessed symptom severity 2) Patient-assessed symptom severity: nasal itching, nasal obstruction, sneezing, running nose, eye irritation, and eye watering graded daily by patients scale of 0 (none) to 3 (severe) 3) Patient global assessment of efficacy: recorded once at end of trial – categorical scale keyed to perceived degree of improvement in symptoms (< 50%, 50-80%, > 80%) 4) Adverse events: Not clear how reported/ recorded	1) Investigator-assessed symptom severity: DO NOT ABSTRACT 2) Patient-assessed symptom severity: 3) Patient global assessment of efficacy: 4) Adverse events:	[IF ARTICLE SHOULD BE EXCLUDED, PLEASE EXPLAIN WHY HERE] Quality Scoring: Notes: Local pollen counts conducted daily during trial.

Table 12. Oxford Centre for Evidence-based Medicine levels of evidence (May 2001)[1]

Level	Therapy/prevention, aetiology/harm	Prognosis	Diagnosis	Differential diagnosis/symptom prevalence study	Economic and decision analyses
1a	Systematic review (SR) (with homogeneity*) of RCTs	SR (with homogeneity*) of inception cohort studies; CDR† validated in different populations	SR (with homogeneity*) of Level 1 diagnostic studies; CDR† with 1b studies from different clinical centres	SR (with homogeneity*) of prospective cohort studies	SR (with homogeneity*) of Level 1 economic studies
1b	Individual RCT (with narrow Confidence Interval‡)	Individual inception cohort study with ≥ 80% follow-up; CDR† validated in a single population	Validating** cohort study with good††† reference standards; or CDR† tested within one clinical centre	Prospective cohort study with good follow-up****	Analysis based on clinically sensible costs or alternatives; systematic review(s) of the evidence; and including multi-way sensitivity analyses
1c	All or none§	All or none case-series	Absolute SpPins and SnNouts††	All or none case-series	Absolute better-value or worse-value analyses ††††
2a	SR (with homogeneity*) of cohort studies	SR (with homogeneity*) of either retrospective cohort studies or untreated control groups in RCTs	SR (with homogeneity*) of Level >2 diagnostic studies	SR (with homogeneity*) of 2b and better studies	SR (with homogeneity*) of Level >2 economic studies
2b	Individual cohort study (including low quality RCT; e.g., <80% follow-up)	Retrospective cohort study or follow-up of untreated control patients in an RCT; Derivation of CDR† or validated on split-sample§§§ only	Exploratory** cohort study with good†††reference standards; CDR† after derivation, or validated only on split-sample§§§ or databases	Retrospective cohort study, or poor follow-up	Analysis based on clinically sensible costs or alternatives; limited review(s) of the evidence, or single studies; and including multi-way sensitivity analyses
2c	"Outcomes" Research; Ecological studies	"Outcomes" Research		Ecological studies	Audit or outcomes research
3a	SR (with homogeneity*) of case-control studies		SR (with homogeneity*) of 3b and better studies	SR (with homogeneity*) of 3b and better studies	SR (with homogeneity*) of 3b and better studies
3b	Individual Case-Control Study		Non-consecutive study; or without consistently applied reference standards	Non-consecutive cohort study, or very limited population	Analysis based on limited alternatives or costs, poor quality estimates of data, but including sensitivity analyses incorporating clinically sensible variations.
4	Case-series (and poor quality cohort and case-control studies§§)	Case-series (and poor quality prognostic cohort studies***)	Case-control study, poor or non-independent reference standard	Case-series or superseded reference standards	Analysis with no sensitivity analysis
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on economic theory or "first principles"

[1] Produced by Bob Phillips, Chris Ball, Dave Sackett, Doug Badenoch, Sharon Straus, Brian Haynes, Martin Dawes since November 1998. Available at: http://163.1.96.10/docs/levels .html#levels. Accessed May 30, 2002.

(continued on next page)

Users can add a minus-sign "-" to denote the level of that fails to provide a conclusive answer because of:
· EITHER a single result with a wide Confidence Interval (such that, for example, an ARR in an RCT is not statistically significant but whose confidence intervals fail to exclude clinically important benefit or harm)
· OR a Systematic Review with troublesome (and statistically significant) heterogeneity.
· Such evidence is inconclusive, and therefore can only generate Grade D recommendations.

*	By homogeneity we mean a systematic review that is free of worrisome variations (heterogeneity) in the directions and degrees of results between individual studies. Not all systematic reviews with statistically significant heterogeneity need be worrisome, and not all worrisome heterogeneity need be statistically significant. As noted above, studies displaying worrisome heterogeneity should be tagged with a "-" at the end of their designated level.
†	Clinical Decision Rule. (These are algorithms or scoring systems which lead to a prognostic estimation or a diagnostic category.)
‡	See note #2 for advice on how to understand, rate and use trials or other studies with wide confidence intervals.
§	Met when all patients died before the Rx became available, but some now survive on it; or when some patients died before the Rx became available, but none now die on it.
§§	By poor quality cohort study we mean one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both exposed and non-exposed individuals and/or failed to identify or appropriately control known confounders and/or failed to carry out a sufficiently long and complete follow-up of patients. By poor quality case-control study we mean one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both cases and controls and/or failed to identify or appropriately control known confounders.
§§§	Split-sample validation is achieved by collecting all the information in a single tranche, then artificially dividing this into "derivation" and "validation" samples.
††	An "Absolute SpPin" is a diagnostic finding whose Specificity is so high that a Positive result rules-in the diagnosis. An "Absolute SnNout" is a diagnostic finding whose Sensitivity is so high that a Negative result rules-out the diagnosis.
‡‡	Good, better, bad and worse refer to the comparisons between treatments in terms of their clinical risks and benefits.
†††	Good reference standards are independent of the test, and applied blindly or objectively to applied to all patients. Poor reference standards are haphazardly applied, but still independent of the test. Use of a non-independent reference standard (where the 'test' is included in the 'reference', or where the 'testing' affects the 'reference') implies a level 4 study.
††††	Better-value treatments are clearly as good but cheaper, or better at the same or reduced cost. Worse-value treatments are as good and more expensive, or worse and the equally or more expensive.
**	Validating studies test the quality of a specific diagnostic test, based on prior evidence. An exploratory study collects information and trawls the data (e.g. using a regression analysis) to find which factors are 'significant'.
***	By poor quality prognostic cohort study we mean one in which sampling was biased in favour of patients who already had the target outcome, or the measurement of outcomes was accomplished in <80% of study patients, or outcomes were determined in an unblinded, non-objective way, or there was no correction for confounding factors.
****	Good follow-up in a differential diagnosis study is >80%, with adequate time for alternative diagnoses to emerge (eg 1-6 months acute, 1-5 years chronic)

Grades of Recommendation

A	consistent level 1 studies
B	consistent level 2 or 3 studies ***or*** extrapolations from level 1 studies
C	level 4 studies ***or*** extrapolations from level 2 or 3 studies
D	level 5 evidence ***or*** troublingly inconsistent or inconclusive studies of any level

"Extrapolations" are where data is used in a situation which has potentially clinically important differences than the original study situation.
"Extrapolations" are where data is used in a situation which has potentially clinically important differences than the original study situation.

(continued on next page)

References

1. Canadian Task Force on the Periodic Health Examination: The periodic health examination. CMAJ 1979;121:1193-1254.
2. Sackett DL. Rules of evidence and clinical recommendations on use of antithrombotic agents. Chest 1986 Feb; 89 (2 suppl.):2S-3S.
3. Cook DJ, Guyatt GH, Laupacis A, Sackett DL, Goldberg RJ. Clinical recommendations using levels of evidence for antithrombotic agents. Chest 1995 Oct; 108(4 Suppl):227S-230S.
4. Yusuf S, Cairns JA, Camm AJ, Fallen EL, Gersh BJ. Evidence-Based Cardiology. London: BMJ Publishing Group, 1998.

Chapter 3. Results

Costs and Work Performance

Introduction

This section addresses key research questions 1 and 2:

1) How do currently clinically available treatments for allergic rhinitis affect costs and work performance?

2) What is the relationship between symptom outcomes or disease-specific quality-of-life measures and work performance among adults with allergic rhinitis? Can data on symptomatic outcomes or quality of life be reliably translated into work performance measures?

To address the first question, we considered burden-of-illness studies of allergic rhinitis, as well as cost-comparison and cost-effectiveness studies. For the second question, we sought data correlating work performance either with symptoms of allergic rhinitis or with disease-specific quality of life. A strong association would permit the use of symptom or quality-of-life data, which are much more commonly reported than work-performance data, in economic analyses comparing treatment approaches.

After consulting with the project's advisory panel of experts, we elected to include data on school performance in children as a proxy for work performance in adults, because of the limited data on adults.

Thirty-two studies were included in the analysis of these questions (Table 13 and Evidence Table 1). Studies of costs included burden-of-illness studies (per-patient burden-of-illness studies of selected populations and total burden-of-illness studies for the US population) and cost-effectiveness studies (including cost-benefit and cost-minimization studies). Table 13 indicates which studies reported work-performance outcomes, and which of these also reported data on symptoms and/or health-related quality of life.

Results

Costs (Key Research Question 1)

The large majority of published articles regarding the cost of allergic rhinitis can be categorized as burden-of-illness studies, which attempt to estimate the direct and indirect costs of allergic rhinitis. "Direct costs" typically refers to the cost of medical resources consumed by patients, but may include non-medical resources as well. "Indirect costs" refers to costs incurred due to decreased job productivity as a result of the condition. Other studies of the cost of allergic rhinitis have used medical insurance claims or administrative data to compare the medical costs of patients with allergic rhinitis to those of patients without allergic rhinitis, or to compare the medical costs of patients with allergic rhinitis plus a co-morbid condition (such as asthma) to those of patients with allergic rhinitis alone (Cuffel, Wamboldt, Borish, et al., 1999; Santos,

Cifaldi, Gregory, et al., 1999; Yawn, Yunginger, Wollan, et al., 1999). Few well-conducted, generalizable studies have investigated the impact of currently available clinical treatments on direct medical costs and on indirect costs due to lost productivity. Most economic evaluations of treatments for allergic rhinitis do not take into account uncertainty about differences in the efficacy of treatments, and essentially boil down to a comparison between drug acquisition costs (Kozma, Schulz, Sclar, et al., 1996; Stahl, van Rompay, Wang, et al., 2000). True cost-effectiveness evaluations that compare both costs and outcomes associated with different treatment strategies are rarely performed, in part due to a lack of a consensus on the appropriate measure of "effectiveness" to be used in the denominator of a cost-effectiveness ratio (Weiss and Sullivan, 2001). Although several standardized instruments exist that assess allergic rhinitis symptoms or disease-specific quality of life (Corey, Kemker, Branca, et al., 2000; Juniper and Guyatt, 1991), these instruments are not yet widely used and do not measure outcomes in units, such as quality-adjusted life-years, that might be comparable across conditions.

Burden-of-illness studies. Several burden-of-illness studies have been undertaken to estimate the total cost of allergic rhinitis in the US. The results of these studies vary several-fold, and none is likely to be representative of current practice patterns because all use data that antedate the introduction of non-sedating antihistamines and nasal inhaled steroids. Two widely cited studies were published by McMenamin (1994) and Malone and colleagues (Malone, Lawson, Smith, et al., 1997). Using multiple sources of data, McMenamin estimated the direct cost (physician and medication costs) of allergic rhinitis in the US to be $1.16 billion in 1990 dollars. Malone and colleagues, using data from the 1997 National Medical Expenditure Survey (NMES), estimated the direct cost to be $1.15 billion in 1994 dollars. When the estimated indirect cost of allergic rhinitis due to decreased productivity was added in, total costs were estimated by McMenamin to be $1.8 billion ($1990), and by Malone and colleagues to be $1.23 billion ($1994). Using data from a 1993 household survey, Storms and colleagues estimated that the direct cost of allergic rhinitis (not including diagnostic testing or allergy shots) was $3.4 billion (year not specified), not including its impact on productivity (Storms, Meltzer, Nathan, et al., 1997). A more recent estimate of the cost of allergic rhinitis in the US from a non-peer-reviewed report puts the figures at $4.5 billion (year not specified) in direct medical costs and $3.4 billion in indirect costs (Mackowiak, 1997). In addition, several studies have focused on the estimation of indirect costs only, with estimates ranging from $601 million ($1995) to $7.7 billion (year not specified) (Crystal-Peters, Crown, Goetzel, et al., 2000; Kessler, Almeida, Berglund, et al., 2001; Ross, 1996).

Many factors contribute to the variation in cost estimates reported in the literature: the time period represented by the study data, the prevalence estimates and cost estimates used, and methodological variations in the estimation of direct and indirect costs. A major limitation of published burden-of-illness estimates for allergic rhinitis is that they are based on information that predates the increased use of non-sedating antihistamines and nasal corticosteroids, resulting in an underestimation of costs for medication and medical care visits. Prescription claims data from 1999 show that approximately two-thirds of patients with allergic rhinitis received treatment with one or more medications from these two drug classes (Liao, Leahy, and Cummins, 2001). Prescription drug sales data from 1999 show that expenditures exceeded $3 billion dollars for prescription antihistamines alone (Nash, Sullivan, and Mackowiak, 2000). Furthermore, with the widespread adoption of these medications into practice, it appears that greater proportions of patients with allergic rhinitis are seeking medical attention for their condition. Based on the 1987 NMES data, only 12.3 percent of patients sought medical care for

allergic rhinitis during the survey year (Malone, Lawson, Smith, et al., 1997). Data based on a 1993 survey revealed that 63 percent of respondents reported visiting a physician to seek treatment for allergic rhinitis in the previous 12 months (Storms, Meltzer, Nathan, et al., 1997). Therefore, the number of physician visits for allergic rhinitis, and the costs attributable to these visits, are also likely to be underestimated in reports based on older data.

National cost estimates are highly dependent on estimates of the prevalence of allergic rhinitis in the US, which range from approximately 10 to 30 percent of adults and up to 40 percent of children (Joint Task Force on Practice Parameters in Allergy, Asthma and Immunology, 1998). Variations in these estimates can result from the age range of the study population, the definition of allergic rhinitis used (seasonal or perennial), and whether the condition is based on a physician diagnosis or self-report. Among studies using self-reported diagnoses, prevalence estimates vary based on whether patients are queried specifically about having allergic rhinitis or hay fever symptoms, or are asked to report all their medical conditions without condition-specific prompts. Even among studies using medical record or claims data, prevalence estimates vary based on whether allergic rhinitis is identified by primary diagnosis code only or by considering allergic rhinitis as a primary or secondary diagnosis. When the determination is based on allergic rhinitis coded as a primary diagnosis, the burden of illness will be underestimated because physicians may undercode or miscode for allergic rhinitis, especially when patients present with co-morbid conditions. Given the high degree of co-morbidity associated with allergic rhinitis, the inclusion or exclusion of patients with conditions such as asthma or sinusitis can have a large impact on estimates of prevalence and costs. In one study, the costs attributable to allergic rhinoconjunctivitis were estimated by including costs for patients with any of 10 airway diseases who would be expected to have a secondary diagnosis of allergic rhinitis (Ray, Baraniuk, Thamer, et al., 1999). When using this methodology, total costs were estimated to be $5.4 billion ($1987).

Multiple challenges arise when estimating the direct cost for medical care in the US. Distinctions must be made between costs, charges, total costs, and out-of-pocket co-payments by patients. Sources of economic data may provide charges, expenditures, or costs, and it has long been noted that charges are not representative of costs for healthcare provided in the US. Some studies do not explicitly state whether cost or charge data were used. Cost estimates based on data obtained in patient surveys can also be limited because patients may not know the full cost of a medical visit or medication due to insurance cost-sharing and complicated billing processes. For instance, expenditures reported in the patient survey used by Storms and colleagues (Storms, Meltzer, Nathan, et al., 1997) did not account for insurance or other payments and thus may have underestimated the prescription drug costs. This could account for the finding that expenditures for prescription and over-the-counter (OTC) medications were equal at $56 ($1993) per patient.

When costs associated with healthcare utilization data are not available, analysts may turn to other sources to construct cost estimates. For example, McMenamin (1994) used prevalence data from the 1988 National Health Interview Survey and the 1985 National Ambulatory Medical Care Survey, in which cost data were not reported. He combined prevalence data from these sources with cost data from the National Health Accounts database of the Health Care Financing Administration (now Centers for Medicare and Medicaid Services). Another limitation of many burden-of-illness studies is that the cost of OTC medications is not included. Only one of the studies we identified (Storms, Meltzer, Nathan, et al., 1997) collected information on the utilization of and expenditures related to OTC medications for allergic rhinitis. The authors reported that a greater proportion of allergic rhinitis sufferers purchased

OTC medications than prescription medications (69 vs. 45 percent). Thus, excluding expenditures on OTC medications from cost-of-illness studies for allergic rhinitis may have resulted in a substantial underestimation of medication costs.

Estimating the indirect costs attributed to allergic rhinitis has also proven challenging. First, although assigning costs to missed work days is relatively straightforward, assigning costs to missed school days is difficult; children's missed school days may impact their parents' productivity because parents might miss work to care for young children with allergic rhinitis. Second, the amount of time lost from work or school is relatively small, around two to three percent and four to five percent, respectively (Reilly, Tanner, and Meltzer, 1996; Tanner, Reilly, Meltzer, et al., 1999). Third, estimates of reduced productivity while at work or school appear to vary a great deal depending on whether they are based on patient-reported estimates of impairment or on objective estimates of reduced productivity (Burton, Conti, Chen, et al., 2001; Cockburn, Bailit, Berndt, et al., 1999a) (see next section). In practice, multiple assumptions are usually necessary for analysts to estimate indirect costs. Some analysts have combined patient national survey data on work productivity reductions associated with sedating antihistamines with estimates of the total number of allergic rhinitis sufferers, the proportion of patients treated with sedating antihistamines, and daily wage data to estimate productivity costs due to sedating antihistamines (Crystal-Peters, Crown, Goetzel, et al., 2000; McMenamin, 1994; Ross, 1996). Others have used patient-reported information on the number of days of impairment and analyst-chosen assumptions to assign a value to the level of impairment (Kessler, Almeida, Berglund, et al., 2001; Malone, Lawson, Smith, et al., 1997). For instance, Kessler and colleagues designed a diary-based survey specifically to estimate the indirect costs of allergic rhinitis (Kessler, Almeida, Berglund, et al., 2001). However, they had to rely on an arbitrary assumption to value decreased work quality. In addition, an implicit assumption is often made by assigning the same level of reduced productivity to persons in different types of professions and job settings.

In conclusion, an updated burden-of-illness study of allergic rhinitis that incorporates data on contemporary practice patterns, valid cost estimates, information on OTC medication use, and an objective measure of productivity loss would fill a void in the medical literature on the cost of allergic rhinitis in the US. In addition, well-conducted, generalizable, randomized controlled trials that compare the economic impact of various treatment strategies for allergic rhinitis would go a long way toward determining whether the dollars expended for treatment of allergic rhinitis can be offset by gains in productivity, and whether the outcomes afforded by these treatment strategies are acceptable from a cost-effectiveness standpoint.

Cost-effectiveness evaluations. Only a handful of cost-effectiveness studies have been published that compare the relative costs and health benefits of various treatments for allergic rhinitis. Furthermore, the usefulness of these studies to decisionmakers is hampered by methodological shortcomings. An underlying assumption that is critical to the validity of a cost-effectiveness analysis is that there is a difference in the clinical effectiveness of the treatment alternatives under comparison. In the absence of such a difference, it is appropriate to conduct a cost comparison to determine which treatment is more cost-effective (cost-minimization analysis). However, many of the economic evaluations reported in the allergic rhinitis literature have used cost-minimization analysis when two treatments have been not been proven to be clinically equivalent with an adequately designed trial powered to demonstrate equivalence. When there is no statistically significant difference in effectiveness between treatments, but clinically important differences in effectiveness have not been excluded (by an adequately powered study), a cost-effectiveness analysis can still be conducted, provided that cost-

effectiveness ratios are presented with confidence intervals or other methods to demonstrate uncertainty in the results (Briggs and O'Brien, 2001).

A study published in the late 1980s was based on a trial of 19 patients randomized to treatment with terfenadine or a combination of chlorpheniramine and pseudoephedrine (Leickly, Sears-Ewald, and Ownby, 1989). The cost comparison was based on the daily average wholesale price for the prescribed dose of each medication. One limitation of the study noted by the authors was its limited statistical power. Despite this caveat, the authors concluded that because there was no statistically significant difference in the side-effect profiles of the medications, physicians should consider the cost of the medications when making prescribing decisions.

Another study was based on data from a randomized trial that compared two nasal inhaled corticosteroids (budesonide and fluticasone) over 6 weeks of treatment (Stahl, van Rompay, Wang, et al., 2000). Because no differences in clinical outcomes were shown, the cost-effectiveness evaluation was simplified to a cost-minimization analysis. The authors extrapolated 6-week study medication costs to 1 year, estimating that the annual cost of budesonide was $118 less than the annual cost of fluticasone (1998 Canadian dollars: 1 $Canadian = 0.67 $US).

Another economic evaluation of budesonide was undertaken to compare two dosage forms of the drug, an aqueous nasal spray and a dry powder nasal spray (Keith, Haddon, and Birch, 2000). A willingness-to-pay approach was employed to value benefits before and after a 4-week study period. The study showed no differences in willingness to pay between the treatment arms. However, when subtracting treatment costs and productivity costs from the benefits, a statistically significant net benefit was sustained ($5.80 per week, 1993 Canadian dollars; 1 $Canadian = 0.78 $US).

Instead of comparing specific pharmacologic treatments, one comparative economic evaluation compared the impact of practice guidelines on the outcomes of patients with allergic rhinitis (Santos, Cifaldi, Gregory, et al., 1999). However, the study did not report what guidelines were used or how they were implemented into practice at the intervention clinics. Also missing from this study were statistical comparisons between clinical, behavioral, and quality-of-life outcomes.

Kozma and colleagues reported a cost-effectiveness analysis based on data from a randomized trial comparing fluticasone, terfenadine, and placebo (Kozma, Schulz, Sclar, et al., 1996). While the fluticasone group showed greater improvement in total nasal symptom severity scores than the terfenadine group, the results based on patients' global assessments of efficacy were dependent on the definition of improvement. The proportion of patients reporting improvement in the fluticasone group was statistically significantly larger than in the terfenadine group when considering patients who reported "mild," "moderate," or "significant" improvement, or only "significant" improvement. When the criteria used to indicate improvement included only "moderate" or "significant" improvement, there was no significant difference between the two treatment groups. Because the collection of data on resource utilization was not prospectively planned as part of the study design, the only costs available retrospectively were those for study medication, and these were the only costs considered. Incremental cost-effectiveness ratios were not reported because fluticasone was shown to be a dominant treatment strategy – less costly and more effective – based on the definition of effectiveness that included responses of mild, moderate, or significant improvement.

One study from Germany evaluated long-term costs and health outcomes associated with a 3-year immunotherapy regimen compared to pharmacologic treatment (Schädlich and Brecht, 2000). An economic model based on multiple data sources was used to evaluate cumulative costs over 10 years of therapy and to estimate the incremental proportion of patients that would be free from asthma symptoms due to treatment of allergic rhinitis with immunotherapy. In their base-case analysis, cumulative costs with immunotherapy were expected to be higher than with pharmacologic treatment over the first 6 years. Between the 6^{th} and 8^{th} year of therapy, the cumulative cost of pharmacologic therapy was expected to become higher than costs of immunotherapy. At 10 years of treatment, the expected net savings associated with immunotherapy were estimated at between 650 and 1190 Deutsche Marks (1995; 1 DM = 0.58 $US) per patient, depending on the assumptions used in the model. The model also estimated that out of a hypothetical cohort of 1,000 patients receiving each treatment option, 161 additional patients would be free from asthma symptoms in the immunotherapy group. A recent study that reported a lower incidence of asthma in children who received immunotherapy for allergic rhinitis (Möller, Dreborg, Ferdousi, et al., 2002) helped to validate the most critical assumption of the model, namely, the reduction in incidence of asthma for patients treated with immunotherapy. The model cited three different published estimates of cumulative incidence and remission rates of asthma for patients treated with immunotherapy and pharmacologic therapy. Another assumption, however, deserves critical examination. The model assumes that all patients would continue immunotherapy for 3 years, but studies have shown that only about one-third of patients complete prescribed regimens for immunotherapy (Donahue, Greineder, Connor-Lacke, et al., 1999).

The lack of a standard definition of effectiveness used in the denominator of cost-effectiveness ratios for allergic rhinitis treatment strategies is restricting (Sullivan and Weiss, 2001) and will continue to limit the role cost-effectiveness analyses can play in clinical decisionmaking. Other methodological issues that limit the utility of the available cost-effectiveness data include the observation that none of the economic analyses were based on prospectively collected cost or resource-utilization data. This necessitates that the analysts rely on assumptions to assign costs. In many studies, the cost of study medications is the only cost included in the analysis (often assuming 100 percent adherence) rather than all disease-related or total healthcare costs. Also, without information on resource utilization, the validity of costs assigned to side effects that occur in a clinical trial setting may be questioned. Finally, many of the studies providing clinical data for the economic evaluations (Keith, Haddon, and Birch, 2000; Kozma, Schulz, Sclar, et al., 1996; Leickly, Sears-Ewald, and Ownby, 1989; Meltzer, Casale, Nathan, et al., 1999; Reilly, Tanner, and Meltzer, 1996; Stahl, van Rompay, Wang, et al., 2000; Sussman, Mason, Compton, et al., 1999; Tanner, Reilly, Meltzer, et al., 1999) are based on short-term randomized controlled trials in patients who may not be similar to the majority of patients suffering from allergic rhinitis. Based on short-term trials, analysts extrapolate findings based on 4- to 6-week outcome data to 1 year or more. Such extrapolation is based on the assumption that the rate of accumulating costs continue in a linear fashion over the extrapolated time period. This assumption is certainly violated in seasonal allergic rhinitis, in which symptoms and medication use can be highly variable over the course of a year.

An ideal definition of effectiveness would not only differentiate between patients who improved with treatment and those who did not, but would also differentiate between different degrees of improvement. Even patients who experience incomplete relief from allergic rhinitis symptoms can experience a significant improvement in their quality of life. One measure

commonly used in the health economics literature is the quality-adjusted life-year. However, we have identified no cost-effectiveness studies in allergic rhinitis that used this measure of effectiveness.

In conclusion, the cost-effectiveness literature for allergic rhinitis is small in quantity and suffers from several methodological shortcomings. Prospectively conducted economic analyses, alongside longer-term randomized trials of treatment alternatives, would be a step in the right direction. While economic modeling is a potential alternative, it would require multiple assumptions to incorporate the results of clinical trials of treatment alternatives conducted with a multitude of various physiologic measures and symptom scales. In addition, an association between these measures and quality of life would be necessary, but experts in the field have noted weak correlation between symptoms in a clinical trial and quality-of-life measures, therefore making this link problematic (de Graaf-in 't Veld, Koenders, Garrelds, et al., 1996; Juniper, 1997). Further, an association between measures of either symptoms or quality of life on measures of productivity would be necessary to measure the impact of treatments for allergic rhinitis on indirect costs. Currently, the number, quality, and generalizability of such studies are limited.

Work Performance (Key Research Question 1)

Over the last several years, the impact of allergic rhinitis and its available treatments on work performance has been the subject of an increasing amount of research. Information on the level of work productivity can be collected using two approaches. In some work settings, the productivity level of an employee can be measured objectively using metrics such as the number of customers served per hour or the number of pages transcribed per hour. In many work settings, however, the level of work productivity cannot be objectively measured and information must be obtained directly from the worker by questionnaire. The Allergy-specific Work Productivity and Activity Impairment questionnaire (WPAI-AS) is a validated instrument that has been used in several studies to collect data on productivity. The questionnaire was designed to assess the impact of allergic rhinitis on the quantity of missed work/classroom hours, as well as the level of impairment experienced at work or school by people with allergic rhinitis (Meltzer, Casale, Nathan, et al., 1999; Reilly, Tanner, and Meltzer, 1996; Sussman, Mason, Compton, et al., 1999; Tanner, Reilly, Meltzer, et al., 1999). The WPAI-AS measures the level of work impairment as the extent to which individuals were limited at work or school over the previous 7 days, and the score is reported as the percentage of productivity at work on work days. To calculate an overall work productivity score, the percentage of time spent working/attending class is multiplied by the percentage of productivity at work/school.

The WPAI-AS has been used in three randomized controlled trials that compared fexofenadine with either placebo or pseudoephedrine or a combination of fexofenadine and pseudoephedrine (Meltzer, Casale, Nathan, et al., 1999; Sussman, Mason, Compton, et al., 1999; Tanner, Reilly, Meltzer, et al., 1999). At baseline, the average amount of work time missed ranged from approximately 1.8 to 4.5 percent. None of the studies showed a significant impact of treatment on time missed from work over the study period. In regard to the overall level of work impairment, baseline averages ranged from approximately 33 to 41 percent. After approximately 2 weeks of study treatment, overall work impairment significantly improved in all three studies by approximately seven to nine percentage points.

While these studies are helpful in measuring the relative impact of various treatment regimens on work productivity, it is largely unknown how measures from the WPAI-AS can be used to value lost productivity. Two recently conducted studies, based on objective measures of worker performance, raise questions as to how the level of impairment reported by workers corresponds to objective measures of worker output. One study showed that health claims processors who filled a prescription for a sedating antihistamine were 7.8 percent less productive than average during the 3-day period after filling the prescription (Cockburn, Bailit, Berndt, et al., 1999a). Conversely, those who filled a prescription for a non-sedating antihistamine were 5.2 percent more productive than average during the 3-day period following the receipt of the medication. Subjects receiving each type of medication had similar levels of productivity prior to filling the prescription. Furthermore, there did not appear to be an effect on productivity in the period preceding the receipt of the medication, indicating that the medical condition for which the medications were prescribed did not have an appreciable impact on worker productivity in this cohort of workers.

Another study assessing the impact of allergy treatment on an objective measure of productivity was conducted in a cohort of telephone customer service operators (Burton, Conti, Chen, et al., 2001). Although this study did not show a difference in the probability of meeting a productivity standard between subjects who reported using sedating and non-sedating antihistamines, it was shown that three percent fewer subjects who reported using either medication met the productivity standard than persons without allergic rhinitis (and who did not use either medication). The study also showed that 10 percent fewer subjects who reported having allergies but used no medication met the productivity standard compared to subjects without allergies. The results of this study are more difficult to put into perspective in terms of the level of impairment resulting from allergy symptoms or their treatment given the dichotomous productivity measure used. It is inappropriate to directly compare results from studies using the WPAI-AS with those using objective measures of worker productivity because of the different types of occupations involved. However, the general findings from these types of studies suggest that the level of impairment reported by workers with the WPAI-AS may overestimate measured percent reduction in productivity. If this is the case, studies that directly assign salary information to reductions in productivity could either overestimate indirect costs associated with allergic rhinitis or overestimate the impact alternative treatments have on indirect costs. Future studies that attempt to compare objective measures of productivity to self-reported measures of impairment would be helpful in elucidating this relationship in order to guide analysts in the appropriate valuation of reduced productivity.

Although the two studies discussed above are significant contributions to the literature on the impact of allergic rhinitis and its treatment on productivity outcomes, many unanswered questions remain. Are these results generalizable to other professions? Why did one study show no difference in productivity between sedating and non-sedating antihistamines (Burton, Conti, Chen, et al., 2001), while the other (Cockburn, Bailit, Berndt, et al., 1999a) showed a significant difference in productivity in patients treated with the two types of medications? Further studies are needed to determine whether decreases in productivity are consistent across workers in different occupations and to understand the association between levels of severity of allergic rhinitis and its impact on worker productivity. Quantification of this association is necessary to conduct economic evaluations of treatment options for allergic rhinitis that incorporate clinical outcomes and their impact on indirect costs.

Associations Between Symptom or Quality-of-Life Outcomes and Work Performance (Key Research Question 2)

Being able to predict the impact of changes in rhinitis symptoms on work performance would be helpful in estimating changes in indirect costs related to allergic rhinitis treatments because nearly all of the evidence on effectiveness of treatment of allergic rhinitis relates to symptoms or quality of life, rather than to work performance. In the previous section, we described the limited data on work performance in allergic rhinitis. In order to address the present question, we sought studies that reported data on work performance and either symptoms of allergic rhinitis or disease-specific quality-of-life measures and reported some measure of association between them.

Even though both symptom/quality-of-life and work-performance measures were collected in several studies, only one study quantitatively linked symptom or quality-of-life outcomes data to productivity data. Reilly and colleagues used data from two multicenter, double-blind randomized controlled trials comparing the effectiveness of terfenadine, fexofenadine, and placebo to correlate work or classroom impairment with symptom score changes (Reilly, Tanner, and Meltzer, 1996). Work and classroom impairment were measured using the WPAI-AS and Classroom WPAI-AS, respectively. The study also measured absenteeism; however, because absenteeism was low, the investigators could not validate the WPAI-AS against absenteeism. Correlations between impairment measures and total symptom score at baseline and weeks 1 and 2 ranged from $r = 0.30$ to 0.55. The correlation between changes in symptom score and changes in work impairment measures were similar ($r = 0.35$ to 0.42).

Although the association between symptoms and self-reported work performance in this study was statistically significant and supported by a firm conceptual model, additional information would be desirable to accurately estimate the impact of treatments on work performance. Parameter estimates from the regression analysis conducted to demonstrate the relationship between changes in symptom severity and work impairment measures were not reported. The R-squared values for the regression models were as high as 0.49 when covariates were considered, but the independent contribution of changes in symptom scores was not reported. The two variables that were consistently shown to predict reductions in impairment were improvement in symptom scores and higher baseline impairment, but it is unknown whether an interaction exists between the variables. It is possible that given the same magnitude of change in symptoms, patients with greater impairment at baseline tend to have a greater reduction in impairment compared to patients with less impairment at baseline. Such an interaction would be important when modeling the cost-effectiveness of various treatments for allergic rhinitis, especially when studies of different treatments have been conducted in patients with varying levels of severity of symptoms.

This study was the first to quantitatively document the relationship between allergic rhinitis symptoms and work impairment. Others have reported both symptom outcomes and measures of work performance, but correlations were not reported. This link should be further studied, preferably along with some objective measures of work performance, if the goal is to estimate and compare indirect costs associated with allergic rhinitis and its treatments.

Conclusions

Allergic rhinitis is associated with enormous direct and indirect costs in the US, with estimates as high as $4.5 billion and $7.7 billion annually, respectively; an updated comprehensive burden-of-illness study is necessary to more precisely estimate direct and indirect costs, for which currently available estimates vary four- to six-fold. The literature on economic evaluations of treatments for allergic rhinitis shows several areas for improvement. Economic evaluations of allergic rhinitis treatments often do not adequately consider uncertainty about estimates of efficacy of treatments, often inappropriately using cost-minimization analyses rather than cost-effectiveness analyses. There is a lack of consensus on an appropriate and clinically meaningful measure of "effectiveness" to be used in the denominator of a cost-effectiveness ratio. The few available standardized instruments that assess allergic rhinitis symptoms are not yet widely used. To better estimate the indirect costs of allergic rhinitis treatments, objective measures of work performance are needed to determine the relationship between symptomatic outcomes, for which many data are available, and work performance, for which few data are available.

Environmental Measures

Introduction

This section addresses key research question 3a: How effective are environmental measures for relief of symptoms in adults with allergic rhinitis? The search strategy for this question was broad-based and sought to identify relevant studies on air-cleaning devices, insect control (including house dust mites), and other allergen avoidance strategies. Two Cochrane Collaboration Reviews, "House dust mite avoidance measures for perennial allergic rhinitis" (Sheikh and Hurwitz, 2002) and "House dust mite control measures for asthma" (Gøtzsche, Johansen, Hammarquist, et al., 2001), were identified and reviewed. We were not able to identify any systematic reviews on environmental control strategies aimed at airborne allergens.

After consulting with the project's advisory panel of experts, we elected to include studies conducted in asthma patients, recognizing that differences in response may occur between these populations, because the mechanisms for allergen avoidance are the same, and because of limited data on rhinitis patients. Although our focus is on working populations, we also elected to include studies of school-age children because of limited data on adult populations and a lack of evidence for differences in allergen exposure mechanisms and responses between adults and children.

Results

Twenty-seven articles were included in the analysis (see Evidence Table 2). In what follows, studies involving patients with asthma (n = 20) and those conducted on patients with rhinitis (n = 4) are discussed separately; studies including patients with both conditions (n = 3) are discussed under both headings since virtually all patients had both conditions. A further division is between studies that focus on control of house dust mites (n = 21) and those that focus on control of airborne allergens with or without dust mite control (n = 6).

Rhinitis – Air Filtration Systems for Control of Airborne Allergens

Four small studies evaluated air filtration systems: three considered room-based high efficiency particulate air (HEPA) filters (Antonicelli, Bilò, Pucci, et al., 1991; Reisman, Mauriello, Davis, et al., 1990; Wood, Johnson, Van Natta, et al., 1998), and one examined a central system (Kooistra, Pasch, and Reed, 1978); one of the three studies added allergen-impervious mattress and pillow covers (Wood, Johnson, Van Natta, et al., 1998). A total of 107 adults and children were enrolled; all were skin-test positive to at least one allergen (house dust mite, cats, or ragweed).

In a 16-week randomized controlled trial (RCT) of crossover design, Antonicelli and colleagues tested an Enviracaire® HEPA filter placed in the bedrooms of nine adults and children with asthma and rhinitis who were sensitive to house dust mites (Antonicelli, Bilò, Pucci, et al., 1991). This underpowered trial showed no significant effect on allergen levels collected from floor samples, on symptom levels, or on medication use.

Reisman and colleagues used an 8-week randomized crossover design to test an Enviracaire® HEPA filter placed in the bedrooms of 40 adults and children sensitive to house dust mites (Reisman, Mauriello, Davis, et al., 1990). Thirty-two completed the study. Airborne particles decreased significantly, but total symptoms, seven individual symptoms, and medication use did not change significantly. Comparing crossover periods, patient global evaluations of the active versus placebo filter periods were: 11 "improved," 14 "no difference," and seven "worse" with the active filter. When analyses were repeated using only the last 2 weeks of each period to reduce carry-over effects, nasal congestion and upper airway itching improved by a statistically significant amount. The relevant data were not reported, so it is unclear whether these differences were clinically significant.

Wood and colleagues used a 3-month RCT to evaluate an Enviracaire® HEPA filter placed in the bedrooms of 38 adults sensitive to cats (Wood, Johnson, Van Natta, et al., 1998). In addition, mattresses and pillows were fitted with impervious covers, and subjects were asked to wash bedding weekly and keep cats out of the bedroom. Thirty-five patients completed the study. Airborne cat allergen decreased in a completers' analysis ($p = 0.045$), but not in an intention-to-treat analysis ($p = 0.152$); settled cat antigen did not decrease significantly. Both nasal and chest symptoms were reported for morning, afternoon, and evening time periods. There were no significant between-group differences for any of these comparisons. Post-hoc analysis suggested that at least 284 patients were needed to have adequate power to test the intervention.

Finally, Kooistra and colleagues used an 8-week RCT of crossover design to test a central air conditioning filter in 20 ragweed-sensitive adults (Kooistra, Pasch, and Reed, 1978). Symptoms decreased overall by six percent ($p = 0.06$); nighttime symptoms decreased by 14 percent ($p = 0.0007$); day and evening symptoms did not change significantly.

In summary, four small trials using varied interventions and patient selection criteria do not show strong evidence that air filtration systems decrease rhinitis symptoms. However, studies were likely underpowered to detect clinically relevant differences.

Rhinitis – House Dust Mite Control Measures

Three small Asian and European studies evaluated house dust mite control measures using varying combinations of an acaricide, impervious covers, and extra house cleaning (Geller-Bernstein, Pibourdin, Dornelas, et al., 1995; Kniest, Young, Van Praag, et al., 1991; Moon and

Choi, 1999). A total of 85 adults and children with hose dust mite sensitivity were enrolled. Sensitivity to house dust mite was confirmed by skin test or radioallergosorbent testing (RAST) in one study (Kniest, Young, Van Praag, et al., 1991) and by skin test in the other two studies.

Geller-Bernstein and colleagues used a 6-month, double-blind RCT to test two applications of Acardust,® cleaning, and bed linen changes in 35 dust-mite-sensitive children with rhinitis and asthma (Geller-Bernstein, Pibourdin, Dornelas, et al., 1995). Allergen levels decreased significantly more in the intervention group (but there were important baseline differences). Results were poorly reported, but patient-assessed symptom severity for rhinitis and asthma decreased significantly more for the intervention group.

Kneist and colleagues used a 1-year, double-blind, parallel-group, controlled trial (unclear whether randomized) to test two applications of Acarosan® and cleaning in 20 adults and children with a clinical history of dust-mite-sensitivity rhinitis (Kniest, Young, Van Praag, et al., 1991). Allergen levels decreased significantly more in the intervention group ($p = 0.045$). Patient-assessed symptom severity for rhinitis decreased significantly more for the intervention group.

Moon and Choi (1999) used a 4-week, apparently unblinded, RCT to test dust-mite-impervious mattress covers, extra cleaning, and bed linen washing in 30 dust-mite-sensitive adults and children with rhinitis. Allergen levels and patient-assessed symptom severity for rhinitis decreased significantly more for the intervention group.

In summary, three small trials in highly selected patients suggest that dust mite control measures may decrease rhinitis symptoms.

Asthma

Twenty-three trials conducted in Europe (n = 14), North America (n = 5), Israel (n = 2), Australia (n = 1), and Taiwan (n = 1) have evaluated house dust mite control measures for patients with asthma. Only two studies had sample sizes exceeding 100 (Cloosterman, Schermer, Bijl-Hofland, et al., 1999; Kroidl, Göbel, Balzer, et al., 1998). Interventions varied as follows: acaricide with dust-mite-impervious covers, with or without housecleaning instructions (n = 7); acaricide with cleaning (n = 4); acaricide only (n = 1); dust-mite-impervious covers with or without cleaning (n = 5); dust-mite-impervious covers with cleaning and air filtration (n = 1); air filtration only (n = 3); and cleaning only (n = 2). Study participants had clinical asthma in 19 of 23 studies, asthma with rhinitis in three, and asthma symptoms in one; 22 studies required positive skin tests, and 10 required spirometry consistent with asthma. Studies enrolled children (n = 10), adults (n = 7), or both (n = 6). Twenty studies used a parallel-group design; three used a crossover design. Ten studies used double-blind methods; four blinded only the patients to the treatment; and in nine, blinding was uncertain. Trial durations were less than 3 months (n = 8), 3 to 5 months (n = 4), 6 months (n = 5), and 1 year (n = 6).

The outcomes reported varied across studies but always included at least one of the following: allergen levels for mattresses and other household locations, asthma symptom severity (using unvalidated scales), global asthma scores, or medication use. House dust mite levels decreased in three studies, decreased in some of the sampled locations in five studies, did not decrease in five studies, and were not reported in six studies. Asthma symptom severity decreased overall in three studies, decreased for selected symptoms in three studies, did not decrease significantly in seven studies, and was not meaningfully reported in six studies. Global asthma symptoms decreased in one of the seven studies reporting this result. Medication use was

decreased in one of the eight studies reporting this result. The single large trial (n = 204) showed mixed effects on asthma symptoms and no significant effect on global symptoms or medication use (Cloosterman, Schermer, Bijl-Hofland, et al., 1999). In summary, these small, heterogeneous trials do not suggest a positive effect on asthma symptoms.

The Cochrane Review by Gøtzsche and colleagues, using different inclusion/exclusion criteria, identified 29 trials of dust mite control for patients with asthma (Gøtzsche, Johansen, Hammarquist, et al., 2001). About 75 percent of these studies were performed among children. The authors concluded that they ". . . were unable to demonstrate any overall clinical benefit to mite sensitive asthmatics of measures designed to reduce mite exposure."

Conclusions

Studies of air filtration systems do not show strong evidence for decreasing rhinitis symptoms; however, studies were likely underpowered to detect clinically relevant differences. A few trials in highly selected patients suggest that dust mite control measures such as an acaricide, impervious covers, and extra house cleaning may decrease rhinitis symptoms. Studies of mite-sensitive asthmatics do not demonstrate any overall clinical benefit of a variety of measures designed to reduce mite exposure.

We do not yet know whether secondary domestic aeroallergen avoidance can be effective. However, currently available intervention studies suggest that it might be, and such studies are too imprecise to prove that environmental measures are ineffective. Affordable and feasible techniques that substantially reduce allergen exposure in the home may prove to be effective at reducing symptoms when targeted at suitable patients. Improved techniques for measuring exposure, improved technologies for reducing exposure, and improved selection of patients for intervention are all important issues for future research.

Immunotherapy

Introduction

This section addresses key research question 3b: How effective is immunotherapy for relief of symptoms in adults with allergic rhinitis? Allergen immunotherapy (IT) for allergic rhinitis was first described and practiced in the early 20th century. It achieved acceptance by patients and physicians despite the fact that evidence of its efficacy was lacking until placebo-controlled studies were conducted in the late 1950s. As a result, a variety of allergen immunotherapy methods emerged with little more than anecdotal evidence of their effectiveness. Since the 1960s, controlled clinical trials have demonstrated the clinical effectiveness of IT. Nevertheless, the generalizability of clinical trials of IT for allergic rhinitis has been hampered by the absence of standardized allergen extracts and the absence of validated clinical response criteria for patients undergoing treatment.

In accordance with a position statement developed by the World Health Organization (Bousquet, Lockey, and Malling, 1998), we restricted our review to studies of immunotherapy delivered by subcutaneous injection and did not consider oral, bronchial, sublingual, or nasal routes of administration. We conducted a search of computerized bibliographic databases (described in the Methodology chapter) and also sought to identify existing systematic reviews on injection immunotherapy. The latter effort identified a published Cochrane Collaboration

protocol on the topic (Alves, Sheikh, Hurwitz, et al., 2002) and a journal-published meta-analysis (Ross, Nelson, and Finegold, 2000). Further investigation revealed that the full Cochrane review was in its early stages and could offer little guidance. The published meta-analysis by Ross and colleagues included 16 trials involving 759 patients (Ross, Nelson, and Finegold, 2000). All but one of the studies concluded that immunotherapy was beneficial in allergic rhinitis. The meta-analysis found evidence for reduction in allergic rhinitis symptom-medication scores in patients undergoing immunotherapy (odds ratio, 1.81; 95 percent confidence interval [95% CI], 1.48 to 2.23; $P < 0.05$). This analysis, however, had several limitations, including: (a) incomplete ascertainment of candidate trials; (b) lack of a threshold for clinically important "improvement"; (c) lack of verification of data abstraction; (d) lack of quality assessment of studies; and (e) no account of the number of excluded studies or reasons for exclusion of candidate studies.

We concluded that a more rigorous review of the topic would be useful. In addition to a fresh review of the literature, we have undertaken a quantitative meta-analysis of placebo-controlled trials of allergen immunotherapy for seasonal allergic rhinitis and report the results below.

Results

Studies Identified

Sixty trials were included (see Evidence Table 3). All were required to report a clinical outcome measure based on patient assessment of symptoms and/or medication use for symptom relief. For the purposes of this discussion, trials have been separated into studies of immunotherapy for seasonal and perennial allergic rhinitis. The rationale for this division is based upon differing patterns of allergen exposure, which often correspond to differing immunotherapy protocols. Patients with seasonal allergic rhinitis symptoms may experience short periods of allergen exposure with relatively asymptomatic periods between exposures, whereas patients with perennial allergic rhinitis may have allergic responses to year-round allergens such as dust mite and cat dander. Alternatively, a significant percentage of patients experience year-round symptoms, but have multiple sensitivities to pollen, mold, and environmental allergens. Regarding immunotherapy protocols, seasonal rhinitis IT may be given continuously year-round or pre-seasonally only. The vast majority of trials considered in this report relate to seasonal allergic rhinitis caused by pollen. Only a small number of placebo-controlled trials have been performed to assess the effectiveness of IT to house dust mite or pet allergens.

Seasonal Allergic Rhinitis

General literature review. Forty-eight trials of IT in the treatment of seasonal allergic rhinitis, with a total enrollment of 2,827 subjects, are summarized in Evidence Table 3. Ragweed pollen was the most commonly studied allergen, followed by grass pollen, tree pollen, and the weed pollen, *Parietaria*. All but 14 of the studies employed a seasonal treatment protocol in which subjects were given IT for 4 to 40 weeks prior to the expected pollen-exposure period. Most subjects were recruited into seasonal allergic rhinitis trials based upon symptoms occurring during the period of known exposure to the study allergen. The majority of studies employed a combined symptom-medication scale to collect patient response data. The method

and grading system used to collect these data varied from study to study. None of the published studies gave detailed descriptions of measures used to ensure compliance with symptom/medication diary recording, and none provided detailed information on the percentage of expected data points that were actually collected. With one exception, all trials employed a single allergen or class of allergens (e.g., ragweed allergen or mixed grass allergen) in the treatment protocol. This is in contrast to the common clinical practice of formulating vaccines that include most or all of the allergens to which a patient is sensitive. A summary of the results of placebo-controlled trials of IT for seasonal allergic rhinitis is provided in Table 14.

Among the 48 included trials were several unique trial designs. Two trials compared a method of low-dose immunotherapy, designated the Rinkel method, with standard IT or placebo (Hirsch, Kalbfleisch, Golbert, et al., 1981; Van Metre, Adkinson, Amodio, et al., 1980). In both trials, the Rinkel method was found to be no more effective than placebo. As a result, expert panels have recommended against using the Rinkel method of immunotherapy (Bousquet, Lockey, and Malling, 1998). Two trials employed a withdrawal of therapy strategy in which subjects receiving maintenance doses of IT were randomized to receive continued immunotherapy or placebo for from 1 to 3 years (Durham, Walker, Varga, et al., 1999; Naclerio, Proud, Moylan, et al., 1997). The intent of these studies was to determine the durability of clinical and immunological responses to standard immunotherapy. At the end of the observation periods, the placebo group in each trial maintained clinical response levels similar to those measured in the group receiving continued treatment, indicating that clinical responses related to IT were durable beyond the actual treatment period.

Three trials compared immunotherapy with active medical treatment. In a 3-year trial comparing grass pollen immunotherapy with ketotifen (a drug approved in several European countries), the results favored immunotherapy (Dolz, Martinez-Cocera, Bartolome, et al., 1996). Two short-term trials compared birch or ragweed IT with nasal corticosteroids (Juniper, Kline, Ramsdale, et al., 1990; Rak, Heinrich, Jacobsen, et al., 2001). The results favored medical therapy over IT. However, it should be noted that the duration of immunotherapy was 6 weeks in each of these studies, which may not have been long enough to allow optimal immunologic response to IT, whereas nasal corticosteroids are known to be effective within this short time frame.

Safety data were reported in 38 of the 48 trials reviewed. The most common adverse events described were local reactions (either immediate or late) at the IT injection site. Systemic reactions characterized by generalized urticaria, increased rhinitis symptoms, increased asthma symptoms, or mild anaphylaxis were less common than local reactions and were apparently easily controlled. The percentage of subjects with systemic reactions varied from zero to approximately 25 percent. There were no reports of hospitalizations or deaths related to IT. No standardized methods for describing the characteristics or severity of allergic reactions to immunotherapy have been devised, making the interpretation of the adverse event data difficult.

Meta-analysis of placebo-controlled trials. We performed a meta-analysis of the placebo-controlled trials of allergen immunotherapy conducted among patients with seasonal allergic rhinitis. Outcome data on total symptoms, medication use, or a combination of these measures was abstracted by one of the investigators (DM or JS) and confirmed from original reports by the other. We attempted to abstract data on the mean, variance, and numbers of subjects per treatment arm in order to estimate an effect size. However, many studies reported medians rather than means and used non-parametric statistical analyses; in such cases, it was not possible to estimate an effect size. Some studies used parametric statistical analysis on original or log-

transformed data (Creticos, Reed, Norman, et al., 1996). When data on variance were not reported, we estimated individual patient data from published graphs and figures when reasonably accurate estimates were possible. We analyzed individual patient data using SAS (The SAS Institute, 2001) to estimate means and variance, using log-transformation if necessary to normalize the data. A description of the data abstracted for the analysis is provided in Table 15.

We calculated and combined effect sizes (Cohen, 1988) and tested for statistical heterogeneity using Comprehensive Meta-analysis statistical software (Biostat, 1999). Studies that did not report sufficient data to estimate effect sizes, including those that used only non-parametric statistical analysis, were omitted from the meta-analysis.

Planned subgroup analyses included the type of outcome measure (total symptom score versus medication use versus combined symptom-medication scores), type of allergen (tree, grass, or weed), type of placebo (inert, fixed histamine concentration, variable histamine concentration), and elements of the quality assessment for which sufficient variability was observed.

Fifteen trials were included in the meta-analysis. The number of subjects in each trial ranged from 23 to 73. Seven trials reported data on total symptom severity, two reported data on medication use, and eight reported data on combined symptom severity and medication use. There was no overlap between the trials reporting total symptom severity and those reporting medication use (although both trials reporting medication use, also reported symptom severity). Our primary analysis of all 15 trials was stratified by outcome (symptom severity versus combined symptom severity and medication use). The effect sizes for individual studies showed no significant heterogeneity among either subgroup ($p = 0.13$ and 0.7, respectively) or the entire collection of studies ($p = 0.76$). Effect size estimates ranged from 0.43 to 1.3 for symptom severity, and from 0.61 to 1.4 for studies reporting combined symptom-medication scores (Figure 2). Summary effect sizes were 0.77 (95% CI, 0.53 to 1.02) for symptom severity and 0.97 (0.72 to 1.21) for combined symptom-medication scores, with an overall summary effect size of 0.87 (0.70 to 1.04).

Further subgroup analyses were performed based on allergen used, type of placebo, and selected quality measures. The effect size was estimated for four grass pollen, eight ragweed pollen and three tree pollen studies, with no significant difference ($p = 0.25$). Similarly, no significant difference was observed when studies were stratified by type of placebo (fixed histamine dose, variable histamine dose, and no histamine; $p = 0.60$). We analyzed for differences in effect size associated with quality assessment variables for which there was sufficient variability among trials, namely, double-blinding and description of dropouts. There was no statistically significant difference, but there was a trend ($p = 0.07$) toward a higher effect size among single-blinded compared to double-blinded studies (1.2 [0.8 to 1.5] versus 0.78 [0.58 to 0.98]). There was no difference between those trials that reported dropouts and those that did not (0.86 [0.64 to 1.1] versus 0.89 [0.61 to 1.2]; $p = 0.85$).

Perennial Allergic Rhinitis

The number of clinical trials of IT in perennial allergic rhinitis is small. We identified 12 randomized controlled trials (540 subjects enrolled) that met our inclusion criteria. Seven trials assessed IT with dust mite allergen, and the others studied a combination of dust mite and pollen

allergen, cat allergen, latex allergen, mold (*Alternaria*), or multiple antigens. Most studies (9 of 12) reported results favoring IT (Table 16).

There are important methodological concerns about some of the included trials. Most trials used an IT treatment program of 52 weeks. However, two trials (D'Souza, Pepys, Wells, et al., 1973; Ewan, Alexander, Snape, et al., 1988) had a short treatment program of 12 weeks. One trial used a Rinkel-type protocol and employed a 2-week treatment program of active IT or placebo, after which patients completed a 2-week washout period and crossed over to the opposite therapy (Radcliffe, Lampe, and Brostoff, 1996). It is unlikely that optimal clinical benefits of immunotherapy could be achieved within these short time frames. One trial reported a 41 percent dropout rate and did not collect adequate symptom and medication data to report results (Blainey, Phillips, Ollier, et al., 1984). Another trial did not collect daily symptom scores, had a high dropout rate (8/18; 44 percent), and did not collect data on concomitant allergy medication use (Krouse and Krouse, 2000).

After studies with significant methodological flaws were excluded, the remaining trials included four studies of dust mite immunotherapy in 241 patients, and three small trials (1 each) of immunotherapy using cat, mold, or latex allergen. The small number of trials and the limited number of patients enrolled in these studies underscore the need for additional clinical trials to assess the effectiveness of IT for the treatment of perennial allergic rhinitis.

Adverse event data were described for nine of 12 studies of IT in perennial allergic rhinitis. As observed in IT for seasonal allergic rhinitis, local injection site reactions were common. Systemic allergic reactions were reported in various studies to occur in from zero to 100 percent of subjects. Most of these reactions were mild. There were no reports of treatment-related hospitalizations or deaths.

Quality Assessment

Most of the immunotherapy trials abstracted in this analysis (48 of 60) enrolled patient populations that were similar to the adult US working population. None of the trials described the racial characteristics of the subjects enrolled. Sex- and age-related differences in clinical responses to IT were not reported in any of the trials. Virtually all of the studies used a single allergen or class of allergen in the treatment group. However, the external validity of this approach is questionable, given that most atopic patients are polysensitized. In contrast, most patients receiving IT in non-research settings have vaccines formulated with most or all of the allergens to which they are sensitive.

A primary clinical outcome measure used in most of the studies was a symptom or symptom-medication score compiled from a patient diary. Usually subjects were asked to score a symptom, such as sneezing, on a scale of 0 to 3. Unfortunately, this outcome measure had not been standardized. The degree to which this scale is responsive to change, and whether ceiling or floor effects occur when it is used, have not been determined. Finally, the degree of change in symptom score necessary to be clinically relevant is not known.

Other quality concerns identified in this review include the virtual absence of meaningful sample size determinations; inadequate description of procedures for generating randomization sequences and concealing them from investigators; incomplete patient follow-up; and failure to perform efficacy analyses according to the intention-to-treat principle.

Conclusions

We analyzed 60 controlled trials of immunotherapy in allergic rhinitis. No serious adverse events were reported, and immunotherapy was generally well tolerated. Our data show that immunotherapy for seasonal allergic rhinitis consistently demonstrates evidence of clinical benefit (effect size, 0.87 [95% CI, 0.70 to 1.04]). The magnitude of this effect equates to a 35 to 40 percent reduction in symptom or symptom-medication scores when individual trials with similar effect sizes are analyzed (Lichtenstein, Norman, and Winkenwerder, 1971; Van Metre, Adkinson, Amodio, et al., 1980). This effect is similar to or slightly better than that observed in clinical trials of antihistamines for seasonal allergic rhinitis (European Agency for Evaluation of Medicinal Products, 2001).

Important flaws in study quality were identified, which may affect the internal validity of the results of this analysis. Most trials enrolled a small number of patients and employed clinical outcome measures that have not been validated. Other concerns include inadequate or poorly described methods for allocation concealment and failure to employ an intention-to-treat analysis. Nevertheless, we could not identify significant differences in effect sizes among trials stratified by the presence or absence of these quality criteria. Since most trials were small, we could not accurately assess the presence of publication bias. Although only 15 of 42 placebo-controlled trials provided appropriate data to estimate effect size, the proportion of trials with statistically significant positive findings was similar for all studies (Table 14) and the subset included in the meta-analysis (Figure 2). Findings among the few studies of perennial rhinitis were consistent with a clinically important effectiveness, although the limited number of studies and important methodological problems preclude a firm conclusion or a quantitative estimate of the magnitude of any effect.

Our analysis also highlights several research needs related to immunotherapy and the treatment of allergic rhinitis. Standardized instruments for assessing clinical symptoms need to be developed. Using these tools, it should be possible to define response criteria that will allow investigators to classify patients as responders or non-responders. Large-scale clinical trials employing vaccines with most or all relevant allergens for each individual should be designed to assess IT as it is administered in most community settings. Additional future research objectives should be focused upon the following: methods to identify patients likely to benefit from IT; cost-effectiveness and quality-of-life analyses of IT; determination of whether IT alters the natural history of allergic rhinitis and reduces possible sequelae such as bacterial sinusitis and asthma; and studies clarifying the optimal duration of IT.

Combined Treatments

Introduction

This section addresses key research question 3c: How effective are combined treatments, such as with antihistamines and nasal steroids or antihistamines and oral decongestants, for relief of symptoms in adults with allergic rhinitis?

Results

Studies Identified

Thirty-one publications describing 32 separate randomized controlled trials met the inclusion and exclusion criteria for this topic (see Evidence Table 4); there were 49 relevant comparisons (some trials had multiple treatment arms). We did not identify any systematic reviews addressing this question.

Most studies evaluated patients with seasonal allergic rhinitis (n = 26, 81 percent), recruited from specialty settings, and included primarily adults, with some adolescents (> 12 years of age). Study durations were ≤ 2 weeks (n = 18, 56 percent), 15 days to 6 weeks (n = 12, 38 percent), and > 6 weeks (n = 2, six percent). The majority of studies were small to moderate in size; sample sizes were < 100 (n = 13, 41 percent), 100 to 200 (n = 5, 15 percent), and > 200 (n = 14, 44 percent). A majority of studies were performed outside the US (53 percent). The most common outcomes reported were individual symptoms, symptom scales, and global symptom ratings. Health-related quality of life using the Medical Outcome Study Short-Form Health Survey (SF-36) or the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) was reported in three studies. One study reported economic effects on work performance. Trials involving terfenadine (Seldane®) and astemizole (Hismanal®) were included even though these medications have been withdrawn from the market due to safety concerns. A description of treatment comparisons and an overview of results are provided in Table 17.

For the comparisons for which there were more than two trials, we attempted a quantitative meta-analysis. We extracted outcome data at 2 weeks for (a) total symptom relief scores and (b) nasal symptom scores and/or nasal congestion scores (Table 18). The 2-week time point was chosen to maximize comparability between trials despite differences in duration of treatment and followup. We used data on continuous measures to calculate effect sizes or standardized mean differences (Cohen, 1988) based on reported means and standard deviations or p-values from parametric statistical analyses using Comprehensive Meta-analysis statistical software (Biostat, 1999). Studies that did not report sufficient data to estimate effect size, including those that used only non-parametric statistical analysis, were omitted from the analysis. Where similar trials provided data, we tested the individual study effect size estimates for homogeneity, and, if homogeneous, used a fixed-effects model meta-analysis to combine the estimates. We planned a priori to compare the effect among subgroups of studies using sedating versus non-sedating antihistamines.

A summary of the results of the meta-analysis is provided in Table 19.

Antihistamines with or without a Decongestant

Thirteen studies, conducted in North America (n = 7), Europe (n = 5), and India (n = 1) compared antihistamines to the combination of an antihistamine with pseudoephedrine. The antihistamines assessed included acrivastine (n = 4), cetirizine (n = 2), azatadine (n = 2), terfenadine (n = 2), and one trial each for loratadine, triprolidine, and fexofenadine. Overall, seven studies showed that the antihistamine-decongestant combination was superior to antihistamine alone for reducing symptoms (Bertrand, Jamart, Marchal, et al., 1996; Dockhorn, Williams, and Sanders, 1996; Falliers and Redding, 1980 [two studies]; Grosclaude, Mees, Pinelli, et al., 1997; Panda and Mann, 1998; Williams, Hull, McSorley, et al., 1996). Three trials

found no statistically significant difference (Henauer, Seppey, Huguenot, et al., 1991; Meran, Morse, and Gibbs, 1990; Sussman, Mason, Compton, et al., 1999). Finally, three other studies showed essentially similar symptom scores (Bronsky, Boggs, Findlay, et al., 1995; Diamond, Gerson, Cato, et al., 1981; Vuurman, van Veggel, Sanders, et al., 1996); no formal statistical tests were reported, so these were interpreted as negative. Interestingly, the studies comparing the combination of a sedating antihistamine and decongestant were more often positive compared to antihistamine alone than similarly designed studies using a non-sedating antihistamine.

To quantitatively examine the variability in findings and to calculate a summary estimate of the effect size, we performed a meta-analysis of these studies for two outcomes, total symptom relief and nasal symptom relief. Eleven of the 13 studies reported a total symptom score. Six studies were excluded from the analysis, two because of study duration less than 2 weeks (Diamond, Gerson, Cato, et al., 1981; Vuurman, van Veggel, Sanders, et al., 1996), and four because an effect size could not be calculated (Bertrand, Jamart, Marchal, et al., 1996; Falliers and Redding, 1980 [two studies]; Panda and Mann, 1998). Effect size estimates for total symptom relief from treatment with combination antihistamine-pseudoephedrine versus antihistamine alone are shown in Figure 3. A test of homogeneity was insignificant ($p = 0.84$). The summary effect size was 0.23 (95 percent confidence interval [95% CI], 0.15 to 0.32), showing that total symptom scores were better, that is, there was a greater reduction in symptoms, in the patients receiving combination therapy.

Studies of non-sedating antihistamines (Bronsky, Boggs, Findlay, et al., 1995; Henauer, Seppey, Huguenot, et al., 1991; Sussman, Mason, Compton, et al., 1999) had a combined effect size of 0.16 (95 % CI, 0.03 to 0.29), while studies employing a sedating antihistamine (Dockhorn, Aaronson, Bronsky, et al., 1999; Grosclaude, Mees, Pinelli, et al., 1997; Meran, Morse, and Gibbs, 1990; Williams, Hull, McSorley, et al., 1996) had a summary effect size of 0.29 (95% CI, 0.18 to 0.39). The difference between the two was not statistically significant ($p = 0.15$).

A meta-analysis of the same studies using a nasal symptom score or nasal congestion score (if the total nasal symptom score was not reported) was also performed. Estimates of the effect of combination antihistamine-pseudoephedrine compared to antihistamine alone, based on the nasal symptom/nasal congestion score, are shown in Figure 4. A test of homogeneity was insignificant ($p = 0.71$). The summary effect size was 0.33 (95% CI, 0.24 to 0.41), showing that relief of nasal congestion was greater in patients receiving combination therapy. There was no significant difference in effect sizes between studies using a sedating ($n = 2$) versus a non-sedating antihistamine ($n = 6$; $p = 0.55$).

A third treatment arm, comparing an antihistamine-decongestant combination with pseudoephedrine alone, was evaluated in 10 of the 13 studies described above. The majority of these studies (eight of 10) showed that the antihistamine-decongestant combination was superior to decongestant alone for the treatment of rhinitis symptoms (Bertrand, Jamart, Marchal, et al., 1996; Dockhorn, Williams, and Sanders, 1996; Falliers and Redding, 1980 [two studies]; Grosclaude, Mees, Pinelli, et al., 1997; Meran, Morse, and Gibbs, 1990; Sussman, Mason, Compton, et al., 1999; Williams, Hull, McSorley, et al., 1996); two of these trials showed there was no statistical difference only in one symptom, namely, nasal congestion. Diamond and colleagues (1981) and Bronsky and colleagues (1995) failed to report any statistical comparison for the symptom scores, but the mean scores for the combination treatment were better than those for the decongestant. The treatment of allergic rhinitis with pseudoephedrine alone failed to

alleviate symptoms such as sneezing, itching, and rhinorrhea, but was beneficial in reducing nasal congestion.

All 10 studies comparing pseudoephedrine alone to antihistamine-pseudoephedrine combination reported a total symptom score. Four studies were excluded from the meta-anlaysis, one because the study duration was less than 2 weeks (Diamond, Gerson, Cato, et al., 1981), and three because an effect size could not be calculated (Bertrand, Jamart, Marchal, et al., 1996; Falliers and Redding, 1980 [two studies]). Estimates of the effect of the combination of antihistamine and pseudoephedrine to decongestant alone are shown in Figure 5. A test of homogeneity was insignificant ($p = 0.67$). The summary effect size was 0.31 (95% CI, 0.22 to 0.39), showing that total symptom scores were better, that is, there was a greater reduction in symptoms, in the patients receiving combination therapy. There was no significant difference in effect sizes between studies using a sedating ($n = 2$) versus a non-sedating antihistamine ($n = 4$; $p = 0.66$).

A meta-analysis using a nasal symptom score/nasal congestion score was performed as well. Estimates of the effect of the combination of an antihistamine and pseudophedrine to decongestant alone, based on the nasal scores, are shown in Figure 6. A test of homogeneity was insignificant ($p = 0.39$). The summary effect size, 0.16 (95% CI, 0.07 to 0.25), shows that relief of nasal congestion was greater for patients receiving combination therapy. There was no significant difference in effect sizes between the single study using a sedating antihistamine compared to the six studies using a non-sedating antihistamine ($p = 0.77$).

Thus, the combination of an antihistamine and a decongestant (pseudoephedrine) provides greater relief of total and nasal symptoms than either an antihistamine alone or pseudoephedrine alone. Furthermore, studies using a sedating versus non-sedating antihistamine found similar results when combined with a decongestant.

Antihistamine With or Without Nasal Glucocorticoid

Ten studies conducted in Europe ($n = 6$) and North America ($n = 4$) compared the combination of an antihistamine with a nasal glucocorticoid with either antihistamine alone ($n = 7$ trials) or nasal glucocorticoid alone ($n = 7$ trials). The combinations studied included terfenadine-flunisolide, terfenadine-budesonide, astemizole-beclomethasone, loratadine-beclomethasone, loratadine-fluticasone, loratadine-flunisolide, cetirizine-mometasone, and cetirizine-fluticasone.

Of the seven studies comparing the combination of antihistamine-nasal glucocorticoid to antihistamine alone, five showed statistically significant differences favoring the combination (Backhouse, Finnamore, and Gosden, 1986; Brooks, Francom, Peel, et al., 1996; Juniper, Kline, Hargreave, et al., 1989; Ratner, van Bavel, Martin, et al., 1998; Simpson, 1994). Two studies did not formally test the significance of the mean symptom scores between the two treatment groups, but the mean symptom scores were better with the antihistamine-nasal glucocorticoid combination than with antihistamine alone (Berger, Fineman, Lieberman, et al., 1999; Wilson, Dempsey, Sims, et al., 2000); we interpreted these two studies as possibly showing superiority of the combination.

Only two of the seven studies reported a total symptom score; therefore we used either the total nasal symptom score or nasal congestion score in a meta-analysis to assess treatment efficacy. One study was excluded because it compared a nasal antihistamine to the combination of an oral antihistamine (a different antihistamine) with a nasal steroid (Berger, Fineman,

Lieberman, et al., 1999). Estimates of the effect of combination antihistamine-nasal steroid to antihistamine alone are shown in Figure 7. A test of homogeneity was insignificant ($p = 0.22$). The summary effect size was 0.44 (95% CI, 0.27 to 0.61), showing that nasal symptom scores were better, that is, there was a larger reduction in symptoms, in the patients receiving combination therapy. No subgroup analysis of non-sedating and sedating antihistamines was performed since only one study used a sedating antihistamine.

Of the seven studies that compared antihistamine-nasal glucocorticoid to nasal glucocorticoid, three found the combination superior for reducing allergic rhinitis symptoms (Drouin, Yang, Horak, et al., 1995; Purello-D'Ambrosio, Isola, Ricciardi, et al., 1999; Ratner, van Bavel, Martin, et al., 1998). The three combinations studies were loratadine-fluticasone, loratadine-flunisolide, and loratadine-beclomethasone. Four studies found no significant difference between the two treatments (Benincasa and Lloyd, 1994; Brooks, Francom, Peel, et al., 1996; Juniper, Kline, Hargreave, et al., 1989; Simpson, 1994).

For the meta-analysis, one study was excluded because data were not available to calculate an effect size for the total nasal score or nasal congestion score (Drouin, Yang, Horak, et al., 1995). Estimates comparing the effect of a combination nasal steroid-antihistamine to nasal steroid alone are shown in Figure 8. A test of homogeneity was insignificant ($p = 0.76$). The summary effect size was 0.09 (95% CI, -0.04 to 0.22), showing that nasal symptom scores were not significantly different between combination therapy and nasal steroid monotherapy. No subgroup analysis of non-sedating and sedating antihistamines was performed since only one study used a sedating antihistamine.

Thus, the addition of a nasal glucocorticoid to antihistamine relieves allergic rhinitis symptoms better than antihistamine alone; however, the combination of antihistamine-nasal glucocorticoid has not been shown to be better than nasal glucocorticoid alone, and confidence intervals suggest that the effect cannot be large.

Antihistamine-Decongestant versus Nasal Glucocorticoid

Only one study assessed the combination of antihistamine-decongestant (astemizole-D) compared to intranasal steroid (beclomethasone) for the treatment of seasonal allergic rhinitis over a 4-week period (Negrini, Troise, Voltolini, et al., 1995). There was no difference in the mean area under the curve for symptom severity in nasal congestion, sneezing, rhinorrhea, nasal itching, or total symptom scores. There was less use of ophthalmic rescue medication in the astemizole-D group compared to beclomethasone.

Antihistamines Combined With Other Therapies

Antihistamines in combination with a non-steroidal anti-inflammatory, ophthalmic antihistamine, ipratropium bromide, or mast cell stabilizer, have been compared to antihistamine alone for the treatment of allergic rhinitis.

A comparison of a nasal antihistamine (levocabastine) with or without a nasal decongestant (oxymetazoline) for 1 week in 977 seasonal allergy patients from the US and Canada found no statistically significant difference between the combination and the nasal antihistamine alone, but found the combination superior to the nasal decongestant alone for the relief of symptoms (Busse, Janssens, and Eisen, 1996). Most frequent side effects were headache or application site reactions (no significant difference, but higher in oxymetazoline and combination groups). The

global assessment of efficacy was higher in the levocabastine and levocabastine-oxymetazoline groups.

A study comparing terfenadine plus ipratropium bromide nasal spray with terfenadine alone for 2 weeks in 305 patients with perennial allergic and non-allergic rhinitis showed reduction in rhinorrhea severity and duration with the combined therapy, but no statistical difference in congestion or sneezing. Compared to terfenadine alone, the patient global assessment favored combined therapy (69 vs. 53 percent, $p = 0.0008$) (Finn, Aaronson, Korenblat, et al., 1998).

A comparison of terfenadine with or without nimesulide (a non-steroidal anti-inflammatory) showed a reduction in symptom severity scores ($p = 0.005$; 30-day treatment, seasonal allergic rhinitis) (Andri, Senna, Betteli, et al., 1992). A 7-day study evaluating terfenadine with or without flurbiprofen for seasonal allergic rhinitis showed differences in mean daily symptom scores for congestion and sneezing on day 3, and for running/blowing nose on day 4. The differences pre- and post-treatment were not compared; the treatment period may have been too short to adequately compare the treatments (Brooks and Karl, 1988).

A study evaluating astemizole with or without nedocromil sodium (1%) nasal spray and placebo control (mast cell stabilizer) showed lower mean symptom summary scores at the end of 4 weeks of treatment for ragweed seasonal allergies (combination > astemizole alone > placebo) (Bukstein, Biondi, Blumenthal, et al., 1996). Likewise, a comparison of loratadine with or without olopatadine ophthalmic solution for seasonal allergic conjunctivitis showed significantly lower itching with combination therapy after 1 week of treatment. RQLQ scores were significantly lower on combination therapy (Lanier, Gross, Marks, et al., 2001).

Nasal Glucocorticoids Combined With Other Therapies

Nasal glucocorticoids in combination with ipratropium bromide or a nasal decongestant have been studied in two trials. A comparison of a nasal steroid (budesonide) plus nasal decongestant (oxymetazoline for the 1st 3 days) versus nasal steroid alone or antihistamine alone showed that the two nasal steroid groups (combination and alone) were better than antihistamine alone for improving all nasal symptoms ($p < 0.05$; 3-week treatment, perennial rhinitis) (Lau, Wei, Van Hasselt, et al., 1990). The addition of oxymetazoline led to faster relief compared to budesonide alone, 1 day versus 7 days ($P < 0.05$). Interestingly, the patient global assessment of efficacy was not significantly different among the three groups.

One study compared ipratropium plus beclomethasone dipropionate nasal spray with ipratropium alone, beclomethasone alone, and placebo (2-week treatment, seasonal allergic rhinitis and non-allergic rhinitis) (Dockhorn, Aaronson, Bronsky, et al., 1999). All three active treatment groups were significantly better than placebo in reducing rhinorrhea severity and duration. Patients treated with the combination of ipratropium plus beclomethasone had greater percentage in the reduction of rhinorrhea severity and duration than ipratropium alone, which was better than beclomethasone alone. Patient global assessment of efficacy (good or excellent control of rhinorrhea) was combination > ipratropium > beclomethasone > placebo. RQLQ scores improved from baseline for all four groups (combined > ipratropium or placebo, $p < 0.05$). Rates of minor adverse events (headache, nasal dryness, epistaxis) were similar among all groups.

Conclusions

In summary, the combination of antihistamine with decongestant (pseudoephedrine) resulted in better overall symptom relief, both for total symptom score and total nasal/nasal congestion score, than did antihistamine or decongestant alone. The combination antihistamine-nasal glucocorticoid resulted in improved nasal symptom/nasal congestion scores when compared to antihistamine alone. However, a comparison of nasal glucocorticooid to the combination antihistamine-nasal glucocorticoid rules out more than a minimal difference in efficacy.

Other combinations have been studied in a small number of trials, and overall show that the addition of ipratropium is beneficial for rhinorrhea symptoms, the addition of ophthalmic antihistamines reduces eye itching, and the addition of the mast cell stabilizer nedocromil sodium or non-steroidal anti-inflammatory drugs to antihistamines may show benefit over antihistamine alone.

Clinician Specialty Differences

Introduction

This section addresses key research question 4: How do different types of healthcare providers (generalists, allergy specialists, and otolaryngologists) treat adults with allergic rhinitis, and how do treatment outcomes vary by provider? Healthcare from a specialist clinician may result in better health outcomes than care from a generalist because the specialist may make a more precise diagnosis, offer better selected or more intensive treatment, or educate or motivate the patient more effectively to use self-management skills. In asthmatic patients, specialist compared to generalist care has been shown to reduce emergency room return visits for acute exacerbations over a 28-week period (Zeiger and Schatz, 2000). Healthcare provided by a generalist may have advantages because the generalist may have a longer and more personalized relationship with the patient, may more fully understand the patient's other medical and social conditions, and may be better able to incorporate the chronic care required into the patient's regular healthcare utilization. A combination of clinicians or collaborative generalist-specialist care might provide the best care. In what follows, we attempt to describe the existing evidence on differences in allergic rhinitis treatment and outcomes by clinician specialty.

The referral of a patient with symptoms of allergic rhinitis to a specialist generally occurs because a generalist has been unable to satisfactorily alleviate the patient's symptoms, provide the needed patient education, or initiate a specific type of treatment, such as immunotherapy. There is general agreement that the generalist is well qualified to manage patients with symptoms of allergic rhinitis initially; however, some recommend that if the patient's symptoms do not improve in 3 to 6 months, then referral to an allergy specialist is indicated (Trotto, 1999). The population of an allergist's practice is highly skewed towards individuals who have been previously treated by a generalist, and it is likely that these patients have more severe allergies not controlled by first-line therapy.

Besides offering immunotherapy, a specialist may have a greater understanding of nasal anatomy and physiology, allowing for a more accurate diagnosis of allergic disorders and other sinonasal disorders that may mimic allergic rhinitis. Moreover, the skill of nasal endoscopy through a rigid or flexible endoscope may be an important aspect of the evaluation by the specialist (Fornadley, Corey, Osguthorpe, et al., 1996).

Much of the medical literature regarding clinician specialty in allergy treatment is not empirical research. The published literature on clinician specialty in the treatment of allergic rhinitis is all authored by allergy specialists (principally internists), otolaryngology allergists, and/or national allergy-related professional associations. Such papers are either reviews of the treatment of allergic rhinitis (usually in support of specialty-specific guidelines), descriptions of the current understanding of the etiology and basis for treatment of allergic rhinitis, or queries of existing databases for prevalence data. Most reviews concern indications for immunotherapy and advocate standardization of the preparation of allergy extracts. No comparisons have been made among specialists regarding outcomes of immunotherapy or allergy management. It has been noted that the surgical training of otolaryngology allergists allows this group of specialists to address anatomic abnormalities that may exacerbate the symptoms of allergic rhinitis (Krouse and Krouse, 1999; Petersson, 1995).

Regarding specific guidelines for treating allergic rhinitis, there is little evidence and no clear consensus in the literature to suggest that either the medically trained allergist or the surgically trained allergist offers any advantage over the other. Some guidelines advocate the position that specialty training in allergy is necessary to fully understand the basis of immunotherapy and that the practice of immunotherapy should use methods of proven efficacy (Royal College of Physicians and Royal College of Pathologists, 1995). Anaphylaxis from immunotherapy may also be best handled by the specialist. Current guidelines on allergic rhinitis also agree in failing to endorse "alternative therapies," including homeopathy, clinical ecology, or treatment for the "yeast syndrome" (Fornadley, Corey, Osguthorpe, et al., 1996; Joint Task Force on Practice Parameters in Allergy, and Asthma and Immunology, 1998; Royal College of Physicians and Royal College of Pathologists, 1995).

Results

A total of 26 articles (all large case series or surveys/analyses of secondary data) were selected for potential abstraction into evidence tables. Eighteen of these did not address our question and were excluded from further review. Of the eight articles included in Evidence Table 5, none directly addressed the question of clinician-specialty differences in treatment recommendations or outcomes; rather, they described the practice patterns of allergy management, patient preferences by clinician type, or effectiveness of patient education interventions.

The primary care clinician is usually the initial point of contact for treatment of adults suffering from symptoms of allergic rhinitis. Patients who continue to have nasal or sinus symptoms are often referred to an allergy specialist for additional evaluation and treatment. In a survey of 2,139 individuals in the UK, patients with perennial (two percent) and seasonal (15 percent) allergic rhinitis were identified; general practitioners were the main contact for advice and treatment for 54 percent of patients (Scadding, Richards, and Price, 2000). Twenty-seven percent sought the advice of their pharmacist; 22 percent did not seek any treatment; seven percent saw a health food consultant, herbalist, or alternative medicine advisor; and two percent consulted a specialist (Scadding, Richards, and Price, 2000).

In a survey of patients seen in an allergy clinic in Switzerland, 63 percent were referred by a generalist because of the severity of their symptoms, while 37 percent had wanted the referral to a specialist principally because of the specialist's skill in the diagnosis and management of allergic rhinitis (Francillon, Burnand, Frei, et al., 1995).

Among a series of 120 patients seen in a community-based otolaryngology practice who had rhinitis or sinusitis, 87 percent had previously seen a generalist, but 42 percent had previously consulted an otolaryngologist (Krouse and Krouse, 1999). Previous therapies included not only traditional therapies such as medications (70 percent), but also complementary treatments, including diet (45 percent), chiropractic manipulation (35 percent), herbal therapy (29 percent), biofeedback (26 percent), and acupuncture (19 percent). Medications used by patients included antihistamines (71 percent), antibiotics (71 percent), over-the-counter sinus medications (71 percent), decongestants (74 percent), steroid nasal sprays (52 percent), saline nasal sprays (52 percent), and saline irrigations (39 percent).

In seeking better treatment outcomes for patients with allergic rhinitis, Brydon (1993) explored the outcomes associated with an allergy management program utilizing allergy-trained nurse practitioners to educate and manage patients with allergic rhinitis. Twenty-three of 39 subjects had allergic rhinitis confirmed by skin testing, and this cohort of patients was followed for 9 months after seeing the allergy-trained nurse practitioners. The study found that the number of prescriptions and general practitioner visits dropped 39 percent and 71 percent, respectively ($p < 0.001$). The improved outcomes were attributed to better patient education provided by the allergy-trained nurse practitioners. However, the design of the study (uncontrolled, pre-post comparison case series) and high dropout rate (25 percent) raise serious concerns about the study's internal validity.

Other, less intensive educational interventions were studied in a randomized controlled trial (Gani, Pozzi, Crivellaro, et al., 2001). This study compared three patient education strategies among patients with allergic rhinitis attending an allergy specialty clinic. All patients were prescribed a nasal glucocorticoid spray, but each was, in addition, randomized to receive one of the following educational interventions: (a) written instructions provided by the drug manufacturer on the use of the nasal spray; (b) brief training and simplified written instructions on the use of the spray; or (c) a 1-hour lesson on allergic rhinitis, its treatment, the proper use of medications, and potential side effects given by a trained allergist. Although no differences in nasal symptoms were seen among the three groups, the untrained patients (group a) had a higher rate of non-adherence to treatment than the trained groups ($p = 0.001$) and the more intensively trained group (group c) had less use of rescue medication than the other groups ($p = 0.02$).

The question of whether generalists manage patients with allergic rhinitis appropriately was explored in a postal survey in the UK (White, Smith, Baker, et al., 1998). Fifty-four percent of allergic rhinitis patients had partially or poorly controlled symptoms on the medications they were using. However, 69 percent of these patients were not taking their medications appropriately. The authors concluded that better outcomes could be achieved by referral to an allergy specialist. No data were presented to support this conclusion, which rested entirely on the observation that specialists could offer immunotherapy to this subset of patients. The study appears to suggest that poor results of treatment in generalist practice may be related to non-compliance, or perhaps to insufficient patient education.

A survey of patients referred to an otolaryngologic clinic for the first time and reporting failure of nasal glucocorticoid treatment to control symptoms of allergic rhinitis described details regarding patients' use of nasal glucocorticoid spray (Camilleri, 1991). The author concluded that no more than 29 percent of treatment failures could be attributed to inadequate dosing which could be improved through patient education interventions.

A survey of 1,321 general practitioners in France reported on 3,026 patients with seasonal allergic rhinitis (Demoly, Allaert, Lecasble, et al., 2002). While half of the patients knew to

what allergens they reacted, only 11 percent had undergone allergy testing, most of whom had previous allergist consultation. Seventy-nine percent of patients believed they had adequate and appropriate information, but 58 percent indicated that they would like more advice. Only 55 percent of patients followed instructions scrupulously, and 44 percent self-medicated often.

Fewer data are published describing specialist clinician practice. One series reports on the treatments and outcomes of a large series of patients referred to otolaryngology specialty care specifically for allergy skin testing (Lane, Pine, and Pillsbury, 2001). The authors note that their experience may be unusual because "the majority of academic otolaryngology clinics do not directly provide [allergy skin testing]." Of 3,329 patients who had allergy skin testing by an otolaryngologist in one academic allergy clinic, 2,653 (79.7 percent) had positive skin test responses. Of those with positive skin test responses, 2,008 (75.7 percent) underwent immunotherapy. Among patients undergoing immunotherapy, average improvement was 3.9 on a scale of one to five. Patients with no improvement in nasal congestion symptoms had an average rating of 3.57, significantly lower than all patients combined ($p = 0.015$). From this case series, a survey of a subset of 275 patients currently undergoing immunotherapy showed that 84 (30.5 percent) had a history of nasal or sinus surgery either before immunotherapy (35.6 percent), after immunotherapy (57.8 percent), or concurrent with immunotherapy (six percent). Nasal congestion was the symptom most often reported to be improved after surgery (74.3 percent). Surgical procedures (131 procedures in 72 patients) included septoplasty (59 patients), reduction of inferior turbinates (38 patients), and endoscopic sinus surgery (34 patients), with 54 percent of patients having more than one procedure. The most frequent combination was septoplasty and reduction of inferior turbinates (18 patients). Mean self-reported effectiveness of immunotherapy was not significantly different between patients who had and had not undergone surgery.

Conclusions

Two studies suggest that clinician-delivered patient education interventions coupled with medical treatment may improve allergic rhinitis symptoms more than medical treatment alone. Several studies point to less than adequate knowledge regarding allergy treatment among patients in general medical practice. Although survey data suggest that many patients are referred from generalist practices to specialist clinicians based on the severity of symptoms, there are no published empirical data to support the view that specialist clinicians see more severely affected patients. A recent review similarly found no empirical evidence for differences in allergic rhinitis outcomes by clinician specialty, but cited some evidence in asthma (Zeiger and Schatz, 2000).

Future research related to generalist versus specialist care may require development of a standardized and validated severity-of-illness scale, which would allow better risk adjustment for comparing outcomes across settings and clinicians. However, prospective studies comparing alternative treatment models would provide more valid evidence to guide management decisions. Key issues would include: (a) comparing symptomatic treatment with allergen identification and specific immunological treatment; (b) comparing routine generalist-delivered symptomatic treatment with specialist-delivered symptomatic treatment; and (c) comparing various types of generalist-specialist collaborative care with traditional referral model care. The availability of clinical practice guidelines for allergic rhinitis (Joint Task Force on Practice Parameters in Allergy, and Asthma and Immunology, 1998) would permit a test of whether their

implementation improves generalist care through, for example, more specific and accurate diagnosis, more appropriate pharmacotherapy, or better patient education.

Racial and Ethnic Variation

Introduction

Susceptibility to allergic disease varies with genetic predisposition and environmental factors. Individuals with a family history of asthma or allergic rhinitis are two to six times more likely to develop allergic rhinitis (Lundback, 1998). Environmental factors such as indoor allergens and occupational exposures are associated with allergic rhinitis (Naclerio and Solomon, 1997). Conceptually, race or ethnicity may be associated with prevalence or treatment because of differing genetic susceptibilities, differing exposures to environmental factors, and different healthcare experiences related to factors such as access to care, quality of care, and patient preferences.

This section addresses key research question 5: In adult patients with symptoms of allergic rhinitis, does the prevalence, treatment patterns, or response to treatment vary according to a patient's race or ethnicity? Because few data were available on adults, we also included studies in children. We identified five studies addressing this question (see Evidence Table 6).

Results

Variation in Prevalence

The prevalence of allergic rhinitis in different racial groups was reported in three studies. The National Health and Nutrition Examination Survey, 1976 to 1980 (NHANESII), was a cross-sectional survey that estimated 1-year prevalence rates for respiratory conditions in the US civilian population (Turkeltaub and Gergen, 1991). To allow for US population-based estimates, results from the 12,742 respondents, aged 12 to 74, were weighted based on sampling methods and population estimates from the US Census Bureau. The interviewer assigned race, and allergic rhinitis was defined as a "physician diagnosis of hay fever or complained of frequent nasal and/or eye symptoms that varied by both season and pollen during the past 12 months, not counting colds or the flu." There was not a consistent relationship between prevalence and race. Allergic rhinitis was more prevalent in whites (7.8 percent, standard error [SE] 0.4) than blacks (5.1 percent, SE 0.6; $p < 0.01$). However, blacks were more likely than whites to report both allergic rhinitis and asthma (3.1 percent, SE 0.5 vs. 2.0 percent, SE 0.2; $p < 0.05$). There was no statistically significant association with race when all patients with allergic rhinitis (with or without asthma) were considered. These unadjusted results were not significantly changed by adjustment for age, sex, smoking status, poverty status, and rural or urban location.

The Cornell Family Illness Study followed 448 New York families to determine the incidence and burden of minor illnesses (Lebowitz, Cassell, and McCarroll, 1972). Diagnoses were established by self-reported symptoms collected through weekly interviews. Rhinitis was defined as a stuffy or runny nose that was not associated with a cold. The incidence of rhinitis varied from 0.7 episodes per person per year in whites to 0.4 episodes in blacks and 0.3 episodes in Puerto Ricans. Although age was identified as a possible confounder, the analysis did not adjust for differing age distributions in the racial groups.

Fagan and colleagues surveyed 2,044 seventh- through 12th-graders in Illinois (Fagan, Scheff, Hryhorczuk, et al., 2001). Rhinitis was defined as "sneezing or a runny or blocked nose not associated with a cold or the flu;" hay fever was defined as a "yes" response to the question, "Have you ever had hay fever?" In both unadjusted analyses and analyses adjusted for age, sex, family history of asthma, active smoking, and dampness exposure, there was no association between race and self-reported rhinitis (odds ratio [OR] 1.00; 95 percent confidence interval [CI], 0.68 to1.47) or hay fever (OR 1.18; 95 percent CI, 0.78 to 1.78).

In summary, three studies reported prevalence rates of allergic rhinitis by racial or ethnic groups. The largest and most representative study, NHANESII (Turkeltaub and Gergen, 1991), did not show a consistent relationship with race.

Finally, a fourth study (Strachan, Sibbald, Weiland, et al., 1997) contributed indirect information on this question. This international survey demonstrated wide variability in the 12-month prevalence of rhinitis and hay fever in children in 56 different countries: the prevalence of rhinitis ranged from 1.5 to 66.6 percent, and the prevalence of hay fever from 0 to 54.4 percent. Study investigators did not directly correlate differences in prevalence with differences in race or ethnicity; however, the wide variability in prevalence observed may be partly due to racial and ethnic differences, in addition to other factors such as language differences, environmental differences, and variations in the availability and use of treatments.

Variation in Treatment Patterns

We identified only one study that examined racial variation in treatment (Lower, Henry, Mandik, et al., 1993). This retrospective case series, based in a university pediatric allergy clinic, examined factors associated with adherence to immunotherapy. Among 315 patients with allergic rhinitis, ranging in age from 5 to 18 years old, 138 had discontinued treatment prior to completing the prescribed course. Whites were more likely to continue treatment than non-whites (61 vs. 36 percent).

Variation in Response to Treatment

We did not identify any studies that examined variation in response to treatment by race or ethnic group. Among the randomized trials reviewed for other questions addressed in this literature synthesis, only 13 (approximately 11 percent) described the racial characteristics of the study population (Berger, Fineman, Lieberman, et al., 1999; Bronsky, Boggs, Findlay, et al., 1995; Dockhorn, Aaronson, Bronsky, et al., 1999; Dockhorn, Williams, and Sanders, 1996; Finn, Aaronson, Korenblat, et al., 1998; Gabriel, Ng, Allan, et al., 1977; Huss, Huss, Squire, et al., 1994; Lanier, Gross, Marks, et al., 2001; Lau, Wei, Van Hasselt, et al., 1990; Ratner, van Bavel, Martin, et al., 1998; Shapiro, Wighton, Chinn, et al., 1999; Sussman, Mason, Compton, et al., 1999; Williams, Hull, McSorley, et al., 1996). None of these studies described results according to race or ethnicity of the subjects.

Conclusions

There are few studies addressing any aspect of racial variation in relation to prevalence, treatment patterns, or response to treatment for patients with allergic rhinitis. Few trials described the racial characteristics of the study population. At a minimum, randomized trials

should report patient characteristics that may allow evaluation of differences in response to treatment.

This review may not have identified all the relevant literature on race and prevalence or treatment for allergic rhinitis. Although we searched multiple databases with terms appropriate to the subject, it is possible that studies reporting treatments by racial groups are not indexed by relevant search terms and thus were not identified by our search.

Figure 2. Meta-analysis of placebo-controlled trials of immunotherapy for seasonal allergic rhinitis

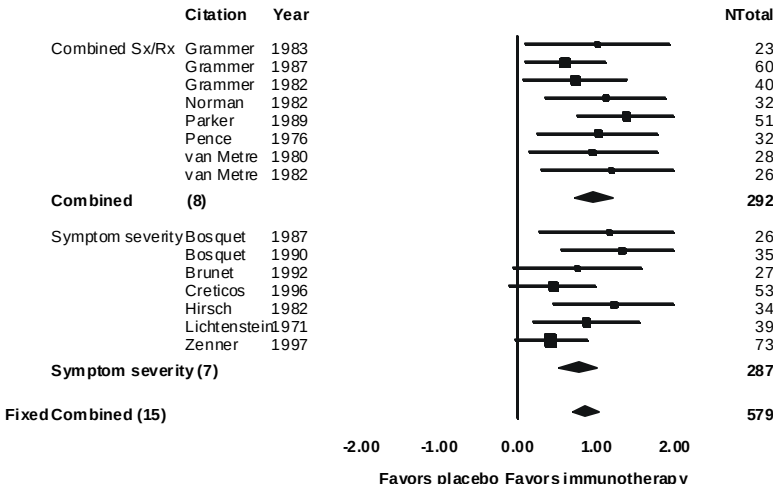

Figure 3. Meta-analysis of trials comparing antihistamine + decongestant combinations versus antihistamine alone: effect size based on differences in total symptom severity

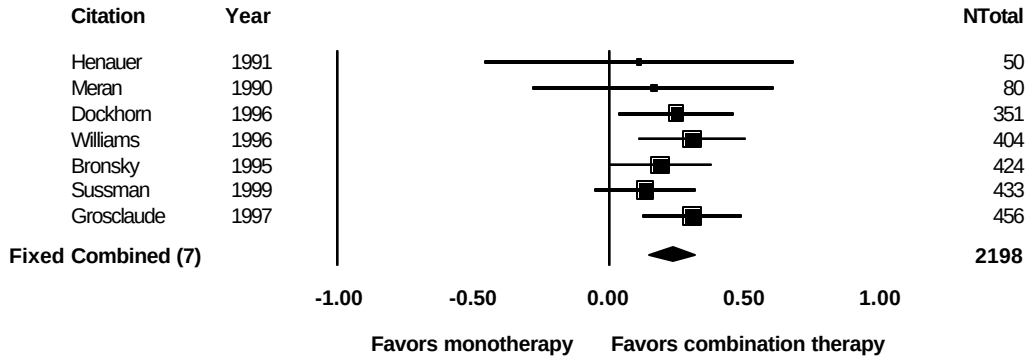

Figure 4. Meta-analysis of trials comparing antihistamine + decongestant combinations versus antihistamine alone: effect size based on differences in nasal symptom severity

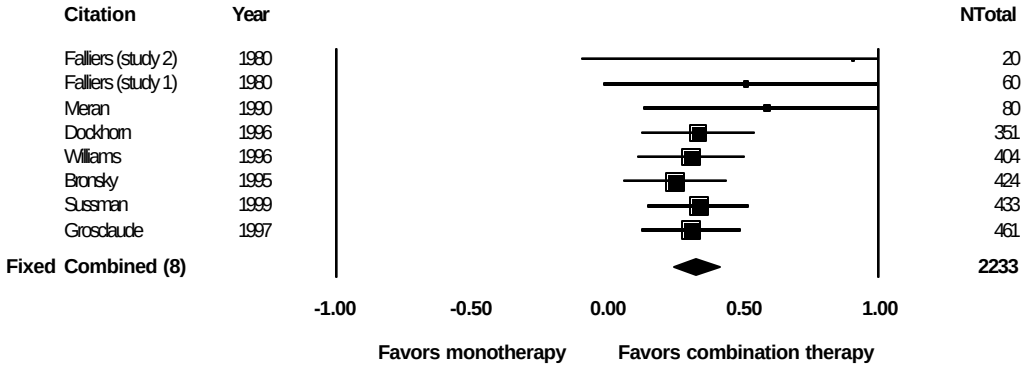

Figure 5. Meta-analysis of trials comparing antihistamine + decongestant combinations versus decongestant alone: effect size based on differences in total symptom severity

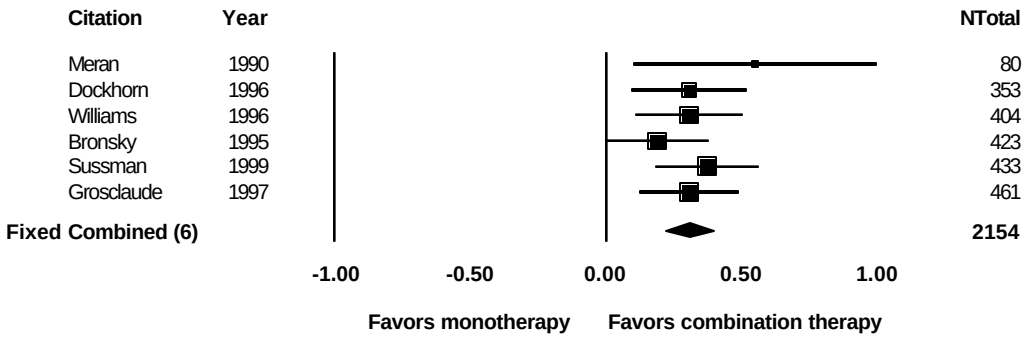

Figure 6. Meta-analysis of trials comparing antihistamine + decongestant combinations versus decongestant alone: effect size based on differences in nasal symptom severity

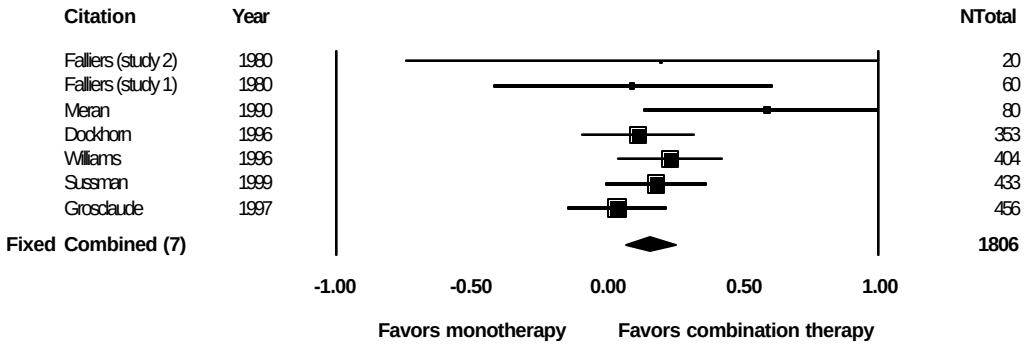

Figure 7. Meta-analysis of trials comparing antihistamine + nasal glucocorticoid combinations versus antihistamine alone: effect size based on differences in nasal symptom severity

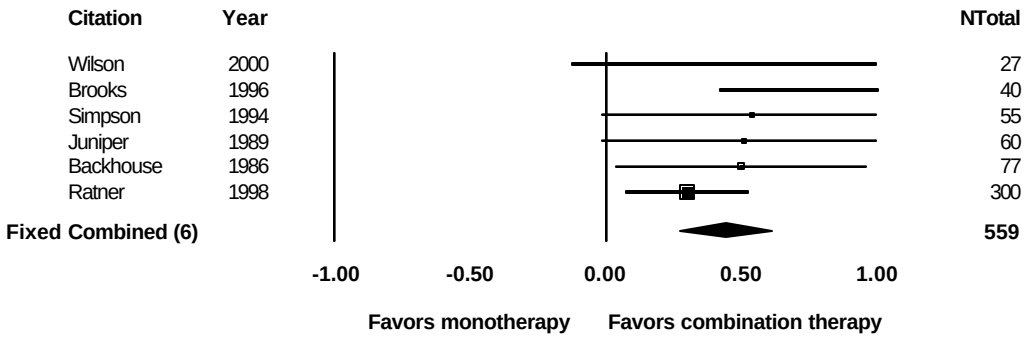

Figure 8. Meta-analysis of trials comparing antihistamine + nasal glucocorticoid combinations versus nasal glucocorticoid alone: effect size based on differences in nasal symptom severity

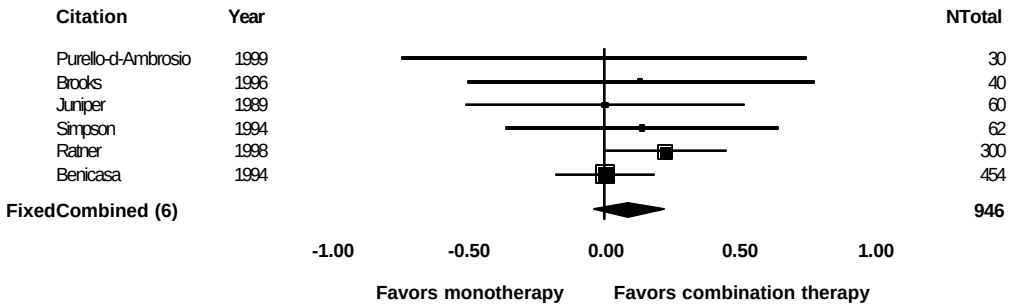

Table 13. Summary of types of data reported in studies abstracted in Evidence Table 1

Study	Data source	Per-patient burden of illness for selected populations	Total burden-of-illness estimates for US population	Cost-effectiveness	Work performance	Symptoms	Health-related quality of life
Blanc, Trupin, Eisner, et al., 2001	Telephone survey	X[1]			X	X	X
Burton, Conti, Chen, et al., 2001	Survey, work productivity data				X		
Cockburn, Bailit, Berndt, et al., 1999a; Cockburn, Bailit, Berndt, et al., 1999b	Prescription claims data, work productivity data				X		
Crystal-Peters, Crown, Goetzel, et al., 2000	1995 National Health Interview Survey and Bureau of Labor Statistics		X[2]				
Cuffel, Wamboldt, Borish, et al., 1999	Health care claims						
Donahue, Greineder, Connor-Lacke, et al., 1999	Health care claims	X					
Fell, Mabry, and Mabry, 1997	Survey	X[1]			X	X	
Gilmore, Alexander, Mueller, et al., 1996	Health care claims						
Keith, Haddon, and Birch, 2000	Randomized controlled trial	X		X[3]			
Kessler, Almeida, Berglund, et al., 2001	Survey	X			X		
Kozma, Schulz, Sclar, et al., 1996	Randomized controlled trial			X		X	
Lee, Cummins, and Okamoto, 2001	Health care claims	X					
Leickly, Sears-Ewald, and Ownby, 1989	Randomized controlled trial					X	
Liao, Leahy, and Cummins, 2001	Health care claims	X					
Malone, Lawson, Smith, et al., 1997	1987 National Medical Expenditure Survey		X				

(continued on next page)

Study	Data source	Per-patient burden of illness for selected populations	Total burden-of-illness estimates for US population	Cost-effectiveness	Work performance	Symptoms	Health-related quality of life
Manor, Matthews, and Power, 2001	Survey					X	
McMenamin, 1994	Multiple national surveys, government statistics		X				
Meltzer, Casale, Nathan, et al., 1999	Randomized controlled trial				X		X
Ray, Baraniuk, Thamer, et al., 1999	Multiple national surveys, expert opinion		X				
Reilly, Tanner, and Meltzer, 1996	Randomized controlled trial				X	X	X
Revicki, Leidy, Brennan-Diemer, et al., 1998	Survey				X	X	X
Ross, 1996	Multple national surveys, government statistics				X		
Santilli, Nathan, Glassheim, et al., 2001	Survey	X[1]				X	
Santos, Cifaldi, Gregory, et al., 1999 (Study 1)	Health care claims	X					
Santos, Cifaldi, Gregory, et al., 1999 (Study 2)	Randomized controlled trials	X			X	X	X
Schädlich and Brecht, 2000	Multiple published estimates			X			
Stahl, van Rompay, Wang, et al., 2000	Randomized controlled trials			X			
Storms, Meltzer, Nathan, et al., 1997	Survey		X		X		
Sussman, Mason, Compton, et al., 1999	Randomized controlled trials				X	X	
Tanner, Reilly, Meltzer, et al., 1999	Randomized controlled trials				X		X

(continued on next page)

Study	Data source	Per-patient burden of illness for selected populations	Total burden-of-illness estimates for US population	Cost-effectiveness	Work performance	Symptoms	Health-related quality of life
Trotter, 2000	Prescription claims	X					
Yawn, Yunginger, Wollan, et al., 1999	Patient registry	X					

[1] Costs not assigned, but estimates of resource utilization reported.
[2] Indirect costs only.
[3] Cost-benefit analysis in which benefits were measured with a willingness-to-pay survey.

Table 14. Placebo-controlled randomized controlled trials of injection immunotherapy (IT) for seasonal allergic rhinitis, by type of allergen

Allergen	Number of trials	Number of subjects	Number of trials favoring IT	Number of trials with negative or equivocal results
Ragweed	18	990	14	4
Grass (any)	13	604	12	1
Tree (any)	7	168	7	0
Parietaria	4	170	4	0

Table 15. Data abstracted for meta-analysis of placebo-controlled trials of immunotherapy (IT) for seasonal allergic rhinitis

Study	Allergen	Symptom measure-ment period	Outcome	IT mean	IT SD	IT n	Placebo mean	Placebo SD	Placebo n	Statistical test	P-value	IPD?
Ariano, Kroon, Augeri, et al., 1999	Tree	7 mo	Combined Sx/Rx	550 (median)	NR	11	1250 (median)	NR	11	Non-parametric	p = 0.02	No
Arvidsson, Löwhagen, and Rak, 2002	Tree	6 wk	Sx severity	1.3 (median)	0-5.2 (range)	22	2.1 (median)	0.6-5.6 (range)	24	Non-parametric	p = 0.05	No
Arvidsson, Löwhagen, and Rak, 2002	Tree	6 wk	Rx use	NR	NR	22	NR	NR	24	Non-parametric	p = 0.004	No
Bernstein, Tennenbaum, Georgakis, et al., 1976	Ragweed	4 wk	Sx severity	1.097 (mean daily score)	NR	58 (est.)	1.378 (mean daily score)	NR	54 (est.)	Not specified	p < 0.05	No
Bernstein, Tennenbaum, Georgakis, et al., 1976	Ragweed	4 wk	Rx use	0.411 (measured score)	NR	58 (est.)	0.584 (measured score)	NR	54 (est.)	Not specified	p < 0.01	No
Bødtger, Poulsen, Jacobi, et al., 2002	Tree	2 wk	Rx use	32.5 (median)	6.0-71.0 (range)	17	51.0 (median)	14.0-76.0 (range)	17	Non-parametric	p < 0.04	No
Bødtger, Poulsen, Jacobi, et al., 2002	Tree	2 wk	Rx use	52.0 (median)	2.0-114.0 (range)	17	102.0 (median)	2.0-186.0 (range)	17	Non-parametric	p < 0.02	No
Bousquet, Frank, Soussana, et al., 1987	Grass	6 wk	Sx severity	61.0	35.0	35	109	33	16	Non-parametric	p < 0.01	No
Bousquet, Hejjaoui, Skassa-Brociek, et al., 1987	Grass	4 wk	Sx severity	9.5 (median)	10.0	15	20.5 (median)	7	11	Non-parametric	p < 0.005	Graph

(continued on next page)

Study	Allergen	Symptom measure-ment period	Outcome	IT mean	IT SD	IT n	Placebo mean	Placebo SD	Placebo n	Statistical test	P-value	IPD?
Bousquet, Hejjaoui, Skassa-Brociek, et al., 1987	Grass	4 wk	Rx use	0.84	2.25	15	2.67	1.54	11	Non-parametric	p < 0.01	Graph
Bousquet, Hejjaoui, Soussana, et al., 1990	Grass	6 wk	Sx severity	63.6	32.5	20	108.6	33.2	15	Non-parametric	p < 0.005	Graph
Bousquet, Hejjaoui, Soussana, et al., 1990	Grass	6 wk	Rx use	38.6	37.6	20	66.4	51.7	15	Non-parametric	p < 0.05	No
Bousquet, Hejjaoui, Soussana, et al., 1990	Grass	6 wk	Sx days	22.9	11.4	20	40.2	7.1	15	Non-parametric	p < 0.01	No
Bousquet, Maasch, Hejjaoui, et al., 1989	Grass	4 wk	Sx severity	14.8	22.9	18	63.5	54.6	14	Non-parametric	p < 0.001	No
Bousquet, Maasch, Hejjaoui, et al., 1989	Grass	4 wk	Rx use	22.9	39.1	18	53.7	54.1	14	Non-parametric	p < 0.001	No
Bousquet, Maasch, Hejjaoui, et al., 1989	Grass	4 wk	Sx days	9.0	10.7	18	26.5	8.6	14	Non-parametric	p < 0.01	Graph
Brunet, Bedard, Lavoie, et al., 1992	Ragweed	4 wk	Sx severity	4.7	0.7 (SEM)	13	7.5	1.2 (SEM)	14	Non-parametric	p < 0.05	Graph
Brunet, Bedard, Lavoie, et al., 1992	Ragweed	4 wk	Rx use	0.9	0.2 (SEM)	13	0.7	0.2 (SEM)	14	Non-parametric	p < 0.6	No

(continued on next page)

Study	Allergen	Symptom measure-ment period	Outcome	IT mean	IT SD	IT n	Placebo mean	Placebo SD	Placebo n	Statistical test	P-value	IPD?
Cockcroft, Cuff, Tarlo, et al., 1977	Ragweed	Not specified	Sx severity	4.95	NR	21	5.75	NR	21	Parametric	p = NS (0.05 < p < 0.10)	No
Cockcroft, Cuff, Tarlo, et al., 1977	Ragweed	Not specified	Sx severity	2.29	NR	21	4.37	NR	21	Parametric	p < 0.05	No
Creticos, Reed, Norman, et al., 1996	Ragweed	4 mo pre-trial observa-tion; year-1 data	Sx severity	3.5 (year 1)	0.5	29	4.3 (year 1)	0.5	24	Parametric	p < 0.1	No
Grammer, Shaughnessy, Bernhard, et al., 1987	Ragweed	5 wk	Combined Sx/Rx	7.76	NR	30	17.4	NR	30	Parametric	p = 0.02	No
Grammer, Shaughnessy, Suszko, et al., 1983	Grass	9 wk	Combined Sx/Rx	210	75 (SEM)	10	500	115 (SEM)	13	Non-parametric	p = 0.02	No
Grammer, Zeiss, Suszko, et al., 1982	Ragweed	7 wk	Combined Sx/Rx	332.	64 (SEM)	21	530	83 (SEM)	19	Parametric	p = 0.022	No
Hirsch, Kalbfleisch, and Cohen, 1982	Ragweed	6 wk	Sx severity	24.8	15.1	20	45.9	18.6	14	Parametric	p < 0.004	No
Hirsch, Kalbfleisch, and Cohen, 1982	Ragweed	6 wk	Rx use	4.0	7.4	20	8.3	2.3	14	Parametric	p < 0.025	No
Iliopoulos, Proud, Adkinson, et al., 1991	Ragweed	Not specified	Combined Sx/Rx	NR	NR	21	NR	NR	20	Non-parametric	p < 0.04	No

(continued on next page)

Study	Allergen	Symptom measure-ment period	Outcome	IT mean	IT SD	IT n	Placebo mean	Placebo SD	Placebo n	Statistical test	P-value	IPD?
Leynadier, Banoun, Dollois, et al., 2001	Grass	12 wk	Sx severity	49.5	NR	16	56	NR	13	Non-parametric	p = NS	No
Leynadier, Banoun, Dollois, et al., 2001	Grass	12 wk	Rx use	11.1	NR	16	40.8	NR	13	Non-parametric	p = 0.005	No
Lichtenstein, Norman, and Winken-werder, 1971	Ragweed	8 wk	Sx severity	7.25	NR	18	11.125	NR	21	Non-parametric	p < 0.01	Graph
McAllen, 1969	Grass	7 wk	Sx severity	54	NR	40	72	NR	20	Non-parametric	p = 0.074	No
McAllen, 1969	Grass	7 wk	Sx days	35	NR	40	28.5	NR	20	Non-parametric	p = 0.087	No
Norman, Lichtenstein, Kagy-Sobotka, et al., 1982	Ragweed	NR	Combined Sx/Rx	5.3	NR	16	8.8	NR	17	Non-parametric	p < 0.01	Graph
Ortolani, Pastorello, Incorvaia, et al., 1994	Tree	4 wk	Combined Sx/Rx	NR	NR	17	NR	NR	14	Non-parametric	p < 0.05	No
Parker, Whisman, Apaliski, et al., 1989	Tree	10 days	Combined Sx/Rx	57.0	NR	26	129.9	NR	25	Non-parametric	p = 0.0001	Yes
Pastorello, Pravettoni, Incorvaia, et al., 1992	Grass	4 wk	Combined Sx/Rx	NR	NR	10	NR	NR	9	Non-parametric	p < 0.01	No
Pence, Mitchell, Greely, et al., 1976	Tree	12 wk	Combined Sx/Rx	5.46	3.22	17	8.83	3.15	15	Parametric	p < 0.01	Yes

(continued on next page)

Study	Allergen	Symptom measure-ment period	Outcome	IT mean	IT SD	IT n	Placebo mean	Placebo SD	Placebo n	Statistical test	P-value	IPD?
Van Metre, Adkinson, Amodio, et al., 1980	Ragweed	8 wk	Combined Sx/Rx	3.0	NR	15	5.0	NR	14	Non-parametric	p < 0.01	Graph
Van Metre, Adkinson, Amodio, et al., 1982	Ragweed	8 wk	Combined Sx/Rx	3.79	NR	15	11.14	NR	11	Non-parametric	p < 0.01	Graph
Varney, Gaga, Frew, et al., 1991	Grass	11 wk	Sx severity	360	NR	21	928	NR	16	Non-parametric	p = 0.001	No
Varney, Gaga, Frew, et al., 1991	Grass	11 wk	Rx use	129	NR	21	627	NR	16	Non-parametric	p = 0.002	No
Walker, Pajno, Limo, et al., 2001	Grass	11 wk (2 seasons: 1996 & 1998)	Grass	Difference between IT and placebo = 1186.5	241.5 to 1928.6	22	See IT mean	See IT SD	22	Non-parametric	p = 0.01	No
Walker, Pajno, Limo, et al., 2001	Grass	11 wk (2 seasons: 1996 & 1998)	Grass	Difference between IT and placebo = 1043.0	332.0 to 2667.1	22	See IT mean	See IT SD	22	Non-parametric	p = 0.007	No
Weyer, Donat, L'Heritier, et al., 1981	Grass	6 wk	Sx severity	16	10	17	24	8	16	Non-parametric	p < 0.09	No
Weyer, Donat, L'Heritier, et al., 1981	Grass	6 wk	Rx use	3	5	17	11	13	16	Non-parametric	p < 0.07	No
Weyer, Donat, L'Heritier, et al., 1981	Grass	6 wk	Combined Sx/Rx	10	7	17	18	15	16	Non-parametric	p < 0.03	No
Zenner, Baumgarten, Rasp, et al., 1997	Grass	10 wk	Sx severity	82.2	10.1	45	116	13.2	41	Non-parametric	p < 0.025	Graph
Zenner, Baumgarten, Rasp, et al., 1997	Grass	10 wk	Rx use	26% of 70 days	NR	45	33% of 70 days	NR	41	Non-parametric	p < 0.296	No

Abbreviations: IPD = individual patient data; IT = immunotherapy; mo = month(s); n = number of patients; NR = not reported; NS = not significant; Rx = medication; SD = standard deviation; SEM = standard error of the mean; Sx = symptom; wk = weeks

Table 16. Placebo-controlled randomized controlled trials of injection immunotherapy (IT) for perennial allergic rhinitis, by type of allergen

Allergen	Number of trials	Number of subjects	Number of trials favoring IT	Number of trials with negative or equivocal results
Dust mite	7	357	5	2
Dust mite and pollen	1	10	0	1
Cat	1	28	1	0
Mold (*Alternaria*)	1	22	1	0
Latex	1	14	1	0
Multiple antigens	1	36	1	0

Table 17. Randomized controlled trials comparing combination pharmacotherapy to monotherapy for allergic rhinitis

Treatment 1	Treatment 2	No. of comparisons	Results
Antihistamine + oral decongestant	Antihistamine	13	7 combination superior, 3 no significant difference, 3 no difference, no statistical test reported
Antihistamine + oral decongestant	Decongestant	10	8 combination superior, 2 possibly superior
Antihistamine + oral decongestant	Nasal glucocorticoid	1	No significant difference
Antihistamine + nasal glucocorticoid	Nasal glucocorticoid	7	3 combination superior, 4 no significant difference
Antihistamine + nasal glucocorticoid	Antihistamine	7	5 combination superior, 2 possibly superior
Antihistamine + mast cell stabilizer	Antihistamine	1	Combination superior
Antihistamine + NSAID	Antihistamine	2	Combination superior (1 study)
Antihistamine + ophthalmic antihistamine	Antihistamine	1	Combination reduced eye itching
Antihistamine + ipratropium	Antihistamine	1	Combination reduced rhinorrhea
Ipratropium + nasal glucocorticoid	Nasal glucocorticoid	1	Combination reduced rhinorrhea
Ipratropium + nasal glucocorticoid	Ipratropium	1	Combination reduced rhinorrhea
Nasal glucocorticoid + 3 days nasal decongestant	Nasal glucocorticoid	1	No significant difference
Nasal glucocorticoid + 3 days nasal decongestant	Antihistamine	1	Combination superior
Nasal antihistamine + nasal decongestant	Nasal antihistamine	1	No significant difference
Nasal antihistamine + nasal decongestant	Nasal decongestant	1	Combination superior

Table 18. Data abstracted for meta-analysis of combination treatment articles

Study	Combination	Mono-therapy	Outcome	Combo mean	Combo SD	Combo n	Mono mean	Mono SD	Mono n	Statistical test	P-value	Possible to calculate ES?
A. Antihistamine + decongestant combinations versus antihistamine alone, total symptom severity (see also Figure 3)												
Bronsky, Boggs, Findlay, et al., 1995	Loratadine+ pseudo-ephedrine	Loratadine	TSS	6.72	NR	212	5.6	NR	212	ANOVA	P < 0.05	Yes
Dockhorn, Williams, and Sanders, 1996	Acrivastine+ pseudo-ephedrine	Acrivastine	TSS	10.3	NR	176	12.3	NR	175	ANCOVA (1-sided)	P < 0.001	Yes
Falliers and Redding, 1980 (study 1)	Azatadine+ pseudo-ephedrine	Azatadine	TSS	70% reduc-tion	NR	30	52% reduc-tion	NR	30	ANOVA	NR	No
Falliers and Redding, 1980 (study 2)	Azatadine+ pseudo-ephedrine	Azatadine	TSS	82% reduc-tion	NR	10	58% reduc-tion	NR	10	ANOVA	NR	No
Grosclaude, Mees, Pinelli, et al., 1997	Cetirizine+ pseudo-ephedrine	Cetirizine	TSS	0.85	NR	230	1.03	NR	226	ANOVA	P < 0.001	Yes
Henauer, Seppey, Hugenot, et al., 1991	Terfenadine+ pseudo-ephedrine	Terfenadine	TSS	NR	NR	25	NR	NR	25	ANOVA	P = 0.69	Yes
Meran, Morse, and Gibbs, 1990	Acrivastine+ pseudo-ephedrine	Acrivastine	TSS	1.66	2.25	40	2.04	2.25	40	ANOVA (log-trans-formed scores)	P = 0.45	Yes
Sussman, Mason, Compton, et al., 1999	Fexofenadine + pseudo-ephedrine	Fexo-fenadine	TSS	2.32	NR	215	2.05	NR	218	ANCOVA	P ~ 0.16	Yes

(continued on next page)

Study	Combination	Mono-therapy	Outcome	Combo mean	Combo SD	Combo n	Mono mean	Mono SD	Mono n	Statistical test	P-value	Possible to calculate ES?
Williams, Hull, McSorley, et al., 1996	Acrivastine+ pseudo-ephedrine	Acrivastine	TSS	8.5	NR	202	9.8	NR	202	ANCOVA	P < 0.001 (1-sided)	Yes
B. Antihistamine + decongestant versus antihistamine alone, nasal symptom severity (see also Figure 4)												
Bertrand, Jamart, Marchal, et al., 1996	Cetirizine+ pseudo-ephedrine	Cetirizine	Nasal obstruc-tion	Graph	NR	70	Graph	NR	70	CMH (categori-cal)	P = 0.005	No
Bronsky, Boggs, Findlay, et al., 1995	Loratadine+ pseudo-ephedrine	Loratadine	NSS	NR	NR	212	NR	NR	212	ANOVA	P < 0.01	Yes
Dockhorn, Williams, and Sanders, 1996	Acrivastine+ pseudo-ephedrine	Acrivastine	NSS	3.8	NR	176	4.7	NR	175	ANCOVA (1-sided)	P < 0.001	Yes
Falliers and Redding, 1980 (study 1)	Azatadine+ pseudo-ephedrine	Azatadine	NSS	68% reduc-tion	NR	30	35% reduc-tion	NR	30	ANOVA	P < 0.05	Yes
Falliers and Redding, 1980 (study 2)	Azatadine+ pseudo-ephedrine	Azatadine	NSS	73% reduc-tion	NR	10	27% reduc-tion	NR	10	ANOVA	P < 0.05	Yes
Grosclaude, Mees, Pinelli, et al., 1997	Cetirizine+ pseudo-ephedrine	Cetirizine	NSS	1.19	NR	230	1.43	NR	226	ANOVA	P < 0.001	Yes
Meran, Morse, and Gibbs, 1990	Acrivastine+ pseudo-ephedrine	Acrivastine	NSS	1.89	NR	40	2.41	NR	40	ANOVA (log-trans-formed scores)	P < 0.01	Yes

(continued on next page)

Study	Combination	Mono-therapy	Outcome	Combo mean	Combo SD	Combo n	Mono mean	Mono SD	Mono n	Statistical test	P-value	Possible to calculate ES?
Sussman, Mason, Compton, et al., 1999	Fexofenadine + pseudo-ephedrine	Fexo-fenadine	NSS	0.56	NR	215	0.36	NR	218	ANCOVA	P < 0.0005	Yes
Williams, Hull, McSorley, et al., 1996	Acrivastine+ pseudo-ephedrine	Acrivastine	NSS	2.3	NR	202	2.7	NR	202	ANCOVA	P < 0.001 (1-sided)	Yes
C. Antihistamine + decongestant combination versus decongestant alone, total symptom severity (see also Figure 5)												
Bronsky, Boggs, Findlay, et al., 1995	Loratadine+ pseudo-ephedrine	Pseudo-ephedrine	TSS	6.72	NR	212	5.32	NR	212	ANOVA	P < 0.05	Yes
Dockhorn, Williams, and Sanders, 1996	Acrivastine+ pseudo-ephedrine	Pseudo-ephedrine	TSS	10.3	NR	176	11.8	NR	177	ANCOVA (1-sided)	P = 0.002	Yes
Falliers and Redding, 1980 (study 1)	Azatadine+ pseudo-ephedrine	Pseudo-ephedrine	TSS	70% reduc-tion	NR	30	43% reduc-tion	NR	30	ANOVA	NR	No
Falliers and Redding, 1980 (study 2)	Azatadine+ pseudo-ephedrine	Pseudo-ephedrine	TSS	82% reduc-tion	NR	10	55% reduc-tion	NR	10	ANOVA	NR	No
Grosclaude, Mees, Pinelli, et al., 1997	Cetirizine+ pseudo-ephedrine	Pseudo-ephedrine	TSS	0.85	NR	230	1.14	NR	231	ANOVA	P < 0.001	Yes
Meran, Morse, and Gibbs, 1990	Acrivastine+ pseudo-ephedrine	Pseudo-ephedrine	TSS	1.66	2.25	40	2.92	2.25	40	ANOVA (log-trans-formed scores)	P = 0.014	Yes

(continued on next page)

Study	Combination	Mono-therapy	Outcome	Combo mean	Combo SD	Combo n	Mono mean	Mono SD	Mono n	Statistical test	P-value	Possible to calculate ES?
Sussman, Mason, Compton, et al., 1999	Fexofenadine + pseudo-ephedrine	Pseudo-ephedrine	TSS	2.32	NR	215	1.42	NR	218	ANCOVA	P < 0.0001	Yes
Williams, Hull, McSorley, et al., 1996	Acrivastine+ pseudo-ephedrine	Pseudo-ephedrine	TSS	8.5	NR	202	10.8	NR	202	ANCOVA	P < 0.001 (1-sided)	Yes
D. Antihistamine + decongestant combination versus decongestant alone, nasal symptom severity (see also Figure 6)												
Bertrand, Jamart, Marchal, et al., 1996	Cetirizine+ pseudo-ephedrine	Pseudo-ephedrine	Nasal obstruc-tion	Graph	NR	70	Graph	NR	70	CMH (categori-cal)	P = 0.025	No
Bronsky, Boggs, Findlay, et al., 1995	Loratadine+ pseudo-ephedrine	Pseudo-ephedrine	NSS	NR	NR	212	NR	NR	212	ANOVA	P = NS	No
Dockhorn, Williams, and Sanders, 1996	Acrivastine+ pseudo-ephedrine	Pseudo-ephedrine	NSS	3.8	NR	176	4.1	NR	177	ANCOVA (1-sided)	P ~ 0.29	Yes
Falliers and Redding, 1980 (study 1)	Azatadine+ pseudo-ephedrine	Pseudo-ephedrine	NSS	68% reduc-tion	NR	30	62% reduc-tion	NR	30	ANOVA	P ~ 0.72	Yes
Falliers and Redding, 1980 (study 2)	Azatadine+ pseudo-ephedrine	Pseudo-ephedrine	NSS	73% reduc-tion	NR	10	63% reduc-tion	NR	10	ANOVA	P ~ 0.65	Yes
Grosclaude, Mees, Pinelli, et al., 1997	Cetirizine+ pseudo-ephedrine	Pseudo-ephedrine	NSS	1.19	NR	230	1.22	NR	231	ANOVA	P ~ 0.68	Yes

(continued on next page)

Study	Combination	Mono-therapy	Outcome	Combo mean	Combo SD	Combo n	Mono mean	Mono SD	Mono n	Statistical test	P-value	Possible to calculate ES?
Meran, Morse, and Gibbs, 1990	Acrivastine+ pseudo-ephedrine	Pseudo-ephedrine	NSS	1.89	NR	40	2.88	NR	40	ANOVA (log-trans-formed scores)	P < 0.01	Yes
Sussman, Mason, Compton, et al., 1999	Fexofenadine+ pseudo-ephedrine	Pseudo-ephedrine	NSS	0.56	NR	215	0.45	NR	218	ANCOVA	P ~ 0.059	Yes
Williams, Hull, McSorley, et al., 1996	Acrivastine+ pseudo-ephedrine	Pseudo-ephedrine	NSS	2.3	NR	202	2.6	NR	202	ANCOVA	P ~ 0.01 (1-sided)	Yes
E. Antihistamine + nasal glucocorticoid versus antihistamine alone, nasal symptom severity (see also Figure 7)												
Backhouse, Finnamore, and Gosden, 1986	Terfenadine+ flunisolide nasal spray	Terfenadine	Nasal con-gestion	1.4	0.7	49	1.8	0.9	50	t-test	P ~ 0.03	Yes
Brooks, Francom, Peel, et al., 1996	Loratadine+ beclo-methasone nasal spray	Loratadine	Nasal con-gestion	NR	NR	20	NR	NR	20	ANOVA	P < 0.001	Yes
Juniper, Kline, Hargreave, et al., 1989	Astemizole+ beclo-methasone nasal spray	Astemizole	Nasal con-gestion	0.322	NR	30	0.594	NR	30	ANOVA	P < 0.05	Yes
Ratner, van Bavel, Martin, et al., 1998	Loratadine+ fluticasone nasal spray	Loratadine	NSS	160	NR	150	232	NR	150	ANOVA	P < 0.01	Yes
Simpson, 1994	Terfenadine+ budesonide nasal spray	Terfenadine	Blocked nose	7	NR	32	14	NR	23	ANOVA	P < 0.05	Yes

(continued on next page)

Study	Combination	Mono-therapy	Outcome	Combo mean	Combo SD	Combo n	Mono mean	Mono SD	Mono n	Statistical test	P-value	Possible to calculate ES?
Wilson, Dempsey, Sims, et al., 2000	Cetirizine+ mometasone nasal spray	Cetirizine	NSS	1.8	0.6 (SEM)	14	3.5	0.7 (SEM)	13	MANOVA with pairwise comparison	P ~ 0.07	Yes
F. Antihistamine + nasal glucocorticoid versus nasal glucocorticoid alone, nasal symptom severity (see also Figure 8)												
Benincasa and Lloyd, 1994	Cetirizine+ fluticasone nasal spray	Fluticasone nasal spray	NSS	1.5	1.6	227	1.5	1.4	227	t-test	P = 1.0	Yes
Brooks, Francom, Peel, et al., 1996	Loratadine+ beclo-methasone nasal spray	Beclo-methasone nasal spray	Nasal con-gestion	NR	NR	20	NR	NR	20	ANOVA	P = 0.66	Yes
Drouin, Yang, Horak, et al., 1995	Loratadine+ belclo-methasone nasal spray	Beclo-methasone nasal spray	NSS	66% im-proved	NR	76	59% im-proved	NR	78	ANOVA	P = NS	No
Juniper, Kline, Hargreave, et al., 1989	Astemizole+ beclo-methasone nasal spray	Beclo-methasone nasal spray	Nasal con-gestion	0.322	NR	30	0.319	NR	30	ANOVA	P ~ 0.98	Yes
Purello-D'Ambro-sio, Isola, Ricciardi, et al., 1999	Loratadine+ flunisolide nasal spray	Flunisolide nasal spray	Nasal blockage	19.9%	NR	15	20%	NR	15	ANOVA	P ~ 1.0	Yes
Ratner, van Bavel, Martin, et al., 1998	Loratadine+ fluticasone nasal spray	Fluticasone nasal spray	NSS	160	NR	150	192	NR	150	ANOVA	P < 0.05	Yes
Simpson, 1994	Terfenadine+ budesonide nasal spray	Budesonide nasal spray	Blocked nose	7	NR	32	5.5	NR	30	ANOVA	P ~ 0.58	Yes

Abbreviations: ANCOVA = analysis of covariance; ANOVA = analysis of variance; CMH = Cochran-Mantel-Haenszel; ES = effect size; MANOVA = multivariate analysis of variance; n = number of patients; NR = not reported; NS = not significant; NSS = nasal symptom severity; SD = standard deviation; TSS = total symptom score

Table 19. Summary of meta-analysis of randomized controlled trials comparing combination pharmacotherapy to monotherapy for allergic rhinitis

Combination	Comparator drug	Number of studies	Total number of patients	Outcome evaluated	Summary effect size (95% confidence interval
Antihistamine-decongestant	Antihistamine	7	2298	Total symptom score	0.23 (0.15 to 0.32)
Antihistamine-decongestant	Decongestant	6	2154	Total symptom score	0.31 (0.22 to 0.39)
Antihistamine-decongestant	Antihistamine	8	2233	Nasal symptom score	0.33 (0.24 to 0.41)
Antihistamine-decongestant	Decongestant	7	1806	Nasal symptom score	0.16 (0.07 to 0.25)
Antihistamine-nasal glucocorticoid	Antihistamine	6	559	Nasal symptom score	0.44 (0.27 to 0.61)
Antihistamine-nasal glucocorticoid	Nasal glucocorticoid	6	946	Nasal symptom score	0.9 (-0.4 to 0.22)

Chapter 4. Conclusions

Allergic rhinitis, as a common illness in the US working-age population, is the subject of a sizable amount of research. A small but growing body of research focuses on the effects of allergic rhinitis and its treatment on outcomes that are particularly relevant to working-age allergic rhinitis sufferers and the clinicians involved in their care, and to employers and health insurers. We addressed several questions that are key to understanding and improving allergic rhinitis care in the US. While many of these questions remain unanswerable based on currently available research, some firm conclusions can be reached, and several high priorities for future research can be identified.

Specific conclusions for each topic considered are summarized below.

Costs and Work Performance

- Allergic rhinitis is associated with enormous direct and indirect costs in the US, with estimates as high as $4.5 billion and $7.7 billion annually, respectively; an updated comprehensive burden-of-illness study is necessary to more precisely estimate direct and indirect costs, for which currently available estimates vary four- to six-fold.

- There are few well-conducted, generalizable studies of direct and indirect costs for currently available clinical treatments.

- Economic evaluations of allergic rhinitis treatments often do not adequately consider uncertainty about estimates of the efficacy of treatments, often inappropriately using cost-minimization analyses rather than cost-effectiveness analyses.

- There is a lack of consensus on an appropriate and clinically meaningful measure of "effectiveness" to be used in the denominator of a cost-effectiveness ratio.

- The few available standardized instruments that assess allergic rhinitis symptoms are not yet widely used.

- Additional studies are needed to better understand how the severity of allergic rhinitis symptoms and the various medications used to treat those symptoms affect productivity.

- In order to better estimate indirect costs of allergic rhinitis treatments, objective measures of work performance are needed to determine the relationship between symptom outcomes and work performance.

Environmental Measures

Based on the pathophysiology of allergic rhinitis, treatments that decrease allergen exposure sufficiently through environmental control measures can be expected to control symptoms. Our systematic review showed that:

- Allergen avoidance measures have been studied more often in children than in adults with allergic rhinitis.

- Studies of air filtration systems do not show strong evidence for decreasing rhinitis symptoms; however, studies were likely underpowered to detect clinically relevant differences.

- A few trials in highly selected patients suggest that dust-mite control measures such as an acaricide, impervious covers, and extra house cleaning may decrease rhinitis symptoms.

- Studies of mite-sensitive asthmatics do not demonstrate any overall clinical benefit of a variety of measures designed to reduce mite exposure. Although the small number of studies evaluating this question did not yield a definitive answer, the data for house dust mite controls are encouraging.

Immunotherapy

- Nearly all of 60 clinical trials of immunotherapy in allergic rhinitis reporting symptom outcomes favored injection immunotherapy over placebo.

- No serious adverse events were reported, and immunotherapy was generally well tolerated.

- A quantitative meta-analysis showed a consistent effect for immunotherapy for seasonal allergic rhinitis, but the conclusion about the effectiveness of immunotherapy for perennial allergic rhinitis was less certain.

- Primary quality concerns in this literature were related to small trial size, lack of standardized clinical outcome assessments, and trial design issues related to blinding.

Combined Treatments

- Combination symptomatic pharmacotherapy with antihistamines plus decongestants has been well studied and overall shows improved total and nasal symptom relief compared to monotherapy with either antihistamines or decongestants alone.

- Combination treatment with antihistamines plus nasal glucocorticoids improves nasal symptoms more than antihistamine alone, but not significantly more than monotherapy with nasal glucocorticoids.

- Other combinations have been studied in a small number of trials and overall show that compared with antihistamines alone: (a) the addition of ipratropium is beneficial for rhinorrhea symptoms; (b) ophthalmic antihistamine reduces eye itching; and (c) the mast cell stabilizer nedocromil sodium and non-steroidal anti-inflammatory drugs improve overall rhinitis symptoms.

Clinician Specialty Differences

Although differences in care and outcomes have been demonstrated between generalist and specialist care in other conditions, including asthma, few data are available in allergic rhinitis.

- Clinician-delivered patient education interventions coupled with medical treatment may improve allergic rhinitis symptoms more than medical treatment alone, as suggested in two studies.

- Several studies point to less-than-adequate knowledge regarding allergy treatment among patients in general medical practice.

- Few objective data are available to describe case mix and practice patterns in generalist and specialist care.

- Although survey data suggest that many patients are referred from generalist practices to specialist providers based on the severity of symptoms, there are no empirical published data to support that specialist practice has more severely affected patients.

Racial and Ethnic Variation

- There are few studies addressing any aspect of racial variation in relation to prevalence, treatment patterns, or response to treatment for patients with allergic rhinitis.

- The largest and most representative study, The National Health and Nutrition Examination Survey, 1976-80, does not show a consistent relationship between allergic rhinitis prevalence and race.

- Among the randomized trials reviewed for other questions addressed in this literature synthesis, only 13 of 116 described the racial characteristics of the study population.

- The only data on variation in treatment patterns with respect to race or ethnicity suggested that in a pediatric population, whites were more likely to continue injection immunotherapy treatment than non-whites.

- No data exist that describe variation in treatment outcomes by race.

Chapter 5. Future Research

Future research priorities were identified by reviewing the available evidence for each question addressed by the report. When the evidence was seriously flawed or insufficient to adequately answer a question, important gaps in evidence and research priorities were identified. These are discussed below. Additional areas for research are also identified in the Agency for Healthcare Research and Quality (AHRQ) evidence report, "Management of Allergic and Nonallergic Rhinitis" (Long, McFadden, DeVine, et al., 2002).

Costs and Work Performance

Although several studies have estimated the burden of illness due to allergic rhinitis, cost estimates vary widely, and both methodological issues and changes in current practice limit the applicability of these studies. Methodological challenges include: the definition of allergic rhinitis (particularly when using administrative datasets); valid cost estimates that include over-the-counter medications; and valid, objective measures of productivity changes. Additional data are needed regarding how allergic rhinitis in children affects working parents' productivity. In addition, existing analyses antedate the increased use of non-sedating antihistamines and nasal glucocorticoids. An updated study that adequately addressed these issues would give a more valid estimate of the direct costs associated with allergic rhinitis.

Ideally, the effects of treatment on work performance would be determined from randomized trials that include objective measures of work performance. Alternatively, one could model the impact of treatments on work performance if valid links existed between symptom outcomes or health-related quality of life (HRQOL) measures and work performance. Unfortunately, we did not identify any studies that establish these links. Since symptom outcomes and HRQOL are typically easier to measure than productivity, studies that would allow one to associate a given change in symptom or HRQOL score with a corresponding change in work productivity across a variety of jobs would be a particularly valuable contribution.

Environmental Measures

Based on the pathophysiology of allergic rhinitis, interventions that decrease allergen exposure through environmental control measures are conceptually appealing. The small number of studies evaluating such interventions did not yield definitive results, but the data for house dust mite controls are encouraging. Future studies will need to overcome a number of conceptual and methodological challenges. Since individuals are often allergic to more than one allergen, allergen avoidance measures may be needed for each significant allergen. Most studies to date have focused environmental controls on house dust mites or indoor aeroallergens. More comprehensive measures, such as those recommended in the National Heart, Lung, and Blood Institute's "Practical Guide for the Diagnosis and Management of Asthma" (National Heart, Lung, and Blood Institute, 1997), should be tested in patients with allergic rhinitis and significant functional impairment. If comprehensive measures are effective, future studies should identify the most critical components, since lifestyle changes are often difficult for patients to adopt. Another practical issue is whether allergen avoidance measures are more effective when tailored

to an individual patient's specific allergic sensitivities, or whether more general recommendations without specific allergy testing are adequate.

Immunotherapy

Immunotherapy (IT) is a potentially important treatment for allergic rhinitis. However, it requires special expertise, a committed patient, and is relatively expensive. Immunotherapy may be administered by injection, nasally, or sublingually, but there are few studies using the latter two routes of administration. Most studies have focused on patients with grass-pollen- or ragweed-induced seasonal allergic rhinitis. To better understand the role of IT in the treatment of allergic rhinitis, we need clinical trials employing vaccines containing most or all of the relevant allergens for each individual, which would allow us to assess IT as it is administered in most community settings. Such polyantigen studies would require new approaches to outcome measurement; currently, studies on seasonal allergens rely on timing symptom assessment to peak allergen levels. Additional future research objectives should be focused on the following: methods to identify patients likely to benefit from IT; cost-effectiveness and quality-of-life analyses of IT; determination of whether IT alters the natural history of allergic rhinitis and reduces possible sequelae such as bacterial sinusitis and asthma; comparisons of immunotherapy and the best available medical management and/or allergen avoidance; and studies clarifying the optimal duration of IT. Studies should be of sufficient duration to evaluate the short- and long-term effects of treatment, and adverse effects should be collected and reported systematically. An important subgroup to study is patients with co-occurring asthma, since effective treatment for allergic rhinitis has the potential to improve asthma symptoms.

Combined Treatments

To develop the most cost-effective management strategies, it is important to determine the relative efficacy of combinations of treatments compared to monotherapy. Compared to monotherapy, combined treatments are significantly more costly, and the potential effects range from no additional benefit to synergistic increases in efficacy.

The combination of an antihistamine plus a decongestant compared to either medication alone has been well studied in a large number of relatively short-term trials. Similarly, antihistamines plus nasal glucocorticoids have been compared adequately evaluated compared to either medication alone. Over 80 percent of these studies were done in patients with seasonal allergic rhinitis; longer duration studies in patients with perennial allergic rhinitis would provide useful efficacy data. In addition, longer duration "effectiveness trials" that included outcomes such as health-related quality of life and cost-effectiveness in primary care populations with clinically diagnosed seasonal or allergic rhinitis could guide policy. Other combinations (antihistamine, mast cell stabilizer, nonsteroidal anti-inflammatory drugs, ophthalmic antihistamine, and ipratropium) have been evaluated in single trials and more data are needed to better understand the efficacy of these combinations.

Clinician Specialty Differences

To understand the quality of current care for patients with allergic rhinitis, we need studies describing current practice patterns. Theoretically, earlier and more aggressive treatments that include allergy avoidance measures, immunotherapy, and medications may lead to better functional status, better work productivity, and fewer disease-related complications. Observational studies that compare treatment patterns and outcomes across specialties will need to pay careful attention to case-mix adjustment. A standardized and validated severity-of-illness scale would facilitate this research. In addition, prospective studies that compare symptomatic treatment to allergen identification with specific treatment would directly address two approaches commonly used in generalist and specialty practices. The development, implementation, and testing of clinical practice guidelines may provide the impetus for studying clinician practice patterns and outcomes as well as a framework for improving practice and evaluating outcomes. Finally, studying patient preferences and expectations for treatment and consulting behavior may provide important insights into clinician specialty case mix, practice patterns, and outcomes.

Racial and Ethnic Variation

Racial variability in disease prevalence, treatment patterns, or response to treatment can serve as cues to underlying differences in genetic susceptibility, environmental exposures, access to care, quality of care, or differing patient preferences for care. The few studies of disease prevalence did not show important differences by race. We did not identify any studies that described differences in treatment patterns or treatment response, in part because study populations were often incompletely described. We recommend that future studies give more complete descriptions of patient populations, including racial descriptors that might permit important subgroup analyses.

Need for Improved and More Uniform Trial Reporting

This evidence report highlights the need to improve the quality and homogeneity of trial reporting. Better reporting would aid interpretation and application of research findings and facilitate future literature syntheses. For clinical trials, the process for recruiting the study population and the population's clinical and demographic characteristics were often inadequately described. Thus the generalizability of study findings was often unclear. Design characteristics that help clinicians assess the validity of trial results were often incomplete, particularly information on randomization, allocation concealment, and, in some instances, blinding. Following the recommendations of the Consolidated Standards of Reporting Trials (CONSORT) statement for reporting trials would improve assessments of generalizabilty and validity (Moher, Schulz, Altman, et al., 2001).

References

Adelsberg BR. Sedation and performance issues in the treatment of allergic conditions. [Review]. Arch Intern Med 1997;157(5):494-500.

Alves B, Sheikh A, Hurwitz B, et al. Allergen injection immunotherapy for seasonal allergic rhinitis (Protocol for a Cochrane Review). In: The Cochrane Library, Issue 1, 2002. Oxford: Update Software.

American Academy of Allergy, Asthma & Immunology. The allergy report. Milwaukee, WI: American Academy of Allergy, Asthma & Immunology, Inc.; 2000.

Anderson HR, Pottier AC, Strachan DP. Asthma from birth to age 23: incidence and relation to prior and concurrent atopic disease. Thorax 1992;47(7):537-42.

Andri L, Senna GE, Betteli C, et al. Combined treatment of allergic rhinitis with terfenadine and nimesulide, a non-steroidal antiinflammatory drug. Allerg Immunol (Paris) 1992;24(8):313-4, 317-9.

Antonicelli L, Bilò MB, Pucci S, et al. Efficacy of an air-cleaning device equipped with a high efficiency particulate air filter in house dust mite respiratory allergy. Allergy 1991;46(8):594-600.

Ariano R, Kroon AM, Augeri G, et al. Long-term treatment with allergoid immunotherapy with Parietaria. Clinical and immunologic effects in a randomized, controlled trial. Allergy 1999;54(4):313-9.

Arvidsson MB, Löwhagen O, Rak S. Effect of 2-year placebo-controlled immunotherapy on airway symptoms and medication in patients with birch pollen allergy. J Allergy Clin Immunol 2002;109(5):777-83.

Backhouse CI, Finnamore VP, Gosden CW. Treatment of seasonal allergic rhinitis with flunisolide and terfenadine. J Int Med Res 1986;14(1):35-41.

Bellanti JA, Wallerstedt DB. Allergic rhinitis update: epidemiology and natural history. [Review]. Allergy Asthma Proc 2000;21(6):367-70.

Benincasa C, Lloyd RS. Evaluation of fluticasone propionate aqueous nasal spray taken alone and in combination with cetirizine in the prophylactic treatment of seasonal allergic rhinitis. Drug Invest 1994;8(4):225-33.

Berger WE, Fineman SM, Lieberman P, et al. Double-blind trials of azelastine nasal spray monotherapy versus combination therapy with loratadine tablets and beclomethasone nasal spray in patients with seasonal allergic rhinitis. Rhinitis Study Groups. Ann Allergy Asthma Immunol 1999;82(6):535-41.

Bernstein IL, Tennenbaum J, Georgakis N, et al. Fraction A: a new immunotherapeutic approach for ragweed pollinosis. Int Arch Allergy Appl Immunol 1976;50(2):181-91.

Bertrand B, Jamart J, Marchal JL, et al. Cetirizine and pseudoephedrine retard alone and in combination in the treatment of perennial allergic rhinitis: a double-blind multicentre study. Rhinology 1996;34(2):91-6.

Biostat. Comprehensive Meta-analysis [computer program]. Version 1.25. Englewood, NJ: Biostat; 1999.

Blainey AD, Phillips MJ, Ollier S, et al. Hyposensitization with a tyrosine adsorbed extract of Dermatophagoides pteronyssinus in adults with perennial rhinitis. A controlled clinical trial. Allergy 1984;39(7):521-8.

Blair H. Natural history of childhood asthma. 20-year follow-up. Arch Dis Child 1977;52(8):613-9.

Blaiss MS. Quality of life in allergic rhinitis. [Review]. Ann Allergy Asthma Immunol 1999;83(5):449-54.

Blanc PD, Trupin L, Eisner M, et al. The work impact of asthma and rhinitis: findings from a population-based survey. J Clin Epidemiol 2001;54(6):610-8.

Bødtger U, Poulsen LK, Jacobi HH, et al. The safety and efficacy of subcutaneous birch pollen immunotherapy -- a one-year, randomised, double-blind, placebo-controlled study. Allergy 2002;57:297-305.

Bousquet J, Bullinger M, Fayol C, et al. Assessment of quality of life in patients with perennial allergic rhinitis with the French version of the SF-36 Health Status Questionnaire. J Allergy Clin Immunol 1994;94(2 Pt 1):182-8.

Bousquet J, Frank E, Soussana M, et al. Double-blind, placebo-controlled immunotherapy with a high-molecular-weight, formalinized allergoid in grass pollen allergy. Int Arch Allergy Appl Immunol 1987;82(3-4):550-2.

Bousquet J, Hejjaoui A, Skassa-Brociek W, et al. Double-blind, placebo-controlled immunotherapy with mixed grass-pollen allergoids. I. Rush immunotherapy with allergoids and standardized orchard grass-pollen extract. J Allergy Clin Immunol 1987;80(4):591-8.

Bousquet J, Hejjaoui A, Soussana M, et al. Double-blind, placebo-controlled immunotherapy with mixed grass-pollen allergoids. IV. Comparison of the safety and efficacy of two dosages of a high-molecular-weight allergoid. J Allergy Clin Immunol 1990;85(2):490-7.

Bousquet J, Lockey R, Malling HJ. Allergen immunotherapy: therapeutic vaccines for allergic diseases. A WHO position paper. [Review]. J Allergy Clin Immunol 1998;102(4 Pt 1):558-62.

Bousquet J, Maasch HJ, Hejjaoui A, et al. Double-blind, placebo-controlled immunotherapy with mixed grass-pollen allergoids. III. Efficacy and safety of unfractionated and high-molecular-weight preparations in rhinoconjunctivitis and asthma. J Allergy Clin Immunol 1989;84(4 Pt 1):546-56.

Bousquet J, van Cauwenberge P, Khaltaev N, et al. Allergic rhinitis and its impact on asthma (ARIA). J Allergy Clin Immunol 2001;108:S147-336.

Briggs AH, O'Brien BJ. The death of cost-minimization analysis? [Review]. Health Econ 2001;10(2):179-84.

Bronsky E, Boggs P, Findlay S, et al. Comparative efficacy and safety of a once-daily loratadine-pseudoephedrine combination versus its components alone and placebo in the management of seasonal allergic rhinitis. J Allergy Clin Immunol 1995;96(2):139-47.

Brooks CD, Francom SF, Peel BG, et al. Spectrum of seasonal allergic rhinitis symptom relief with topical corticoid and oral antihistamine given singly or in combination. Am J Rhinol 1996;10(3):193-9.

Brooks CD, Karl KJ. Hay fever treatment with combined antihistamine and cyclooxygenase-inhibiting drugs. J Allergy Clin Immunol 1988;81(6):1110-7.

Brunet C, Bedard PM, Lavoie A, et al. Allergic rhinitis to ragweed pollen. I. Reassessment of the effects of immunotherapy on cellular and humoral responses. J Allergy Clin Immunol 1992;89(1 Pt 1):76-86.

Brydon M. The effectiveness of a peripatetic allergy nurse practitioner service in managing atopic allergy in general practice--a pilot study. Clin Exp Allergy 1993;23(12):1037-44.

Bukstein DA, Biondi RM, Blumenthal MM, et al. Tilarin in combination with astemizole. Allergy 1996;51(28 Suppl):20-7.

Burton WN, Conti DJ, Chen CY, et al. The impact of allergies and allergy treatment on worker productivity. J Occup Environ Med 2001;43(1):64-71.

Busse W, Janssens M, Eisen G. A multicenter, double-blind, randomized, placebo-controlled trial comparing the efficacy and tolerability of levocabastine-oxymetazoline nasal spray with levocabastine and oxymetazoline alone in the symptomatic treatment of seasonal allergic rhinitis. Am J Rhinol 1996;10(2):105-11.

Camilleri AE. Information leaflets in the rhinitis clinic? J Laryngol Otol 1991;105(4):282-4.

Centers for Disease Control and Prevention, National Center for Health Statistics. Current estimates from the National Health Interview Survey, 1996. Vital and Health Statistics, Series 10, No. 200. DHHS Publication No. (PHS) 99-1528. Hyattsville, MD: US Department of Health and Human Services. October 1999.

Cloosterman SG, Schermer TR, Bijl-Hofland ID, et al. Effects of house dust mite avoidance measures on Der p 1 concentrations and clinical condition of mild adult house dust mite-allergic asthmatic patients, using no inhaled steroids. Clin Exp Allergy 1999;29(10):1336-46.

Cockburn IM, Bailit HL, Berndt ER, et al. Loss of work productivity due to illness and medical treatment. J Occup Environ Med 1999a;41(11):948-53.

Cockburn IM, Bailit HL, Berndt ER, et al. Costing out care: when antihistamines go to work. Bus Health 1999b;17(3):49-50.

Cockcroft DW, Cuff MT, Tarlo SM, et al. Allergen injection therapy with glutaraldehyde-modified--ragweed pollen-tyrosine adsorbate. A double-blind trial. J Allergy Clin Immunol 1977;60(1):56-62.

Cohen J. Statistical power analysis for the behavioral sciences. Hillsdale, NJ: L. Erlbaum Associates; 1988.

Cook PR, Farias C. The safety of allergen immunotherapy: a literature review. [Review]. Ear Nose Throat J 1998;77(5):378-9, 383-8.

Corey JP, Kemker BJ, Branca JT, et al. Health status in allergic rhinitis. Otolaryngol Head Neck Surg 2000;122(5):681-5.

Creticos PS, Reed CE, Norman PS, et al. Ragweed immunotherapy in adult asthma. N Engl J Med 1996;334(8):501-6.

Crystal-Peters J, Crown WH, Goetzel RZ, et al. The cost of productivity losses associated with allergic rhinitis. Am J Manag Care 2000;6(3):373-8.

Cuffel B, Wamboldt M, Borish L, et al. Economic consequences of comorbid depression, anxiety, and allergic rhinitis. Psychosomatics 1999;40(6):491-6.

D'Souza MF, Pepys J, Wells ID, et al. Hyposensitization with Dermatophagoides pteronyssinus in house dust allergy: a controlled study of clinical and immunological effects. Clin Allergy 1973;3(2):177-93.

de Graaf-in 't Veld T, Koenders S, Garrelds IM, et al. The relationships between nasal hyperreactivity, quality of life, and nasal symptoms in patients with perennial allergic rhinitis. J Allergy Clin Immunol 1996;98(3):508-13.

Demoly P, Allaert F-A, Lecasble M, et al. ERASM, a pharmacoepidemiologic survey on management of intermittent allergic rhinitis in every day general medical practice in France. Allergy 2002;57:546-54.

Diamond L, Gerson K, Cato A, et al. An evaluation of triprolidine and pseudoephedrine in the treatment of allergic rhinitis. Ann Allergy 1981;47(2):87-91.

Dockhorn R, Aaronson D, Bronsky E, et al. Ipratropium bromide nasal spray 0.03% and beclomethasone nasal spray alone and in combination for the treatment of rhinorrhea in perennial rhinitis. Ann Allergy Asthma Immunol 1999;82(4):349-59.

Dockhorn RJ, Williams BO, Sanders RL. Efficacy of acrivastine with pseudoephedrine in treatment of allergic rhinitis due to ragweed. Ann Allergy Asthma Immunol 1996;76(2):204-8.

Dolz I, Martinez-Cocera C, Bartolome JM, et al. A double-blind, placebo-controlled study of immunotherapy with grass-pollen extract Alutard SQ during a 3-year period with initial rush immunotherapy. Allergy 1996;51(7):489-500.

Donahue JG, Greineder DK, Connor-Lacke L, et al. Utilization and cost of immunotherapy for allergic asthma and rhinitis. Ann Allergy Asthma Immunol 1999;82(4):339-47.

Drouin MA, Yang WH, Horak F, et al. Adding loratadine to topical nasal steroid therapy improves moderately severe seasonal allergic rhinoconjunctivitis. Adv Ther 1995;12(6):340-9.

Durham SR, Walker SM, Varga EM, et al. Long-term clinical efficacy of grass-pollen immunotherapy. N Engl J Med 1999;341(7):468-75.

European Agency for Evaluation of Medicinal Products. Committee for Proprietary Medicinal Products European Public Assessment Report (EPAR): Neoclarityn. 2001. Available at: http://www.eudra.org/humandocs/humans/epar/neoclarityn/neoclarityn.htm. Accessed August 31, 2002.

Ewan PW, Alexander MM, Snape C, et al. Effective hyposensitization in allergic rhinitis using a potent partially purified extract of house dust mite. Clin Allergy 1988;18(5):501-8.

Fagan JK, Scheff PA, Hryhorczuk D, et al. Prevalence of asthma and other allergic diseases in an adolescent population: association with gender and race. Ann Allergy Asthma Immunol 2001;86(2):177-84.

Falliers CJ, Redding MA. Controlled comparison of anew antihistamine-decongestant combination to its individual components. Ann Allergy 1980;45(2):75-80.

Fell WR, Mabry RL, Mabry CS. Quality of life analysis of patients undergoing immunotherapy for allergic rhinitis. Ear Nose Throat J 1997;76(8):528-32, 534-6.

Finn AF Jr, Aaronson D, Korenblat P, et al. Ipratropium bromide nasal spray 0.03% provides additional relief from rhinorrhea when combined with terfenadine in perennial rhinitis patients; a randomized, double-blind, active-controlled trial. Am J Rhinol 1998;12(6):441-9.

Fornadley JA, Corey JP, Osguthorpe JD, et al. Allergic rhinitis: clinical practice guideline. Committee on Practice Standards, American Academy of Otolaryngic Allergy. Otolaryngol Head Neck Surg 1996;115(1):115-22.

Francillon C, Burnand B, Frei P, et al. Referral pattern to the allergist for hay fever in a health-care system with open access to specialists. Allergy 1995;50(12):959-63.

Gabriel M Sister, Ng HK, Allan W G, et al. Study of prolonged hyposensitization with D. pteronyssinus extract in allergic rhinitis. Clin Allergy 1977;7(4):325-39.

Gani F, Pozzi E, Crivellaro MA, et al. The role of patient training in the management of seasonal rhinitis and asthma: clinical implications. Allergy 2001;56:65-8.

Geller-Bernstein C, Pibourdin JM, Dornelas A, et al. Efficacy of the acaricide: acardust for the prevention of asthma and rhinitis due to dust mite allergy, in children. Allerg Immunol (Paris) 1995;27(5):147-54.

Gilmore TM, Alexander BH, Mueller BA, et al. Occupational injuries and medication use. Am J Industrial Med 1996;30(2):234-9.

Gøtzsche PC, Johansen HK, Hammarquist C, et al. House dust mite control measures for asthma (Cochrane Review). In: The Cochrane Library, Issue 2, 2001. Oxford: Update Software.

Grammer LC, Shaughnessy MA, Bernhard MI, et al. The safety and activity of polymerized ragweed: a double-blind, placebo-controlled trial in 81 patients with ragweed rhinitis. J Allergy Clin Immunol 1987;80(2):177-83.

Grammer LC, Shaughnessy MA, Suszko IM, et al. A double-blind histamine placebo-controlled trial of polymerized whole grass for immunotherapy of grass allergy. J Allergy Clin Immunol 1983;72(5 Pt 1):448-53.

Grammer LC, Zeiss CR, Suszko IM, et al. A double-blind, placebo-controlled trial of polymerized whole ragweed for immunotherapy of ragweed allergy. J Allergy Clin Immunol 1982;69(6):494-9.

Grosclaude M, Mees K, Pinelli ME, et al. Cetirizine and pseudoephedrine retard, given alone or in combination, in patients with seasonal allergic rhinitis. Rhinology 1997;35(2):67-73.

Henauer S, Seppey M, Huguenot C, et al. Effects of terfenadine and pseudoephedrine, alone and in combination in a nasal provocation test and in perennial rhinitis. Eur J Clin Pharmacol 1991;41(4):321-4.

Hirsch SR, Kalbfleisch JH, Cohen SH. Comparison of Rinkel injection therapy with standard immunotherapy. J Allergy Clin Immunol 1982;70(3):183-90.

Hirsch SR, Kalbfleisch JH, Golbert TM, et al. Rinkel injection therapy: a multicenter controlled study. J Allergy Clin Immunol 1981;68(2):133-55.

Huss RW, Huss K, Squire EN, et al. Mite allergen control with acaricide fails. J Allergy Clin Immunol 1994;94(1):27-32.

Iliopoulos O, Proud D, Adkinson NF, et al. Effects of immunotherapy on the early, late, and rechallenge nasal reaction to provocation with allergen: changes in inflammatory mediators and cells. J Allergy Clin Immunol 1991;87(4):855-66.

Joint Task Force on Practice Parameters in Allergy, Asthma and Immunology. Diagnosis and management of rhinitis: complete guidelines of the Joint Task Force on Practice Parameters in Allergy, Asthma and Immunology. Joint Task Force on Practice Parameters in Allergy, Asthma and Immunology, representing the American Academy of Allergy, Asthma and Immunology; the American College of Allergy, Asthma and Immunology; and the Joint Council of Allergy, Asthma and Immunology. Ann Allergy Asthma Immunol 1998;81(5 Pt 2):478-518.

Jüni P, Witschi A, Bloch R, et al. The hazards of scoring the quality of clinical trials for meta-analysis. JAMA 1999;282(11):1054-60.

Juniper EF. Measuring health-related quality of life in rhinitis. [Review]. J Allergy Clin Immunol 1997;99(2):S742-9.

Juniper EF, Guyatt GH. Development and testing of a new measure of health status for clinical trials in rhinoconjunctivitis. Clin Exp Allergy 1991;21(1):77-83.

Juniper EF, Kline PA, Hargreave FE, et al. Comparison of beclomethasone dipropionate aqueous nasal spray, astemizole, and the combination in the prophylactic treatment of ragweed pollen-induced rhinoconjunctivitis. J Allergy Clin Immunol 1989;83(3):627-33.

Juniper EF, Kline PA, Ramsdale EH, et al. Comparison of the efficacy and side effects of aqueous steroid nasal spray (budesonide) and allergen-injection therapy (Pollinex-R) in the treatment of seasonal allergic rhinoconjunctivitis. J Allergy Clin Immunol 1990;85(3):606-11.

Keith PK, Haddon J, Birch S. A cost-benefit analysis using a willingness-to-pay questionnaire of intranasal budesonide for seasonal allergic rhinitis. Rhinocort Study Group. Ann Allergy Asthma Immunol 2000;84(1):55-62.

Kessler RC, Almeida DM, Berglund P, et al. Pollen and mold exposure impairs the work performance of employees with allergic rhinitis. Ann Allergy Asthma Immunol 2001;87(10):289-95.

Kniest FM, Young E, Van Praag MC, et al. Clinical evaluation of a double-blind dust-mite avoidance trial with mite-allergic rhinitic patients. Clin Exp Allergy 1991;21(1):39-47.

Kooistra JB, Pasch R, Reed CE. The effects of air cleaners on hay fever symptoms in air-conditioned homes. J Allergy Clin Immunol 1978;61(5):315-9.

Kozma CM, Schulz RM, Sclar DA, et al. A comparison of costs and efficacy of intranasal fluticasone propionate and terfenadine tablets for seasonal allergic rhinitis. Clin Ther 1996;18(2):334-46.

Kroidl RF, Göbel D, Balzer D, et al. Clinical effects of benzyl benzoate in the prevention of house-dust-mite allergy. Results of a prospective, double-blind, multicenter study. Allergy 1998;53(4):435-40.

Krouse JH, Krouse HJ. Patient use of traditional and complementary therapies in treating rhinosinusitis before consulting an otolaryngologist. Laryngoscope 1999;109(8):1223-7.

Krouse JH, Krouse HJ. Efficacy of immunotherapy based on skin end-point titration. Otolaryngol Head Neck Surg 2000;123(3):183-7.

Lane AP, Pine HS, Pillsbury HC III. Allergy testing and immunotherapy in an academic otolaryngology practice: a 20-year review. Otolaryngol Head Neck Surg 2001;124(1):9-15.

Lanier BQ, Gross RD, Marks BB, et al. Olopatadine ophthalmic solution adjunctive to loratadine compared with loratadine alone in patients with active seasonal allergic conjunctivitis symptoms. Ann Allergy Asthma Immunol 2001;86(6):641-8.

Lau SK, Wei WI, Van Hasselt CA, et al. A clinical comparison of budesonide nasal aerosol, terfenadine and a combined therapy of budesonide and oxymetazoline in adult patients with perennial rhinitis. Asian Pac J Allergy Immunol 1990;8(2):109-15.

Lebowitz MD, Cassell EJ, McCarroll J. Health and the urban environment. XI. The incidence and burden of minor illness in a healthy population: methods, symptoms, and incidence. Am Rev Respir Dis 1972;106(6):824-34.

Lee J, Cummins G, Okamoto L. A descriptive analysis of the use and cost of new-generation antihistamines in the treatment of allergic rhinitis: a retrospective database analysis. Am J Manag Care 2001;7(4 Suppl):S103-12.

Leickly FE, Sears-Ewald D, Ownby DR. A comparative cost-effectiveness study of two treatment modalities for ragweed hay fever. Am J Rhinol 1989;3(2):99-104.

Leynadier F, Banoun L, Dollois B, et al. Immunotherapy with a calcium phosphate-adsorbed five-grass-pollen extract in seasonal rhinoconjunctivitis: a double-blind, placebo-controlled study. Clin Exp Allergy 2001;31(7):988-96.

Liao E, Leahy M, Cummins G. The costs of nonsedating antihistamine therapy for allergic rhinitis in managed care: an updated analysis. Am J Manag Care 2001;7(15 Suppl):S459-68.

Lichtenstein LM, Norman PS, Winkenwerder WL. A single year of immunotherapy for ragweed hay fever. Immunologic and clinical studies. Ann Intern Med 1971;75(5):663-71.

Long A, McFadden C, DeVine D, et al. Management of allergic and nonallergic rhinitis. Evidence Report/Technology Assessment No. 54 (Prepared by New England Medical Center Evidence-based Practice Center under Contract No. 290-97-0019). AHRQ Publication No. 02-E024. Rockville, MD: Agency for Healthcare Research and Quality. May 2002.

Lower T, Henry J, Mandik L, et al. Compliance with allergen immunotherapy. Ann Allergy 1993;70(6):480-2.

Lundback B. Epidemiology of rhinitis and asthma. [Review]. Clin Exp Allergy 1998;(Suppl 2):3-10.

Mackowiak JI. The health and economic impact of rhinitis. Am J Manag Care 1997;3:S8-S18.

Malone DC, Lawson KA, Smith DH, et al. A cost of illness study of allergic rhinitis in the United States. J Allergy Clin Immunol 1997;99(1 Pt 1):22-7.

Manor O, Matthews S, Power C. Self-rated health and limiting longstanding illness: inter-relationships with morbidity in early adulthood. Int J Epidemiol 2001;30(3):600-7.

McAllen MK. Hyposensitisation in grass pollen hay fever. A double blind trial of alumn precipitated pollen extract and depot emulsion pollen extract compared with placebo injections. Acta Allergol 1969;24(6):421-31.

McMenamin P. Costs of hay fever in the United States in 1990. Ann Allergy 1994;73(1):35-9.

Meltzer EO, Casale TB, Nathan RA, et al. Once-daily fexofenadine HCl improves quality of life and reduces work and activity impairment in patients with seasonal allergic rhinitis. Ann Allergy Asthma Immunol 1999;83(4):311-7.

Meran A, Morse J, Gibbs TG. A cross-over comparison of acrivastine, pseudoephedrine and their combination in seasonal allergic rhinitis. Rhinology 1990;28(1):33-40.

Moher D, Cook DJ, Jadad AR, et al. Assessing the quality of randomised trials: current issues and future directions. Int J Tech Assess Health Care 1996;12(2):195-208.

Moher D, Schulz KF, Altman D, et al. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. [Review]. JAMA 2001;285(15):1987-91.

Möller C, Dreborg S, Ferdousi HA, et al. Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT-study). J Allergy Clin Immunol 2002;109(2):251-6.

Moon JS, Choi SO. Environmental controls in reducing house dust mites and nasal symptoms in patients with allergic rhinitis. Yonsei Med J 1999;40(3):238-43.

Mosbech H, Osterballe O. Does the effect of immunotherapy last after termination of treatment? Follow-up study in patients with grass pollen rhinitis. Allergy 1988;43(7):523-9.

Naclerio R, Solomon W. Rhinitis and inhalant allergens. [Review]. JAMA 1997;278(22):1842-8.

Naclerio RM, Proud D, Moylan B, et al. A double-blind study of the discontinuation of ragweed immunotherapy. J Allergy Clin Immunol 1997;100(3):293-300.

Nash DB, Sullivan SD, Mackowiak J. Optimizing quality of care and cost effectiveness in treating allergic rhinitis in a managed care setting. Am J Manag Care 2000;6(1 Suppl):S3-15; quiz S19-20.

National Heart Lung and Blood Institute. Practical guide for the diagnosis and management of asthma. NIH Publication No. 97-4053. Rockville, MD: National Institutes of Health, 1997.

National Institute of Allergy and Infectious Diseases, National Institutes of Health. Allergy statistics. NIAID Fact Sheet. Bethesda, MD: National Institute of Allergy and Infectious Diseases. January 2002.

National Institutes of Health. Fighting seasonal allergies. NIH Word on Health. Bethesda, MD: National Institutes of Health. June 2002.

Negrini AC, Troise C, Voltolini S, et al. Oral antihistamine/decongestant treatment compared with intranasal corticosteroids in seasonal allergic rhinitis. Clin Exp Allergy 1995;25(1):60-5.

Nimmagadda SR, Evans R 3rd. Allergy: etiology and epidemiology. [Review]. Pediatr Rev 1999;20(4):111-5; quiz 116.

Norman PS, Lichtenstein LM, Kagey-Sobotka A, et al. Controlled evaluation of allergoid in the immunotherapy of ragweed hay fever. J Allergy Clin Immunol 1982;70(4):248-60.

Ortolani C, Pastorello EA, Incorvaia C, et al. A double-blind, placebo-controlled study of immunotherapy with an alginate-conjugated extract of Parietaria judaica in patients with Parietaria hay fever. Allergy 1994;49(1):13-21.

Oxford Centre for Evidence-based Medicine. Levels of evidence. May 2001. Produced by Phillips B, Ball C, Sackett D, et al., since November 1998. Available at: http://163.1.96.10/docs/levels.html#levels. Accessed May 30, 2002.

Panda NK, Mann SB. Comparative efficacy and safety of terfenadine with pseudoephedrine and terfenadine alone in allergic rhinitis. Otolaryngol Head Neck Surg 1998;118(2):253-5.

Parikh A, Scadding GK. Seasonal allergic rhinitis. BMJ 1997;314:1392-5.

Parker WA, Whisman BA, Apaliski SJ, et al. The relationships between late cutaneous responses and specific antibody responses with outcome of immunotherapy for seasonal allergic rhinitis. J Allergy Clin Immunol 1989;84(5 Pt 1):667-77.

Pastorello EA, Pravettoni V, Incorvaia C, et al. Clinical and immunological effects of immunotherapy with alum-absorbed grass allergoid in grass-pollen-induced hay fever. Allergy 1992;47(4 Pt 1):281-90.

Pedersen PA, Weeke ER. Asthma and allergic rhinitis in the same patients. Allergy 1983;38(1):25-9.

Pence HL, Mitchell DQ, Greely RL, et al. Immunotherapy for mountain cedar pollinosis. A double-blind controlled study. J Allergy Clin Immunol 1976;58(1 Pt 1):39-50.

Petersson G. Allergy practice and the otolaryngologist. Curr Opin Otolaryngol Head Neck Surg 1995;3(3):218-23.

Purello-D'Ambrosio F, Isola S, Ricciardi L, et al. A controlled study on the effectiveness of loratadine in combination with flunisolide in the treatment of nonallergic rhinitis with eosinophilia (NARES). Clin Exp Allergy 1999;29(8):1143-7.

Radcliffe MJ, Lampe FC, Brostoff J. Allergen-specific low-dose immunotherapy in perennial allergic rhinitis: a double-blind placebo-controlled crossover study. J Investig Allergol Clin Immunol 1996;6(4):242-7.

Ragusa FV, Passalacqua G, Gambardella R, et al. Nonfatal systemic reactions to subcutaneous immunotherapy: a 10-year experience. J Investig Allergol Clin Immunol 1997;7(3):151-4.

Rak S, Heinrich C, Jacobsen L, et al. A double-blinded, comparative study of the effects of short preseason specific immunotherapy and topical steroids in patients with allergic rhinoconjunctivitis and asthma. J Allergy Clin Immunol 2001;108(6):921-8.

Ratner PH, van Bavel JH, Martin BG, et al. A comparison of the efficacy of fluticasone propionate aqueous nasal spray and loratadine, alone and in combination, for the treatment of seasonal allergic rhinitis. J Fam Pract 1998;47(2):118-25.

Ray NF, Baraniuk JN, Thamer M, et al. Direct expenditures for the treatment of allergic rhinoconjunctivitis in 1996, including the contributions of related airway illnesses. J Allergy Clin Immunol 1999;103(3 Pt 1):401-7.

Reilly MC, Tanner A, Meltzer EO. Work, classroom and activity impairment instruments: validation studies in allergic rhinitis. Clin Drug Invest 1996;11:278-88.

Reisman RE, Mauriello PM, Davis GB, et al. A double-blind study of the effectiveness of a high-efficiency particulate air (HEPA) filter in the treatment of patients with perennial allergic rhinitis and asthma. J Allergy Clin Immunol 1990;85(6):1050-7.

Revicki DA, Leidy NK, Brennan-Diemer F, et al. Development and preliminary validation of the multiattribute Rhinitis Symptom Utility Index. Qual Life Res 1998;7(8):693-702.

Ross RN. The costs of allergic rhinitis. Am J Manag Care 1996;2:285-90.

Ross RN, Nelson HS, Finegold I. Effectiveness of specific immunotherapy in the treatment of allergic rhinitis: an analysis of randomized, prospective, single- or double-blind, placebo-controlled studies. Clin Ther 2000;22(3):342-50.

Royal College of Physicians, Royal College of Pathologists. Good allergy practice--standards of care for providers and purchasers of allergy services within the National Health Service. Clin Exp Allergy 1995;25(7):586-95.

Santilli J, Nathan R, Glassheim J, et al. Patients receiving immunotherapy report it is effective as assessed by the rhinitis outcomes questionnaire (ROQ) in a private practice setting. Ann Allergy Asthma Immunol 2001;86(2):219-21.

Santos R, Cifaldi M, Gregory C, et al. Economic outcomes of a targeted intervention program: the costs of treating allergic rhinitis patients. Am J Manag Care 1999;5(4 Suppl):S225-34.

Scadding GK, Richards DH, Price MJ. Patient and physician perspectives on the impact and management of perennial and seasonal allergic rhinitis. Clin Otolaryngol Allied Sci 2000;25(6):551-7.

Schädlich PK, Brecht JG. Economic evaluation of specific immunotherapy versus symptomatic treatment of allergic rhinitis in Germany. Pharmacoeconomics 2000;17:37-52.

Settipane GA. Allergic rhinitis--update. Otolaryngol Head Neck Surg 1986;94(4):470-5.

Settipane RJ, Hagy GW, Settipane GA. Long-term risk factors for developing asthma and allergic rhinitis: a 23-year follow-up study of college students. [Review]. Allergy Proc 1994;15(1):21-5.

Shapiro GG, Wighton TG, Chinn T, et al. House dust mite avoidance for children with asthma in homes of low-income families. J Allergy Clin Immunol 1999;103(6):1069-74.

Sheikh A, Hurwitz B. House dust mite avoidance measures for perennial allergic rhinitis (Cochrane Review). In: The Cochrane Library, Issue 1, 2002. Oxford: Update Software.

Simpson RJ. Budesonide and terfenadine, separately and in combination, in the treatment of hay fever. Ann Allergy 1994;73(6):497-502.

Skoner DP. Allergic rhinitis: definition, epidemiology, pathophysiology, detection, and diagnosis. [Review]. J Allergy Clin Immunol 2001;108(1 Suppl):S2-8.

Spector SL. Overview of comorbid associations of allergic rhinitis. [Review]. J Allergy Clin Immunol 1997;99(2):S773-80.

Stahl E, van Rompay W, Wang EC, et al. Cost-effectiveness analysis of budesonide aqueous nasal spray and fluticasone propionate nasal spray in the treatment of perennial allergic rhinitis. Ann Allergy Asthma Immunol 2000;84(4):397-402.

Storms W, Meltzer EO, Nathan RA, et al. The economic impact of allergic rhinitis. J Allergy Clin Immunol 1997;99:S820-4.

Strachan D, Sibbald B, Weiland S, et al. Worldwide variations in prevalence of symptoms of allergic rhinoconjunctivitis in children: the International Study of Asthma and Allergies in Childhood (ISAAC). Ped Allergy Immunol 1997;8(4):161-76.

Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. [Review]. JAMA 2000;283(15):2008-12.

Sullivan SD, Weiss KB. Health economics of asthma and rhinitis. II. Assessing the value of interventions. J Allergy Clin Immunol 2001;107(2):203-10.

Sussman GL, Mason J, Compton D, et al. The efficacy and safety of fexofenadine HCl and pseudoephedrine, alone and in combination, in seasonal allergic rhinitis. J Allergy Clin Immunol 1999;104(1):100-6.

Tanner LA, Reilly M, Meltzer EO, et al. Effect of fexofenadine HCl on quality of life and work, classroom, and daily activity impairment in patients with seasonal allergic rhinitis. Am J Manag Care 1999;5(4 Suppl):S235-47.

The SAS Institute. The SAS System for Windows [computer program]. Release 8.02. Cary, NC: The SAS Institute, Inc.; 2001.

Thompson AK, Juniper E, Meltzer EO. Quality of life in patients with allergic rhinitis. [Review]. Ann Allergy Asthma Immunol 2000;85(5):338-48.

Trotter JP. The treatment of seasonal allergic rhinitis: cost implications of pharmacotherapy for managed care. Manag Care Interface 2000;13(1):60-2.

Trotto NE. Asthma, rhinitis, sinusitis, urticaria. Patient Care 1999;33(1):115-39.

Turkeltaub PC, Gergen PJ. Prevalence of upper and lower respiratory conditions in the US population by social and environmental factors: data from the second National Health and Nutrition Examination Survey, 1976 to 1980 (NHANES II). Ann Allergy 1991;67(2 Pt 1):147-54.

Van Metre TE, Adkinson NF, Amodio FJ, et al. A comparison of immunotherapy schedules for injection treatment of ragweed pollen hay fever. J Allergy Clin Immunol 1982;69(2):181-93.

Van Metre TE, Adkinson NF Jr, Amodio FJ, et al. A comparative study of the effectiveness of the Rinkel method and the current standard method of immunotherapy for ragweed pollen hay fever. J Allergy Clin Immunol 1980;66(6):500-13.

Varney VA, Gaga M, Frew AJ, et al. Usefulness of immunotherapy in patients with severe summer hay fever uncontrolled by antiallergic drugs. BMJ 1991;302(6771):265-9.

Vuurman EFPM, van Veggel LMA, Sanders RL, et al. Effects of Semprex-D and diphenhydramine on learning in young adults with seasonal allergic rhinitis. Ann Allergy Asthma Immunol 1996;76(3):247-52.

Walker SM, Pajno GB, Lima MT, et al. Grass pollen immunotherapy for seasonal rhinitis and asthma: a randomized, controlled trial. J Allergy Clin Immunol 2001;107(1):87-93.

Weiler JM, Bloomfield JR, Woodworth GG, et al. Effects of fexofenadine, diphenhydramine, and alcohol on driving performance. A randomized, placebo-controlled trial in the Iowa driving simulator. Ann Intern Med 2000;132(5):354-63.

Weiss KB, Sullivan SD. The health economics of asthma and rhinitis. I. Assessing the economic impact. [Review]. J Allergy Clin Immunol 2001;107(1):3-8.

Weyer A, Donat N, L'Heritier C, et al. Grass pollen hyposensitization versus placebo therapy. I. Clinical effectiveness and methodological aspects of a pre-seasonal course of desensitization with a four-grass pollen extract. Allergy 1981;36(5):309-17.

White P, Smith H, Baker N, et al. Symptom control in patients with hay fever in UK general practice: how well are we doing and is there a need for allergen immunotherapy? Clin Exp Allergy 1998;28(3):266-70.

Williams BO, Hull H, McSorley P, et al. Efficacy of acrivastine plus pseudoephedrine for symptomatic relief of seasonal allergic rhinitis due to mountain cedar. Ann Allergy Asthma Immunol 1996;76(5):432-8.

Wilson A, Dempsey OJ, Sims EJ, et al. Evaluation of treatment response in patients with seasonal allergic rhinitis using domiciliary nasal peak inspiratory flow. Clin Exp Allergy 2000;30(6):833-8.

Wood RA, Johnson EF, Van Natta ML, et al. A placebo-controlled trial of a HEPA air cleaner in the treatment of cat allergy. Am J Respir Crit Care Med 1998;158(1):115-20.

Yawn BP, Yunginger JW, Wollan PC, et al. Allergic rhinitis in Rochester, Minnesota residents with asthma: frequency and impact on health care charges. J Allergy Clin Immunol 1999;103(1 Pt 1):54-9.

Zeiger RS, Schatz M. Effect of allergist intervention on patient-centered and societal outcomes: allergists as leaders, innovators, and educators. [Review]. J Allergy Clin Immunol 2000;106(6):995-1018.

Zenner HP, Baumgarten C, Rasp G, et al. Short-term immunotherapy: a prospective, randomized, double-blind, placebo-controlled multicenter study of molecular standardized grass and rye allergens in patients with grass pollen-induced allergic rhinitis. J Allergy Clin Immunol 1997; 100(1):23-9.

Evidence Table 1: Costs and Work Performance

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Blanc, Trupin, Eisner, et al., 2001	Design: Population-based telephone survey Intervention(s): NA Duration of study treatment: NA Dates: May 28-July 21, 1999 Location: Northern California rural, suburban, and urban regions Setting: Community Type(s) of providers: NA	No. of subjects at start: 5,304 contacts made with individual households; 1,411 refused; 227 excluded (language); 254 excluded (no asthma or rhinitis) Dropouts/withdrawals: NA No. of subjects at end: 125 asthma; 175 rhinitis (and no asthma) Inclusion criteria: Age 18-50; self-reported physician-diagnosed asthma (asthma group) or self- or physician-diagnosed "allergic rhinitis, sinusitis or hay fever" or "chronic post-nasal drip" (rhinitis group) Exclusion criteria: Emphysema or cystic fibrosis Age: NR Sex: 72% women Race: 74% White, 16% Latino, 9% Asian/Other, 2% Black Other: Smoking status: Current 16% Former 28% Never 57% Insured for healthcare: 89%	1) Severity of respiratory symptoms (self-reported) 2) Medication use 3) Quality of life (SF-12) 4) Health care utilization 5) Employment status 6) Work effectiveness	1) Severity of respiratory symptoms (self-reported): Severe: 22% Moderate: 49% Mild: 29% 2) Medication use: Past 2 weeks: Rx inhaler: 9% Rx nasal spray: 25% Antihistamine: 59% Ever use steroids for breathing: 13% 3) Quality of life (SF-12): Functional status scores (mean ± SD): SF-12 physical component: 49 ± 10 SF-12 mental component: 48 ± 11 Activity limitations due to condition (in previous month): 30% 4) Health care utilization, past 12 months, for condition: Urgent care visit: 32% ED visit: 6% 5) Employment status: Labor force participation since onset: 97% Labor force participation given onset < 18 years of age: 99% Changed jobs or duties due to condition: 18% Currently employed: 23% 6) Work effectiveness (last 4 weeks): Any partial or complete lost work days: 23% Any partial lost work days: 20% Any complete lost work days: 13% Self-rated effectiveness on job < 90%: 36%	Quality Scoring: Population similar: Yes Intervention(s) described: No Comorbidities described: Yes Diagnosis by MD: No Objectively confirmed: Not applicable Outcome measures valid: No Level of evidence: 1b Notes: Survey failed to screen for COPD (only emphysema). Study designed to compare asthma group to rhinitis-only group. No comparison possible to subjects with no respiratory illness.

Evidence Table 1: Costs and Work Performance (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Burton, Conti, Chen, et al., 2001	Design: Prospective survey of customer service representatives, weekly productivity data and Health Risk Appraisal (HRA) information from employer, and pollen counts in the community. To measure productivity impact of AR and its treatment Intervention(s): NA Duration of study treatment: NA Dates: June 1998 through October 1998 Location: Elgin, IL Setting: Large employer Type(s) of providers: NA	No. of subjects at start: Surveys sent to 1600 telephone customer service representatives in June 1998; 54% (634 subjects) completed and returned. The follow-up survey sent out in October 1998 was completed by 72% (459 subjects). Of the study population, HRA information was available for 299 in the AR group and 269 in the non-AR group. Dropouts/withdrawals: NR No. of subjects at end: 634 subjects were included in analyses of productivity Inclusion criteria: NR Exclusion criteria: NR Age: 20.5% < 25; 36.1% 25-34; 23.3% 35-44; 20.3% 45+ Sex: 88.6% women Race: Asian: 2.4%; Black:7.7%; White: 81.4%; Hispanic: 8.4%; Native American: 0.2%	1) Proportion of patients with self-reported AR who reported using no medications, OTC medications, or prescription medications 2) Likelihood of meeting the productivity standard during weeks when the pollen count was high 3) Impact of allergies on meeting the productivity standard before or after allergy season 4) Impact of allergies on meeting the productivity standard during the allergy season 5) Impact of no medication among those with allergies on productivity during the allergy season 6) Impact of using antihistamines (sedating or nonsedating) on productivity during the allergy season 7) Impact of type of antihistamine on productivity during the allergy season	1) 21.7% reported no medication use for AR; 41.6% reported OTC medication use; and 36.7% reported prescription medication use. 2) 7% fewer employees with allergies met the productivity standard when pollen counts were high compared with employees without allergies 3) Employees with or without allergies met the productivity standard as often before and after the allergy season 4) 5% fewer employees with allergies met the productivity standard during allergy season compared with employees without allergies 5) 10% fewer employees with allergies who reported using no medication met the productivity standard compared to employees without allergies 6) 3% fewer employees who reported using nonsedating or sedating antihistamines met the productivity standard compared to employees without allergies 7) No difference in productivity was observed between those reporting the use of sedating or nonsedating antihistamines among those who used medication	Quality Scoring: Population similar: Yes Intervention(s) described: No Comorbidities described: Yes Diagnosis by MD: No Objectively confirmed: Not applicable Outcome measures valid: Yes Level of evidence: 4 Notes: Weekly productivity was measured as a dichotomous variable classified as either meeting or not meeting the overall productivity standard. As the final measure, the average of all weekly scores was computed. Those meeting the weekly productivity standard more than half the time were classified as meeting the productivity standard. The results on medication type and productivity are misleading. Instead of reporting the % reduction in the likelihood of meeting the productivity standard, the authors report these percentages as the percent reduction in productivity. This interpretation is carried out through the discussion when making a case for the cost-benefit of providing pharmacy coverage for people with AR.

Evidence Table 1: Costs and Work Performance (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Cockburn, Bailit, Berndt, et al., 1999a **and** **Cockburn, Bailit, Berndt, et al., 1999b**	Design: Retrospective analysis of claims data and daily work output records To test the impact of antihistamine use on productivity, work output observations of insurance claims processors were classified into periods directly preceding and following the date on which the prescription was filled. Time periods of 3, 5, 7, 10, and 14 days were tested. Intervention(s): NA Duration of study treatment: NA Dates: January 1993-July 1995 Location: NR Setting: Community, large insurance company Type(s) of providers: NA	No. of subjects at start: Health claims for 5,888 individuals Dropouts/withdrawals: NA No. of subjects at end: After removing outliers, 183,301 observations on daily work output were available for 682 individuals Inclusion criteria: Individuals with prescription claim(s) for antihistamines Exclusion criteria: Age: Mean, 32 Sex: 94% female Race: NR Other:	1) Effect of antihistamines (all types combined) on average level of productivity 2) Effect of sedating and nonsedating antihistamines on average level of productivity 3) Effect of sedating antihistamines on average level of productivity when extending the analysis time period 4) Daily cost of lost output based on hourly pay of $11.50 5) Net monetary benefit of treatment with non-sedating antihistamines compared to sedating antihistamines	1) When not controlling for the type of antihistamine, there was not a statistical difference in productivity during the 3-day period prior to filling the prescription or the 3-day period following the filling of a prescription for an antihistamine. 2) During the 3-day period after filling a prescription for a sedating antihistamine, workers were on average 7.8% less productive ($p < 0.01$). Conversely, during the 3-day period after filling a prescription for a nonsedating antihistamine, workers were 5.2% more productive on average ($p < 0.01$). 3) When extending the time period during which productivity is measured following a sedating antihistamine, the negative effect on productivity remains significant ($p < 0.01$) out to 14 days (max period tested). However, the size of the effect lessened to 3.1%. 4) Daily cost of lost output: $9 per day (ranging from $7 to $11) 5) Net monetary benefit of treatment with non-sedating antihistamines compared to sedating antihistamines: $7.50- $8 per day assuming an incremental cost of $1-$1.50/day for nonsedating antihistamines	Quality Scoring: Population similar: Yes Intervention(s) described: No Comorbidities described: No Diagnosis by MD: No Objectively confirmed: Not applicable Outcome measures valid: Yes Level of evidence: 4 Note: Study limitation: Claims for prescription drugs could have been prescribed for dependants, not employees.

Evidence Table 1: Costs and Work Performance (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Crystal-Peters, Crown, Goetzel, et al., 2000	Design: Cost of illness study (indirect costs only) based on a synthesis of data from: 1) 1995 National Health Interview Survey; 2) Bureau of Labor Statistics Intervention(s): NA Duration of study treatment: NA Dates: 1995 Location: US Setting: Community Type(s) of providers: NA	No. of subjects at start: NA Dropouts/withdrawals: NA No. of subjects at end: NA Inclusion criteria: Respondents with self-reported diagnostic information that was coded as allergic rhinitis Exclusion criteria: Age: Of those reporting AR, 18.2% < 18, 72.9% 18-64, 8.9% ≥ 65 Sex: Of those reporting AR, 53.6% women Race: NR	1) Prevalence of AR 2) Prevalence of AR by age group 3) Average annual number and total number of work days lost per person with AR 4) Indirect costs of lost work days 5) Total number of at-work reduced activity days 6) Indirect costs of at-work productivity losses 7) Indirect costs of reduced activity due to sedating antihistamines 8) Total indirect costs of AR	1) Prevalence of AR: 9.8% (25.7 million) 2) Prevalence of AR by age group: < 18yo: 6.6%; 18-64yo: 11.7%; ≥ 65yo: 9.8% 3) Average annual number and total number of work days lost per person with AR: 0.24 days per year, 3.6 million lost work days 4) Indirect costs of lost work days: $445.3 million ($1995) 5) Total number of at-work reduced activity days: Nearly 3 million at-work reduced activity days 6) Indirect costs of at-work productivity losses: $92.8 million ($1995) 7) Indirect costs of reduced activity due to sedating antihistamines: $4.6 billion ($1998) 8) Total indirect costs of AR: $5.2 billion ($1998)	Quality Scoring: Population similar: Yes Intervention(s) described: No Comorbidities described: No Diagnosis by MD: No Objectively confirmed: Not applicable Outcome measures valid: No Level of evidence: 2b Notes: Assumptions used in cost calculations: 1) At-work productivity losses were based on NHIS-reported number of days that respondents cut down on usual activities by more than half of the day and were valued at 25% of the respondent's daily salary. 2) Assumed that at-work reduced activity days reported in NHIS do not consider the effects of sedating antihistamines. 3) To assign indirect costs of reduced productivity due to sedating antihistamines, it was assumed based on unpublished survey data that 82% of AR patients use some treatment, and that 57% use OTC sedating antihistamines. 4) 1989 Gallup poll: People with AR who used sedating (OTC) antihistamines reported a 25% reduction in productivity for 14 work days per year. This analysis double-counts productivity losses. It uses

(continued on next page)

Evidence Table 1: Costs and Work Performance (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
					NHIS data to estimate lost productivity due to missed work days and at-work reduced productivity days. It assumes that reduced activity resulting from sedating antihistamines is not included in these estimates. Therefore, it uses the results from the 1989 Gallup poll and unpublished survey data to estimate indirect costs resulting from the use of sedating antihistamines.
Cuffel, Wamboldt, Borish, et al., 1999	Design: Retrospective analysis of health care claims This analysis was designed to: 1) estimate the prevalence of coexistent AR, depression and anxiety disorder; 2) estimate the effects of the comorbid conditions on costs; and 3) determine whether treatment of AR had an impact on overall costs when these conditions were comorbid. Intervention(s): NA Duration of study treatment: NA Dates: 1995 Location: US Setting: NA Type(s) of providers: NA	No. of subjects at start: Claims data from 600,000 persons Dropouts/withdrawals: NA No. of subjects at end: 13% (85,298) with AR diagnosis; 9.3% (59,529) with diagnosis of depression and 2.2% (14,582) with diagnosis of anxiety Inclusion criteria: Diagnosis of AR based on ≥ 2 prescriptions for allergy medication or diagnosis of AR Exclusion criteria: None specified Age: 0-17yo: 16.1%; 18-34yo: 17.6%; 35-44yo: 21.3%, 45-54yo: 25.6%, 55-64yo: 18.9%; ≥65yo: 0.4% Sex: 61% women Race: NR	1) Prevalence of AR 2) Proportion of AR patients with depression or anxiety disorder or both conditions 3) Odds ratio (OR) of a depressive disorder among people with AR compared to people without AR 4) Odds ratio (OR) of a anxiety disorder among people with AR compared to people without AR 5) Additional annual expense from having a diagnosis of AR and depression versus a diagnosis of either AR or depression alone 6) Additional annual expense from having a diagnosis of AR and anxiety disorder versus a diagnosis of either AR or	1) 13.3% (85,298/641,205) 2) Depression, 12%; anxiety disorder, 1.5%; depression and anxiety disorder, 1.5% 3) OR = 1.7 (95% CI, 1.63-1.73) 4) OR = 1.41 (95% CI, 1.35-1.47) 5) $363 additional per person per year 6) $207 additional per person per year	Quality Scoring: Population similar: Yes Intervention(s) described: No Comorbidities described: No Diagnosis by MD: No Objectively confirmed: Not applicable Outcome measures valid: No Level of evidence: 2b

(continued on next page)

Evidence Table 1: Costs and Work Performance (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
			anxiety disorder alone		
			7) Economic impact of AR treatment on total costs when AR and depression were comorbid	7) $83 reduction per person per year	
			8) Economic impact of AR treatment on total costs when AR and anxiety disorder were comorbid	8) $141 reduction per person per year	
Donahue, Greineder, Connor-Lacke, et al., 1999	Design: Retrospective analysis based on HMO claims data Intervention(s): NA Duration of study treatment: NA Dates: April 1988 through December 1994 Location: Northeast US Setting: Staff model HMO Type(s) of providers: NA	No. of subjects at start: 122,196 diagnosed with asthma or rhinitis; of which 2,677 (2%) received ≥ 1 immunotherapy injection Dropouts/withdrawals: NA No. of subjects at end: 603 met all duration of membership, pharmacy coverage, and automated record eligibility requirements and were deemed to have actually received an immunotherapy injection Inclusion criteria: Subjects were required to have a minimum of 4 years of continuous enrollment in the HMO. Medical records were used to confirm the accuracy of asthma and rhinitis diagnoses. Exclusion criteria: Age: 7% age < 10 years; 15% age 10-29; 55% age 20-39; 23% age ≥ 40 Sex: 56% women Race: NR	1) Median duration of immunotherapy (2-6 years of follow-up per patient) 2) Distribution of number of treatments per person 3) Correlates of duration of therapy 4) Compliance with immunotherapy (see Notes for definition)	1) 2.7 years. Bivariate analyses showed that duration did not differ by age or gender, but duration was longest for patients with both asthma and rhinitis. Duration was similar among those with cat, ragweed and other allergens, but was shorter among patients with undocumented allergen. 2) The distribution was bimodal with peaks at ~5 and ~65 injections per patient, 23% had no injections after the first month. 3) Multivariate analyses showed that duration of immunotherapy was shortest among females, those aged 10-20 years, and those for whom the allergen type was not documented. 4) Of those with sufficient follow-up for assessment, 33% were classified as completing immunotherapy. 43% of those with both asthma and rhinitis completed therapy compared to 28% of those with rhinitis and 13% of those with asthma only. Patients with ragweed allergen were more likely to complete treatment and those with undocumented allergen were less likely.	Quality Scoring: Population similar: No Intervention(s) described: No Comorbidities described: Yes Diagnosis by MD: No Objectively confirmed: Not applicable Outcome measures valid: No Level of evidence: 2b Note: Compliance with immunotherapy was evaluated by determining the proportion of patients who received at least 50% of the recommended number of injections in each interval according to the following recommendations: ≥ 20 injections in 1st 6 months, ≥ 30 injections in 1st year, an additional 31 injections over next 2.5 years, and a total of ≥ 61 injections over 3.5 y ears.

(continued on next page)

Evidence Table 1: Costs and Work Performance (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
		Diagnoses: 58% had rhinitis without asthma, 39% had rhinitis plus asthma, 3% had only asthma Allergens: 6% cat (no ragweed) 45% ragweed (no cat) 20% other or combination 29% no documented	5) Total cost of immuno-therapy (allergy testing, immunotherapy visits, visits for adverse reactions). 6) Immunotherapy and nonimmunotherapy costs for people who completed therapy compared to those who did not compete therapy	5) $438 per person-year: $212 for people with asthma, $416 for people with rhinitis, and $496 for people with both conditions. 6) $698 per person-year among those who completed immunotherapy vs. $247 for those who did not. Non-immunotherapy costs were $508 among people who completed immunotherapy and $421 among people who did not.	
Fell, Mabry, and Mabry, 1997	Design: Case series, survey Patients administered the survey were asked to rate their nasal symptoms and QOL before undergoing immunotherapy and at the time they completed the survey. Intervention(s): Immunotherapy Duration of study treatment: NA Dates: NR Location: Texas Setting: Outpatient Type(s) of providers: Patients from 1 provider represented	No. of subjects at start: 60 Dropouts/withdrawals: 0 No. of subjects at end: 60 Inclusion criteria: patients with IgE-mediated allergy who had undergone 1or more years of immunotherapy Exclusion criteria: NR Age: Men: ages 27-70; women: ages 29-72 Sex: 60% men Race: NR	1) Nasal symptoms currently and before immunotherapy. 2) General health currently and before immunotherapy. 3) Tolerance of exercise, outdoor activities, participation in social activities and energy level for every day activities currently and before immunotherapy. 4) Productivity at work currently and before immunotherapy and causes for changes in productivity. 5) Work days missed currently and before immunotherapy.	1) 92% reported a signif icant improvement in symptoms 2) 62% reported that their general health was much better since beginning immunotherapy. 3) 38% reported an increase in exercise tolerance. Of the 34 patients who reported regularly participating in outdoor activities, 74% were better able to perform these activities; 63% reported improvement in their social lives, and 55% reported an increased energy level. 4) Of the 56 patients who were employed, 59% reported that their allergies caused them to be less productive at work, and all of these patients reported increased productivity since beginning immunotherapy. 5) 31 of 56 (55%) reported missing work as a consequence of allergies. Prior to beginning immunotherapy, 29 of the 31 missed between 1 and 6 days of work over a 6-month period. The other 2 patients reported missing 12-18	Quality Scoring: Population similar: Yes Intervention(s) described: No Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 4 Note: These results are limited by recall bias and selection bias as only patients who continued immunotherapy were included in the survey and all were under the care of the 2nd author. Furthermore, it was not reported how these patients were selected to participate in the survey. In addition, no statistical testing was used to compare responses.

(continued on next page)

Evidence Table 1: Costs and Work Performance (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
				work days within 6 months. Compared to the period before immunotherapy, patients missed work 4.2 fewer days after initiation of immunotherapy.	
			6) Number of physician visits to treat severe allergy symptoms or infections currently and before immunotherapy.	6) The 63% of patients making frequent physician visits for allergies prior to immunotherapy had a decrease in the number of office visits by 3.8 per 6-month period after initiation of immunotherapy.	
			7) Quantity of medications currently and before immunotherapy.	7) 63% were able to decrease the amount of each medication taken. Of the 36 people who reported taking more than 3 courses of antibiotics per year, 89% were able to decrease antibiotic use by at least 50% since starting immunotherapy.	
			8) Patients' assessment of whether immunotherapy was worthwhile and time until they noticed a benefit of immunotherapy.	8) 92% reported that they felt that immunotherapy was worthwhile and the average amount of time they received immunotherapy before noting a benefit was 4.2 months when excluding one patient who reported 24 months.	

Evidence Table 1: Costs and Work Performance (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Gilmore, Alexander, Mueller, et al., 1996	Design: Case-control study using a large managed care database Intervention(s): NA Duration of study treatment: NA Dates: 1992-1993 Location: Washington state Setting: Community, staff-model HMO Type(s) of providers: NR	No. of subjects at start: NA Dropouts/withdrawals: NA No. of subjects at end: 3,394 incident visits for traumatic work-related injury Inclusion criteria: Cases: people who had a clinic or emergency room visit for an acute work-related injury in 1992-1993 Controls: matched to cases on sex, decade of birth date, and employer Case:Control Ratio: 1:2 Exclusion criteria: NA Age: 18 years or older Sex: 58.2% male Race: NR	1) Odds Ratio for increased risk of work-related injury within 30 days following use of antihistamines	1) Open wounds and contusions: OR = 1.5 (95%CI: 1.1 to 1.9); burns: OR = 3.1 (95%CI: 1.0-9.7); and fractures: OR = 1.7 (95%CI: 0.9-3.3).	Quality Scoring: Population similar: Yes Intervention(s) described: No Comorbidities described: No Diagnosis by MD: No Objectively confirmed: Not applicable Outcome measures valid: No Level of evidence: 3b Notes: Antihistamines in this study were almost always sedating, as non-sedating antihistamines were not available on the formulary during the study period. Limitation of analysis: Exposure to medication was based on purchase of medication within 30 days prior to the date of injury. However, misclassification was not expected to differ between cases and controls.

Evidence Table 1: Costs and Work Performance (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Keith, Haddon, and Birch, 2000	Design: RCT, parallel-group, method of randomization not described Intervention(s): 1) Intranasal budesonide delivered as a dry powder (Rhinocort® Turbuhaler® 400 µg), once per day (n = 121) 2) Intranasal budesonide delivered as an aqueous spray (Rhinocort® Aqua® 256 µg), once per day (n = 121) Duration of study treatment: 4 weeks Loratidine and sodium cromoglycate or naphazoline HCl-antazoline phosphate eyedrops "provided for rescue" (instructions for using not described) Trial preceded by 7- to 10-day placebo run-in period Dates: 1993 ragweed pollen season Location: Canada Setting: Allergy clinic Type(s) of providers: NR	No. of subjects at start: 242 (randomized and received treatment) Dropouts/withdrawals: No. of subjects at end: 242 received treatment, 241 completed both willingness-to-pay questionnaires Inclusion criteria: Age ≥ 18 years; positive skin prick test to ragweed (≥ 3 mm); symptoms of rhinitis or a clear exacerbation of perennial rhinitis symptoms during ≥ 1 previous ragweed season Exclusion criteria: None specified Age: 36 Sex: 54.5% female Race: NR	1) Costs: Included costs for study and rescue meds; any immunotherapy received; unscheduled visits to physician and services provided at such visits; visits to other physicians or hospital outpatient departments; and time off work or school 2) Benefits: Indirectly assessed by willingness-to-pay questionnaire administered at beginning and end of study 3) Cost-benefit analysis (including sensitivity analysis)	1) Costs: Cost data were provided in figures. Therefore, exact cost estimates are not available from the article. 2) Benefits: Prior to treatment, subjects were willing to pay an average of $15.89 (1993 Canadian$) per week for an allergy treatment that would relieve all symptoms. Following treatment, subjects were willing to pay an average of $12.95 (1993 Canadian$) per week to take the drug they had been using during subsequent allergy seasons. The reduction in willingness-to-pay was significant. 3) Cost-benefit analysis (including sensitivity analysis): The net benefit was significantly higher than costs incurred by $5.80 per week. The net benefit was highest ($7.39) among those who felt they had fewer symptoms than in previous ragweed seasons. When excluding the time lost from work or school from the calculation of costs, the net benefit was higher at $8.30 per week. In the sensitivity analysis, the estimates that were most sensitive to change were the cost of study medication, days missed from work or school and rescue medications. Only when the cost of each was at its highest assumed value was the net benefit negative.	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: Mo Level of evidence: 4 Note: Double-dummy blinding technique employed.

Evidence Table 1: Costs and Work Performance (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Kessler, Almeida, Berglund, et al., 2001	Design: Population-based daily diary survey used to estimate indirect costs of AR Intervention(s): NA Duration of study treatment: NA Dates: March 1996 to May 1997 Location: US Setting: Community Type(s) of providers: NA	No. of subjects at start: The National Survey of Daily Experience (NSDE) (n = 3,032) was a substudy of the MacArthur Foundation Midlife Development in the US Survey (MIDUS). 83% of the target sample (n = 1,242) consented by telephone to participate. Dropouts/withdrawals: NA No. of subjects at end: 114 w/out AR, 625 with self-reported AR Inclusion criteria: Age 25 to 74; self-reported "hay fever or other seasonal allergies" among a list of conditions Exclusion criteria: None specified Age: Of those with allergic rhinitis: 35.5% 25-34, 34.7% 35-49,29.7% ≥ 50 Sex: 60.5% women Race: NR	1) Associations between impaired work quality and sociodemographic variables 2) Associations between impaired work quantity and sociodemographic variables 3) Average monthly indirect cost during periods of high pollen/mold exposure per person 4) Projected US annual indirect cost of AR during high pollen/mold exposure	1) Impaired work quality was inversely related to age, higher in the western areas of the US, and lower in the fall than other seasons. 2) Impaired work quantity was higher in women and higher in the western areas of the US 3) $156.27 SE = $20.04 ($1997) 4) $7.7 billion ($1997)	Quality Scoring: Population similar: Yes Intervention(s) described: No Comorbidities described: No Diagnosis by MD: No Objectively confirmed: Not applicable Outcome measures valid: No Level of evidence: 1b Notes: Assumptions used in cost calculations: 1) Data on work impairment (work quality and work quantity) was collected using self-administered diaries during 8 consecutive days (periods were randomly assigned). 2) Impaired work quality was measured using yes/no response options. Work quantity was measured on a 0-10 scale, then dichotomized as impaired (0-5) and not impaired (6-10). 3) Individual-level wage data were combined with results from regression analyses to estimate indirect costs. It was assumed that impaired work quality was equal to 25% of the respondent's daily wage and impaired work quantity was equal to 75% of daily wage.

Evidence Table 1: Costs and Work Performance (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Kozma, Schulz, Sclar, et al., 1996	Design: Secondary analysis of data from previously reported RCT (see Notes) Intervention(s): 1) Fluticasone propionate nasal spray, 2 sprays per nostril, once per day (total dose 200 µg) (n = 78) 2) Terfenadine 60 mg bid (n = 77) Duration of study treatment: 14 days No mention of rescue med Trial preceded by 4- to 7-day run-in period Dates: NR Location: Texas Setting: Allergy clinic Type(s) of providers: NR	No. of subjects at start: 232 in original trial; 77 subjects randomized to placebo were excluded from the cost-effectiveness analysis Dropouts/withdrawals: No. of subjects at end: 155 Inclusion criteria: Based on four 0-100 point visual analog scales for sneezing, nasal obstruction, rhinorrhea, and nasal itching, patients had to have had a combined score ≥ 200 on 4 of 7 days prior to the intervention Exclusion criteria: NR Age: 39 years (mean) Sex: 52% female Race: White: 81.3%; Black: 3.2%; Hispanic: 15.5%; Other: 0%	1) Efficacy: 1a) Patient-assessed symptom severity: sneezing, nasal obstruction, rhinorrhea, and nasal itching graded daily using 0- to 100-point visual analog scales 1b) Patient global assessment of efficacy: overall response to treatment graded at end of trial on scale of 1 (significant improvement) to 7 (significant worsening) 2) Costs: Included only direct cost for study med (average wholesale price) 3) Cost-efficacy analysis (including sensitivity analysis)	1) Efficacy: 1a) There were no differences in total symptom severity scores prior to treatment. However, scores were significantly lower in the fluticasone group during the treatment period (159 vs 201, p = 0.003). The average decrease in scores between baseline and treatment periods was also greater for the fluticasone arm (-116 vs -80, p = 0.007). 1b) More patients in the fluticasone arm indicated that they improved during the treatment period (mild, moderate or significant improvement) compared to patients in the terfenadine arm (85% vs 69%, p = 0.007). 5% in the fluticasone arm and 2% in the terfenadine arm reported worsening. A greater proportion of patients in the terfenadine arm reported no change (29% vs 9%). When the criteria used to indicate improvement included only those reporting significant or moderate improvement, there was not a significant difference between treatment arms (64% vs 53%, p = 0.154). When only a significant improvement was used as the criterion, more patients in the fluticasone arm were deemed to have improved (38% vs. 19%, p = 0.007). 2) Cost of terfenadine during study period: $24.81; cost of fluticasone during study period: $18.14 3) Incremental cost-effectiveness ratios were not reported as fluticasone was found to be less costly and more effective than terfenadine when the standard for improvement included only those indicating significant	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: No Outcome measures valid: No Level of evidence: 2b Notes: Efficacy assessed through a secondary analysis of data from a previously published trial (van Bavel J, Findlay S, Hampel F, et al. Intranasal fluticasone propionate is more effective than terfenadine tablets for seasonal allergic rhinitis. Arch Intern Med 1994;154:2699-704). Original trial included a placebo arm, which was not included in this re-analysis. Double-dummy blinding technique employed in original trial.

(continued on next page)

Evidence Table 1: Costs and Work Performance (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
				improvement or when the standard for improvement included those indicating significant, moderate or mild improvement.	
Lee, Cummins, and Okamoto, 2001	Design: Retrospective analysis of health care claims Intervention(s): NA Duration of study treatment: NA Dates: 1997 and 1998 Location: US Setting: National managed care organization Type(s) of providers: NA	No. of subjects at start: > 16 million people in data set Dropouts/withdrawals: NA No. of subjects at end: 202,426 Inclusion criteria: People diagnosed with AR during 1997 or 1998 and with at least one prescription claim within the 12-month period following AR diagnosis. All prescription claims within the 12-month period following the first prescription claim were analyzed. Exclusion criteria: Patients who were not continuously enrolled during the study period Age: Mean, 34 Sex: 61.4% women Race: NR Geographic region: Midwest: 27.7% Northeast: 12.0% Southeast: 51.8% West: 9.0%	1) Proportion of patients who received treatment with second-generation antihistamines ± nasal steroids, plus breakdown by treatment 2) Prevalence of comorbid conditions 3) Average annual charges by department 4) Total average annual charges 5) Proportion of total costs attributed to prescription drugs and outpatient medical services	1) Treatment included second-generation antihistamine and/or nasal steroid: 90.7%; Monotherapy with second-generation antihistamines: 41.4%; Monotherapy with nasal steroids: 19.7%; Combination therapy with second-generation antihistamines and nasal steroids: 29.7% 2) Upper respiratory infection: 32.2%; Lower respiratory infection: 3.3%; depression: 6.5%; sinusitis: 34.2%; Asthma: 14.8%; emphysema: 0.2%; COPD: 0.9%; otitis media: 11.5% 3) Inpatient: $8.28; outpatient: $216.31; ancillary: $4.43; emergency: $0.16; pharmacy-related: $236.02 4) $465.21 5) Prescription drugs: 51%; outpatient medical services: 46%	Quality Scoring: Population similar: Yes Intervention(s) described: No Comorbidities described: No Diagnosis by MD: No Objectively confirmed: Not applicable Outcome measures valid: No Level of evidence: 2c Notes: Patients' treatment was classified based on initial treatment selection. Switches or augmentations were not considered.

Evidence Table 1: Costs and Work Performance (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Leickly, Sears-Ewald, and Ownby, 1989	Design: RCT, parallel-group Intervention(s): 1) Terfenadine 60 mg twice per day (n = 10) 2) Chlorpheniramine 4 mg + pseudoephedrine 60 mg, one capsule in morning and two at night (n = 9) Patients in both groups permitted to use nasal cromolyn as rescue med, if study med failed to relieve symptoms adequately Duration of study treatment: 38 days (during ragweed season) Dates: August- September 1986 Location: Detroit, MI Setting: Allergy clinic Type(s) of providers: NR	No. of subjects at start: 20 Dropouts/withdrawals: 1 No. of subjects at end: 19 Inclusion criteria: History of late summer-early fall ragweed-induced allergic rhinitis for at least 2 years and a positive skin test to ragweed Exclusion criteria: Perennial allergic rhinitis, poorly controlled asthma, daily systemic steroid use, or long period of absence from study location Age: Mean, 32 years; range, 18-59 Sex: 53% women Race: NR	1) Daily cost to druggist for study meds (based on average wholesale prices, December 1986) 2) Patient-assessed symptom severity: sneezing; stuffy nose; runny nose; red, itchy nose; cough/wheeze; and shortness of breath graded twice daily on scale of 0 (none) to 6 (very severe) 3) Adverse effects: drowsiness and irritability graded twice daily on scale of 0 (none) to 6 (very severe); GI complaints noted, but not scored 4) Treatment compliance 5) Patient global evaluation of efficacy of treatment: experience during study rated relative to previous ragweed seasons 6) Patient satisfaction: pts asked at end of trial whether they would use the study med again	1) Daily cost to druggist for study meds: $0.92 for terfenadine, $0.37 for chlorpheniramine/pseudoephedrine 2) Patient-assessed symptom severity: No significant differences in any individual symptom (p-values from 0.32 to 0.90) or combined symptoms (p = 0.97) 3) Adverse effects: No significant difference in any individual adverse effect (p-values from 0.07 to 0.77), but terfenadine had significantly fewer total adverse effects (p = 0.03). 4) Treatment compliance: 1 patient in the terfenadine group reported 3 days of noncompliance 5) Patient global evaluation of efficacy of treatment: 6 of 10 in the terfenadine group and 8 of 9 in the chlorpheniramine/ pseudoephedrine group stated that this was their 'best year'. 6) Patient satisfaction: 7 of 10 patients treated with terfenadine would stated that they would use the medication again; 8 of 9 chlorpheniramine/ pseudoephedrine patients reported that they would use the medication again.	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 4 Note: Unable to determine how they calculated their symptom scores. Scores were collected twice daily using a 0-6 scale. They state that the average symptom scores represent the total score for the group for that symptom divided by the number of days in the study, providing an average symptoms treatment group score per day. If they did add up the scores for pts in each arm of the trial (n = 9 and n = 10) and then divide by the number of days, these results will not be valid because (1) there are more patients in one group versus the other (2) because observations are not on a per-patient basis but a per-day basis.

Evidence Table 1: Costs and Work Performance (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Liao, Leahy, and Cummins, 2001	Design: Retrospective analysis of health care claims Intervention(s): NA Duration of study treatment: NA Dates: 1999 Location: US Setting: National managed care organization Type(s) of providers: NA	No. of subjects at start: ~13 million people in data set Dropouts/withdrawals: NA No. of subjects at end: 105,696 Inclusion criteria: People diagnosed with AR during 1999 with at least one prescription claim for a nonsedating antihistamine within the 12-month period following AR diagnosis. Exclusion criteria: NR Age: Mean, 36 (SD 19); 16% age < 12; 10% age 13-18; 39% age 19-45; 29% age 46-65; 7% age > 65 Sex: 61.8% women Race: NR Geographic Region: Midwest: 14.1% Northeast: 13.9% Southeast: 63.9% West: 8.1%	1) Proportion of patients who received treatment with second-generation antihistamines ± nasal steroids, plus breakdown by treatment. Patients' treatment was classified based on initial treatment selection. Switches or augmentations were not considered. 2) Prevalence of comorbid conditions 3) Average annual charges by department 4) Total average annual charges 5) Proportion of total costs attributed to prescription drugs and outpatient medical services	1) Treatment included second-generation antihistamine and/or nasal steroid: 66.3%; Monotherapy with second-generation antihistamines: 24.8%; Monotherapy with nasal steroids: 12.0%; Combination therapy with second-generation antihistamines and nasal steroids: 29.5% 2) Prevalence of comorbid conditions: Upper respiratory infection: 29.0%; lower respiratory infection: 4.7%; depression: 7.4%; sinusitis: 32.0; asthma: 18.4%; emphysema: 0.3%; COPD: 6.9%; otitis media: 8.9% 3) Average annual charges by department: inpatient: $14.71; outpatient: $358.84; ancillary: $5.44; emergency: $0.30; pharmacy-related: $171.32 4) Total average annual charges: $550.61 5) Proportion of total costs attributed to prescription drugs and outpatient medical services: Prescription drugs: 31%; Outpatient medical services: 65%	Quality Scoring: Population similar: No Intervention(s) described: No Comorbidities described: Yes Diagnosis by MD: No Objectively confirmed: Not applicable Outcome measures valid: No Level of evidence: 3b Notes: The results are not consistent with the inclusion criteria. The inclusion criteria defined cases as patients with a prescription claim for a nonsedating antihistamine, yet in the results a proportion of patients received monotherapy with steroids or neither steroids nor nonsedating antihistamines. Also, this study was intended to update the results of the study by Lee, Cummins, and Okamoto (2001), above. However, there are substantial differences between the results of these study for some outcomes such as the proportion of pts receiving neither nasal steroids nor nonsedating antihistamines (33.7% vs. 9.3%), the proportion receiving nasal steroids only (12.0% vs. 19.7%), and average costs for pharmaceuticals ($171.32 vs. $236.02). The authors attribute these differences to differences in the study populations.

Evidence Table 1: Costs and Work Performance (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Malone, Lawson, Smith, et al., 1997	Design: Cost of illness study based on data from the 1987 National Medical Expenditure Survey (NMES) Intervention(s): NA Duration of study treatment: NA Dates: 1987 Location: US Setting: Community Type(s) of providers: Allergist, 17%; ENT, 4%; GP or family practitioner, 6%; internist, 3%; pediatrician, 9%; nurse, 24%; other, 20%; not certain, 10%	No. of subjects at start: 36,259 respondents to NMES Dropouts/withdrawals: No. of subjects at end: Inclusion criteria: Non-institutionalized civilians in the US Exclusion criteria: Federal, military, and Department of Veterans Affairs populations, plus residents of nursing homes and other institutions Age: NR Sex: 45% male (of respondents with AR) Race: Native American: 328,921 (1%) Asian/Pacific: 606,762 (1%) Black: 4,215,059 (11%) White: 32,728,023 (84%) Other: 1,116,999 (3%)	1) Prevalence of AR 2) Proportion of AR patients who sought medical treatment 3) Number and cost of prescriptions for AR 4) Number and cost of office or clinic visits to medical providers for AR 5) Number and cost of outpatient hospital visits for AR 6) Number and cost of emergency room visits for AR 7) Number of missed work days and associated productivity loss 8) Number of missed school days and associated productivity loss 9) Productivity loss associated with reduced activity days 10) Total direct cost of AR 11) Total indirect cost of AR 12) Total direct and indirect cost of AR	1) Prevalence of AR: 38.9 million (26.7 million adults and 12.3 million children) 2) Proportion of AR patients who sought medical treatment: 12.1% (4.7 million persons) 3) Number and cost of prescriptions for AR: 11.5 million prescriptions, $184 million ($1987), $301 million ($1994) 4) Number and cost of office or clinic visits to medical providers for AR: 16.7 million visits, $418 million ($1987), $648 million ($1994) 5) Number and cost of outpatient hospital visits for AR: 734,000 visits, $96 million ($1987), $180 million ($1994) 6) Number and cost of emergency room visits for AR: 101,000 visits, $9.5 million ($1987), 17.7 million ($1994) 7) Number of missed work days and associated productivity loss: 811,000 missed work days, $37 million ($1987), $47 million ($1994) 8) Number of missed school days and associated productivity loss: 824,000 missed school days, $13 million ($1987), $17 million ($1994) 9) Productivity loss associated with reduced activity days: 4,230,000 reduced activity days, $17 million ($1987), $23 million ($1994) 10) Total direct cost of AR: $708 million ($1987), $ 1.15 billion ($1994)	Quality Scoring: Population similar: Yes Intervention(s) described: No Comorbidities described: No Diagnosis by MD: No Objectively confirmed: Not applicable Outcome measures valid: No Level of evidence: 3b Notes: Assumptions used in cost calculations: 1) Restricted activity days collected in NMES were valued at 25% of the respondent's daily salary. 2) Restricted activity days for those less than 18 years of age were not included. 3) Indirect costs for missed school days based on parent's income. 4) Cost of OTC medications not included.

(continued on next page)

Evidence Table 1: Costs and Work Performance (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
				11) Total indirect cost of AR: $67 million ($1987), $ 86 million ($1994) 12) Total direct and indirect cost of AR: $775 million ($1987), $ 1.23 billion ($1994)	
Manor, Matthews, and Power, 2001	Design: Longitudinal survey of a 1958 birth cohort administered at ages 23 and 33 Intervention(s): NA Duration of study treatment: NA Dates: Surveys administered in 1981 and 1991 Location: England, Wales, and Scotland Setting: Community Type(s) of providers: NR	No. of subjects at start: At age 23: n = 12,525 Dropouts/withdrawals: 1,252 No. of subjects at end: At age 33: n = 11,273 Inclusion criteria: Born in England, Wales, or Scotland during one week in March 1958 Exclusion criteria: NA Age: Survey administered when respondents were 23 and 33 years of age Sex: 50% male Race: NR	1) Prevalence of hay fever at age 23 and age 33 in men and women 2) Relationships between 2 global health measures and (self-rated health and limiting longstanding illness) and specific health problems. Self-rated health was grouped into 2 categories: fair/poor and good/excellent. Limiting longstanding illness was determined by asking whether respondents had a longstanding illness, disability, or infirmity that limited their daily activities in any way compared to people of their same age. Hay fever was one of the specific health problems examined. Others included psychological distress, respiratory problems, obesity, asthma, backache, eczema, diabetes, epilepsy, cancer, heart trouble, high blood pressure, arthritis, and menstrual or other gynecologic problems. 3) Association between changes in self-reported	1) Prevalence of hay fever by age and sex: Age 23: men 16.6%; women 16.4% Age 33: men 15.6%; women 16.3% 2) Self-rated health and limiting illness were associated with all specific health problems except among men for hay fever and obesity. In women, those who reported hay fever were more likely to report fair/poor health - lowest odd ratio reported for any health condition [OR = 1.47 (age 23) and 1.33 (age 33)]. The association between reporting longstanding illness and hay fever was significant in men and women at age 23 (OR = 1.38 and 1.98, respectively), but only for women at age 33 (OR = 1.74). These associations were considered weak. 3) No association between changes in self-rated health and changes in	Quality Scoring: Population similar: Yes Intervention(s) described: No Comorbidities described: No Diagnosis by MD: No Objectively confirmed: Not applicable Outcome measures valid: No Level of evidence: 1b Notes: *(continued on next page)*

Evidence Table 1: Costs and Work Performance (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
			health and changes in specific health problems reported	reporting hay fever or eczema were found. Significant associations were found for other health problems.	
Mc-Menamin, 1994	Design: Cost of illness study based on a synthesis of data from multiple sources: 1) 1988 National Health Interview Survey; 2) 1985 National Ambulatory Medical Care Survey; 3) 1989 Gallup Poll; 4) National Health Accounts from the Health Care Financing Administration 5) wage data from US Dept of Labor Intervention(s): NA Duration of study treatment: NA Dates: Vary Location: US Setting: Community Type(s) of providers: NA	No. of subjects at start: NA Dropouts/withdrawals: NA No. of subjects at end: NA Inclusion criteria: NA Exclusion criteria: Federal, military, and Department of Veterans Affairs populations, plus residents of nursing homes and other institutions Age: NR Sex: NR Race: NR	1) Prevalence estimate from NHIS: no. of people reporting hay fever in 1988 2) Number and cost of physicians' office visits for AR 3) Cost of medications for AR 4) Direct medical costs for AR (physician visits and medications) 5) Number of lost work days 6) Indirect costs of AR 7) Total costs (direct + indirect)	1) Prevalence estimate from NHIS: no. of people reporting hay fever in 1988: 22.4 million; 9.3% prevalence rate 2) Number and cost of physicians' office visits for AR: 9.8 million visits, $881 million ($1990) 3) Cost of medications for AR: $276 million ($1990) 4) Direct medical costs for AR (physician visits and medications): $1.16 billion ($1990) 5) Number of lost work days: 3.4 million 6) Indirect costs of AR: $639 million ($1990) 7) Total costs (direct + indirect): $1.8 billion ($1990)	Quality Scoring: Population similar: Not adequately described Intervention(s) described: No Comorbidities described: No Diagnosis by MD: No Objectively confirmed: Not applicable Outcome measures valid: No Level of evidence: 3b Notes: Assumptions used in cost calculations: 1) 5% growth in population from 1985 to 1990. 2) 1989 Gallup poll: People with AR who used sedating (OTC) antihistamines reported a 25% reduction in productivity for 14 work days per year. 3) Proportion Treated with OTC antihistamines: 1989 Gallup poll: 50%. 4) Medication costs were based on the ratio of prescription and OTC medication costs to total physician costs as estimated in the National Health Accounts for HCFA (37.93%). 5) Cost of office visit: $50, cost of office visit with tests: $100 6) Average daily earnings: $96.05. 7) Productivity losses based on (1) total lost work days; (2) 25% of wage earners' reduced activity days; (3) 25% of home workers reduced activity days less 5%.

Evidence Table 1: Costs and Work Performance (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Meltzer, Casale, Nathan, et al., 1999	Design: RCT, parallel-group, method of randomization not described Intervention(s): 1) Fexofenadine 180 mg once per day (n = 275) 2) Fexofenadine 120 mg once per day (n = 284) 3) Placebo (n = 286) Duration of study treatment: 2 weeks No mention of rescue med Trial preceded by 1-week placebo run-in period Dates: August-November 1997 Location: US Setting: Community Type(s) of providers: NR	No. of subjects at start: 845 Dropouts/withdrawals: No. of subjects at end: 845 (610 eligible for inclusion in analyses of work impairment, 238 for classroom impairment) Inclusion criteria: Age 12-65; moderate to severe seasonal AR; history of AR during previous 2 fall seasons; positive skin prick test; symptom score ≥ 6 (max score: 16), with 2 or more symptoms rated as moderate-to-severe. After 1-week placebo run-in period, patients needed a symptom score ≥5 with ≥ 2 individual symptoms rated as moderate or severe. Exclusion criteria: Patients with individual symptoms rated as very severe; URI within 30 days of study; lack of response to antihistamines; clinically significant underlying medical disorder; receipt of immunotherapy; pregnancy; inability to read or understand English Age: Mean, 32-33 Sex: 64.6% female Race: 88.2% Caucasian; 11.8% Other Average no. of years since onset of seasonal AR: 17	1) Disease-specific quality of life: assessed using the Rhinoconjunctivities Quality of Life Questionnaire (RQLQ) at baseline and at 1 and 2 weeks 2) Performance impairment due to allergy symptoms: assessed using the Work Productivity and Activity Impairment (WPAI) instrument at baseline and at 1 and 2 weeks 3) Overall health impressions/generic quality of life: measured using 3 generic domains of the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) (Role-Physical, General Health Perceptions, Change in Health)	1) Disease-specific quality of life: Mean overall RQLQ score at baseline: 2.7; patients treated with both doses of fexofenadine experienced greater improvement in overall RQLQ scores. The 180-mg group reported greater improvement than placebo for all 7 RQLQ domains. The 120-mg group reported greater than placebo for 4 of the 7 RQLQ domains: practical problems, nasal symptoms, eye symptoms, and emotions. 2) Performance impairment due to allergy symptoms: Overall work impairment significantly decreased 7.1% in the 120-mg group and 8.7% in the 180-mg group, compared to a 1.8% reduction in the placebo group. There were also significant reductions in both fexofenadine groups relative to placebo in activity impairment. There were no significant differences between treatment groups in the percentage of time missed from work. There were also no significant differences in classroom impairment measures. 3) Overall health impressions/generic quality of life: There were significant improvements in both fexofenadine groups as measured by the SF-36 Role-Physical domain compared to placebo. Significantly more patients treated with fexofenadine reported an improvement in health from baseline to Week 1 compared to placebo. However, there was not a significant difference between treatment groups from week 1 to week 2.	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: Yes Level of evidence: 1b Notes:

Evidence Table 1: Costs and Work Performance (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Ray, Baraniuk, Thamer, et al., 1999	Design: Cost of illness study based on data from 1994 National Hospital Discharge Survey, 1994 National Ambulatory Medical Care Survey, 1994 National Hospital Ambulatory Medical Care Survey, 1994 National Survey of Ambulatory Surgery, 1987 National Medical Expenditure Survey, and estimates gathered from 4 experts using a 3-round modified consensus Delphi procedure The study objective was to estimate direct medical costs associated with treatment of allergic rhinoconjuctivitis. The analysis was based on the assumption that AR is a predisposing factor for other airway disorders. The Delphi procedure was used to obtain estimates of the proportion of patients with specific airway disorders who would also be assumed to have allergic rhinoconjunctivitis (AR/AC). Intervention(s): NA Duration of study treatment: NA Dates: 1994 data extrapolated to 1996 values Location: US Setting: All medical settings Type(s) of providers: All	No. of subjects at start: NR Dropouts/withdrawals: NA No. of subjects at end: NR Inclusion criteria: All survey records with a primary diagnosis of AR or atopic conjunctivitis were attributed to AR/AC Exclusion criteria: Federal, military, and Department of Veterans Affairs populations, plus residents of nursing homes and other institutions Age: NR Sex: NR Race: NR	1) Total number of outpatient physician visits attributed to AR/AC in US 2) Total number of hospital outpatient visits attributed to AR/AC in US 3) Total number of emergency department visits attributed to AR/AC in US 4) Total number of hospitalizations attributed to AR/AC in US 5) Total medical costs attributed to AR/AC in US Costs were estimated by the expert panel. These estimated costs were multiplied by the total number of encounters for each of 10 airway disorders (e.g. chronic otitis media, sinusitis, asthma) to estimate resource use attributable to AR/AC	1) Total number of outpatient physician visits attributed to AR/AC in US: 24,200,183 outpatient physician visits 2) Total number of hospital outpatient visits attributed to AR/AC in US: 1,410,779 hospital outpatient visits 3) Total number of emergency department visits attributed to AR/AC in US: 1,887,448 emergency department visits 4) Total number of hospitalizations attributed to AR/AC in US: 97,349 hospitalizations 5) Total medical costs attributed to AR/AC in US: $5.93 billion ($1987), of which 31.4% was for treatment of AR/AC coded as the primary diagnosis, 25% for comorbid chronic otitis media or eustachian tube disorders, and 17% for comorbid sinusitis and 17% for comorbid asthma	Quality Scoring: Population similar: Yes Intervention(s) described: No Comorbidities described: Yes Diagnosis by MD: No Objectively confirmed: Not applicable Outcome measures valid: No Level of evidence: 4 Notes: This study may overestimate the cost of allergic rhinoconjunctivitis because the total cost of visits that have a primary diagnosis of 1 of 10 airway diseases were attributed to allergic rhinoconjunc tivitis. It is also likely to overestimate the number of inpatient/outpatient/ER encounters because even though AR may be assumed to be a secondary diagnosis in many cases where another diagnosis is the primary, exacerbation or treatment of the principal diagnosis precipitated the medical encounter. For example, the majority of hospital costs were attributable to the assumption that 30% of those with asthma would have AR.

Evidence Table 1: Costs and Work Performance (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Reilly, Tanner, and Meltzer, 1996	Design: Validation study of the Allergy-specific Work Productivity and Activity Impairment (WPAI-AS) using data from 2 multicenter, double-blind, randomized, placebo-controlled trials Intervention(s): 1) Terfenadine 2) Fexofenadine 3) Placebo Duration of study treatment: Dates: 1993 autumn allergy season for the work/activity impairment cohort (Study 1) and 1994 spring allergy season for the classroom impairment cohort (Study 2) Location: US Setting: Allergy clinic Type(s) of providers: NR	No. of subjects at start: 574 in the intent-to-treat dataset for Study 1, 422 completed WPAI-AS at baseline, week 1, and week 2; 962 in the intent-to-treat dataset for Study 2, 241 were students who completed Classroom WPAI-AS at baseline, week 1, and week 2 Dropouts/withdrawals: NR No. of subjects at end: NR Inclusion criteria: Moderate to severe AR Exclusion criteria: Patients with asthma were NOT specifically excluded, but patients with severe asthma were not eligible because patients taking concomitant corticosteroids or cromolyn medications were excluded Age (mean): Study 1, 33; Study 2, 22.8 Sex: Study 1, 63% female; Study 2, 51.5% female Race: Study 1, 84.8% Caucasian; Study 2, 84.2% Caucasian Years of seasonal AR: Study 1, 17.5; Study 2, 12.6	1) Discriminative validity: Correlations between time missed from work or classroom and total symptom score at baseline and weeks 1 and 2. 2) Discriminative validity: Correlations between impairment measures and total symptom score at baseline and weeks 1 and 2. 3) Discriminative validity: Results of regression analysis for total symptom scores on the prediction of work and activity impairment 4) Discriminative validity: Results of regression analysis for total symptom scores on the prediction of classroom impairment 5) Evaluative validity: Correlation between average change in total symptom scores and change in time missed from work or classroom 6) Evaluative validity: Correlation between changes in total symptom scores and work and classroom impairment measures 7) Evaluative validity: Results of regression	1) Correlations were generally low: work: r = 0.11 to 0.16; classroom: r = 0.13 to 0.27 2) Correlations were higher than with time missed measures: work: r = 0.30 to r = 0.55; classroom: r = 0.25 to 0.41 3) Higher total symptom scores were significant predictors of greater work and activity impairment, but not time missed from work at all time points. 4) Higher total symptom scores were significant predictors of classroom impairment at all time points. Higher total symptom scores were also predictive of more classroom time missed at weeks 1 and 2. 5) There was virtually no correlation (work: r = -0.06; classroom: r = 0.05 to 0.14). 6) Correlations were positive (work: r = 0.35 to 0.42; classroom: r = 0.24 to 0.27) 7) Average change in total symptom score was a significant predictor of all	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: Yes Level of evidence: 4 Note: The discriminative and evaluative validity of the WPAI-AS impairment measures (work impairment, overall work impairment, activity impairment, classroom impairment and overall classroom impairment) was established. Because absenteeism from work and school was relatively low (1.7% for work and 4.7% for classroom), establishing the validity of work time missed and classroom time missed was not possible.

(continued on next page)

Evidence Table 1: Costs and Work Performance (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
			analysis for changes on total symptom score and changes in work and classroom impairment measures	impairment measures except work or classroom time missed.	
			8) Responsiveness: changes in mean total symptom scores and WPAI-AS scores for the 5% of patients with the most improvement and the 5% of patients with the least improvement	8) Among the 5% of patients with the most improvement, the level of work and classroom impairment decreased dramatically. Among the 5% of patients with the least improvement, the level of work and classroom impairment generally increased or stayed about the same.	
			9) Responsiveness: changes in total symptom scores and impairment measures for responders and nonresponders (as measured by physician evaluation)	9) For responders in Study 1 and Study 2, total symptom scores and impairment measures decreased dramatically. For nonresponders in Study 1 and Study 2, symptom scores and impairment measures either decreased slightly or stayed about the same.	
			10) Sample size implications	10) To detect a 5% difference in overall work impairment, 201 patients per treatment group would be necessary for 80% power and 5% Type 1 error for a 2-sided hypothesis test. To detect a 5% difference in overall classroom impairment, 192 patients per treatment group would be necessary.	

Evidence Table 1: Costs and Work Performance (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Revicki, Leidy, Brennan-Diemer, et al., 1998	Design: Cross-sectional surveys for instrument development The objective of the study was to design a preference-weighted instrument for rhinitis that could be used to construct rhinitis symptom-adjusted life years (distinct from quality-adjusted life years) in order to quantify outcomes of care for cost-effectiveness analyses. Intervention(s): NA Duration of study treatment: NA Dates: NR Location: Baltimore Setting: Allergy clinic Type(s) of providers: NR	No. of subjects at start: 100 patients, of whom 20 were randomly selected to be retested at 2 weeks to evaluate test-retest reliability Dropouts/withdrawals: NR No. of subjects at end: 100 Inclusion criteria: Receiving care at the Johns Hopkins University Asthma and Allergy Center Exclusion criteria: NR Age: Mean: 36.9 years Sex: 60% women Race: 77% Caucasian; 15% African-American; 8% Asian or other ethnic group Other: Mean duration of illness: 21 years Mean age of onset: 16 years Concurrent diagnosis of asthma: 52% <u>Clinical and health-related measures:</u> To evaluate concurrent and construct validities with the Rhinitis Symptom Utility Index (RSUI), 6 additional measures were used: (1) physician-reported disease severity; (2) disability days; (3) disease-specific quality of life using the RQLQ; (4) generic health utility using the Health Utilities Index Mark 2 (HUI2); (5) Visual Analog Scale (VAS); and (6) Standard Gamble (SG)	1) Average number of days over the previous month when the patient was in bed most or all of the day, had restricted activity for at least ½ day, and the number of days the patient missed school or work 2) RSUI scores 3) Reproducibility of RSUI over 2 weeks. 4) Construct validity of the RSUI 5) Correlations between the RSUI and total and subscale scores for the RQLQ.	1) Average number of bed disability days: 0.63; restricted activity days: 2.49; and missed work days: 0.45. 2) RSUI scores ranged from 0.15 to 1.0. Most scores were > 0.70. The mean was 0.72 (SD 0.23), the median score was 0.78. 3) Intraclass correlation coefficient (ICC) was 0.40. (ICCs for RQLQ ranged from 0.17 to 0.77 due to instability of allergic rhinitis symptoms over time). 4) The RSUI was able to discriminate between levels of disease severity. The mean RSUI for none/mild allergic rhinitis was 0.79 and the mean RSUI for the moderate/severe group was 0.67 ($p < 0.05$). Mean RSUI scores were also higher for patients with HUI2 scores ≥ 0.75 (0.76) than patients with HUI2 scores 0.75 (0.57). Also, mean RSUI scores were higher for patients with no bed disability days (0.76) compared to patients with ≥ 1 bed disability day (0.62). 5) Correlation between the RSUI and total score was -0.67 ($p = 0.0001$). Correlation between the RSUI and each subscale was -0.47 for activity limitations, -0.58 for sleep, -0.51 for non-hay fever symptoms, -0.61 for eye symptoms, -0.69 for nasal symptoms, -0.49 for emotional symptoms, and -	Quality Scoring: Population similar: Yes Intervention(s) described: Not applicable Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: Yes Level of evidence: 4 *(continued on next page)*

Evidence Table 1: Costs and Work Performance (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
		Multiattribute utility assessment methods were used to derive the preference weighting scheme to estimate the RSUI score.		0.61 for practical problems (p = 0.0001 for each).	
Ross, 1996	Design: Cost of illness study (indirect costs only) based on a synthesis of data from multiple sources: 1) 1983-1985 survey from US Department of Health and Human Services; 2) 1994 Statistical Abstract of the United States; and 3) 1989 Gallup Poll The study was designed to estimate the indirect costs associated with the use of first-generation, sedating antihistamines. Intervention(s): NA Duration of study treatment: NA Dates: 1983-1986 prevalence estimates; 1993 wages Location: US Setting: Community Type(s) of providers: NR	No. of subjects at start: NA Dropouts/withdrawals: NA No. of subjects at end: NA Inclusion criteria: Member of US work force Exclusion criteria: NA Age: NR Sex: 51.6% men, Race: NR	1) Prevalence estimate – no. of people with AR in US workforce 2) Prevalence estimate – no. of people with AR classified into 1 of 11 employment categories for men and women 3) Lost productivity due to treatment of AR with sedating (OTC) antihistamines using Assumption #2 (see Notes) 4) Lost productivity if 10%, 20%, 30% of workers with AR lost 1 day of work per year due to AR	1) 12.6 million 2) 11.1 million 3) $3.79 billion ($2.39 billion for men and $1.40 billion for women) 4) 10%: $108 million; 20%: $216 million; 30%: $324 million	Quality Scoring: Population similar: Yes Intervention(s) described: No Comorbidities described: No Diagnosis by MD: No Objectively confirmed: Not applicable Outcome measures valid: No Level of evidence: 3b Notes: Assumptions used in cost calculations: 1) 5% growth in population during previous decade 2) Reduced productivity: 1989 Gallup poll: People with AR who used sedating (OTC) antihistamines reported a 25% reduction in productivity for 14 work days per year. 3) Proportion Treated with OTC antihistamines: 1989 Gallup poll: 50%

Evidence Table 1: Costs and Work Performance (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Santilli, Nathan, Glassheim, et al., 2001	Design: Survey Intervention(s): NA Duration of study treatment: NA Dates: NR Location: Bridgeport, CT; Colorado Springs, CO; Fresno, CA Setting: Private allergy practices Type(s) of providers: Specialists	No. of subjects at start: 175 Dropouts/withdrawals: 0 No. of subjects at end: 175 Inclusion criteria: Immunotherapy for one allergen or a combination of pollens, molds, mites and animal dander for at least 1 year Exclusion criteria: NR Age: NR Sex: 68% female Race: NR Other: Average duration of immunotherapy 3.3 years	1) Rhinitis Outcomes Questionnaire (ROQ) consisting of 26 symptom questions each scored using a 0 to 5 Likert scale. A total score of 130 is possible, representing the most severe combination of allergy symptoms. 2) Percent of patients reporting that immunotherapy was effective 3) Change in antibiotic use, emergency room visits, days lost from work or school, and hospital admissions 4) Change in number of daily medications	1) Prior to immunotherapy, the average score on the ROQ was 52. The average score decreased to 25 following immunotherapy. 2) 81% reported that they believed immunotherapy was effective, and 19% of patients were unsure. 3) Patients reported a 67% decrease in antibiotic use, 68% decrease in emergency room visits, a 75% decrease in days lost from work or school, and a 79% decrease in hospital admissions. 4) Patients did not report a decrease in the number of daily medications after immunotherapy.	Quality Scoring: Population similar: Not adequately described Intervention(s) described: No Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: Yes Level of evidence: 4 Note: Patients who discontinued immunotherapy prior to 1 year were not included in the study. Also, the study is limited by recall bias, as patients completed the survey twice at one sitting (once to recall symptoms prior to immunotherapy and once to evaluate current symptoms). The absolute numbers of patients reporting antibiotic use, ER visits, lost work/school days, or hospital admission were not reported, and no statistical tests were used for comparisons.

Evidence Table 1: Costs and Work Performance (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Santos, Cifaldi, Gregory, et al., 1999 **Study 1 (= retro-spective review of annual medical costs of treating allergic rhinitis)**	Design: Retrospective analysis based on HMO claims data Intervention(s): None – billing encounter data analyzed to compute utilization of HMO system resources (specifically, service encounters and prescriptions) over a 1-year period for selected cohorts of patients with and without allergic rhinitis Duration of study treatment: NA Dates: 1996 Location: New Mexico Setting: Community, network model HMO Type(s) of providers: NR	No. of subjects at start: 15,872 (7936 allergic rhinitis patients + 7936 age- and sex-matched non-allergic rhinitis controls) Dropouts/withdrawals: NA No. of subjects at end: 15,872 Inclusion criteria: Age 12-64; HMO member in 1996 with continuous enrollment from 1994 to 1995; evidence of allergies based on one of the following: a visit for an allergen skin test, an ICD-9-CM code of allergic rhinitis, or a prescription for an allergy medication during the spring or fall allergy seasons Exclusion criteria: NR Age: mean: ~41 years Sex: 58% women Race: NR	1) Total cost to the HMO for medical care provided to the AR group and the matched control group in 1996 2) Cost of prescription medication to HMO for AR group and matched control group in 1996 3) Among the AR group, costs and distribution of prescriptions for allergic rhinitis 4) Average AR prescription costs per person with AR 5) Percent of AR population who filled at least one prescription.	1) AR group: $5.38 million; matched control group: $3.46 million 2) <u>All medication</u>: AR group: $2.06 million; matched control group: $1.05 million. <u>AR medication only</u>: AR group: $1.08 million; matched control group: $0.22 million <u>AR medication as a % of total Rx cost</u> AR group: 53%, matched control group: 21% 3) <u>Antibiotics</u>: 34.6% of AR prescriptions, 12.9% of total medication costs; <u>Oral Steroids</u>: 4.7% of AR prescriptions, 0.3% of total medication costs; <u>Antihistamines</u>: 29.4% of AR prescriptions; 21.8% of total medication costs; <u>Nasal Anti-inflammatory</u>: 27.2% of AR prescriptions; 16.5% of total medication costs; <u>Combination/cold</u>: 4.0% of AR prescriptions, 1.1% of total medication costs. 4) <u>All AR medications</u>: $190.70; <u>Antibiotics</u>: $68.49; <u>Oral Steroids</u>: $10.06; <u>Antihistamines</u>: $187.00; <u>Nasal Anti-inflammatory</u>: $125.30; <u>Combination/cold</u>: $42.71 5) 72%	Quality Scoring: Population similar: Yes Intervention(s) described: No Comorbidities described: No Diagnosis by MD: No Objectively confirmed: Not applicable Outcome measures valid: No Level of evidence: 4 Notes: Assumptions used in cost estimation: 1) Relative value units (RVUs) were used to estimate costs for the HMO ($38.82/RVU in 1996 US$). 2) Prescription drug prices based on October 1997 AWP plus dispensing fee

Evidence Table 1: Costs and Work Performance (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Santos, Cifaldi, Gregory, et al., 1999 **Study 2 (= prospective RCT comparing two types of clinics for treating patients with allergic rhinitis)**	Design: RCT, parallel-group, method of randomization not described Intervention(s): 1) Intervention clinics – used practice guidelines designed to improved and standardize treatment of patients with allergic rhinitis; interventions/ practice guidelines used not described (n = 247 patients) 2) Control clinics – did not alter diagnostic and treatment practices (n = 255 patients) Duration of study treatment: 4 weeks Dates: 1996 fall allergy season Location: New Mexico Setting: Community, network model HMO Type(s) of providers: NR	No. of subjects at start: 502 Dropouts/withdrawals: NR No. of subjects at end: Inclusion criteria: Age 12-65; HMO members for ≥ 12 months prior to start of intervention; present evidence of fall allergies involving nasal symptoms Exclusion criteria: NR Age: NR Sex: NR Race: NR	1) Direct medical costs: included service encounters, prescriptions, and OTC medications (recorded by patients in daily symptom diaries) 2) Indirect costs: Estimated by measuring declines in work and school productivity using the Work Productivity and Activity Impairment Index – Allergy Specific (WPAI-AS) 3) Patient-assessed symptom severity: stuffy nose, sneezing, runny nose, itchy nose/palate/ throat, and itchy/watery eyes graded daily on scale of 0 (no symptoms) to 4 (physician visit needed); these data supplemented (how?) by data gathered in enrollment survey and periodic phone surveys 4) Behavior index – measured compliance with suggested preventive behavior (medical compliance, avoiding smoke, wearing a dust mask, etc.); scores ranged from 0 (no action) to 11 (maximum); not clear when assessed 5) Quality of life: assessed using an index "based on items from the Rhinoconjunctivitis Quality	1) Direct medical costs: Total direct medical costs: Intervention group: $56,515; Control group: $58,402 Direct medical costs per person: Intervention group: $229; Control group: $229 2) Indirect costs (productivity/activity impairment): Total indirect costs: Intervention group: $16,561; Control group: $21,372 Indirect costs per person: Intervention group: $67; Control group: $84 3) Patient-assessed symptom severity: Intervention group vs. control group: Stuffy nose: 1.60 vs 1.55; Sneezing: 1.02 vs 0.97; Runny Nose: 1.15 vs 1.10; Itchy Nose/Palate/Throat: 1.16 vs 1.02; Itchy/Watery Eyes: 1.27 vs 1.09 4) Average behavior index score: Intervention group: 4.60; Control group: 4.30 5) Quality of life measured using the RQLQ Index: Intervention Group: 2.9; Control group: 2.4	Quality Scoring: Population similar: Not adequately described Intervention(s) described: No Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 4 Notes: Results of statistical comparisons were not reported to compare differences in costs or patient outcomes. Not relevant to key question about correlating symptom outcomes/disease-specific quality of life with workplace performance data – estimates of statistical variation (SD or SE) are not reported, nor are the results of statistical comparisons

(continued on next page)

Evidence Table 1: Costs and Work Performance (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
			of Life Questionnaire (RQLQ)"; scores ranged from 0 to 10, with higher scores indicating lower quality of life		
Schädlich and Brecht, 2000	Design: Cost-effectiveness analysis using a model based on secondary data. Separate models were developed for seasonal and perennial allergic rhinitis. Intervention(s): Specific immunotherapy (SIT) for 3 years versus pharmacologic treatment Duration of study treatment: Model was based on a 10-year follow-up period Dates: NA Location: Germany Setting: NA Type(s) of providers: NA	No. of subjects at start: NA Dropouts/withdrawals: NA No. of subjects at end: NA Inclusion criteria: NA Exclusion criteria: NA Age: NR Sex: NR Race: NR <u>Cost-Effectiveness Model:</u> <u>Time period:</u> model was based on a 10-year period. <u>Health Outcome</u>: the presence or absence of asthma symptoms at 10 years. Clinical trial, observational, and epidemiological data were used to model the health outcome. <u>Costs:</u> Costs in the model were valued from 3 perspectives: society, the healthcare system, and the statutory health insurance provider (SHI). Cost estimates were derived from a variety of sources including public pharmacies for the cost of drugs and allergen extracts, government payment schedules, and published estimates. Costs were discounted at 5% per annum.	1) Break-even point of accumulated costs and cost difference at 10 years between SIT and pharmacologic treatment 2) Incremental number of patients free from asthma due to SIT 3) Cost per additional patient free from asthma symptoms at 10 years 4) Results of sensitivity analyses	1) In the base-case analysis, cumulative costs in both arms were equal during year 7. At 10 years, cumulative costs in the SIT arm were approximately DM670 (DM; DM 1 = $US 0.5764, 1997 values) lower in the SIT group. 2) Out of 1000 hypothetical patients, the model showed that 161 additional patients were free from asthma symptoms at 10 years. 3) In the best case scenario for pollen allergy, the break even point for costs was reached at 1 year, resulting in a cost savings of DM 3,620 at 10 years with 212 additional patients free from asthma. In the worst case scenario, the break even point was never reached, resulting in additional costs in the SIT arm of DM 1,420 at 10 years with 88 additional patients free from asthma. 4) Sensitivity analyses: The following variables had an important effect on cost-effectiveness: a) Direct medical cost of anti-allergic pharmacotherapy (symptomatic treatment); b) Cost of SIT; c) Increase in asthma prevalence with symptomatic treatment of allergic rhinitis.	Quality Scoring: Population similar: Yes Intervention(s) described: No Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: No Outcome measures valid: No Level of evidence: 1b Note: 100% compliance with immunotherapy was assumed, the measure of effectiveness modeled was the additional patient free of asthma symptoms based on cumulative incidence and remission rates from different published sources for SIT and symptomatic treatment.

Evidence Table 1: Costs and Work Performance (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Stahl, van Rompay, Wang, et al., 2000	Design: Retrospective cost-minimization analysis based on data from a randomized, double-blind, parallel group study Intervention(s): 1) Budesonide 256µg once daily 2) Fluticasone 200 µg once daily 3) Placebo Duration of study treatment: 6 weeks Dates: November 1994 to July 1995 Location: Canada and Spain Setting: Allergy clinic Type(s) of providers: NR	No. of subjects at start: 314 Dropouts/withdrawals: NR No. of subjects at end: NR Inclusion criteria: Perennial allergic rhinitis Exclusion criteria: None specified Age: NR Sex: NR Race: NR	1) Cost of study drugs for 12 months in 1998 Canadian dollars 2) Cost of medical management (physician visits, comedication, laboratory tests/ examinations) of perennial AR for 12 months in 1998 Canadian dollars based on expert opinion 3) Cost of medical management due to lack of efficacy and side effects over 12 months in 1998 Canadian dollars 4) Treatment cost for both active treatment study arms (placebo was not considered a relevant comparator and was not included in the cost minimization analysis)	1) Budesonide: $95.80; fluticasone: $214.01; difference = $118.21 2) Physician visits: $114.23; laboratory tests/examinations: $48.23; co-medications: $38.96; total = $201.41 3) Lack of efficacy: $75.18; side effects: $17.46 4) Because effectiveness and side effect profiles for both medications were not different, the difference in costs is attributable to the difference in drug costs. The total 12-month cost for budesonide was estimated at $389.85 and the total 12-month cost for fluticasone was estimated at $508.06. Difference = $118.21.	Quality Scoring: Population similar: Not adequately similar Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: No Outcome measures valid: No Level of evidence: 4 Notes: The clinical data used in the study included all patients from Canada and Spain. However, the cost-minimization analysis was conducted using practice patterns (from an expert panel) and costs from Canada. Drug costs for study medications determined the results.

Evidence Table 1: Costs and Work Performance (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Storms, Meltzer, Nathan, et al., 1997	Design: Population-based mail surveys Intervention(s): NA Duration of study treatment: NA Dates: 1993 Location: US Setting: Co mmunity Type(s) of providers: NR	No. of subjects at start: Surveys initially sent to 15,000 households; 66.3% responded; a sample of 1450 persons were sent a 2nd survey to gather further information about AR; 73.4% responded Dropouts/withdrawals: NA No. of subjects at end: 481 respondents Inclusion criteria: Self-reported seasonal or perennial AR and ≥ 7 days of symptoms during previous year Exclusion criteria: Respondents who selected one of the following options as best describing their nasal/ocular symptoms that lasted ≥ 7 days during previous year: common cold, an allergy only when exposed to certain triggers, sinus problems, or other condition Age: 11.9% < 18; 20.6% 18-34; 33.5% 35-49; 19.1% 50-64; 10.8% ≥ 65 Sex: 56% female Race: 93% white	1) Proportion who reported not taking medications for AR, proportion filling a prescription for AR, proportion reporting an average monthly expenditure for OTC medications for AR 2) Proportion reporting any missed work or school days or unable to perform normal activities 3) Proportion who sought treatment from a physician for AR symptoms 4) Average per-patient expenditure on prescription and OTC medications for AR 5) Total US expenditures for prescription and OTC medications for AR 6) Total US expenditures for physician visits for AR 7) Total direct medical costs for AR	1) No medication: 13.5%; prescription medication: 45%; OTC medication: 69%. 2) 5% 3) 63% (22.6 million people) 4) Prescription: $56 ($1993); OTC: $56 ($1993) 5) Prescription: $907 million ($1993); OTC: $1.39 billion ($1993); Total: $2.3 billion 6) $1.13 billion ($1993) 7) $3.4 billion ($1993)	Quality Scoring: Population similar: Yes Intervention(s) described: No Comorbidities described: No Diagnosis by MD: No Objectively confirmed Not applicable Outcome measures valid: No Level of evidence: 4 Notes: It is not clear whether self-reported "expenses" represent total costs or out-of-pocket expenditures. Assumptions used in cost calculations: 1) Cost of office visit: $50. Assumed that physician visits did not include any diagnostic tests. 2) Self-reported expenses equal to direct medical costs.

Evidence Table 1: Costs and Work Performance (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Sussman, Mason, Compton, et al., 1999	Design: RCT, parallel-group, method of randomization not described Interventions: 1) Fexofenadine 60 mg + pseudoephedrine 120 mg (extended-release), twice per day (n = 215) 2) Fexofenadine 60 mg twice per day (n = 218) 3) Pseudoephedrine 120 mg (extended-release) twice per day (n = 218) Duration of study treatment: 14-20 days Rescue med not permitted Trial preceded by a 3- to 5-day placebo run-in period; no other washout period described Dates: NR Location: Canada Setting: Allergy clinic Type(s) of providers: NR	No. of subjects at start: 710 were screened for study; 651 randomized and treated with study drug(s) Dropouts/withdrawals: 9.7% discontinued the study; 2.8% due to adverse events; 3.8% due to subject/investigator decision. No. of subjects at end: 651 included in intent-to-treat analysis Inclusion criteria: Age 12-65; history of ragweed allergy confirmed by a positive skin prick test; evidence of a clinical response to antihistamines. At the initial visit, subjects had to have a total symptom score ≥ 6 for the previous 12 hours, with nasal congestion and ≥ 2 symptoms rated as moderate or severe. After the placebo lead-in phase, subjects had to have a total symptom score ≥ 6, moderate or severe nasal congestion, and at least 2 symptoms rated as moderate or severe for 2 of the 3 most recent evening assessments. Exclusion criteria: History of alcoholism or drug abuse; hypersensitivity to terfenadine, fexofenadine, or pseudoephedrine; URI or sinusitis within 30 days of 1st study visit; pregnant or lactating women; any symptoms rated as very severe Age: Mean ~33 years Sex: 57.8% female	1) Patient-assessed symptom severity: sneezing; rhinorrhea; itchy nose, palate, and/or throat; itchy, watery, or red eyes; and nasal congestion graded twice each day (7 PM and bedtime) on scale of 0 (symptom absent) to 4 (symptom so severe as to warrant an immediate visit to the physician). 2) Adverse events: Patients "were required to record any adverse events" 3) Work-related productivity: Assessed using the Work Productivity Activities Index (WPAI), completed at baseline and at end of treatment	1) Patient-assessed symptom severity: When using the efficacy endpoint used to evaluate all symptoms except nasal congestion, symptoms were improved to a greater extent with combination therapy than with pseudoephedrine alone, but not when compared with fexofenadine alone. When using the efficacy endpoint to evaluate nasal congestion symptoms, again, there was a significant improvement in the combination therapy arm compared to pseudoephedrine, but not compared to fexofenadine alone. 2) Adverse events: 43% of patients experienced ≥ 1 adverse event. There was no difference between the combination (51.2%) and pseudoephedrine only (45.4%) groups. However, the incidence of adverse events was significantly lower in the fexofenadine group (32.6%). The most frequently reported events were headache and insomnia. 3) Work-related productivity: At baseline, all patients reported an average of 44% impairment in daily activities. Working patients reported a 1.8% loss in work time, 38.7% work impairment, and 39.3% overall work impairment during the placebo lead-in phase. After treatment, daily activity impairment decreased by 9.8% in the fexofenadine group, 7.9% in the pseudoephedrine group, and 13% in the combination therapy group. Among working patients, there was a significant improvement in work productivity in the combination group (9.3%) compared to the pseudoephedrine group (6.2%). There was no improvement between the	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: Yes Level of evidence: 4 Note: Double-dummy blinding technique employed. *(continued on next page)*

Evidence Table 1: Costs and Work Performance (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
		Race: White: 86.9%; Black: 5.4%; Asian: 6.4%; Multiracial: 1.2% Other: Average years since first episode of seasonal AR: ~15.3 years.		combination and fexofenadine group (8.1%). Overall work productivity in the combination (8.5%) and the fexofenadine (8.0%) groups increased compared to the pseudoephedrine group (4.9%).	
Tanner, Reilly, Meltzer, et al., 1999	Design: Results of 2 RCTs pooled, both parallel-group, method of randomization not described Intervention(s): 1) Fexofenadine 60 mg bid (n = 389) 2) Placebo (n = 387) 3) (See Notes) Duration of study treatment: 2 weeks Use of meds with antihistamine or decongestant activity, corticosteroids, and immunotherapy in changing doses prohibited during trial No run-in/washout period described; patient using meds with antihistamine or decongestant activity within 48 hours, corticosteroids within 30 days, or immunotherapy in changing doses within 60 days excluded Dates: Spring 1994 Location: US	No. of subjects at start: 1957 randomized; 1948 had baseline and at least one other QOL assessment; 776 of these assigned to analyzed interventions (fexofenadine 60 mg bid and placebo) Dropouts/withdrawals: No. of subjects at end: 1948 Inclusion criteria: Diagnosis of moderate to severe seasonal allergic rhinitis based on a positive skin prick test within previous 15 months; ≥ 2 of the following symptoms rated as moderate or severe by the investigator: sneezing, rhinorrhea, itchy nose, palate and/or throat; or itchy, watery eyes; history of positive response to previous antihistamine use Exclusion criteria: Symptoms rated as very severe; pregnant or lactating women; significant hepatic, neurologic, endocrine, or major systemic disease Age (mean): Study 1, 32 (range, 11-65); Study 2, 33 (range, 12-68) Sex: Study 1, 58% femal; Study	1) Disease-specific quality of life: assessed using the Rhinoconjunctivities Quality of Life Questionnaire (RQLQ) at baseline and at 1 and 2 weeks 2) Performance impairment (at work and in classroom) due to allergy symptoms: assessed using the Allergy-Specific Work Productivity and Activity Impairment Questionnaire (WPAI-AS) at baseline and at 1 and 2 weeks 3) Generic quality of life: measured using 3 generic domains of the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) (Role-Physical, General Health Perceptions, Change in Health)	1) Disease-specific quality of life: Average overall RQLQ score at baseline: 2.7; linear regression revealed significantly lower mean RQLQ scores at weeks 1 and 2 in the fexofenadine group compared to the placebo group. At week 1, patients randomized to fexofenadine had significant reductions in all RQLQ domains except sleep. By week 2, a significant reduction remained in the following domains only: activity, practical problems and nasal symptom scores. 2) Performance impairment due to allergy symptoms: Patients taking fexofenadine had significant reductions in the percentage of daily activity impairment at weeks 1 and 2. By week 2, patients taking fexofenadine had greater reductions in the percentage of overall work impairment. At baseline, only approximately 3% of usual work time was missed due to allergy symptoms. There was not a significant difference in the percent of usual work time missed between treatment groups at Week 1 or Week 2. Reductions in classroom time missed, classroom impairment or overall impairment in the classroom were significantly lower in the fexofenadine group at Week 1, but there was no difference at Week 2.	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: Yes Level of evidence: 4 Notes: Unspecified range of fexofenadine doses tested in original trials; present analysis considers 60-mg bid dose vs. placebo. No separate publications referenced for 2 RCTs here pooled.

(continued on next page)

Evidence Table 1: Costs and Work Performance (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	Setting: 32 centers throughout the US Type(s) of providers: NR	2, 55% female Race: Study 1, 85% Caucasian, 15% Other; Study 2, 80% Caucasian, 20% Other Average number of years of seasonal allergic rhinitis: Study 1, 16; Study 2, 17		3) Generic quality of life: No significant differences on the generic QOL measures were detected between treatment groups at any time point.	
Trotter, 2000	Design: Retrospective analysis of prescription claims Intervention(s): NA Duration of study treatment: NA Dates: April 1997 - April 1998 Location: US Setting: Outpatient Type(s) of providers: NR	No. of subjects at start: Prescription records from > 60 million people Dropouts/withdrawals: NA No. of subjects at end: 121,524 patients met inclusion criteria Inclusion criteria: Claim for initial prescription for = 1 of the following medications: azelastine, fexofenadine, loratadine, fluticasone, beclomethasone, or cetirizine. Initiating therapy was defined as the absence of a prior prescription claim for the AR medications or other medications, including antihistamines, nasal steroids, and medications for cough/cold. Patients had to be eligible for prescription plan benefits for the full study year. Exclusion criteria: NR Age: NR Sex: NR Race: NR	1) Average number of prescriptions received annually 2) Total prescription costs for AR drugs for patients initiating therapy with various AR medications 3) Percentage of patients receiving monotherapy with each medication	1) Average number of prescriptions received annually: Azelastine 2.2 Beclomethasone 2.4 Cetirizine 2.5 Fluticasone 2.6 Loratadine NR Fexofenadine 2.7 2) Total prescription costs for AR drugs for patients initiating therapy with various AR medications: Azelastine $111 Beclomethasone $118-$129 Cetirizine $134 Fluticasone $137 Loratadine $171 Fexofenadine $222 3) Percentage of patients receiving monotherapy with each medication: Azelastine 46.6% Beclomethasone 43.3% Cetirizine 46.2% Fluticasone 38.1% Loratadine 40.3% Fexofenadine 38.9%	Quality Scoring: Population similar: Not adequately described Intervention(s) described: No Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: No Outcome measures valid: No Level of evidence: 2b Notes: The study aim was to estimate the total cost of treatment for patients initiating treatment with selected medications. Assumption used in cost estimation: Unit size (e.g., no of tablets, inhalations) of each prescription was combined with average wholesale price to estimate medication costs. It is not clear whether 12 months of data were available beyond the date on which the initial AR medication was filled because the claims used in the analysis covered only a 13-month period. Therefore, patients who filled their first AR

(continued on next page)

Evidence Table 1: Costs and Work Performance (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
					medication 6 months into the study period may have had data available for only 7 months, not 1 year.
Yawn, Yunginger, Wollan, et al., 1999	Design: Analysis of population-based registry of patients with asthma The study was designed to estimate the prevalence and incremental medical care charges (not including medications) of AR among patients with asthma. Intervention(s): NA Duration of study treatment: NA Dates: Charge data, 1987-1996 Location: Olmstead County, Minnesota Setting: Community Type(s) of providers: NA	No. of subjects at start: Random sample of 1245 patients with asthma Dropouts/withdrawals: Patients > 65 years were excluded from analysis No. of subjects at end: Analysis of charge data was based on 1065 patients; analysis of clinical data was based on 1245 patients Inclusion criteria: Diagnosed with "definite asthma" based on patient history or clinical findings Exclusion criteria: Bullous emphysema or pulmonary fibroses on chest radiograph; PiZZ α_1-antitrypsin; cystic fibrosis; other major chest disease Age: Mean, 31 (in 1987); median, 24 Sex: 53% male Race: NR	1) Proportion of asthma patients diagnosed with AR 2) Tri-mean (dollars/year) for patients with asthma only (total medical care charges not including medications) 3) Tri-mean (dollars/year) for patients with asthma and AR (total medical care charges not including medications) 4) Tri-mean (dollars/year) for patients with asthma only (total medical care charges not including medications), stratified by gender 5) Tri-mean (dollars/year) for patients with asthma and AR (total medical care charges not including medications), stratified by gender	1) 52.4% with concomitant AR 2) $249.89 ($1987) 3) $335.82 ($1987) 4) $160.26 for men ($1987) $392.18 for women ($1987) 5) $226.93 for men ($1987) $543.96 for women ($1987)	Quality Scoring: Population similar: Yes Intervention(s) described: ?? Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: No Outcome measures valid: No Level of evidence: 1b Notes: Annual medical charges were computed for each patient and adjusted to 1987 dollars using the Medical Consumer Price Index. Charges did not include charges for medication. The 'tri-mean' is computed as the mean of the 1st quartile (Q_1), 2 times the median (Q_2), and the 3rd quartile (Q_3): (tri-mean = $(Q_1+2Q_2+Q_3)/4$).

[†] Quality scoring criteria were as follows:
Population similar: Was the study population described and reasonably similar to an adult working US population? (Yes [described and similar], No [described, but not similar], Not adequately described)
Intervention(s) described: Were the intervention protocols referenced or described in sufficient detail to replicate? (Yes, No)
Comorbidities described: Was the presence of comorbid asthma (or other upper respiratory conditions) described in the study population? (Yes, No)
Diagnosis by MD: Was the diagnosis of allergic rhinitis based on physician diagnosis? (Yes, No, Not applicable [asthma patients only])
Objectively confirmed: If physician-diagnosed, was the diagnosis supported by objective evidence of allergy (e.g., skin prick or serum IgE antibody testing)? (Yes, No, Not applicable)

Outcome measures valid: Were the main outcomes of interest to us measured in a way that has been demonstrated empirically to be valid and reliable (e.g., using a standardized scale such the RQLQ or SF-36)? (Yes, No, Not adequately described)
Level of evidence: Based on Oxford Center for Evidence-Based Medicine Levels of Evidence (1a, 1b, 1c, 2a, 2b, 2c, 3a, 3b, 4, 5)

Evidence Table 2: Environmental Measures

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Antonicelli, Bilò, Pucci, et al., 1991	Design: RCT, crossover Interventions: 1) HEPA filter (Enviracaire®) + routine house cleaning. HEPA filter device placed in bedroom and used 24 hours/day for 8 weeks. 2) Routine house cleaning alone. Duration of study treatment: 8 weeks each treatment period; no washout between periods Dates: 10/1988-2/1989 Location: Italy Setting: NR Type(s) of providers: NR	No. of subjects at start: 9 Dropouts/withdrawals: 0 No. of subjects at end: 9 Inclusion criteria: Rhinitis and mild asthma; dust mite sensitivity by skin test Exclusion criteria: Long-term corticosteroid therapy, immunotherapy Age: 16 (range 10-28) Sex: 7 male; 3 female (misreported?) Race: NR Other:	1) Allergen levels: dust collected monthly from bedroom floor on day after usual room cleaning 2) Patient-assessed symptom severity: rhinitis, cough, and dyspnea graded daily on scale of 0 (asymptomatic) to 3 (maximum symptoms) 3) Use of symptomatic medication (terfenadine tablets, salbutamol inhalations): recorded daily in study diaries 4) Spirometry (morning and evening peak flow rates, FEV1, and bronchial reactivity [metacholine challenge test])	1) Allergen levels: Results reported graphically; no significant differences between groups in floor samples. 2) Patient-assessed symptom severity: Results reported graphically; significant period effect on rhinitis symptoms but no intervention effect. No significant effects on cough, wheezing. 3) Use of symptomatic medication: Results reported graphically; no significant effect. 4) Spirometry: Not abstracted	Quality Scoring: Population similar: No Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: No Blinding adequate: Not applicable Dropouts described: Yes Intention-to-treat: Yes Note: No assessment of carry-over effect, period effect, or treatment-by-period interaction. Statistical power not addressed.

Evidence Table 2: Environmental Measures (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Bahir, Goldberg, Mekori, et al., 1997	Design: RCT, parallel-group Interventions: 1) Acaricide (Acardust® = esdepallethin 0.9% and piperonyl butoxide 7.2%) + continuous avoidance measures (n = 13). Acaricide applied twice to mattress and floors (at start of study and at 3 months); avoidance measures described below. 2) Placebo acaricide (applied to mattress and floor at start of study and at 3 months) + continuous avoidance measures (described below) (n = 17) 3) Continuous avoidance measures only (described below) (n = 16) Avoidance measures (all 3 groups): Start of trial: Change bed-clothes, mattresses, rugs, curtains, upholstered furniture, toys, etc. Every object prone to accumulate dust to be removed. Pillows or blankets made of goose, feather, or wool forbidden. Synthetic pillows and blankets only. Daily: wash floors and dust furniture with damp cloth; shake bedclothes outside bedroom and leave on window sill Weekly: vacuum mattresses on both sides; thoroughly clean shelves, pictures,	No. of subjects at start: 62 Dropouts/withdrawals: 16 No. of subjects at end: 46 Inclusion criteria: Mild to moderate asthma by ATS criteria; duration ≥ 1 year; reversible airway disease document by FEV1 or PEF Exclusion criteria: Respiratory tract infection, steroid use, or sodium cromoglycate within past month; immunotherapy or hospitalization for asthma in past 6 months Age: Range, 6-16.5 Sex: NR Race: NR Other:	1) Allergen levels: dust collected by vacuum and analyzed by investigators; allergenicity of dust graded on scale of 0 (none) to 4 (strong) 2) Spirometry (FEV1, peak flow rates) 3) Patient-assessed symptom severity: quality of sleep, dyspnea, wheezing, cough, sputum, rhinitis, and sneezing graded daily on scale of 0-12 4) Use of ß$_2$-agonists and concurrent medication (topical steroids, cromoglycate): recorded by patients daily 5) Parents' global assessment of severity of asthma at end of study compared to beginning (same, better, worse)	1) Allergen levels: Baseline and f/u; p = ns Gp1: 3.6 ± 0.7; 3.3 ± 0.9 Gp2: 3.3 ± 0.6; 2.9 ± 0.8 Gp3: 3.5 ± 0.6; 2.7 ± 0.8 2) Spirometry: Not abstracted 3) Patient-assessed symptom severity: Reported graphically; p = ns 4) Use of ß$_2$-agonists and concurrent medication: Reported graphically; p = ns 5) Parents' global assessment of severity of asthma at end of study compared to beginning; p = ns Gp 1: 7 better; 6 same; 0 worse Gp 2: 9 better; 8 same; 0 worse Gp 3: 6 better; 9 same; 1 worse	Quality Scoring: Population similar: No Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Not applicable Objectively confirmed: Not applicable Outcome measures valid: No Level of evidence: 1b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: No Note: Power: 80% power to detect a 0.75 difference in house dust mite antigen.

(continued on next page)

Evidence Table 2: Environmental Measures (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	furniture, walls, drawers, and cupboards; change bed sheets and wash them in washing machine at 60° C or hotter Monthly: Wash blankets and pillows at 60° C or hotter Duration of study treatment: 6 months Trial preceded by 2-week run-in period Dates: NR Location: Israel Setting: Pediatric Health Centers Type(s) of providers: NR				
Burr, Dean, Merrett, et al., 1980	Design: RCT, parallel-group Interventions: 1) Avoidance measures (n = 26), as follows: mattress vacuumed at start of trial and weekly thereafter; blankets and sheets laundered at start, and blankets beaten in open air at least once every 2 weeks; sheets, pillow-cases, and other washable bedding laundered weekly; feather pillows replaced with synthetic pillows or enclosed in impervious cover; all pillows beaten weekly in open air; quilts and eiderdowns removed unless < 6 months old and washable; soft toys removed or washed, brushed,	No. of subjects at start: 55 Dropouts/withdrawals: 2 No. of subjects at end: 53 Inclusion criteria: Asthma; positive skin test for dust mites Exclusion criteria: "Asthma seemed to be exacerbated by other allergens" Age: 9 (range, 4.5-14) Sex: 36 male; 17 female Race: NR Other:	1) Spirometry (morning and evening peak flow rates) 2) Mother and investigator global evaluation of efficacy: at end of trial (8 weeks), clinician assessed child's progress "in light of the mother's report of symptoms and the changes in physical signs and lung function;" child's condition graded as much better, better, same, worse, or much worse 3) Allergen levels: dust samples obtained from bedding of treated group at start of trial and from	1) Spirometry: Not abstracted 2) Mother and investigator global evaluation of efficacy: Intervention: 5/26 much better; 11/26 better Control: 6/27 much better; 9/27 better 3) Allergen levels: Only reported pre-post for intervention group. Between-group comparisons not made.	Quality Scoring: Population similar: No Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Not applicable Objectively confirmed: Not applicable Outcome measures valid: No Level of evidence: 1b Randomized: Yes Allocation concealed: Not described Double-blind: No Blinding adequate: Not applicable Dropouts described: Yes Intention-to-treat: No *(continued on next page)*

Evidence Table 2: Environmental Measures (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	or vacuumed every week; bedroom carpets vacuumed several times every week; upholstery vacuumed every 2 weeks. 2) Placebo avoidance measures (n = 27), as follows: importance of dust in living room emphasized; living room dusted daily using special duster, and other rooms similarly dusted once per week; spray-on polish recommended before each dusting; upholstered chairs in living room vacuumed or brushed at least twice a week; carpet in living room vacuumed daily. Duration of study treatment: 8 weeks Trial preceded by 1-week run-in period, during which baseline data collected Dates: NR Location: UK Setting: Pediatric outpatient clinic Type(s) of providers: Pediatricians		both groups at end of trial; collected using special suction device		Note: Power not addressed

Evidence Table 2: Environmental Measures (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Burr, Neale, Dean, et al., 1980	Design: RCT, crossover Interventions: 1) Avoidance measures, as follows: each child issued with new sleeping bag, pillow, and blankets (if required); mattress completely enclosed in impervious plastic bag; all other bedding either enclosed in impervious bags or removed; carpets in bedroom vacuumed several times every week. 2) No special avoidance measures. Duration of study treatment: 1 month each treatment period; no washout between periods Dates: NR Location: UK Setting: Pediatric outpatient clinic Type(s) of providers: Pediatricians	No. of subjects at start: 21 Dropouts/withdrawals: 0 No. of subjects at end: 21 Inclusion criteria: Asthma; positive skin test for dust mites Exclusion criteria: "Asthma seemed to be exacerbated by other allergens" Age: NR, but is a subset of Burr, Dean, Merrett, et al., 1980, above Sex: NR, but is a subset of Burr, Dean, Merrett, et al., 1980, above Race: NR Other:	1) Spirometry (morning and evening peak flow rates) 2) Mother's global evaluation of efficacy: at end of treatment period, mother asked whether child's asthma better or worse 3) Allergen levels: mites contained in bedding counted at end of each treatment period	1) Spirometry: Not abstracted 2) Mother's global evaluation of efficacy: Intervention period compared to control: 6 improved, 14 no change, 1 worse (no test for significance) 3) Allergen levels: Not meaningfully reported	Quality Scoring: Population similar: No Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Not applicable Objectively confirmed: Not applicable Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: No Blinding adequate: Not applicable Dropouts described: Yes Intention-to-treat: Can't determine Notes: All patients had participated in trial by Burr, Dean, Merrett, et al., 1980, described above. No assessment of carry-over effect, period effect, or treatment-by-period interaction. Power not addressed.

Evidence Table 2: Environmental Measures (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Carswell, Birmingham, Oliver, et al., 1996	Design: RCT, parallel-group Interventions: 1) Acaricide (Acarosan®) + avoidance measures (n = 35). At start of trial, Acarosan® powder (benzyl benzoate 5%) applied to bedroom carpet and Acarosan® foam (benzyl benzoate 1.6%) applied to mattresses, duvets, pillows, and any upholstered furniture. All items thoroughly vacuumed with Medivac® vacuum before application of acaricide, 24 hours later, and 4 weeks later. Allergen exclusion covers (Intervent®) fitted to mattresses, duvets, and pillows and left in place for 24 weeks. All bed linens to be washed at 60° C each week. Softy toys removed or washed at 60° C. 2) Placebo acaricide + placebo avoidance measures (n = 35). At start of trial, placebo powder (chalk dust) applied to bedroom carpet and water spray applied to mattresses, duvets, pillows, and any upholstered furniture. All items thoroughly vacuumed with Medivac® vacuum before application, 24 hours later, and 4 weeks later. Placebo covers (cotton) fitted to mattresses, duvets, and pillows and left in place for 24 weeks. All bed linens to be washed at 40° C each week. Softy toys removed or washed at 40° C.	No. of subjects at start: 70 randomized; 62 started treatment Dropouts/withdrawals: 19 No. of subjects at end: 51 (49 completers) Inclusion criteria: Asthma (wheezing, breathlessness); skin test positive for house-dust mite; high dust-mite antigen in mattress Exclusion criteria: Cat allergen sensitive and cat in house; no duvet or not sleeping in single bed Age: 9.8 (range, 7-10) Sex: 44 males; 26 females Race: NR Other:	1) Allergen levels: dust collected by vacuum and Petri dishes "from potentially mite allergen-rich sites" pretreatment and at 2, 6, 14 and 24 weeks 2) Spirometry (peak flow rates) 3) Bronchial histamine sensitivity 4) Patient-assessed symptom severity: presence/absence of asthma symptoms of wheeze, cough, activity impairment, and sleep disturbance recorded whenever peak flow rates measured (3 times per day during four different 2-week periods) 5) Use of symptomatic medication: recorded whenever peak flow rates measured (3 times per day during four different 2-week periods)	1) Allergen levels: Mattress: Median change, $p < 0.0001$ Intervention: 480 ng Control: 215 ng Carpets: reported graphically; no significant difference 2) Spirometry: Not abstracted 3) Bronchial histamine sensitivity: Not abstracted 4) Patient-assessed symptom severity: results reported graphically; total symptoms decreased significantly more in the intervention group (about 30% fewer patients with symptoms vs. no change in control, $p<0.05$). No significant difference in individual symptoms of daytime wheeze and cough. 5) Use of symptomatic medication: 50% of intervention patients took medication vs. 80% in control group, $p< 0.02$. (From graph: about a 30% difference in bronchodilator use and about 20% difference in inhaled steroid use.)	Quality Scoring: Population similar: No Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Not applicable Objectively confirmed: Not applicable Outcome measures valid: No Level of evidence: 1b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: No Notes: 10 subjects excluded because of incomplete treatment or non-adherence. Power: a priori sample size calculation showing 50 completers needed. Looked at potential confounders and found no difference except fewer cats in placebo group.

(continued on next page)

Evidence Table 2: Environmental Measures (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	Duration of study treatment: 24 weeks Dates: NR Location: UK Setting: Schools Type(s) of providers: Family practitioners				
Chang, Becker, Ferguson, et al., 1996	Design: RCT, parallel-group Interventions: 1) Acaracide (Acarosan® = benzyl benzoate) + avoidance measures (n = 12). Acaracide applied once at start of study to carpet in bedroom, carpet in most commonly used room, and mattress; avoidance measures described below. 2) Avoidance measures only (described below) (n = 14) Avoidance measures (both groups): Vacuum home at least once per week, wash bedding in hot water (> 58° C), and encase mattresses and pillows with vinyl covers Duration of study treatment: 3 months Trial preceded by 1-month run-in period, during which allergen levels tested; patients completed diary cards for 1 month pre-trial	No. of subjects at start: 26 Dropouts/withdrawals: 0 No. of subjects at end: 26 Inclusion criteria: Asthma; dust-mite sensitivity by skin test; mite allergens > 1 µg/g of dust from mattress or bedroom floor Exclusion criteria: None specified Age: 11 children, 15 adults Sex: NR Race: NR Other:	1) Allergen levels (mattress and floor): dust collected by vacuum at baseline, 1 week, and 1 and 3 months 2) Patient-assessed symptom severity: cough, wheeze, and breathlessness graded daily on score of 0 (no symptoms) to 3 (severe) 3) Spirometry (FEV1, morning peak expiratory flow rate, evening peak expiratory flow rate) 4) Methacholine inhalation test	1) Allergen levels (baseline; 3 months): Mattress: p = ns Gp 1: 2.17 ± 2.64; 0.06 ± 1.12 Gp 2: 1.68 ± 2.22; 0.28 ± 1.32 Floor: p < 0.05 Gp 1: 2.38 ± 2.24; 0.50 ± 1.71 Gp 2: 2.05 ± 2.05; 1.10 ± 2.17 2) Patient-assessed symptom severity (baseline; 1; 2; and 3 months): p = ns Gp 1: 1.5 ± 2.1; 1.5 ± 1.9; 1.6 ± 2.2; 1.1 ± 1.7 Gp 2: 0.6 ± 0.8; 1.2 ± 1.6; 0.7 ± 1.7; 0.4 ± 0.5 3) Spirometry: Not abstracted 4) Methacholine inhalation test: Not abstracted	Quality Scoring: Population similar: Yes Intervention(s) describe: Yes Comorbidities described: Yes Diagnosis by MD: Not applicable Objectively confirmed: Not applicable Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: No Blinding adequate: Not applicable Dropouts described: No Intention-to-treat: Can't determine Notes: Important baseline differences between groups in symptoms. Power: not addressed.

(continued on next page)

Evidence Table 2: Environmental Measures (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	Dates: 12/1993-4/1994 Location: Canada Setting: NR (subset of participants in another study) Type(s) of providers: NR				
Chen and Hsieh, 1996	Design: RCT, parallel-group Interventions: 1) Avoidance measures (n = 29). Patients provided with new Microstop®-treated mattresses, quilts, pillows, bed linens, and quilt covers. 2) Placebo avoidance measures (n = 29). Patients provided with new non-Microstop®-treated mattresses, quilts, pillows, bed linens, and quilt covers. 3) No avoidance measures (n = 15). Patients continue to use their regular bedding. Duration of study treatment: 12 months Trial preceded by run-in period of at least 1 month, during which baseline data collected Dates: 1/1994 - 4/1995 Location: Taiwan Setting: Allergy clinic at Women and Childrens Hospital	No. of subjects at start: 73 Dropouts/withdrawals: 29 No. of subjects at end: 44 Inclusion criteria: Asthma and positive to house dust-mite Exclusion criteria: Pets, immunotherapy, inhaled steroids Age: 8.23 ± 2.56 Sex: 55 male; 18 female Race: NR Other:	1) Allergen levels: dust samples collected by vacuum from mattress, quilt, and pillows at baseline and after 1, 2, 3, 6, 9, and 12 months 2) Patient-assessed symptom severity: asthma symptoms of sleep disturbance, chest tightness on awakening, daytime symptoms, and cough graded twice daily on scale of 0 (none) to 4 (severe [different definitions for various specific outcomes]) 3) Spirometry (morning and evening peak flow rates)	1) Allergen levels: (reported graphically) Mattress: Intervention showed significant decreases compared to baseline. Placebo groups did not show significant decreases. No between-group differences reported. Quilt: Intervention and placebo avoidance showed significant differences compared to baseline. No between-group differences reported. Pillow: Intervention showed lower mite count compared to placebo and control groups (p = not significant). 2) Patient-assessed symptom severity: (reported graphically). Intervention group showed significantly decreased symptoms compared to baseline for 10 of 12 months. No between-group comparisons reported. 3) Spirometry: Not abstracted	Quality Scoring: Population similar: No Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Not applicable Objectively confirmed: Not applicable Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: No Notes: Power: no discussion. High number of dropouts. No between-group comparisons.

(continued on next page)

Evidence Table 2: Environmental Measures (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	Type(s) of providers: NR				
Clooster-man, Hofland, Lukassen, et al., 1997	Design: RCT, parallel-group, randomization stratified by type of floor covering (textile vs. smooth) and initial FEV1 Interventions: 1) Acaracide (Acarosan® = benzyl benzoate) + avoidance measures (n = 16). Acaricide applied to bedroom and living room floors once at start of study; avoidance measures consisted of encasing mattresses, pillows, and duvets in covers impermeable to house dust mites and house dust mite allergens. 2) Placebo acaracide (water) + placebo avoidance measures (cotton covers permeable to house dust mites and house dust mite allergens (n = 13). Patients in both groups were instructed to vacuum bedroom and living room floors and wash bedding once per week. Duration of study treatment: 6 weeks Trial preceded by 2-week baseline period Dates: 1993 Location: The Netherlands Setting: Recruited from	No. of subjects at start: 29 Dropouts/withdrawals: 11 (5 treatment, 6 placebo) No. of subjects at end: 18 (11 treatment, 7 placebo) Inclusion criteria: Positive skin test for house dust mite; skin test reaction to dogs, cats, and *Spergillus fumigatus* < reaction to house dust mite; (all patients had mild symptoms of asthma but this was not an inclusion criteria) Exclusion criteria: Confirmed diagnosis of asthma; history of receiving anti-inflammatory medication; peak flow variability > 15% or FEV1 increase by > 15% after salbutamol Age: Gp 1: 32.4 ± 11.5; Gp 2: 23.5 ± 6.3 (p = 0.04) Sex: 17/29 women Race: NR Other:	1) Spirometry (peak flow rates, peak flow variability) 2) Patient-assessed symptom severity: cough, breathlessness, wheezing, expectoration, tiredness, and disturbed sleep (due to cough, wheeze, or breathlessness) graded on scale of 0 (no symptoms) to 10 (severe symptoms)	1) Spirometry: Not abstracted 2) Patient-assessed symptom severity: Selected symptoms (sleep, breathlessness, wheeze, overall score) reported graphically; no data given for other symptoms; only within-group p-values given. Between-group differences given for only one symptom (wheeze) at one time point, week 5 (Gp 1 change from baseline of -0.31 ± 0.1 vs Gp 2 +0.53 ± 0.24; p = "significant").	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: No Objectively confirmed: Yes Outcome measures valid: No (?) Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: No Blinding adequate: Not applicable Dropouts described: Yes Intention-to-treat: No Notes: Stratification and randomization resulted in unbalanced distribution of patients to treatment groups. Appear to be important baseline differences in symptoms and demos. Patients were minimally symptomatic. Sample size based on peak flow; 80% power to detect a 15 l/min difference; no post-hoc power calculation on symptoms.

(continued on next page)

Evidence Table 2: Environmental Measures (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	patients referred for skin testing Type(s) of providers: General practitioners				
Clooster-man, Schermer, Bijl-Hofland, et al., 1999	Design: RCT, parallel-group Interventions: 1) Acaracide (Acarosan® = benzyl benzoate) + avoidance measures (n = 76). Acaricide applied to carpets and rugs in bedroom and living room once at start of study; avoidance measures consisted of encasing mattresses, pillows, and duvets in covers impermeable to house dust mites and house dust mite allergens. 2) Placebo acaracide (water) + placebo avoidance measures (cotton covers permeable to house dust mites and house dust mite allergens (n = 81). Duration of study treatment: 20 weeks Trial preceded by 4-week baseline period During trial, patients used only bronchodilators, and in a standardized way; exacerba-tions treated with prednisone and, if necessary, antibiotics in a standardized way Dates: 10/1993-9/1996	No. of subjects at start: 258 eligible; 204 randomized Dropouts/withdrawals: 58 No. of subjects at end: 146; 157 ITT Inclusion criteria: Asthma; positive skin test for house dust mite; FEV1 > 50% and > 65% after salbutamol; PC20 = 8 mg/ml or reversibility of obstruction after salbutamol Exclusion criteria: Oral steroids; inhaled corticosteroids dependency; skin test reactivity to pets > reaction to dust mite if pets in house Age: Gp 1: 32.7 ± 11; Gp 2: 33.9 ± 11.1 Sex: 82 men; 75 women Race: NR Other:	1) Allergen levels: dust collected by vacuum from mattress and floors at baseline and at 8, 14, and 20 weeks 2) Spirometry (peak flow rates, peak flow variability, FEV1, bronchial hyper-responsiveness) 3) Patient-assessed symptom severity: cough, breathlessness, wheezing, expectoration, tiredness, and disturbed sleep (due to cough, wheeze, or breathlessness) graded on scale of 0 (no symptoms) to 10 (severe symptoms)	1) Allergen levels: Reported graphically (Der P 1): Mattress: ng/g, p = 0.0001 Gp 1: 860 (95% CI, 537-1376), declined by 90.6% Gp 2: 931 (95% CI, 602-1439), declined by 31.5% Bedroom floor (p = 0.883) and living room floor (p = 0.9422) – only graphical 2) Spirometry: Not abstracted 3) Patient-assessed symptom severity: Reported graphically only; no significant differences, p = 0.5474	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Not applicable Objectively confirmed: Not applicable Outcome measures valid: No (?) Level of evidence: 1b Randomized: Yes Allocation concealed: Not described Double-blind: No Blinding adequate: Not applicable Dropouts described: Yes Intention-to-treat: Yes Note: Power not addressed

(continued on next page)

Evidence Table 2: Environmental Measures (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	Location: The Netherlands Setting: Allergy laboratory records with GP and Pulmonologists Type(s) of providers: General practitioners and pulmonologists				
Dietemann, Bessot, Hoyet, et al., 1993	Design: RCT, parallel-group Interventions: 1) Acaracide (Acarosan® = benzyl benzoate) (n = 11). Applied to all mattresses and upholsteries in home and to all carpets and rugs at the start of the trial and once again after an interval of at least 6 months. 2) Placebo acaracide, applied as above (n = 12). Duration of study treatment: 1 year Dates: NR Location: France Setting: Chest clinic Type(s) of providers: Pulmonologists?	No. of subjects at start: 26 Dropouts/withdrawals: 3 No. of subjects at end: 23 Inclusion criteria: Definite history of asthma; positive skin test to *Dermatophagoides pteronssinus*; RAST for Dp > 3 using pharmacia screening system; Acarex value ≥ ++ Exclusion criteria: None specified Age: 35 ± 14.9 Sex: 12 men; 12 women Race: NR Other:	1) Investigator-assessed symptom severity ("clinical scores"): graded every 3 months during clinic visits on scale of 0 = no asthmatic episodes, 1 = at least one asthmatic episode per month, 2 = at least one asthmatic episode per week, 3 = at least one asthmatic episode per day,] 2) Patient-assessed symptom severity: graded every 3 months during clinic visits on VAS scale of 0 (severe dyspnea) to 10 (no dyspnea) 3) Medication use: graded every 3 months during clinic visits on following scale: 0 = no medication; 1 = no more than 4 inhalations per day of ß2-agonists or disodium cromoglycate intake or both; 2 = continuous bronchodilator treatment with ß2-agonists, with or without long-acting theophylline (twice per day), and beclomethasone	1) Investigator-assessed symptom severity ("clinical scores"): Baseline and % change, p = ns Gp 1: 2.54 (95% CI, ± 1.5); -45% Gp 2: 2.0 (95% CI, ± 0.4); -41% 2) Patient-assessed symptom severity: Baseline and % change, p = ns Gp 1: 5.7 (95% CI, ± 0.84); +36% Gp 2: 5.0 (95% CI, ± 0.78); +46.6% 3) Medication use: Baseline and % change, p = ns Gp 1: 2.27 (95% CI, ± 0.66); -12% Gp 2: 1.92 (95% CI, ± 0.50); -19.8% 4) Spirometry: Not abstracted 5) Allergen levels: Baseline µg/g and % change of Der p I + Der f I Mattress: p = ns Gp 1: 43.53 (95% CI, ± 24.6); -19.7% Gp 2: 84.66 (95% CI, ± 52.5); -17% Upholstery elements: p = ns Gp 1: 30.4 (95% CI, ± 31.5); -67% Gp 2: 40.0 (95% CI, ± 18.4); - 61% Carpets: p = ns Gp 1: 4.95 (95% CI, ± 3.23); -74% Gp 2: 13.0 (95% CI, ± 6.6); -27%	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Not applicable Objectively confirmed: Not applicable Outcome measures valid: No Level of evidence: 1b Randomized: Yes Allocation concealed: Not applicable Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: No Notes: No diary recording of symptoms. Symptom outcomes based on data collected at 3-monthly clinic visits. Power not addressed.

(continued on next page)

Evidence Table 2: Environmental Measures (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
			dipropionate at dose ≤ 1000 µg/day; 3 = ß2-agonist inhalation with or without long-acting theophylline, and beclomethasone dipropionate at dose ≥ 1000 µg/day 4) Spirometry (FEV1, FVC, FEF 25-75, peak flow rates) 5) Allergen levels: dust collected by vacuum from mattresses, carpets, and upholstery at baseline and 12 months		
Dorward, Colloff, MacKay, et al., 1988	Design: RCT, parallel-group Interventions: 1) Avoidance measures (n = 9). Mattresses and bedroom carpets soaked with liquid nitrogen at start of trial. Entire surface of bed vacuumed weekly. Blankets, pillows, and duvets cleaned at the start of trial; sheets and pillow cases washed weekly; blankets and upper sheets or duvets folded back each morning to allow mattress to air. Hard surfaces damp-dusted weekly. Plants, soft toys, cushions, and upholstered furniture removed from bedroom. 2) No avoidance measures (n = 9). Patients instructed to continue with their normal cleaning activities.	No. of subjects at start: 21 Dropouts/withdrawals: 3 No. of subjects at end: 18 Inclusion criteria: Stable asthma; positive skin test to house dust-mite; FEV1 >60% predicted Exclusion criteria: Requirement for oral steroids, theophylline, sodium cromoglycate or dog or cat at home Age: 25.6 (range 13-48) intervention; 24.8 control (range 14-53) Sex: 8 males; 10 females Race: NR Other:	1) Patient-assessed symptom severity: presence/absence and duration of wheezing recorded daily; overall severity of asthma graded daily on 10-cm linear analog scale 2) Use of salbutamol inhaler: number of puffs used recorded daily 3) Spirometry (morning and evening peak flow rates) 4) Bronchial reactivity (PC_{20} histamine values) 5) Allergen levels: dust samples collected from mattresses and carpets at baseline and at 4 and 8 weeks	1) Patient-assessed symptom severity: (reported graphically as mean % change) Wheezing hours decreased significantly in intervention group (about -50% vs. + 10%, $p < 0.05$); wheezing days did not differ (about -20% vs. 0%); asthma severity decreased but not significantly different (about -45% vs. +10%). 2) Use of salbutamol inhaler: No significant difference (about -10% vs. +10%) 3) Spirometry: Not abstracted 4) Bronchial reactivity: Not abstracted 5) Allergen levels: (Mattress, # intact mites/0.25 m2/min) Intervention: 6.56 ± 6.25 baseline; 0.33 ± 1.33 8 weeks, $p< 0.01$ for within-group change Control: 7.0 ± 6.98 baseline; 4.22 ±	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Not applicable Objectively confirmed: Not applicable Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: No Blinding adequate: Not applicable Dropouts described: Yes Intention-to-treat: No Note: Power: no discussion *(continued on next page)*

Evidence Table 2: Environmental Measures (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	Duration of study treatment: 8 weeks Trial preceded by 2- to 3-week run-in period Dates: 1/1984 – 6/1984 Location: Scotland Setting: Hospital respiratory clinic Type(s) of providers: NR		6) IgE and allergen-specific IgE antibody levels	4.94 8 weeks , p > 0.05 for within-group change No between-group comparison made 6) IgE and allergen-specific IgE antibody levels: Not abstracted	
Frederick, Warner, Jessop, et al., 1997	Design: RCT, crossover Interventions: 1) Avoidance measures, consisting of encasing mattresses, pillows, and duvets in covers impermeable to house dust mites and house dust mite allergens (Intervent®). Patients instructed to wipe down covers with a damp cloth once per week. 2) Placebo avoidance measures (polycotton covers, no weekly wipe-down). Duration of study treatment: 3 months each treatment period, with a 1-month washout between periods Trial preceded by 2-week run-in period Dates: 11/1992 – 11/993 Location: UK	No. of subjects at start: 31 Dropouts/withdrawals: 0 No. of subjects at end: 31 Inclusion criteria: Documented perennial asthma; positive skin test or RAST ≥ grade 3 to house dust mite Exclusion criteria: None specified Age: 9 (range 5-15) Sex: 20 male; 11 female Race: NR Other:	1) Allergen levels: dust collected from mattress, duvet, and pillow at baseline and end of each period 2) Patient-assessed symptom severity: asthma last night, daytime wheeze, and exercise tolerance measured (twice?) daily on scale of 0-3 (not described) 3) Spirometry (morning and evening peak flow rates, FEV1, PC_{20}) 4) Use of bronchodilator (ß2-agonist): recorded daily by patients in diary 5) Blood assays (ECP, EPX, EPO, sIL-2R)	1) Allergen levels: Median ng/g (with range), baseline and 3 months: Mattress: (active and placebo crossover), p = 0.0012 Gp 1 (active): 12,403 (616-24,138); 1,246 (0-66,667) Gp 2 (active): 8,500 (354-50,000); 1,086 (0-6,452) Gp 1 (placebo): 7,275 (100-30,519); 2,737 9(53-97,143) Gp 2 (placebo): 14,759 (0-82,500); 13,500 (900-63,830) Duvet (p < 0.000) and pillow (p < 0.0001) antigen levels also decreased significantly 2) Patient-assessed symptom severity: Baseline; month 3; median and (range) Asthma: p = ns Active: 0.2 (0-1.9); 0.1 (0-0.8) Placebo: 0.09 (0-2.5); 0.09 (0-1.7) Asthma, wheeze, and exercise tolerance did not differ significantly between groups 3) Spirometry: Not abstracted 4) Use of bronchodilator (ß2-agonist):	Quality Scoring: Population similar: No Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Not applicable Objectively confirmed: Not applicable Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: No Double-blind: No Blinding adequate: Not applicable Dropouts described: Yes Intention-to-treat: Yes Notes: Intervention bias (i.e., no weekly wipe-down in placebo group); could lead to unblinding. No assessment of period effect or treatment-by-period interaction.

(continued on next page)

Evidence Table 2: Environmental Measures (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	Setting: General Pediatric Hospital Type(s) of providers: ?			Baseline; 3 months, median µg (range) Active: 120 (0-986); 80 (0-312) Placebo: 60 (0-542); 40 (0-372) 5) Blood assays: Not abstracted	Power not addressed.
Geller-Bernstein, Pibourdin, Dornelas, et al., 1995	Design: RCT, parallel-group Interventions: 1) Acaricide (Acardust® = esdepallethin 0.9% and piperonyl butoxide 7.2%), applied at baseline and 3 months to mattress (and more widely throughout bedroom?) (n = 17) 2) Placebo acaricide, applied as above (n = 15) Subjects in both groups cleaned their bedrooms regularly using the same procedures (change of bedsheet every week, change of blanket every month, daily dust removal with damp cloth, and weekly vacuuming of carpets and furniture). Duration of study treatment: 6 months Trial preceded by 1-month run-in period Dates: NR Location: Israel Setting: Pediatric Allergy Clinic Type(s) of providers: ?	No. of subjects at start: 35 Dropouts/withdrawals: 3 No. of subjects at end: 32 Inclusion criteria: Age 4-12 with asthma or rhinitis severe enough to require continuous medications for the 3 months prior to entry; in asthmatics, a peak flow or FEV1 ≥ 15% below predicted; positive skin test to house dust mite; Acarex test ≥ 2+ in child's mattress dust Exclusion criteria: Allergy due to non-house dust mite allergens; use of an acaricide w/in 3 months of study entry Age: Gp 1: 9.7 ± 2.6; Gp 2: 8.1 ± 2.6 Sex: 23 male; 12 female Race: NR Other:	1) Patient-assessed symptom severity (diary data): asthma severity, nasal secretion, nasal obstruction, sneezing, ocular pruritus, and lacrimation graded twice weekly (so text; abstract has "daily") on scale of 0 (no symptoms) to 3 (severe symptoms) 2) Patient-assessed symptom severity (clinic visits): disruption of daily activities, wheezing frequency, severity of rhinitis symptoms, frequency of rhinitis crisis graded at monthly clinic visits on scale of 0 (no symptoms/less than once per month) to 3 (severe symptoms/permanently) 3) Investigator-assessed symptom severity (monthly clinic visits) 4) Use of concurrent medication: recorded by patients in diary (frequency unclear) 5) Adverse events: patients instructed to record "any unusual events, symptoms or other	Outcomes reported monthly; data reported below are for baseline and 6 months. 1) Patient-assessed symptom severity (diary data): means (no variance given), p = 0.001? Gp 1: 34.83; 5.47 Gp 2: 29.88; 6.60 2) Patient-assessed symptom severity (clinic visits): means (no variance given) Daily Activity Disruption (p = 0.02) Gp 1: 1.17; 0.13 Gp 2: 0.94; 0.27 Wheezing frequency (p = 0.10) Gp 1: 1.94; 0.67 Gp 2: 2.06; 0.73 Nasal secretion – graphical results only, p = 0.01 favoring Acardust® Other rhinitis symptoms – graphical results only, p = 0.02 favoring Acardust® 3) Investigator-assessed symptom severity (monthly clinic visits): Not abstracted 4) Use of concurrent medication: Graphical results only, p = 0.01 favoring Acardust® 5) Adverse events: None	Quality Scoring: Population similar: No Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 1b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: No Notes: Poorly reported trial. Often difficult to know whether outcomes reported are based on patient-diary or clinic-visit data. 32 patients had rhinitis; 31 had asthma. Power not addressed.

(continued on next page)

Evidence Table 2: Environmental Measures (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
			illnesses" in their diaries 6) Patient/parent monthly global evaluation of asthma severity: graded at monthly clinic visits using VAS from 0-100 mm 7) Investigator monthly global evaluation of asthma severity 8) Investigator final global evaluation of improvement (6 months) 9) Spirometry (morning and evening peak flow, PFF, FEV1) 10) Blood tests (total and dust mite farinae-specific IgE levels) 11) Allergen levels: dust collected by vacuum from mattress at baseline and 2, 3, 4, and 6 months	6) Patient/parent monthly global evaluation of asthma severity: Graphical results only, p = 0.001 favoring Acardust® 7) Investigator monthly global evaluation of asthma severity: Not abstracted 8) Investigator final global evaluation of improvement (6 months): Not abstracted 9) Spirometry: Not abstracted 10) Blood tests: Not abstracted 11) Allergen levels: p = 0.02 Gp 1: 10.05 ± 13.74; 4.15 ± 6.51 Gp 2: 6.01 ± 8.01; 3.01 ± 4.33	

Evidence Table 2: Environmental Measures (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Gillies, Littlewood, and Sarsfield, 1987	Design: RCT, parallel-group Interventions: 1) Avoidance measures (n = 13). Mattress completely enclosed by special cover; pillows enclosed in plastic covers; soft toys and pets excluded from bedroom; synthetic bedding used; damp-dusting performed weekly; bed, mattress, and bed base vacuumed thoroughly (interval not specified). 2) No avoidance measures (n = 12). Patients instructed to continue their normal domestic cleaning practice. Duration of study treatment: 6 weeks (controlled portion of trial) Dates: 11/1984?-4/1985? Location: UK Setting: NR Type(s) of providers: NR	No. of subjects at start: 26 Dropouts/withdrawals: 1 No. of subjects at end: 25 Inclusion criteria: Children; mild to moderate asthma; positive skin test to dust mite allergen Exclusion criteria: Requiring regular asthma medication Age: 9.7 (range 6-16) Sex: NR Race: NR Other:	1) Allergen levels: dust collected from mattresses using a standard dusting technique at baseline and 6 weeks 2) Total and allergen-specific IgE antibody levels 3) Bronchial reactivity (PC_{20} histamine values) 4) Patient-assessed symptom severity: day- and nighttime cough and wheeze and daytime activity recorded daily 5) Use of bronchodilators: recorded daily 6) Spirometry (morning and evening peak flow rates)	1) Allergen levels: Mattress (dust mite counts mites/m2, baseline - 6 weeks) Intervention: 40.0 ± 64.24; 1.23 ± 1.74 Control: 21.75 ± 20.3; 10.33 ± 16.22 (no between-group statistical comparison) 2) Total IgE antibody levels: Not abstracted 3) Bronchial reactivity: Not abstracted 4) Patient-assessed symptom severity: reported in text as "no significant changes in …[symptom scores, medication requirements]…" 5) Use of bronchodilators: reported in text as "no significant changes in …[symptom scores, medication requirements]…" 6) Spirometry: Not abstracted	Quality Scoring: Population similar: No Intervention(s) described: No Comorbidities described: Yes Diagnosis by MD: Not applicable Objectively confirmed: Not applicable Outcome measures valid: ?? Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: ?? Blinding adequate: ?? Dropouts described: ?? Intention-to-treat: ?? Notes: All patients employed avoidance measures during weeks 7-12. Power: no discussion Poorly reported trial. No data given for symptoms, no between-group comparisons.

Evidence Table 2: Environmental Measures (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Huss, Huss, Squire, et al., 1994	Design: RCT, parallel-group Interventions: 1) Acaracide (Acarosan® = benzyl benzoate) + avoidance measures (n = 6). Acaracide applied to bedroom and living room carpets at baseline and 6 months; avoidance measures described below. 2) Placebo acaracide (applied as above) + avoidance measures (described below) (n = 6) Avoidance measures: patients in both groups had already (at start of trial) implemented avoidance measures such as encasing mattresses, box springs, and pillows in allergen-impermeable covers and washing bed linens in hot water. During trial, were instructed to vacuum carpets weekly. Duration of study treatment: 1 year Dates: 10/1990-11/1991 Location: US Setting: NR Type(s) of providers: NR	No. of subjects at start: 12 Dropouts/withdrawals: 0 No. of subjects at end: 12 Inclusion criteria: Symptomatic asthma using standardized criteria; positive skin test to house dust mite; high levels of house dust mite in carpets Exclusion criteria: "Significant" severity to dog, cat, feathers, or other potentially relevant indoor allergens Age: 44; (range 25-65) Sex: 4 male; 8 female Race: 10 white; 1 black; 1 other Other:	1) Allergen levels: collected from bedroom and living room carpets by vacuum at baseline and at 3, 6, 9, and 12 months 2) Spirometry (morning and evening peak flow, FEV1, FEF_{25-75}, peak flow variability) 3) Experience using acaracide/difficulty of use/time involved: assessed by interview at end of study (12 months) 4) Patient global assessment of efficacy: graded once, at 12 months; patient asked whether he/she felt treatment had improved his/her asthma (yes/no/unsure) 5) Patient global assessment of adverse events: graded once, at 12 months; patient asked whether he/she had felt any adverse effects as result of treatment (yes/no) 6) Medication use: Not clear how assessed	1) Allergen levels: Results shown graphically; no within-group or between-group differences. 2) Spirometry: Not abstracted 3) Experience using acaracide/difficulty of use/time involved: Not abstracted 4) Patient global assessment of efficacy: Not reported by group 5) Patient global assessment of adverse events: No adverse events reported. 6) Medication use: No data reported; statement of "not significantly different"	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Not applicable Objectively confirmed: Not applicable Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: No Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: Yes Notes: Small sample size (6 patients per group). Very little patient-assessed symptom data reported. No daily recording of symptoms. Power not addressed.

Evidence Table 2: Environmental Measures (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Kniest, Young, Van Praag, et al., 1991	Design: Controlled trial (patients assigned "arbitrarily" – doesn't say randomly), parallel-group, matched-pairs design (matched by age, IgE and skin testing to house dust mite, symptoms, guanine exposure and dwelling) Interventions: 1) Acaracide (Acarosan® = benzyl benzoate) + avoidance measures (n = 10). Acaracide applied to all textile objects in home (carpets, padded furniture, upholstery, mattresses, stuffed animals) at baseline and 6 months; avoidance measures described below. 2) Placebo acaracide (applied as above) + avoidance measures (described below) (n = 10) Avoidance measures (both groups): Described as "normal but intensive household cleaning" Duration of study treatment: 1 year Dates: 6/1988 – 6/1989 Location: The Netherlands Setting: Allergy Department Type(s) of providers: NR	No. of subjects at start: 20 Dropouts/withdrawals: 0 No. of subjects at end: 20 Inclusion criteria: House dust mite induced perennial rhinitis more evident than other allergic symptoms Exclusion criteria: None specified Age: 20; (range 12-35) Sex: NR Race: NR Other:	1) Patient-assessed symptom severity: itching of eye and nose, sneezing, nose secretion, nose bleeding, eye irritation, and nasal blockage graded daily on scale of 0 (no symptoms) to 3 (symptoms present for more than 2 hours) 2) Medication use: use of steroid nasal spray, cromoglycate nasal spray, and terfenadine recorded daily 3) Physician global evaluation of efficacy 4) Blood tests (IgE, eosinophils) 5) Allergen levels: dust collected from all textile objects in home by vacuum at baseline and at 3, 6, and 12 months	1) Patient-assessed symptom severity: Gp 1 improved more than Gp 2 (p = 0.025, matched-pairs analysis, subject level scores given) 2) Medication use: No between-group differences in medication index (no p-value or means reported) 3) Physician global evaluation of efficacy: Not abstracted 4) Blood tests (IgE, eosinophils): Not abstracted 5) Allergen levels: Graphical results given; guanine exposure dropped more for group 1 (70% of baseline) than group 2 (97% of baseline; p = 0.45, matched-pairs analysis)	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 3b Randomized: No Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: Yes Notes: Uncertain if truly randomized. Concealment: NR Power not addressed.

Evidence Table 2: Environmental Measures (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Kooistra, Pasch, and Reed, 1978	Design: RCT, crossover; groups matched for skin test sensitivity to ragweed and *Alternaria* Interventions: 1) Air conditioning + home air cleaner (Space Gard®, removes particles 6.0 µ and larger with 99% efficiency) 2) Air conditioning + placebo air cleaner (no filter) Duration of study treatment: 4 weeks each treatment period; no wash-out between periods Dates: 8/10/1976-10/4/1976 Location: USA Setting: Allergy clinic? Type(s) of providers: Allergists?	No. of subjects at start: 20 Dropouts/withdrawals: 0 No. of subjects at end: 20 Inclusion criteria: ≥ 5-year history of seasonal hay fever symptoms; skin test ≥ 2+ for ragweed extract Exclusion criteria: Significant allergy to house dust mite, or animal dander; nasal polyps. No patients were using corticosteroids. None had had immunotherapy in past 2 years. Age: Range 15-68 Sex: 11 men; 9 women Race: NR Other:	1) Patient-assessed symptom severity: duration of sneezing, nasal congestion, and itchy eyes, and amount of medication used, recorded for 3 periods each day (day = 8 AM to 5 PM; evening = 5-10 PM; night = 10 PM to 8 AM); values of 0-3 assigned (by investigators?) to each parameter 2) Pollen concentrations (indoor and outdoor): recorded at 2 and 4 weeks during each study period	1) Patient-assessed symptom severity: (difference between cleaner out – cleaner in) Daytime: 0.15 (4% reduction); p = ns Evening: 0.03 (.9% reduction); p = ns Night: 0.35 (14% reduction); p = 0.0007 Total 24 hours: 0.52 (6% reduction); p = 0.06 2) Pollen concentrations: Results seem uninterpretable given the crossover design. Outdoor allergen levels differ between filter-in and filter-out time periods.	Quality Scoring: Population similar: Not adequately described Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: No Dropouts described: Yes Intention-to-treat: Yes Notes: No statistical test for period effect. Treatment-by-period interaction assessed: "order of placement of the air cleaner (first half or second half) . . . had no statistical effect on the symptoms of hay fever." Power not addressed. All patients had allergic rhinitis; 6 had symptoms of mild asthma.

Evidence Table 2: Environmental Measures (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Korsgaard, 1983	Design: RCT, parallel-group Interventions: 1) Avoidance measures (n = 23), as follows: mattresses vacuumed twice a week; bedding replaced with new synthetic quilts and pillows; bed linen changed and washed twice a week; bedroom floor changed, if necessary, to linoleum or wood and cleaned twice a week; bedroom thoroughly aired for at least 20 minutes every day, and one window left half-open for 24 hours; window in living room open for at least 20 minutes every day; indoor clothes drying to be avoided, if possible; no flowers or plants in bedroom; water-vapor producing activities to be followed by thorough airing 2) No special avoidance measures (n = 23) Duration of study treatment: 12 weeks Trial preceded by 12-week run-in period Dates: 12/1979-3/1981 Location: Denmark Setting: Hospital Chest Clinic Type(s) of providers: NR	No. of subjects at start: 46 Dropouts/withdrawals: 0 No. of subjects at end: 46 Inclusion criteria: Asthma; positive skin test to house dust mites; RAST class ≥ 3 to house dust mite; positive bronchial provocation test to house dust mite Exclusion criteria: Skin test reaction to other indoor allergens (e.g., mold); unable to safely use B2 agonists Age: Median 30 (range 21-34) Sex: 32 men; 14 women Race: NR Other:	1) Adherence to prescribed avoidance measures: assessed by questionnaire at baseline and 12 weeks 2) Spirometry (morning and evening peak flow) 3) Medication use (terbutaline spray): assessed a) by weighing container when exchanged for a new one (every 4 weeks), and b) by daily diary recordings 4) Patient-assessed symptom score: shortness of breath, coughing, and wheezing graded on scale of 0-3 (not described) twice daily (once for 24 hours overall and once for nighttime only) 5) Indoor absolute humidity: measured during weeks -8, -4, 1, 5, 9, and 12 6) Allergen levels: dust collected from mattress and bedroom and living room floors (frequency not reported)	1) Adherence to prescribed avoidance measures: Intervention group increased cleaning of bed linen, mattress, bedroom and living room floor, and airing of the bedroom significantly. 2) Spirometry: Not abstracted 3) Medication use (terbutaline spray): Baseline (12 weeks); 12 weeks following intervention, median (IQR); p = 0.163 Gp 1: 0.54 g/month (0.26-2.29); 0.33 (0.09-1.33) Gp 2: 0.71 g/month (0.42-1.15); 0.40 (0.14-1.41) 4) Patient-assessed symptom score: Baseline (12 weeks); 12 weeks following intervention, median (IQR); 24 hour score: p = 0.0184 Gp 1: 9.0 (5.5-14.5); 3.0 (1.0-10.5) Gp 2: 9.0 (3.0-16.5); 7.5 (2.0-10.5) Night score: p = 0.0716 Gp 1: 5.0 (0.0-8.5); 0.5 (0.0-4.0) Gp 2: 4.0 (0.0-9.5); 3.0 (0.0-7.0) 5) Indoor absolute humidity: Not abstracted 6) Allergen levels: median (IQR) in 0.10 g of dust Mattress: p = 0.1532 Gp 1: 55 (23-346); 122 (18-230) Gp 2: 44 (5-398); 64 (8-378) Bedroom floor: p = 0.0001 Gp 1: 52 (8-204); 16 (5-30) Gp 2: 47 (6-201); 74 (21-463) Living room floor: p = 0.676 Gp 1: 6 (2-41); 14 (4-71) Gp 2: 8 (2-49); 8 (3-70)	Quality Scoring: Population similar: Yes Intervention(s) described: No Comorbidities described: Yes Diagnosis by MD: Not applicable Objectively confirmed: Not applicable Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: No Blinding adequate: Not applicable Dropouts described: Yes Intention-to-treat: Yes Notes: Power not addressed. 34 patients had allergic rhinitis.

Evidence Table 2: Environmental Measures (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Kroidl, Göbel, Balzer, et al., 1998	Design: RCT, parallel-group Interventions: 1) Acaracide (Acarosan®), applied (by patients) according to manufacturer's written instructions (n = 55). Applied at the start of trial and again at 6 months. 2) Placebo acaracide (as above, but without active ingredient [benzyl benzoate]) (n = 63). Duration of study treatment: 12 months Dates: NR Location: Germany Setting: NR Type(s) of providers: NR	No. of subjects at start: 118 Dropouts/withdrawals: 40 No. of subjects at end: 78 Inclusion criteria: Asthma requiring regular treatment; skin test and RAST positive for house dust mite Exclusion criteria: "Patients with other relevant allergies;" smoking within 5 years Age: Range 8-50 (mean not reported) Sex: 67 males; 51 females Race: NR Other:	1) Patient global evaluation of efficacy: at end of trial, symptoms assessed as "worse," "same," or "better" 2) Investigator global evaluation of efficacy 3) Allergen-specific IgE antibody levels 4) Skin reactivity 5) Bronchial reactivity	1) Patient global evaluation of efficacy: (reported graphically) – no significant difference (approximately 61% better in intervention group vs. 64% in control; p = 0.098) 2) Investigator global evaluation of efficacy: Not abstracted 3) Allergen-specific IgE antibody levels: Not abstracted 4) Skin reactivity: Not abstracted 5) Bronchial reactivity: Not abstracted	Quality Scoring: Population similar: Not adequately described Intervention(s) described: ?? Comorbidities described: Yes Diagnosis by MD: Not applicable Objectively confirmed: Not applicable Outcome measures valid: No Level of evidence: 1b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: No Notes: No outcomes based on daily recording of symptoms. 70/118 patients had allergic rhinitis. Power: no discussion.

Evidence Table 2: Environmental Measures (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Marks, Tovey, Green, et al., 1994	Design: RCT, parallel-group Interventions: 1) Acaricide (Allersearch DMS®) + avoidance measures (n = 17). Acaricide applied once at start of study to both sides of mattress, pillows, duvet, and blankets, as well as to carpets and bedroom and living room furniture. Avoidance measures consisted of placing impermeable covers over mattress, pillows, and duvets. 2) Placebo acaricide (applied as above) (n = 18) Duration of study treatment: 6 months Trial preceded by a 3-month run-in period Dates: 1989-1990 Location: Australia Setting: Hospital asthma and allergy clinics; general practices Type(s) of providers: NR	No. of subjects at start: 35 Dropouts/withdrawals: 5 No. of subjects at end: 30 Inclusion criteria: Clinical diagnosis of asthma; reversible airflow obstruction; (all had positive skin tests to at least one inhaled allergen and all but two were positive to house dust mite) Exclusion criteria: None specified Age: mean 35 Sex: 18 female; 17 male Race: NR Other:	1) Allergen levels: dust samples collected from bed, bedroom floor, and living room floor at baseline and at 2 weeks, 3 months, and 6 months 2) Patient-assessed symptom severity: Symptoms assessed twice daily, as follows: a) Sleep disturbance due to asthma (0 = none, to 3 = awake most of the night); b) Chest tightness on awakening (0 = not present and didn't require extra bronchodilator during the night, to 2 = present); c) Duration and frequency of daytime wheeze and breathlessness (0 = none, to 3 = most or all of the day); d) Severity of daytime wheeze and breathlessness (0 = none, to 2 = moderate to severe, distressing and/or had to limit activities); e) Cough (0 = none, to 2 = more than occasional). 3) Spirometry (peak flow rates, peak flow variability, FEV1, airway responsiveness [PD20 FEV1])	1) Allergen levels: Results presented graphically and as mean change. Over 3 sites (bed, bedroom floor, living room floor), Der p I levels decreased significantly at 2 weeks (p = 0.038) but not at 3 months (p = 0.33) or 6 months (p = 0.76) 2) Patient-assessed symptom severity: No significant differences at 1,3, or 6 months. 6-month mean change (95% CI), p = 0.20: Gp 1: 0.14 (-0.08-037) Gp 2: -0.06 (-0.31-0.19) 3) Spirometry: Not abstracted	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Not applicable Objectively confirmed: Not applicable Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: No Blinding adequate: Not applicable Dropouts described: yes Intention-to-treat: Can't determine Note: Power not addressed

Evidence Table 2: Environmental Measures (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Moon and Choi, 1999	Design: RCT, parallel-group Interventions: 1) "Routine care" (not defined) + avoidance measures (n = 15). Avoidance measures consisted of wrapping mattress in vinyl cover, washing top bedding cover in hot (55° C) water every 2 weeks, removing soft furniture from bedroom, and wet cleaning bedroom floor every day. 2) "Routine care" alone (n = 15). Other treatments continued including immunotherapy (52%) and symptomatic treatment (28%). Duration of study treatment: 4 weeks Dates: 7/1995-10-1995 Location: Korea Setting: Allergy clinic of University Hospital Type(s) of providers: Allergy clinic nurse	No. of subjects at start: 30 Dropouts/withdrawals: 1 No. of subjects at end: 29 Inclusion criteria: Allergic rhinitis; skin test ≥ 3+ to house dust mite; positive RAST; skin test for other "common inhalant allergens" was negative Exclusion criteria: None specified Age: 15.6 (range 6-31) Sex: 12 female; 17 male Race: NR Other:	1) Allergen levels: dust samples collected by vacuum from bedroom floor, bedding, and mattress at baseline and 1 month 2) Patient-assessed symptom severity: symptoms graded [daily or once at beginning and once at end??] as follows: Sneezing (0 = no sneezing attacks, to 3 = more than 10 sneezing attacks); Rhinorrhea (0 = no nose blowings, to 3 = more than 10 nose blowings); Nasal obstruction (0 = no nasal obstruction, to 3 nasal obstruction with predominant mouth breathing)	1) Allergen levels: p<0.05 Mean change Gp 1: -32.5 Gp 2: 15.8 2) Patient-assessed symptom severity: p < 0.05 Mean change Gp 1: -2.9 Gp 2: -0.3	Quality Scoring: Population similar: No Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: No Blinding adequate: Not applicable Dropouts described: Yes Intention-to-treat: No Note: Power not addressed

Evidence Table 2: Environmental Measures (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Reisman, Mauriello, Davis, et al., 1990	Design: RCT, crossover Interventions: 1) Active HEPA filter (ENVIRACAIRE® with active filter) placed in bedroom 2) Placebo HEPA filter (ENVIRACAIRE® with blank filter) placed in bedroom Duration of study treatment: 4 weeks each treatment period; no washout between periods Dates: Mid-Nov to March (year?) Location: US Setting: NR Type(s) of providers: NR	No. of subjects at start: 40 Dropouts/withdrawals: 8 No. of subjects at end: 32 Inclusion criteria: Perennial rhinitis; positive skin test to house dust or house dust mite Exclusion criteria: None specified Age: 27.5 (range 6-61) Sex: 12 male; 20 female Race: NR Other:	1) Airborne particle counts: measured at baseline, 4 weeks (end of 1st period), and 8 weeks (end of 2nd period) 2) Patient-assessed symptom severity: severity and duration of sneezing; nasal discharge; nasal congestion; itchy eyes, ears, nose, and throat; and asthma graded twice each day (for 7 AM to 7 PM and for 7 PM to 7 AM) on scale of 1 (mild/30 minutes) to 3 (severe/ more than 2 hours) 3) Medication use: graded (twice?) daily as follows: 1 = antihistamine or decongestant tablets; 2 = theophylline tablet; 3 = nasal or systemic steroid dose 4) Patient global evaluation of response: graded as “improved” or “no difference” at 4 and 8 weeks (end of each treatment period)	1) Airborne particle counts: Patient level data given; summary data given as % change without p value Gp 1: 73.4% decrease Gp 2: 3.6% increase 2) Patient-assessed symptom severity: For 7 individual symptoms and total symptoms compared separately for night- and daytime periods, there were no significant between-group differences (data presented for individual but not total scores) Analysis restricted to final 2-week period of placebo vs. active filter showed improvement for active filter on nasal congestion (p = 0.007) and upper airway itching (p = 0.017); data not reported, only p values given 3) Medication use: No significant differences; data not presented 4) Patient global evaluation of response: Active filter period: 11/32 improved Placebo filter period: 7/32 improved 14 found no difference	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: No Notes: Carry-over effect reduced by comparing last 2 weeks on treatment. No tests for period effect or treatment-by-period interaction. Power not addressed. 11 patients had asthma.

Evidence Table 2: Environmental Measures (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Shapiro, Wighton, Chinn, et al., 1999	Design: RCT, parallel-group Interventions: 1) Aggressive environmental control program (n = 22). Consisted of: application of dust mite impermeable covers to mattress, box spring, and pillow; laundry service delivery of a clean blanket and 4 sets of bed linens every months; and tannic acid acaricide application to bedroom and living room carpet every 2 months. Families instructed to dust and vacuum weekly and to avoid clutter. 2) Standard environmental control program (n = 22). Consisted of: general discussion of need to dust and vacuum house weekly and avoid clutter in the bedroom, and the application of placebo tannic acid acaricide every 2 months. Duration of study treatment: 1 year Trial preceded by 4-week run-in period Dates: NR Location: US Setting: Clinics serving low SES neighborhoods Type(s) of providers: NR	No. of subjects at start: 44 Dropouts/withdrawals: 8 No. of subjects at end: 36 Inclusion criteria: Mild to moderate persistent asthma by NHLBI criteria; ≥ 1 urgent care visit in past 6 months; albuterol use ≥ 5 times/month; positive methacholine challenge at ≤ 10 mg/ml; skin test positive to house dust mite Exclusion criteria: Already carrying out environmental control measures Age: 9.5 (range 6-15) Sex: 14 male; 22 female Race: 21 White; 9 African-American; 3 Asian-Pacific; 1 Hispanic; 2 other Other:	1) Parents' global evaluation of symptom severity: graded as mild, moderate, or severe at baseline, 6 months, and 12 months 2) Parents' global evaluation of quality of life: graded on scale of 0 (no symptoms) to 14 (many symptoms) at baseline, 6 months, and 12 months 3) Asthma exacerbations: measured in terms of hospitalizations, ED visits, and steroid bursts 4) Spirometry (FEV1, bronchial hyper-responsiveness (PD_{20}) 5) Allergen levels: dust collected from mattress, bedroom carpet, living room furniture and carpet, and kitchen floor at baseline and at 4, 8, and 12 months	1) Parents' global evaluation of symptom severity: "No significant changes from baseline"; no data or p-values given. 2) Parents' global evaluation of quality of life: "Similar for groups and did not change during the course of the year"; no data or p-values given 3) Asthma exacerbations: "Similar for the two groups" 4) Spirometry (FEV1, bronchial hyper-responsiveness (PD_{20}): Not abstracted 5) Allergen levels: Dust mite concentration categorized as low (<2 µg/g), moderate (2-<10 µg/g), or high (≥ 10 µg/g). 50% of Gp 1 and 16.7% of Gp 2 changed to a lower category (p = 0.03). Mean dust mite levels decreased 19.6% in Gp 1 and increased 33% in group 2 (p = 0.20).	Quality Scoring: Population similar: No Intervention(s) described: No Comorbidities described: Yes Diagnosis by MD: Not applicable Objectively confirmed: Not applicable Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: No Notes: No symptom data based on daily recordings. Investigators reported that "attempts to collect daily symptom and peak flow diaries were futile." Power not addressed.

Evidence Table 2: Environmental Measures (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Walshaw and Evans, 1986	Design: RCT, parallel-group Interventions: 1) Avoidance measures (n = 25). Mattress thoroughly vacuumed and covered with a plastic cover; cover to be damp-dusted at least weekly. Pillows also enclosed in plastic covers. Feather bedding replaced with synthetic polyester or avoided; woolen blankets replaced with cotton c ellular or polyester equivalents. All bedding to be washed at least weekly and/or shaken outside frequently. Bedroom carpet to be vacuumed at regular intervals or (preferably) replaced with linoleum, which was to be washed frequently. Soft furnishings and plants to be removed from bedroom. Bathroom door to be kept closed during and immediately after bathing, etc., and kitchen door during and immediately after cooking. Bedroom to be thoroughly ventilated on dry days only. Lounge floor to be vacuumed frequently. 2) No avoidance measures (n = 25). Duration of study treatment: 1 year Dates: 11/1982 – 4/1984 Location: UK Setting: Hospital-based chest	No. of subjects at start: 50 Dropouts/withdrawals: 8 No. of subjects at end: 42 Inclusion criteria: Adults with asthma; strongly positive skin test to house dust mite Exclusion criteria: Other chest disease Age: Intervention 33 ± 2 (SEM); Control 34 ± 2 (SEM) Sex: 22 male; 28 female Race: NR Other:	1) Allergen levels: dust samples collected at baseline and every 4 months thereafter from mattresses and bedroom and lounge floors using a modified hand-held vacuum 2) Relative humidity in the bedroom: measured at baseline and every 4 months thereafter 3) Spirometry (FEV1, FVC, peak flow rates) 4) Bronchial reactivity (PC_{20}) 5) Use of symptomatic medication (inhaled cromoglycate, broncho-dilators, and steroids; oral steroids): not clear how assessed 6) Patient- and investigator-assessed symptom severity: symptoms assessed at each 4-monthly clinic visit by means of a detailed history 7) Total IgE, IgA, IgM, and IgG antibody levels	1) Allergen levels: reported graphically, mattress and bedroom floor mite levels fell significantly for intervention group but not the control group; no between-group comparison given 2) Relative humidity in the bedroom: Fell significantly in 2 of 3 measures for intervention group and 1 of 3 measures for control group compared to baseline; no between-group comparisons 3) Spirometry: Not abstracted 4) Bronchial reactivity: Not abstracted 5) Use of symptomatic medication: Results stratified by RAST positive/negative. Only within-group analysis given. 6) Patient- and investigator-assessed symptom severity: (reported graphically) Results stratified by RAST positive/negative. Only the RAST positive intervention group showed improvement; no statistical tests reported; no between-group analysis reported. 7) Total IgE, IgA, IgM, and IgG antibody levels: Not abstracted	Quality Scoring: Population similar: No Intervention(s) described: No Comorbidities described: Yes Diagnosis by MD: Not applicable Objectively confirmed: Not applicable Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: No Blinding adequate: Not applicable Dropouts described: Yes Intention-to-treat: No Notes: Power: no discussion. Analysis is a multiple time points with no analysis for overall effect and no consideration of multiple testing.

(continued on next page)

Evidence Table 2: Environmental Measures (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	clinics Type(s) of providers: NR				
Warburton, Niven, Pickering, et al., 1994	Design: RCT, crossover Interventions: 1) HEPA filter placed in main living room. Patients advised to leave unit running continuously and to keep external windows closed as much as possible. 2) Placebo HEPA filter (same external unit, internal HEPA and charcoal filters removed), employed as above. Duration of study treatment: Mean duration of active treatment was 30.3 days (range, 21-45); mean duration of placebo treatment was 24.0 days (range, 20-33) Trial preceded by run-in period of unspecified length Dates: NR Location: UK Setting: NR Type(s) of providers: NR	No. of subjects at start: 13 Dropouts/withdrawals: 1 No. of subjects at end: 12 Inclusion criteria: Volunteers with asthma; positive skin test to house dust mite antigen and to ≥ 1 of 3 fungal species Exclusion criteria: NR Age: 45.5 (range 19-64) Sex: 8 male, 4 female Race: NR Other:	1) Patient-assessed symptom severity: cough, phlegm production, wheeze, breathlessness, and chest tightness graded daily on visual analog scale; frequency of nocturnal wakening also recorded 2) Use of symptomatic medication (broncho-dilators): recorded daily 3) Spirometry (FEV1, FVC, morning and evening peak flow rates) 4) Bronchial reactivity (PD_{20}) 5) Airborne allergen levels: measured using Rotheroe and Mitchell pumps at height of 1.5 m in living room; measured at baseline and at end of each treatment period	1) Patient-assessed symptom severity: No significant difference in mean symptom scores for any individual symptom (no variance given for means) 2) Use of symptomatic medication: No significant difference in mean bronchodilator use (no variance given for means) 3) Spirometry: Not abstracted 4) Bronchial reactivity: Not abstracted 5) Airborne allergen levels: Intervention period: 0.038 ± 0.025 mg/m^3 Control period: 0.028 ± 0.015 mg/m^{-3} No significant difference	Quality Scoring: Population similar: Yes Intervention(s) described: No Comorbidities described: Yes Diagnosis by MD: Not applicable Objectively confirmed: Not applicable Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: No Dropouts described: Yes Intention-to-treat: No Notes: No assessment of carry-over effect, period effect, or treatment-by-period interaction. Power: no discussion.

Evidence Table 2: Environmental Measures (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Wood, Johnson, Van Natta, et al., 1998	Design: RCT, parallel-group Interventions: 1) Active HEPA filter (Envirocare® with active filter) in bedroom + avoidance measures (described below) (n = 18) 2) Placebo HEPA filter (Envirocare® with filter removed) in bedroom + avoidance measures (described below) (n = 17) Avoidance measures (both groups): bed fitted with impervious mattress and pillow covers; subjects instructed to wash bedding once a week and to keep cats from entering bedroom at all times Duration of study treatment: 3 months Trial preceded by 1-month baseline period Dates: NR Location: US Setting: Advertisement; University Allergy Clinic Type(s) of providers: NR	No. of subjects at start: 38 Dropouts/withdrawals: 3 No. of subjects at end: 35 Inclusion criteria: Adults with asthma or allergic rhinitis and symptoms associated with cat contact; symptoms requiring medication use on ≥ 50% of days; positive skin prick test and RAST to cat allergen; home with ≥ 1 cat Exclusion criteria: Severe asthma Age: 36.3 (range 23-60) Sex: 10 male; 25 female Race: NR Other:	1) Allergen levels: dust collected from carpet or upholstered furniture; air samples obtained with small portable pump 2) Patient-assessed symptom severity: nasal congestion, rhinorrhea, sneezing, coughing, wheezing, and chest tightness graded on scale of 0 (none) to 3 (severe) three times per day; sleep difficulty recorded daily (yes/no) 3) Medication use: recorded in daily diaries 4) Spirometry (morning and evening peak flow rates, FEV1, MCh reactivity, cat RAST levels)	1) Allergen levels: Baseline; 3-month Airborne Fel d 1, ng/m3; p = 0.045 for completers analysis; p = 0.152 for ITT Gp 1: 3.0 ± 1.1; 1.7 ± 1.7 Gp 2: 2.6 ± 1.2; 2.8 ± 1.8 Settled dust Fel d 1; ug/g; p = 0.407 completers analysis Gp 1: 10.1 ± 2.3; 10.5 ± 1.6 Gp 2: 11.8 ± 0.9; 10.6 ± 1.1 2) Patient-assessed symptom severity: Results presented separately for nasal and chest symptoms at 3 time periods (morning, afternoon, night). No significant between-group differences for any of the 6 comparisons Nasal am: Gp 1: 1.40 ± 0.60; 0.91 ± 0.61 Gp 2: 1.22 ± 0.63; 0.88 ± 0.64 p = 0.769 Nasal pm: Gp 1: 1.16 ± 0.62; 0.74 ± 0.59 Gp 2: 1.04 ± 0.58; 0.82 ± 0.66 p = 0.534 Nasal night: Gp 1: 1.01 ± 0.64; 0.67 ± 0.71 Gp 2: 0.70 ± 0.55; 0.64 ± 0.69 p = 0.138 Chest am: Gp 1: 0.82 ± 0.61; 0.29 ± 0.38 Gp 2: 0.86 ± 0.63; 0.55 ± 0.60 p = 0.388 Chest pm: Gp 1: 0.71 ± 0.60; 0.28 ± 0.39 Gp 2: 0.80 ± 0.59; 0.59 ± 0.56 p = 0.179 Chest night: Gp 1: 0.62 ± 0.62; 0.29 ± 0.49 Gp 2: 0.56 ± 0.53; 0.37 ± 0.60 p = 0.215 3) Medication use: Reported for nasal	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 1b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: Yes Notes: 28/35 patients had asthma; 35/35 had allergic rhinitis Compliance: assessed using internal timers; machines operated at least 80% of the 3 months by 83% of intervention and 94% of placebo group. Post-hoc power analysis estimated 284-14,744 subjects needed depending on outcome addressed.

(continued on next page)

Evidence Table 2: Environmental Measures (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
				and chest medications, prn and maintenance medications. No significant differences for any of the 4 comparisons. 4) Spirometry: Not abstracted	
Zwemer and Karibo, 1973	Design: RCT, crossover Interventions: 1) Pure-zone System® clean air head board (air filtering system built into head board of bed). 2) Placebo system (same as above, but with filter removed). Duration of study treatment: 2 weeks each treatment period Dates: Winter season Location: USA Setting: University practices Type(s) of providers: Pediatric allergists	No. of subjects at start: 18 Dropouts/withdrawals: 6 No. of subjects at end: 12 Inclusion criteria: Asthma; positive skin tests to house dust and other indoor allergenic materials; receiving hyposensitization and advised to practice environmental control Exclusion criteria: None Age: range 6-16 Sex: 7 male; 11 female Race: NR Other:	1) Patient-assessed symptom severity: day- and nighttime cough and wheezing graded daily on scale of 0 (none) to 6 (severe, intolerable); sick days (from school), number of asthma attacks, nights with normal sleep, and number of times awakened by symptoms also recorded daily 2) Use of symptomatic medication: recorded daily	1) Patient-assessed symptom severity: 7 excellent improvement; 4 good improvement; 1 fair improvement 2) Use of symptomatic medication: 5 reduced treatment	Quality Scoring: Population similar: No Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Not applicable Objectively confirmed: Not applicable Outcome measures valid: No Level of evidence: 3b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: No Dropouts described: Yes Intention-to-treat: No Notes: No assessment of carry-over effect, period effect, or treatment-by-period interaction. Power: Not addressed Poorly reported; no analytic plan given and no statistics reported. Reports some failure of blinding (patients detected assignment).

[†] Quality scoring criteria were as follows:
Population similar: Was the study population described and reasonably similar to an adult working US population? (Yes [described and similar], No [described, but not similar], Not adequately described)
Intervention(s) described: Were the intervention protocols referenced or described in sufficient detail to replicate? (Yes, No)

Comorbidities described: Was the presence of comorbid asthma (or other upper respiratory conditions) described in the study population? (Yes, No)
Diagnosis by MD: Was the diagnosis of allergic rhinitis based on physician diagnosis? (Yes, No, Not applicable [asthma patients only])
Objectively confirmed: If physician-diagnosed, was the diagnosis supported by objective evidence of allergy (e.g., skin prick or serum IgE antibody testing)? (Yes, No, Not applicable)
Outcome measures valid: Were the main outcomes of interest to us measured in a way that has been demonstrated empirically to be valid and reliable (e.g., using a standardized scale such the RQLQ or SF-36)? (Yes, No, Not adequately described)
Level of evidence: Based on Oxford Center for Evidence-Based Medicine Levels of Evidence (1a, 1b, 1c, 2a, 2b, 2c, 3a, 3b, 4, 5)
Randomized: Was the study described as "randomized"? (Yes, No)
Allocation concealed: If the method for concealing allocation from the investigators was described, was it *adequate* (table of random numbers, computer-generated, coin tossing, etc.) or *inadequate* (alternating, date of birth, hospital number, etc.)? (Not described, Yes [described and adequate], No [described, but inadequate])
Double-blind: Was the study described as "double-blind"? (Yes, No)
Blinding adequate: If the method of double-blinding was described, was it *adequate* (e.g., identical placebo, active placebo, injection vs. tablet with double dummy) or *inadequate* (e.g., tablet vs. injection with no double dummy)? (Not described, Yes [described and adequate], No [described, but inadequate])
Dropouts described: Did the study describe dropouts and withdrawals so that all patients entering the trial could be accounted for? (Yes, No)
Intention-to-treat: Was the analysis performed according to the intention-to-treat principle? (Yes, No, Can't determine)

Evidence Table 3: Immunotherapy

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Alvarez-Cuesta, Cuesta-Herranz, Puyana-Ruiz, et al., 1994	Design: RCT, parallel-group Interventions: 1) Biologically standardized cat dander extract, quantified with monoclonal antibodies (100 biological units [BU] = 33 µg of *Fel d* I antigen, 650 µg of albumin, and 99 µg of *Fel d* Bd/K30 antigen) (n = 14). Gradually increasing doses administered twice weekly until dose of 13.2 µg of *Fel d* I or maximum tolerated dose reached; maintenance dose then repeated monthly with extract absorbed in aluminum hydroxide gel. Average maintenance dose 11.3 ± 4.7 µg of *Fel d* I (34.4 ± 14.3 BU); average total cumulative dose 170 µg *Fel d* I (515 BU). 2) Placebo (constituents not described) (n = 14) Duration of study treatment: 1 year Symptomatic medication permitted, but not described Dates: NR Location: Spain Setting: University hospitals Type(s) of providers: Specialists	No. of subjects at start: 28 Dropouts/withdrawals: 0 No. of subjects at end: 28 Inclusion criteria: Rhino-conjunctivits and asthma; 18+ months duration; exacerbated by exposure to cat; positive skin test and specific IgE to cat Exclusion criteria: Prior immunotherapy; sensitization to other perennial antigens (not specified); contraindication to immunotherapy Age: 15-65 years old; mean 24 active 29 placebo Sex: 6M/22F Race: NR Other:	1) Adverse reactions 2) Patient global evaluation of efficacy (PSE): at end of study, patients asked to grade their symptoms during direct contact with cats in relation to such symptoms before trial on scale of 0% (complete failure) to 100% (total success) 3) Patient-assessed symptom severity and use of symptomatic medication (combined in a single measure): unspecified symptoms graded daily on scale of 0-3 (not described); use of symptomatic medication recorded daily in study diaries 4) Skin reactivity 5) Conjunctival reactivity 6) Bronchial reactivity	1) Adverse reactions: 10 subjects had 14 "reactions," 7 local and 3 systemic. 2) Patient global evaluation of efficacy: Average 81.3 ± 15.5% improvement active vs. 20.7 ± 33.2% placebo; $p < 0.001$ 3) Patient-assessed symptom severity and use of symptomatic medication (combined in a single measure): 0.14 ± 0.35 active vs. 1.42 ± 0.51 placebo; $p < 0.001$ 4) Skin reactivity: Not abstracted 5) Conjunctival reactivity: Not abstracted 6) Bronchial reactivity: Not abstracted	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 1b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Not described Dropouts described: Yes Intention-to-treat: Yes Notes: Subjects also had to take environmental precautions for 12 months prior to immunotherapy, which included removing cat from home.

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Ariano, Kroon, Augeri, et al., 1999	Design: RCT, parallel-group Interventions: 1) Allergoid extract of *Parietaria* (wall pellitory) pollen (Purethal™-*Parietaria*) (n = 13). Glutaraldehyde-modified allergoid obtained from equal parts *Parietaria judaica* and *P. officinalis* pollens. Extract standardized to 20,000 AUeq per ml. Build-up phase: increasing doses (1,000; 2,000; 4,000; 6,000; 8,000; and 10,000 AUeq) injected each week. Maintenance phase: 10,000 AUeq injected each month. In event of AEs, dose repeated or temporarily reduced, according to international guidelines. 2) Placebo (same as above, except for allergen) (n = 12) Duration of study treatment: 1 year (RCT phase); trial followed by 2-year open study during which all patients received active treatment Symptomatic medication permitted: Loratadine or cetirizine (10 mg/day), beclomethasone nasal spray (100 µg/puff), and inhaled albuterol (100 µg/puff) Dates: October 1990-1991 Location: Presumably Italy, but not stated	No. of subjects at start: 25 Dropouts/withdrawals: 0 (at end of year 1) No. of subjects at end: 25 (end of year 1) Inclusion criteria: Single sensitization to *Parietaria* by skin test and RAST; 2 years of disease; rhinoconjunctivitis Exclusion criteria: Anatomic alteration of upper airway; immunodeficiency; malignancies; severe psychologic disorders; chronic steroids; beta-blockers; SIT in last 5 years; pregnant or lactating women Age: 13-62 (mean 32.1) Sex: 17 F Race: NR Other: 5 subjects had mild asthma (3 active, 2 placebo)	1) Adverse reactions: classified according to following scale: 1 = mild local = wheal/flare < 5 cm, granuloma persisting < 1 week, slight pain; 2 = moderate local = wheal/flare < 10 cm, granuloma persisting < 3 weeks; 3 = severe local = wheal/flare > 10 cm, granuloma persisting > 3 weeks, pain requiring medications; 4 = mild systemic = rhinitis, conjunctivitis, asthma, and urticaria not requiring treatment; 5 = severe systemic = as above (4), but requiring pharmacologic treatment 2) Patient-assessed symptom severity and medication use (combined in a single measure): sneezing, rhinorrhea, nasal obstruction, nasal/conjunctival itching, lacrimation, cough, and wheezing graded daily on scale of 0 (no symptom) to 2 (severe); use of symptomatic medication recorded in daily diaries (each dose recorded as score of 1) 3) Patient global evaluation of efficacy: assessed at 1 year in two ways: a) with a questionnaire on	1) Adverse reactions: Placebo: no systemic or local reactions Active: 2 moderate (asthma), 3 mild (rhinitis) systemic reactions. 5 mild, 3 moderate, 4 severe local reactions. All during buildup phase. 2) Patient-assessed symptom severity and medication use (combined in a single measure): Median symptom score after 1 year ~1,250 placebo and ~550 active (p = 0.02). However, baseline scores not given. (Values estimated from figure.) 3) Patient global evaluation of efficacy: (Active vs. Placebo) Frequency of symptoms: (p = 0.001) Decr-10 v 1 Unch-3 v 9 Incr- 0 v 2 Physical Performance (p = 0.043) Imp-6 v 1 Unch-6 v 9 Worse-1 v 2 Duration of symptoms (p = 0.024) Short-5 v 0 Unch-8 v 7 Leng-0 v 5 Satisfaction (p = 0.002) Yes-11 v 0 Indiff-1 v 0 No-1 v 11 VAS % improvement Active 31.6 v Placebo -15.0 (p = 0.01) 4) Skin reactivity: Not abstracted 5) Allergen-specific IgG_4 and IgE levels: Not abstracted	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: Yes Notes: No histamine in placebo injection.

(continued on next page)

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	Setting: Presumably academic Allergy and Immunology Department, but not stated Type(s) of providers: Presumably allergists		frequency of symptoms, physical performance, duration of complaints, and global satisfaction (each graded as "improved," "unchanged," or "worsened"); and b) with a visual analog scale running from + (clinical condition improved) to - (worsening of clinical condition) 4) Skin reactivity 5) Allergen-specific IgE and IgG4 antibody levels		
Arvidsson, Löwhagen, and Rak, 2002	Design: RCT, parallel-group Interventions: 1) Aluminum-adsorbed birch pollen (*Betula verrucosa*) extract (Alutard® SQ) (n = 24). Clustered protocol, with 14 gradually increasing doses (from 10 to 100,000 SQ-U) given over 7 to 8 weeks. Maintenance injections (100,000 SQ-U) given every 6 weeks for remainder of study. 2) Placebo (diluent + histamine dihydrochloride) (n = 25). Duration of study treatment: Up to 2 years over 2 pollen seasons Symptomatic medication permitted: Acrivastine capsule 8 mg; terbutaline inhalation 0.5 mg; salbutamol	No. of subjects at start: 49 Dropouts/withdrawals: 3 No. of subjects at end: 46 Inclusion criteria: History of birch pollen-induced symptoms from the upper airways; positive skin prick test (> 3 mm wheal) to *Betula verrucosa;* positive RAST; positive conjunctival provocation test Exclusion criteria: perennial symptoms from upper or lower airways; sensitivity to house dust mit or mold; previous treatment with SIT; treatment with topical steroids Age: mean 32 years (range 19 to 46 years) Sex: 59% women Race: NR	1) Patient-assessed symptom severity: evaluated in two ways: a) runny nose/sneezing, blocked nose, eye symptoms, and bronchial symptoms graded daily during pollen season on scale of 0 (none) to 3 (severe); and b) patient's perception of severity of symptoms graded once per week during pollen season on a VAS (0-10, end points not described) 2) Use of symptomatic medication: recorded daily during pollen season; scored as follows: 1 point: acrivastine capsule, terbutaline inhalation, or salbutamol inhalation; 2 points: sodium	1) Patient-assessed symptom severity: Median symptom scores 1st pollen season SIT 1.3 (range 0-5.2) Pl 2.1 (range 0.6-5.6) P=0.05 2nd pollen season SIT 2.6 (range 0-6.5) Pl 4.3 (range 2.4-9.1) P=0.005 2) Use of symptomatic medication: The placebo group used significantly more rescue medication than the active group during both seasons (p=0.004 in 1997 and p=0.004 in 1998) 3) Adverse reactions: SIT placebo Total AE 71 81 # pts 22 20 general sx 40.7% 46.7% respiratory 27.6% 19.8% (rhinitis or cough) post-injection 4 7	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: No Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: No Notes: Long-term study *(continued on next page)*

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	inhalation 0.4 mg; and sodium cromoglycate eye drops (40 mg/ml) and nasal spray (5.2 mg/ml); if needed, patients could request topical steroids (budesonide nasal powder [100 µg/dose] or inhalation powder [200 µg/dose]) Dates: Treatment began Nov 1996 to Jan 1997; study ended June 1998 Location: Goteborg, Sweden Setting: Allergy clinic Type of providers: Allergists	Other: 21 patients also sensitive to grass pollen; 30 patients also sensitive to animal dander, but none had exposure to pets during the study	cromoglycate eye drop or nasal spray puff; 4 points: budesonide nasal powder or inhalation powder dose 3) Adverse reactions	(all mild)	
Bernstein, Tennen-baum, Georgakis, et al., 1976	Design: RCT, parallel-group (matched-pairs design) Interventions: 1) Alum-adsorbed Fraction A (partially purified derivative of aqueous ragweed extract) (n = 68). Cumulative dose of 24,000 PNU to be attained in 20 doses, but more injections required when large local or systemic reactions occurred. Goal for 1972 pre-season (injections given weekly) was to attain maximum individual dose of 6,000 PNU. During season, ½ of maximum pre-seasonal dose given every week. This dose continued every 4 weeks after end of season until 2 months prior to 1973 season, when maximum dose again reached at weekly intervals.	No. of subjects at start: 148 Dropouts/withdrawals: 17 13 lost to followup (10 P v 3 A); 4 serious systemic reaction No. of subjects at end: 131 completed 1972 season. Inclusion criteria: Definite seasonal history; clinical findings of ragweed hayfever 3+ years; no IT for at least 1 year; positive skin test to Fraction A Exclusion criteria: None specified Age: Mean age 30 Sex: 63 F Race: NR Other: 1/3 recipients had previous ragweed immunotherapy	1) Investigator global assessment of treatment response 2) Patient-assessed symptom severity: unspecified symptoms graded daily during pollen season on scale of 0 (no symptoms/ no significant symptoms) to 3 (significant symptoms not controlled by regular medication, but controlled by steroids) 3) Use of symptomatic medication: recorded daily during pollen season as 0 (no medication taken) or 1 (medication taken) 4) Immunologic parameters (hemagglutinating antibodies, RAST)	1) Investigator global assessment of treatment response: Not abstracted 2) Patient-assessed symptom severity: Assessed in only 112 patients. Data lost in mail on 19. Symptom Score (active v placebo): 1.097 v 1.378 ($p < 0.05$) 3) Use of symptomatic medication: Drug Score (active v placebo): 0.411 v 0.584 ($p < 0.05$) 4) Immunologic parameters (hemagglutinating antibodies, RAST): Not abstracted 5) Adverse reactions: Systemic effects in 17 patients (1.4% of injections) in active group and 6 patients in placebo group. Of these 6 active and 2 placebo treated patients had serious systemic reactions. 3 of 6 active group patients tolerated subsequent injections. Local reactions	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 1b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: No Notes: Results reported for 1st year of 2-year trial. No histamine in placebo.

(continued on next page)

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	2) Placebo (n = 63) Duration of study treatment: Approx. 2 years; protocol began with pre-seasonal treatment before 1972 ragweed season and extended through 1973 season Symptomatic medication permitted: Not described Dates: 1972 Ragweed season Location: Cincinatti, OH Setting: Academic immunology practice Type(s) of providers: Specialists		5) Adverse reactions	in 24 active group patients (2.3% of injections).	
Blainey, Phillips, Ollier, et al., 1984	Design: RCT, parallel-group Interventions: 1) Tyrosine-adsorbed extract of *Dermatophagoides pteronyssinus* (house dust mite) (Migen®) (n = 17). Build-up phase: 6 injections at weekly intervals, with doses increasing from 4 to 400 Noon units (10^{-6} g of whole allergen in ml of solution). Maintenance phase: 10 monthly injections at highest dose (400 Noon units), starting 4 weeks after last weekly injection. 2) Placebo (tyrosine-	No. of subjects at start: 39 Dropouts/withdrawals: 16 4 patients did not complete initial 6 weekly injection series (3 placebo patients withdrew for "social" reasons, 1 active patient had severe reaction). 10 patients withdrew during the monthly injection phase due to lack of response (9/18 placebo and 3 of 17 active). No. of subjects at end: 23 Inclusion criteria: Not specified, but all had history of perennial rhinitis exacerbated by dust from mattresses and bedding. All had positive ST or nasal provocation	1) Patient-assessed symptom scores (clinic visits): nasal blockage, sneezing, rhinorrhea, and sleep disturbance graded at each clinic visit on 10-cm visual analog scale running from "no symptoms" to "very severe symptoms" 2) Nasal reactivity 3) Total IgE, specific IgE, and specific IgG antibodies 4) Skin reactivity 5) Use of symptomatic	1) Patient-assessed symptom scores (clinic visits): No data. 2) Nasal reactivity: Not abstracted 3) Total IgE, specific IgE, and specific IgG antibodies: Not abstracted 4) Skin reactivity: Not abstracted 5) Use of symptomatic medication: (see Notes) No data. 6) Patient global evaluation of efficacy of treatment: 11 patients in active group and 5 patients in placebo group considered treatment effective ($p < 0.05$)	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: No *(continued on next page)*

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	containing suspension) (n = 18) Duration of study treatment: 13 months (including 4-week run-in); final post-treatment results taken from 1 month after last maintenance treatment (14 months) Trial preceded by 4-week run-in phase during which patients were treated with beclomethasone dipropionate nasal spray and house dust mite avoidance measures Symptomatic medication permitted: Beclomethasone dipropionate or xylometazoline; patients "encouraged to reduce therapy if they felt able to do so without recurrence of troublesome symptoms" Dates: Enrollment over 2 successive years – not specified Location: London Setting: Not specified, but presumably academic respiratory unit Type(s) of providers: Specialists	study. All were non-responders to topical corticosteroids and avoidance measures. 15 patients had symptoms after contacting domestic animals or had seasonal exacerbation between May and August. Exclusion criteria: None specified Age: 17-36 (mean age 26) Sex: 20 F after initial 6 week injections. Race: NR Other:	medication: recorded daily in study diaries 6) Patient global evaluation of efficacy of treatment: assessed at end of study by asking patients, "Did your symptoms (blocked or runny nose and sneezing attacks) improve after the course of injections?" 7) Adverse reactions	7) Adverse reactions: 1 withdrawal for severe reaction. 5 patients in active group and 6 in placebo group with local reaction. Exacerbation of rhinitis or asthma in 3 active and 5 placebo patients.	Notes: Symptoms scored daily in study diaries, but results not reported because study participants "not thorough enough in completing their diary cards, particularly for drug usage." High dropout rate. No histamine in placebo.

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Bødtger, Poulsen, Jacobi, et al., 2002	Design: RCT, parallel-group Interventions: 1) Aluminum-adsorbed birch pollen (*Betula verrucosa*) extract (Alutard® SQ) (n = 17). Clustered protocol, with 11 injections of gradually increasing doses (from 10 to 100,000 SQ-U) given over 7 weeks. Dose modifications made in the event of local or systemic adverse reactions. Maintenance injections (100,000 SQ-U) given 2 and 6 weeks after maximum dose achieved, then every 8 weeks for remainder of treatment period. 2) Placebo (diluent with gradually increasing concentrations of histamine dihydrochloride) (n = 18). Duration of study treatment: 10 months (Jan to Nov); symptoms monitored for one allergy season (April-May); 1-year follow-up Symptomatic medication permitted: Acrivastine 8 mg; levocabastine eye drops (0.5 mg/ml) and nasal spray (50 µg/dose); and salbutamol inhalations (200 µg/dose); if necessary, a 1-week course of oral prednisone (12.5 mg/day) could be prescribed Dates: Jan 2000 through autumn 2001	No. of subjects at start: 35 Dropouts/withdrawals: 1 No. of subjects at end: 34 Inclusion criteria: At least 2 seasons of severe allergic symptoms in April and May (birch pollen season); poor symptom control in previous seasons on regular antiallergic treatment; positive skin prick tests (> 3 mm wheal) to *Betula verrucosa; positive RAST* Exclusion criteria: Previous SIT toward birch; lactation or pregnancy at start of injection therapy; perennial rhinitis or asthma; continuous use of systemic beta-blockers. Age: median 27 years (range 19 to 46) Sex: 60% women Race: NR Other: 14 patients had seasonal asthma symptoms; 20 patients had self-reported allergy to grass pollen	1) Patient-assessed symptom severity: symptoms of the nose, eyes, and lungs graded daily from 13 March to 21 May on scale of 0 (none) to 3 (severe) 2) Use of symptomatic medication: recorded in study diaries from 13 March to 21 May; scored as follows: 1 point: each drop or spray of levocabastine or inhalation of salbutamol; 2 points: each dose of acrivastine or prednisolone 3) Patient global evaluation of efficacy: assessed at 1-year follow-up in two ways: a) with a visual analog scale (not described) describing the overall severity of the pollen season; and b) with a non-validated questionnaire asking patients whether they had experienced any effect of treatment, a reduction in symptoms, a reduction in medication use, or increased well-being during the pollen season (yes/no for each question) 4) Conjunctival reactivity 5) Nasal reactivity 6) Skin reactivity	1) Patient-assessed symptom severity: IT 31.5 (6.0-50.0) Pl 44.0 (14.0-75) P < 0.05 2) Use of symptomatic medication: IT 52.0 (2.0-114.0) Pl 102 (2.0-186) P < 0.02 3) Patient global evaluation of efficacy: SIT (Y/N) Pl Effect of treatment 15/2 8/9 P < 0.03 Symptom decrease 14/3 8/9 p > 0.07 Medication reduced 10/7 5/12 P = 0.17 Increased well-being 14/3 5/12 P < 0.006 4) Conjunctival reactivity: Not abstracted 5) Nasal reactivity: Not abstracted 6) Skin reactivity: Not abstracted 7) Histamine release: Not abstracted 8) Total and specific IgE: Not abstracted 9) Adverse reactions: SIT placebo Grade 3-4 0 0 Grade 1-2 7 16 Immediate SE 7 14 Late SE 0 2	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: No Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: No Notes:

(continued on next page)

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	Location: Copenhagen, Denmark Setting: Allergy clinic Type(s) of providers: Allergists		7) Histamine release 8) Total and specific IgE 9) Adverse reactions		
Bousquet, Frank, Soussana, et al., 1987	Design: RCT, parallel-group Interventions: 1) Formalinized high-molecular-weight mixed grass pollen allergoid (n = 40 or 39). Administered "using a rather aggressive protocol." Maximum dose reached in 9 injections (time frame not described). Mean total dose received 25,649.5 ± 17,704.3 PNU (range, 5,695 to 73,800). 2) Placebo (constituents not described) (n = 20 or 19). Duration of study treatment: NR (9 injections, but time frame not indicated); outcomes measured during single pollen season Symptomatic medication permitted: NR Dates: NR Location: Montpelier, France (Northern Mediterranean area) Setting: Allergy clinic Type(s) of providers: Allergists	No. of subjects at start: 59 Dropouts/withdrawals: 0 No. of subjects at end: 59 Inclusion criteria: Severe grass pollen-induced rhinitis; volunteers Exclusion criteria: None stated Age: 25.2 ± 12.1 years Sex: NR Race: NR Other:	1) Adverse reactions 2) Nasal reactivity 3) Patient-assessed symptom severity: nasal symptoms evaluated during peak of pollen season (May 1 to June 15); symptoms scored and scale used not described 4) Allergen-specific IgG antibody levels	1) Adverse reactions: 6/39 allergoid-treated pts had systemic reactions (5 mild, 1 urticaria with asthma requiring treatment) 1/20 placebo-treated pts had mild systemic reaction 2) Nasal reactivity: Not abstracted 3) Patient-assessed symptom severity: significantly reduced in allergoid group compared to placebo group (nasal symptom score 61± 35 versus 109 ± 33) 4) Allergen-specific IgG antibody levels: Not abstracted	Quality Scoring: Population similar: Yes Intervention(s) described: No Comorbidities described: No Diagnosis by MD: No Objectively confirmed: No Outcome measures valid: Not adequately described Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: No Blinding adequate: Not applicable Dropouts described: Yes Intention-to-treat: Can't determine Notes: No significant correlation between IgG titer and nasal provocation test or symptom scores. Article reports conflicting numbers of patients in the two treatment groups (n = 39 or 40 for allergoid group; n = 19 or 20 for placebo group).

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Bousquet, Hejjaoui, Skassa-Brociek, et al., 1987	Design: RCT, parallel-group Interventions: 1) Standardized orchard grass-pollen extract (n = 15). Treatment started in December or January. Rush protocol used, with rapid increase in allergen dose; maintenance dose (2 IR) reached in 4 days. Maintenance dose then given every week for 4 weeks, then every 2 weeks until April 1. Co-seasonal immunotherapy (dose reduced by half) then given every 2 weeks until October 1. 2) Mixed grass-pollen (six species) allergoid (n = 19). Treatment started in January or February. Rush protocol used, with rapid increase in allergoid doses over 3 days; doses subsequently increased weekly to reach maintenance dose of 1000 PNU. Increases stopped if/when systemic reaction or large local reaction (diameter > 10 cm) occurred, and maintenance dose defined as dose reached before this reaction. Maintenance dose then given every week for 4 weeks, then every 2 weeks until April 1. Co-seasonal immunotherapy (dose reduced by half) then given every 2 weeks. 3) Placebo (0.9% NaCl, 0.4% phenol, and 0.5 to 0.005 mg/ml histamine	No. of subjects at start: 45 Dropouts/withdrawals: 0 No. of subjects at end: 45 Inclusion criteria: Rhinitis during grass-pollen season; positive prick test (to 1/100 wt/vol standardized extract) and IgE (at RAST class 3 to 4) indicating allergy to orchard grass pollen Exclusion criteria: Multiple pollen allergy; previous specific immunotherapy to grass pollens; use of systemic corticosteroids Age: Mean 24.1 ± 10.1 years (range, 12 to 43) Sex: NR Race: NR Other: "More than half also had symptoms of asthma and/or conjunctivitis" asthma 71% conjunctivitis 58% "Duration of symptoms during pollen season ranged from 3 to 19 years"	1) Adverse reactions 2) Use of symptomatic medication: graded daily during pollen season, as follows: No medication: 0 Disodium cromoglycate nasal spray: 1 Beclomethasone nasal spray: 2 Terfenadine: 3 Oral prednisolone: 4 3) Patient-assessed symptom severity: symptoms graded daily during pollen season, as follows: No symptom: 0 > 5 episodes sneezing: 1 Nasal blockage: 1 or 2 Rhinorrhea: 1 or 2 Nasal pruritus: 1 4) Skin reactivity 5) Allergen-specific IgE and IgG	1) Adverse reactions: Allergoid group 37% Allergen group 20% Placebo group 0% 2) Use of symptomatic medication: Results presented in graph only (could be interpolated) Allergen < Placebo ($p < 0.01$) Allergoid < Placebo ($p < 0.05$) Allergen vs. Allergoid (p = NS) 3) Patient-assessed symptom severity: Results presented in graph only (could be interpolated) Allergen < Placebo ($p < 0.005$) Allergoid < Placebo ($p < 0.01$) Allergen vs. Allergoid (p = NS) 4) Skin reactivity: Not abstracted 5) Allergen-specific IgE and IgG: Not abstracted	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: Yes Note: Only the placebo (3) versus allergoid (2) comparison was double-blind because of different protocol used for allergen group (1).

(continued on next page)

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	hydrochloride) (n = 11). Duration of study treatment: Approximately 10 months (December-September) Symptomatic medication permitted: Disodium cromoglycate nasal spray, beclomethasone nasal spray, terfenadine, oral prednisolone Dates: NR Location: Montpellier, France (Northern Mediterranean area) Setting: Allergy clinic Type(s) of providers: Allergists				
Bousquet, Hejjaoui, Soussana, et al., 1990	Design: RCT, parallel-group Interventions: 1) Formalinized high-molecular-weight allergoid prepared from a six grass-pollen extract, *high-dose schedule* (n = 20). Grasses were: *Dactylis glomerata, Festuca elatior, Holcus lanatus, Lolium perenne, Phleum pratense,* and *Poa pratensis.* Maximal single dose (10,000 PNU) achieved with 8th injection on day 28. This dose administered three times at weekly intervals, then reduced by ½ and administered every 2 weeks during allergy season. Mean cumulative dose received 45,433 ± 14,001 PNU.	No. of subjects at start: 57 Dropouts/withdrawals: 2? (unclear) No. of subjects at end: 55? (unclear) Inclusion criteria: Symptoms of rhinitis during grass-pollen season, positive prick test to 1/100 (wt/vol) standardized orchard-grass pollen extract; positive RAST to orchard-grass pollen Exclusion criteria: previous specific immunotherapy to pollen extract Age: 26.8 ± 10.4 years (range 11 to 45)	1) Adverse reactions 2) Patient-assessed symptom severity: symptoms of rhinitis (rhinorrhea, sneezing, and nasal obstruction), conjunctivitis (watery eyes, red eyes, and pruritus), and asthma (wheezing and shortness of breath) graded twice daily on scale of 0 to 5 (not described) 3) Use of symptomatic medication: recorded daily by patients in study diaries; system for scoring not described 4) Nasal reactivity	1) Adverse reactions: large local reactions (> 10cm diameter and lasting > 24hr) in 9 patients (4/19 low dose group; 5/20 high dose); mild systemic reactions (flushing of face, rhinitis, or urticaria; resolved w/o treatment) in 8 pts (3 placebo; 2 low dose; 3 high dose) severe reaction (urticaria, rhinitis, asthma w/o hypotension) 2) Patient-assessed symptom severity: Mean rhinitis symptom scores (± SD): High dose: 63.6 ± 32.5 Low dose: 57.8 ± 37.5 Placebo: 108.6 ± 33.2 $p < 0.005$, high dose vs. placebo; $p < 0.001$, low dose vs. placebo; p = NS, high dose vs. low dose Mean asthma symptom scores (± SD): High dose: 17.4 ± 20.2	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: No Intention-to-treat: Can't determine Note: Exact scores given for subgroups of pts with asthma *(continued on next page)*

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	2) Formalinized high-molecular-weight allergoid prepared from a six grass-pollen extract (as above), *low-dose schedule* (n = 19). Schedule as above, except maximal single dose 2,000 PNU. Mean cumulative dose received 10,570 ± 2,808 PNU. 3) Placebo (saline, phenol, and histamine dihydrochloride 0.005 to 0.5 mg/ml) (n = 18). Duration of study treatment: 6 weeks pre-season, plus maintenance treatment during single allergy season Symptomatic medication permitted: Nasal and ocular cromoglycate, nasal beclomethasone, terfenadine, oral corticosteroids, inhaled salbutamol, and theophylline; used according to a pre-specified protocol and only when symptoms present Dates: Spring 1987 Location: Montpelier, France Setting: Allergy clinic Type(s) of providers: Allergists	Sex: 24 men Race: NR Other:	5) Skin reactivity 6) Allergen-specific IgE and IgG antibody levels	Low dose: 12.8 ± 16.8 Placebo: 54.8 ± 23.0 p < 0.001, high dose and low dose vs. placebo; p = NS, high dose vs. low dose 3) Use of symptomatic medication: Mean medication score (± SD) High dose: 38.6 ± 37.6 Low dose: 35.3 ± 44.5 Placebo: 66.4 ± 51.7 p < 0.05, low dose (and high dose? – table unclear) vs. placebo No p-value reported for high dose vs. low dose 4) Nasal reactivity: Not abstracted 5) Skin reactivity: Not abstracted 6) Allergen-specific IgE and IgG antibody levels: Not abstracted	experience or rhinitis experience, but number of subjects in these subgroups is not provided.

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Bousquet, Maasch, Hejjaoui, et al., 1989	Design: RCT, parallel-group Interventions: 1) Standardized and lyophilized orchard-grass pollen (*Dactylis glomerata*) extract (n = 18). Rush protocol used, with rapid increase in allergen dose; maintenance dose (3,000 BU) reached in 3 days. Four maintenance injections then given. Co-seasonal immuno-therapy (dose reduced by half) then given every 2 weeks from April 1 to October 1. Mean cumulative dose: 3678 ± 567 PNU. 2) Mixed-grass pollen unfractionated and lyophilized allergoid, prepared from pollens of 6 grasses (*Dactylis glomerate, Festuca elatior, Holcus lanatus, Lolium perenne, Poa pratensis,* and [sixth species?]) (n = 15). Injections of gradually increasing dose (50 to 2,000 PNU) given over 5 weeks (3 injections during week 1, 2 during week 2, 1 per week thereafter). Four maintenance injections (2,000 PNU) given before April 1st. Co-seasonal immunotherapy (dose reduced by half) given bimonthly from April 1 to October 1. Mean cumulative dose: 9,096 ± 6,304 PNU. 3) High-molecular-weight, formalinized and lyophilized mixed-grass pollen allergoid,	No. of subjects at start: 70 Dropouts/withdrawals: 0 No. of subjects at end: 70 Inclusion criteria: Rhinitis during grass-pollen season; positive prick test (to 1/100 wt/vol standardized extract) and IgE (at RAST class 3 to 4) indicating allergy to orchard grass pollen Exclusion criteria: Previous specific immunotherapy to grass pollens Age: Mean 25.2 ± 12.1 years (range, 12 to 46) Sex: NR Race: NR Other: Asthma 54% Conjunctivitis 67%	1) Adverse reactions 2) Patient-assessed symptom severity: rhinorrhea, sneezing, nasal obstruction, watery eyes, red eyes, pruritus, wheezing, and shortness of breath graded (twice?) daily during allergy season on scale of 0-5 (not described) 3) Use of symptomatic medication: recorded daily during allergy season; method of scoring not described 4) Skin reactivity 5) Specific IgG and IgE levels	1) Adverse reactions: Placebo 0 GOID 67% HMW-GOID 42% Std-ext 72% 2) Patient-assessed symptom severity: Symptom score: Placebo 63.5 ± 54.6 GOID 38.1 ± 27.4 HMW-GOID 20.4 ± 18.1 Std-ext 14.8 ± 22.9 Std-ext < Placebo (p < 0.001) HMW-GOID < Placebo (p < 0.001) HMW-GOID < GOID (p < 0.02) GOID vs Placebo (p = NS) Number of days of rhinitis symptoms: Placebo 26.5 ± 8.6 GOID 20.9 ± 10.0 HMW-GOID 9.15 ± 9.5 Std-ext 9.0 ± 10.7 Std-ext < Placebo (p < 0.001) HMW-GOID < Placebo (p < 0.001) Std-ext < GOID (p < 0.05) HMW-GOID < GOID (p < 0.05) GOID vs Placebo (p = NS) 3) Use of symptomatic medication (medication score): Placebo 53.7 ± 54.1 GOID 33.1 ± 41.0 HMW-GOID 30.5 ± 32.8 Std-ext 22.9 ± 39.1 Std-ext < Placebo (p < 0.01) 4) Skin reactivity: Not abstracted 5) Specific IgG and IgE levels: Not abstracted	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Not described Dropouts described: No Intention-to-treat: Can't determine Note: Group receiving standardized orchard-grass pollen extract not blinded.

(continued on next page)

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	prepared from pollens of the 6 grasses described above (n = 13). Protocol same as 2), above. Mean cumulative dose: 13,735 ± 6,355 PNU. 4) Placebo, with increasing doses of histamine dihydrochloride (n = 14) Duration of study treatment: 7 months Symptomatic medication permitted: For conjunctivitis, ocular cromoglycate, followed by H1 blocker, if necessary; for asthma, inhaled salbutamol (200-600 µg), plus theophylline, if necessary; patients asked to take drugs only if they had symptoms Dates: NR Location: Montpellier, France (Northern Mediterranean area) Setting: Allergy clinic Type(s) of providers: Allergists				

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Bruce, Norman, Rosenthal, et al., 1977	Design: RCT, parallel-group (matched-pairs design) Interventions: 1) Lyophilized aqueous extract of ragweed containing 10 µg AgE/ml or 3570 PNU/ml (n = 14). Weekly injections given from January through August of 1973 and 1974. Mean cumulative doses in terms of antigen E were 11.7 µg (4180 PNU) in 1973 and 31.2 µg (11,140 PNU) in 1974. 2) Placebo containing histamine (n = 18) Duration of study treatment: 2 years; injections given January through August of both years, symptoms monitored through ragweed pollen seasons (August to mid-October) of both years Symptomatic medication permitted: For hay fever, decongestants and chlorpheniramine; for asthma, aminophylline, steroids, ephedrine, and nebulized bronchodilators Dates: 9/72-3/73 Location: Baltimore, MD Setting: Academic allergy practice Type(s) of providers: Specialists	No. of subjects at start: 39 Dropouts/withdrawals: Unclear. Not specified at 1-year time point. No. of subjects at end: 32 patient data points at 1 year shown in Fig 2. 29 patients described as continuing thru second year. Inclusion criteria: Symptomatic asthma during ragweed season; positive skin test to ragweed Exclusion criteria: Perennial asthma; IT in previous 2 years Age: NR Sex: NR Race: NR Other:	1) Investigator-assessed severity of *asthma* symptoms 2) Investigator-assessed severity of *hay fever* symptoms 3) Patient-assessed severity of *asthma* symptoms and use of asthma medications (combined in a single measure): patients recorded following items twice daily during ragweed season (Aug to mid-Oct): duration of difficulty breathing and cough, number and duration of asthma attacks, amount of sputum produced, and asthma medication taken 4) Patient-assessed severity of *hay fever* symptoms and use of hay fever medications (combined in a single measure): patients recorded following items twice daily during ragweed season (Aug to mid-Oct): duration of sneezing, stuffy or runny nose, red itchy eyes, and hay fever medication taken 5) Bronchial reactivity 6) Leukocyte histamine release 7) IgE and IgG antibodies	1) Investigator-assessed severity of *asthma* symptoms: Not abstracted 2) Investigator-assessed severity of *hay fever* symptoms: Not abstracted 3) Patient-assessed severity of *asthma* symptoms and use of asthma medications (combined in a single measure): No significant difference. 4) Patient-assessed severity of *hay fever* symptoms and use of hay fever medications (combined in a single measure): No significant difference. 5) Bronchial reactivity: Not abstracted 6) Leukocyte histamine release: Not abstracted 7) Allergen-specific IgE and IgG blocking antibody: Not abstracted	Quality Scoring: Population similar: Not adequately described Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: No Intention-to-treat: No Notes:

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Brunet, Bédard, Lavoie, et al., 1992	Design: RCT, parallel-group Interventions: 1) Alum-precipitated ragweed extract (n = 13). Weekly injections given over 9 weeks in following doses: 50; 100; 200; 500; 1,000; 2,000; 3,000; 3,000; and 3,000 PNU. 2) Placebo (alum-precipitated human serum albumin, with histamine phosphate and caramelized glucose) (n = 14) Duration of study treatment: Injections given over 9 weeks during allergy preseason (May to July); outcomes assessed during one allergy season (mid-August to mid-September) Symptomatic medication permitted: Chlorpheniramine 4-mg tablets; pseudoephedrine 60-mg tablets; and naphazoline HCl, pheniramine maleate, eyedrops Dates: NR Location: Quebec, Canada Setting: University Type(s) of providers: Specialists	No. of subjects at start: 27 Dropouts/withdrawals: 0 No. of subjects at end: 27 Inclusion criteria: Ragweed allergic rhinitis without asthma; positive prick skin test and IgE antibody to ragweed Exclusion criteria: NR Age: 19-56 Sex: Active 10M/3F; placebo 8M/6F Race: NR Other: None had other serious disease or prior immunotherapy	1) Allergen-specific IgE and IgG antibody levels 2) Patient-assessed symptom severity: sneezing, itchy nose, rhinorrhea, nasal obstruction, lacrimation, and itchy eyes graded twice per day during allergy season on scale of 0 (none, no symptoms evident) to 3 (severe, disabling and/or interfering with daily activities and/or sleep) 3) Investigator-assessed symptom severity 4) Use of symptomatic medication: type and amount used recorded daily by patients in study diaries 5) Nasal reactivity 6) Allergen-induced basophil histamine release 7) Adverse reactions	1) Allergen-specific IgE and IgG antibody levels: Not abstracted 2) Patient-assessed symptom severity: Score: 4.7 ± 0.7 active vs. 7.5 ± 1.2 placebo; $p < 0.05$ 3) Investigator-assessed symptom severity: Not abstracted 4) Use of symptomatic medication: Score: 0.9 ± 0.2 active vs. 0.7 ± 0.2; $p = 0.6$ 5) Nasal reactivity: Not abstracted 6) Allergen-induced basophil histamine release: Not abstracted 7) Adverse reactions: Unspecified number of local reactions; one subject with late phase reaction of 8 cm associated with wheezing – continued in study	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 1b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: Yes Notes:

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Cockcroft, Cuff, Tarlo, et al., 1977	Design: RCT, parallel-group (matched-pairs design) Interventions: 1) Glutaraldehyde-modified ragweed tyrosine adsorbate (MRTA) (n = 21). Four weekly injections given in doses of 300; 700; 2,000; and 4,000 NU per 0.5 ml. 2) Placebo (tyrosine base) (n = 22) Duration of study treatment: Injections given over 4 weeks in July; outcomes measured through one allergy season (end of September) Symptomatic medication permitted: Chlorpheniramine maleate 4-mg tablets; naphazoline-antazoline eyedrops (0.05 mg/ml and 0.5 mg/ml, respectively); beclomethasone dipropionate nasal aerosol (50 µg/spray); medrysone (1%) eyedrops; and prednisone 5-mg tablets. Used according to pre-defined protocol. Minimum dose required to control symptoms used. Dates: NR Location: Hamilton, Ontario, Canada Setting: University practice Type(s) of providers: Specialists	No. of subjects at start: 43 Dropouts/withdrawals: 1 withdrew from placebo group for reasons unrelated to the trial. 6 patients in active treatment group could not complete IT regimen but continued in trial (see AEs) No. of subjects at end: 42 Inclusion criteria: Moderate to severe allergic rhinitis during August/September; positive prick skin tests to ragweed Exclusion criteria: Positive prick skin test to mold Cladosporium and Alternaria Age: 29.9 active; 33.2 placebo Sex: 7M/14F active; 8M/14F placebo Race: NR Other: 7 active and 5 placebo patients had receive prior immunotherapy 7 active and 6 placebo patients with mild asthma	1) Patient-assessed symptom severity: sneezing, stuffy and/or runny nose, itchy eyes, and cough graded twice per day on scale of 0 (none) to 3 (lasted longer than 3 hours) 2) Use of symptomatic medication: types and doses used recorded daily by patients in study diaries 3) Patient global assessment of efficacy: patients asked at end of trial whether result of injections "very good" (minimal symptoms, minimal medication requirement), "good" (noticeably better than previous years), or "poor" (slight or no improvement) 4) Allergen-specific IgE and IgG antibody levels, eosinophil counts 5) Adverse reactions	1) Patient-assessed symptom severity: Symptom score (active vs. placebo) Sneezing 1.42 vs. 1.32 (ns) Rhinorrhea congestion 2.06 vs. 2.38 (ns) Eye 0.92 vs. 1.49 (ns) Cough 0.52 vs. 0.58 (ns) Total 4.95 vs. 5.75 (ns) 2) Use of symptomatic medication: Number subjects requiring (active vs. placebo): Chlorpheniramine 20 vs. 20 (ns) Beclomethasone 9 vs. 15 (ns) Eye drops 10 vs. 14 (ns) Medrysone eye drops 0 vs. 1 (ns) Prednisone 1 vs. 2 (ns) Mean daily consumption: Chlorpheniramine 0.77 vs. 0.96 (ns) Beclomethasone 1.01 vs. 2.10; $p < 0.05$ Eye drops 0.50 vs. 1.24 (ns) Total 2.29 vs. 4.37; $p < 0.05$ 3) Patient global assessment of efficacy: (active vs. placebo) Very good 5 vs. 3 Good 9 vs. 5 Poor 7 vs. 13 (ns) 4) Allergen-specific IgE and IgG antibody levels, eosinophil counts: Not abstracted 5) Adverse reactions: Late swelling > 10 cm resulted in stopping injections in 3 patients after second injection and after third injection in another 3. These subjects were followed in intention-to-treat manner.	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Yes Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: Yes Notes:

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Corrado, Pastorello, Ollier, et al., 1989	Design: RCT, parallel-group Interventions: 1) Standardized extract of *Dermatophagoides pteronyssinus* (house dust mite) conjugated to alginate and containing known amounts of antigen P1 (Conjuvac®) (n = 22). Build-up phase: 11 weekly injections of doses increasing from 56 x 10^1 to 448 x 10^3 IU *D. pteronyssinus*. Maintenance phase: 15 monthly injections, each containing 448 x 10^3 IU *D. pteronyssinus.* 2) Placebo (lyophilized sodium alginate diluent ± 5 µg histamine dihydrochloride) (n = 29). Duration of study treatment: 18 months Symptomatic medication permitted: Beclomethasone dipropionate, xylometazoline, or sodium cromoglycate nasal sprays, and chlorpheniramine; patients "encouraged to reduce their medication as much as possible" Dates: 11/83-3/85 Location: Italy and UK Setting: 3 academic centers Type(s) of providers: Specialists	No. of subjects at start: 66 Dropouts/withdrawals: 15 (11 active, 3 placebo): 6 withdrawn for pregnancy, 4 with severe local reactions, 2 with late or generalized reactions, one for lack of benefit, and 2 lost to followup No. of subjects at end: 51 Inclusion criteria: Not specified, although all were determined to have *D. pter*. as "main cause of symptoms on basis of history and nasal provocation and skin prick testing. Exclusion criteria: Pregnancy; nasal polyps or other nasal deformity; proven sensitivity to animals and pets kept in home; systemic corticosteroid use Age: 17-55 (mean 29.5) Sex: 40 F Race: NR Other: 34/66 also had asthma	1) Nasal reactivity 2) Patient-assessed symptom severity (diary data): nasal blockage, sneezing, and rhinorrhea graded twice daily on a scale of 0-3 (not described) 3) Peak flow rates 4) Patient-assessed symptom severity (clinic visits): nasal blockage, sneezing, and rhinorrhea graded on 10-cm visual analog scale (running from "no symptoms" to "could not be worse") during clinic visits at baseline and after 5, 9, and 15 months of maintenance therapy 5) Use of symptomatic medication: recorded in daily study diaries and monitored via tablet counts and nasal spray canister weights 6) Adverse reactions: Prior to each injection, patients asked, "Did you notice anything unusual after the last injection?" Reported problems classified as local or systemic and early or late (> 30 min after injection)	1) Nasal reactivity: Not abstracted 2) Patient-assessed symptom severity (diary data): Last observation carried forward for dropouts. Questionable compliance with diary card collections. Significant difference (p = 0.028) for final diary recordings for AM score, but not PM score (p = 0.12). Actual data not given. 3) Peak flow rates: Not abstracted 4) Patient-assessed symptom severity (clinic visits): Not significant except for congestion subscore (p < 0.01). Data not given. 5) Use of symptomatic medication: No data given. Both groups used little medication at end of study. 6) Adverse reactions: No immediate systemic reactions. Immediate local reaction of < 5 cm in 29% A v 1% placebo, > 5 cm in 1% A and 0% placebo. Delayed systemic reactions in 3% active and 1% placebo. Local < 5 cm 12% v 2. Local > 5 cm 23% v 1%. No anaphylaxis.	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: Yes Notes:

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Creticos, Reed, Norman, et al., 1996	Design: RCT, parallel-group Interventions: 1) Lyophilized extract of short-ragweed pollen, prepared by a professional lab (n = 37). Initial dose of 0.05 ml of a 1:10,000 dilution of extract (0.001 mg of Amb a 1) doubled every week until maximum tolerated dose or 0.5 ml of a 1:10 dilution (10 µg of Amb a 1) reached (19 weeks). Maintenance doses then administered every 2 weeks for 3 months and every 4 weeks thereafter. 2) Placebo (n = 40) Duration of study treatment: 2 years Symptomatic medication permitted: Rhinitis medication not described; asthma medications permitted and adjusted by investigators every 3 weeks during period in which diaries were kept Trial preceded by 4-month observation phase (July 1 through October 31) Dates: NR Location: Baltimore and Rochester, MN Setting: Academic centers Type(s) of providers: Specialists	No. of subjects at start: 90 randomized; 77 began treatment phase Dropouts/withdrawals: 13 dropouts between randomization and treatment. No reason given. 13 dropped out in year 1, 11 in year 2. 8 active group dropouts: 4 moved, 3 withdrew, 1 became pregnant 16 placebo dropouts: 3 moved, 11 withdrew, 1 had worsened asthma, 1 possible adverse reaction No. of subjects at end: 53 Inclusion criteria: Age 16-70; asthma for 1+ year with exacerbation during fall season requiring medication; positive skin test to ragweed with less reactivity to other possible confounding allergens; drop in FEV1 of 20% after methacholine inhalation of less than 25 mg/ml Treatment phase inclusions criteria: Worsened asthma symptom scores during ragweed season, worsening peak flow, and worsening medication scores, return 80% of symptom diaries Exclusion criteria: Asthma requiring 2+ hospitalizations in previous year; inability to wean from long-term oral steroids or cromolyn; sensitivity to animals on regular exposure; current smoking; IT in previous 3 years, or ragweed IT; systemic illness; pregnancy; inability to undergo	1) Peak flow rates 2) Use of asthma medication: recorded daily in study diaries from July 1 through October 31 each year 3) Patient-assessed severity of *asthma* symptoms: unspecified symptoms of asthma recorded twice daily and graded on scale of 0 (none) to 6 (incapacitating) from July 1 through October 31 each year 4) Patient-assessed severity of *rhinitis* symptoms: unspecified symptoms of rhinitis recorded twice daily and graded on scale of 0 (none) to 6 (incapacitating) from July 1 through October 31 each year 5) Bronchial reactivity (antigen and methacholine challenges) 6) Allergen-specific IgE and IgG antibodies 7) Skin reactivity 8) Adverse reactions	1) Peak flow rates: Not abstracted 2) Use of asthma medication: Score 19 active v 43 placebo in year 1 (p = 0.01), and 29 v 33 in year 2 (p = 0.7). 3) Patient-assessed severity of *asthma* symptoms: Not significant in year 1 or 2. Numbers not given. 4) Patient-assessed severity of *rhinitis* symptoms: Baseline: 4.1 A v 4.5 P Year 1: 3.5 A v 4.3 P (p = 0.1) Year 2: 3.1 A v 3.8 P (p = 0.04) 5) Bronchial reactivity: Not abstracted 6) Allergen-specific IgE and IgG antibodies: Not abstracted 7) Skin reactivity: Not abstracted 8) Adverse reactions: Year 1: 7 patients in active group had 14 systemic reactions. 5 were mild, 9 rhinitis, generalized urticaria, angioedema, or combination requiring antihistamine or epinephrine. 2 patients dropped out after several systemic reactions. 4 placebo patients had moderate reactions and received treatment. One patient in placebo group received active treatment by mistake and had severe reaction with bronchospasm and hypotension. Recovered.	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: Can't determine Notes:

(continued on next page)

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
		diagnostic tests Age: Mean 36.0 A v 35.1 P Sex: Active 18 F; placebo 20 F Race: NR Other:			
Cvitanovic, Zekan, Capkun, et al., 1994	Design: RCT, parallel-group Interventions: 1) Partially purified, characterized, and standardized pollen extract of *Parietaria officinalis* (alum-absorbed depot preparation) (n = 40). Increasing doses administered weekly until the appearance of a local reaction, then decreased and slowly increased until a new local reaction occurred; "after some time," injections given on biweekly basis. Injections given pre-seasonally, from beginning of November to mid-March. 2) Oral ketotifen 1 mg twice per day from March 15 to end of June (n = 35) Duration of study treatment: 3 years Symptomatic medication permitted, but not described Dates: NR Location: Split, Croatia	No. of subjects at start: 90 Dropouts/withdrawals: 10/50 active: 6 for incomplete evaluation and 4 for anaphylaxis to IT 5/40 study medication: cause not listed No. of subjects at end: 40 active; 35 drug Inclusion criteria: 2-year history of seasonal rhinoconjunctivitis; positive skin test and specific IgE antibody to *P. officinalis* Exclusion criteria: NR Age: Active (after dropouts) 19-45 years Ketotifen (after dropouts) 18-35 years Sex: Active 20M/20F; Ketotifen 17M/18F Race: NR Other: All subjects were non-allergic, but testing regimen not described. No prior corticosteroids or immiunotherapy.	1) Adverse reactions 2) Allergen-specific IgE and IgG antibody levels 3) Histamine serum concentration 4) Skin reactivity 5) Eosinophil levels 6) Patient-assessed symptom severity: nasal secretion, congestion, itching, and sneezing graded daily on scale of 0 (no symptoms) to 3 (severe symptoms) 7) Use of symptomatic medication: graded daily on scale of 0-3 (as above), with 1 point given for each dose of symptomatic medication	1) Adverse reactions: Active: 4 anaphylaxis in active group. 15 patients with reduced IT dose because of local reactions or rhinorrhea. 2) Allergen-specific IgE and IgG antibody levels: Not abstracted 3) Histamine serum concentration: Not abstracted 4) Skin reactivity: Not abstracted 5) Eosinophil levels: Not abstracted 6) Patient-assessed symptom severity: Score (active vs. ketotifen) Year 1 12.2 ± 5.0 vs. 22.2 + 7.6 Year 2 9.3 ± 3.5 vs. 15.8 ± 4.3 Year 3 8.1 ± 1.2 vs. 12.3 ± 3.1 7) Use of symptomatic medication: Score (active vs. ketotifen) Year 1 5.6 ± 2.3 vs. 15.5 ± 2.8 Year 2 5.9 ± 1.2 vs. 11.2 ± 3.0 Year 3 3.8 ± 1.0 vs. 12.1 ± 2.6	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 1b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: No Dropouts described: Yes Intention-to-treat: No Notes: 15 of 40 patients failed to achieve maintenance dose because of local reactions. IT dosing not standardized. Presumably not blinded.

(continued on next page)

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	Setting: University practice Type(s) of providers: Specialists	Antihistamines stopped 1 month before study.			
Dolz, Martínez-Cócera, Bartolomé, et al., 1996	Design: RCT, parallel-group Interventions: 1) Aluminum hydroxide-adsorbed grass-pollen extract containing allergens PDL *(Phleum, Dactylis, Lolium)* (Alutard® SQ) (n = 18). Rush protocol followed using aqueous extract. Doses ranging from 0.1 ml x 100 USQ/ml to 1.0 ml x 100,000 USQ/ml given over 4 days. Depot extract used after maximum dose of aqueous extract reached; repeated every 4 weeks until end of study. Regime modified if any adverse reaction occurred. 2) Placebo (0.01 mg histamine hydrochloride and 0.4 mg human serum albumin) (n = 10). Duration of study treatment: 3 years Symptomatic medication permitted: Cromoglycate, oral antihistamines, inhaled bronchodilators, and inhaled corticoids Dates: 1990-1992 Location: Madrid, Spain Setting: Allergy clinic	No. of subjects at start: 30 Dropouts/withdrawals: 2 excluded (1 due to initiation of beta-blocker treatment; 1 for personal reasons) No. of subjects at end: 28 Inclusion criteria: Allergy to grass pollen by history, skin test, conjunctival provocation test, and positive specific IgE Exclusion criteria: Previous immunotherapy; sensitization to other pollens or aeroallergens Age: Mean 19.4 (range 15 to 35) Sex: NR Race: NR Other: Asthma: 21%	1) Skin reactivity 2) Conjunctival reactivity 3) Bronchial reactivity 4) Total IgE and allergen-specific IgE, IgG, and IgG4 5) Adverse reactions 6) Patient-assessed symptom severity: nasal symptoms (itching, sneezing, rhinorrhea, and obstruction), ocular symptoms (itching, reddening, photophobia, and sensation of foreign body), and bronchial symptoms (pharyngeal and palatal itching, persistent coughing, dyspnea, and wheezing) graded daily during pollen season an a scale of 0 (no symptoms) to 3 (severe) 7) Use of symptomatic medication: graded daily during pollen season, as follows: Cromoglycate: 1 Oral antihistamines: 2 Inhaled bronchodilators: 3 Inhaled corticoids: 4	1) Skin reactivity: Not abstracted 2) Conjunctival reactivity: Not abstracted 3) Bronchial reactivity: Not abstracted 4) Total IgE and allergen-specific IgE, IgG, and IgG4: Not abstracted 5) Adverse reactions: Local 4 Systemic 7 6) Patient-assessed symptom severity: Results presented in graph only (cannot be interpolated, because daily scores are not aggregated to a single parameter) Nasal symptoms significantly improved compared to placebo in 2nd and 3rd year ($p < 0.001$) 7) Use of symptomatic medication: Results presented in graph only (cannot be interpolated, because daily scores are not aggregated to a single parameter) Medication score significantly improved compared to placebo in 2nd and 3rd year ($p < 0.01$)	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Not described Dropouts described: Yes Intention-to-treat: No Notes: Duration of follow-up longer than most. Absence of statistically significant benefit during first year suggests early benefit of rush IT.

(continued on next page)

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	Type(s) of providers: Allergists				
Dorward, Waclawski, and Kerr, 1984	Design: RCT, parallel-group Interventions: 1) Alum-precipitated five-grass extract (Allpyral®) (n = 18). Five grasses: timothy, rye, cocksfoot, Yorkshire for, and meadow grass. Nine weekly injections starting with a dose of 20 PNU and rising to 4,000 PNU. Dose reduced in event of severe local reaction. Injections completed 2-4 weeks before start of pollen season. No maintenance injections given. 2) Two-grass conjugated extract (Conjuvac®) (n = 21). Two grasses: timothy and cocksfoot. Eleven weekly injections rising from 1 AUR (activity units by RAST) to 800 AUR. Dose reduced in event of severe local reaction. Injections completed 2-4 weeks before start of pollen season. No maintenance injections given. Duration of study treatment: Injections given over 9-11 weeks during allergy pre-season; outcomes assessed during single pollen season (mid-May to end of July) Symptomatic medication permitted: oral antihistamines	No. of subjects at start: 39 Dropouts/withdrawals: 1 discontinued due to adverse reaction; 10 failed to completed diary cards; 4 did not have antibody levels for before and after treatment No. of subjects at end: 25 (could be analyzed for both antibody results and diary scores) Inclusion criteria: Seasonal pollen rhinitis for at least 2 years; attending allergy clinic; positive skin-prick tests to pollen extract Exclusion criteria: None stated Age: 23.6 (range 8 to 52) Sex: NR Race: NR Other: 22 patients had had immunotherapy in the past	1) Adverse reactions 2) Patient-assessed symptom severity: itching eyes, swelling of eyes, watery eyes, sneezing, nasal blockage, runny nose, and wheezing graded daily on scale of 1 (mild) to 3 (severe) 3) Total IgE and allergen-specific IgE and IgG antibody levels 4) Patient global evaluation of efficacy: number of patients who thought that treatment had improved their symptoms 5) Patient satisfaction: number of patients who would repeat the same treatment again next year 6) Use of symptomatic medication: Number of patients requiring antihistamine treatment to control symptoms during the pollen season	1) Adverse reactions: Severe local requiring d/c treatment (Conjuvac) n = 1 Local Minor 10 Conjuvac; 9 Allpyral Frequent 0 Conjuvac; 2 Allpyral Severe 9 Conjuvac; 4 Allpyral Systemic Wheeze 1 Conjuvac; 2 Allpyral Rhinitis 1 Conjuvac; 0 Allpyral Requiring d/c treatment 1 conjuvac; 0 Allypyral 2) Patient-assessed symptom severity: Allpyral significantly higher than Conjuvac (1.31 ± 0.29 versus 0.81 ± 0.18; $p < 0.05$) 3) Total IgE and allergen-specific IgE and IgG antibody levels: Not abstracted 4) Patient global evaluation of efficacy: Allypyral 12/18 cases Conjuvac 16/18 cases 5) Patient satisfaction: Allypyral 15/18 Conjuvac 17/18 6) Use of symptomatic medication: Allpyral 4/18 Conjuvac 3/18	Quality Scoring: Population similar: Yes Intervention(s) described: No Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: No (alternate allocation) Double-blind: No Blinding adequate: Not applicable Dropouts described: Yes Intention-to-treat: No Notes:

(continued on next page)

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	Dates: Spring/summer 1982 Location: Glasgow, Scotland Setting: Allergy clinic Type(s) of providers: Allergists				
D'Souza, Pepys, Wells, et al., 1973	Design: RCT, parallel-group Interventions: 1) Extract of *Dermatophagoides pteronyssinus* (house dust mite) prepared by professional laboratory (n = 45). A 1-g sample of mites and mite excreta, separated from the culture medium, was extracted in 100 ml of glycerinated extraction fluid to make a 1% extract. Three concentrations of vaccine made (0.005%, 0.04%, and 0.33%). Build-up phase: increasing injections of 0.1, 0.2, 0.4, and 0.8 ml given weekly from each vial in order, starting with the lowest concentration (0.005%). Dose repeated or reduced in event of adverse reactions. Treatment stopped after 12 injections (3 months), regardless of whether top dose reached or not. 2) Placebo (carbol saline solution) (n = 46) Patients in both groups were advised to vacuum their mattresses and pillows, damp-dust their bedrooms, and	No. of subjects at start: 96 Dropouts/withdrawals: 5 (2 placebo, 3 active); 2 failed to return after 12 injections, 2 dropped out without reason given, 1 mild asthmatic reaction and was excluded No. of subjects at end: 91 Inclusion criteria: Positive skin test to *D. pter.;* history of symptoms induced by house dust or positive nasal challenge with *D. pter.* Exclusion criteria: Steroid therapy within previous 3 months; house dust IT within 3 years Age: 10-41+ Sex: 16 F/46 placebo, 21 F/45 active Race: NR Other: 10 subjects in each group previously received house dust IT	1) Adverse reactions: As observed by investigators and recorded by patients in study diaries 2) Patient global assessment of efficacy: following parameters graded as "improved" (very much, moderately, or slightly), "not changed," or "worse" (slightly, moderately, or very much) at 1 and 3 months: Asthma Rhinitis Exercise tolerance Dust tolerance (3 months only) Time off work Drug use (3 months only) Overall assessment 3) Nasal reactivity 4) Skin reactivity 5) Patient-assessed symptom severity: wheeze, rhinitis, and night asthma graded daily on scale of 0-3 6) Use of permitted symptomatic medication:	1) Adverse reactions: Active: Local reaction in 34 patients 18 patients mild asthma and/or rhinitis 4 short term generalized urticaria 3 fainting and dizziness Placebo: 2 discontinued treatment because of mild asthma 2) Patient global assessment of efficacy: At 1 and 3 months, 91 patients assessed. No difference at 1 month in any parameter. Results at 3 mo. (%) (active v plac): Asthma improved: 33 v 62.5 p = 0.02 Rhinitis improved: 29 v 22 NS Exercise tolerance better: 35 v 19 NS Dust tolerance better: 55 v 30 p = 0.05 Time off work less: 25 v 14 NS Drug use less: 43 v 19 p = 0.05 Overall very much better: 35 v 19 NS 3) Nasal reactivity: Not abstracted 4) Skin reactivity: Not abstracted 5) Patient-assessed symptom severity: Adequate data for 70 patients. No difference between groups with both groups improving. 6) Use of permitted symptomatic medication:	Quality Scoring: Population similar: No Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: No Notes: *(continued on next page)*

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	wash their blankets every 6-8 weeks, and to exclude feathers from their beds. Duration of study treatment: 3 months Symptomatic medication permitted: Antihistamines, Mogadon®, isoprenaline inhaler, Ventolin® inhaler, and Intal® Dates: NR Location: London Setting: Academic unit Type(s) of providers: Specialists		recorded daily in study diaries 7) Total IgE, and allergen-specific IgE and IgG antibody levels 8) Lymphocyte transformation and leucocyte inhibition 9) Histamine release	No difference. 7) Total IgE, and allergen-specific IgE and IgG antibody levels: Not abstracted 8) Lymphocyte transformation and leucocyte inhibition: Not abstracted 9) Histamine release: Not abstracted	
Durham, Walker, Varga, et al., 1999	Design: RCT, parallel-group Interventions: All patients had received 3-4 years of active immuno-therapy as described by Varney, Gaga, Frew, et al., 1991 and Durham, Varney, Gaga, et al., 1991, below. At start of this phase of the trial, all were randomized to one of following: 1) Continued maintenance immunotherapy (n = 16). Monthly injections of a standardized, aluminum hydroxide-adsorbed grass pollen extract (Alutard®), each containing 100,000 SQ units. Dose reduced by 40% during pollen season.	No. of subjects at start: 32 Dropouts/withdrawals: 5 No. of subjec ts at end: 27 Inclusion criteria: Participation in IT group of previous RCT of IT for allergic rhinitis for timothy grass pollen allergy Exclusion criteria: None specified Age: Median 40 Sex: 19 men, 13 women Race: NR Other:	1) Patient-assessed symptom severity (daily diary): breathlessness, coughing, wheezing, chest tightness, sneezing, blocked nose, running nose, itching eyes, red eyes, streaming eyes, swollen eyes, and itching and dryness of mouth and throat graded daily from May through September on visual analog scale of 0 (no symptoms) to 3 (severe symptoms) 2) Use of symptomatic medication: scored daily from April to October as follows: Each eye drop, nasal spray, or albuterol	1) Patient-assessed symptom severity (daily diary): No differences Nose symptoms: Year Difference b/w Maint & d/c 1993 -74 (-325 to 266) 1994 67 (-287 to 490) 1995 -5 (-462 to 462) p = NS 2) Use of symptomatic medication: No differences Year Difference b/w Maint & d/c 1993 54 (-724 to 2009) 1994 4 (-1064 to 2121) 1995 11 (-689 to 1488) p = NS 3) Patient-assessed symptom severity (every 2 weeks): No differences Year Difference b/w Maint & d/c	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 1b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: No Notes: Randomized patient population same as in Varney, Gaga, Frew, *(continued on next page)*

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	2) Placebo maintenance immunotherapy (diluent plus 0.01 mg of histamine per ml) (n = 16) Duration of study treatment: 3 years Symptomatic medication permitted: Cromolyn sodium eye drops and nasal spray, acrivastine, and albuterol; 7-day course of prednisolone could be given, if necessary Dates: 1992-1995 Location: London, UK Setting: Allergy clinic Type(s) of providers: Allergists		inhalation: 1 Each acrivastine or prednisolone: 2 3) Patient-assessed symptom severity (every 2 weeks): During pollen season, patients asked to grade their overall symptoms every 2 weeks on a visual analog scale from 0 (minimal symptoms) to 10 (maximal symptoms) in response to question, "How has your hay fever been during the past week?" 4) Conjunctival reactivity 5) Skin reactivity 6) CD3 and T cells, and interleukin-4 mRNA 7) Adverse reactions	1993 -1 (-2.6 to 0.3) 1994 0 (-3 to 3.1) 1995 0.2 (-1.9 to 1.6) p = NS 4) Conjunctival reactivity: Not abstracted 5) Skin reactivity: Not abstracted 6) CD3 and T cells, and interleukin-4 mRNA: Not abstracted 7) Adverse reactions: No substantial immediate or late systemic reactions were observed Less than 2% of injections resulted in early or delayed local reactions.	et al., 1991 and Durham, Varney, Gaga, et al., 1991, below. Paper also described 15 matched natural-history controls who had never received immunotherapy and were not randomized to treatment in this trial. Only trial examining effect of discontinuing maintenance treatment.

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Eriksson, Ahlstedt, and Lövhagen, 1979	Design: RCT, parallel-group Interventions: 1) Birch, alder, and hazel allergen extract (Allpyral®) (n = 17). Injections given once a week until highest tolerated dose or maximum dose of 4,000 PNU reached; this dose then given as a maintenance dose every 6-8 weeks. 2) Allpyral® (as above) plus other aqueous tree pollen extracts, as identified by nasal provocation tests using other tree pollens (n = 16). Aqueous allergen extracts given twice a week in increasing doses until highest tolerated dose reached; this dose then administered every 4 weeks. 3) No immunotherapy (n = 14) Patients in groups 1) and 2) who were also allergic to grass and/or compositae pollen were given immunotherapy with those allergens as well. Duration of study treatment: 3 years ("as a rule") Symptomatic medication permitted: antihistamine tablets (brompheniramine 40 mg + phenylpropanololamine 167 mg) for mild symptoms and prednisolone 5 mg if symptoms intolerable in spite	No. of subjects at start: 47 Dropouts/withdrawals: Not specified, but analysis based on smaller number of patients than originally treated. No. of subjects at end: Estimated at 46 Inclusion criteria: Adult hay fever patients with positive nasal provocation test to birch pollen Exclusion criteria: NR Age: Group 1 (15-46) Group 2 (15-33) Group 3 (14-45) Sex: Group 1 8M/9F Group 2 8M/8F Group 3 7M/7F Race: NR Other:	1) Nasal reactivity 2) Patient-assessed symptom severity and use of symptomatic medication (combined in a single measure): sneezing, rhinorrhea, and eye symptoms graded daily during pollen season in year 1 on scale of 0 (no symptoms) to 3 (severe symptoms); number of antihistamine and prednisolone tablets taken also scored from 0 to 3 3) Patient global evaluation of treatment efficacy: at end of pollen season in year 1, patients asked to grade their symptoms relative to previous year's symptoms on scale of 0 (no symptoms) to 4 (worse) 4) IgE and non-IgE antibody levels (against birch and beech allergens) 5) Allergen-induced histamine release	1) Nasal reactivity: Not abstracted 2) Patient-assessed symptom severity and use of symptomatic medication (combined in a single measure): Data presented as graph with score vs. time. Values for medication significant $p < 0.01$ and symptoms scores $p < 0.05$. 3) Patient global evaluation of treatment efficacy: Less troublesome symptoms: Group 1 83% Group 2 93% Group 3 64% all ns 4) IgE and non-IgE antibody levels (against birch and beech allergens) : Not abstracted 5) Allergen-induced histamine release: Not abstracted	Quality Scoring: Population similar: Not adequately described Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 1b Randomized: Yes Allocation concealed: Not described Double-blind: No Blinding adequate: Not applicable Dropouts described: No Intention-to-treat: No Note: Not blinded

(continued on next page)

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	of treatment with antihistamine Dates: Treatment preceded 1974 pollen season Location: Sweden Setting: University clinic Type(s) of providers: Specialists				
Ewan, Alexander, Snape, et al., 1988	Design: RCT, parallel-group Interventions: 1) Standardized, partially purified, freeze-dried extract of *Dermatophagoides pteronyssinus* (house dust mite) (Pharmalgen®) (n = 16). Modified "semi-rush" technique used. Injections given at 1- to 2-week intervals, using aqueous extracts in gradually increasing concentrations. Initial dose was 70 BU (20 + 50); planned top dose was 100,000 BU. Dose increased until a reaction occurred, then reduced and slowly increased again until a second phase of reaction encountered. Dose just below this (maximum tolerated dose) then used for maintenance injections, in depot diluent, which were given monthly for remainder of 3-month period. 2) Placebo extract (contained histamine) (n = 20). Also given in gradually increasing doses.	No. of subjects at start: 38 Dropouts/withdrawals: NR. However, before and after skin test data provided on only 34 patients No. of subjects at end: NR Inclusion criteria: Perennial rhinitis ± asthma; history suggesting allergy to *D. pter*. and no other active perennial allergy Exclusion criteria: IT within last 3 years; systemic corticosteroids within last 1 year Age: 16-55 Sex: 17 F Race: NR Other: Assessment made after 3 months of treatment. All had positive skin test response, positive nasal challenge, and serum IgE antibodies to *D. pter.*	1) Skin reactivity 2) Nasal reactivity 3) Patient-assessed symptom severity: (unspecified) nasal symptoms graded 1 month before treatment and 3 months after start of treatment on visual analog scale (10-cm line, with "no symptoms" at 0 cm, "minimal symptoms" at 1 cm, "slight symptoms" at 4 cm, "moderate symptoms" at 7 cm, and "severe symptoms" at 10 cm) 4) Allergen-specific IgE antibody levels 5) Adverse reactions	1) Skin reactivity: Not abstracted 2) Nasal reactivity: Not abstracted 3) Patient-assessed symptom severity: VAS symptoms: Active: 66.8 to 28.8 Placebo: 50.2 to 39.3 Drop in active group significantly greater than in placebo group ($p < 0.01$). 4) Allergen-specific IgE levels: Not abstracted 5) Adverse reactions: 31 generalized reactions (15% of injections) in active group. 8 were serious or potentially serious and classified as anaphylaxis. Patients responded to epinephrine. Some patients received oxygen, nebulized b-agonists and parenteral steroids. 7 had asthma exacerbation, 5 asthma/uricaria, 3 rhinitis exacerbation, 5 erythema or pruritis, 3 erythema with "other" symptoms. All were early reactions. 13 generalized reactions (5% of injections) in placebo group. All were mild: 10 with generalized pruritis and	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: No Intention-to-treat: No Notes: Article reports interim (3-month) results of trial scheduled to last 1 year. No daily symptom data analyzed. Potentially significant differences in baseline symptom scores may influence result if there was a "floor" effect on reduction of symptoms. *(continued on next page)*

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	Duration of study treatment: 3 months (see Notes) Symptomatic medication permitted: Beclomethasone nasal spray or short-acting antihistamines (chlor-pheniramine or terfenadine) Dates: NR Location: London Setting: Hospital-based allergy department Type(s) of providers: Specialists			erythema, 2 with rhinitis, 1 with asthma. Localized reactions in 6% of active group (induration) and mild flare in 3% and 2% of active and placebo group respectively.	
Gabriel, Ng, Allan, et al., 1977	Design: RCT, parallel-group Interventions: 1) Extract of *Dermato-phagoides pteronyssinus* (house dust mite) made up in four concentrations in a solution of 50% aqueous glycerine containing 0.5% phenol (n = 37). Vaccines prepared in concentrations of 0.0004% (for children under 12 only), 0.003%, 0.025% and 0.20%. Build-up phase: weekly injections of gradually increasing doses, with variations according to age; children aged 8-11 could complete course in 22 weeks, older children in 19 weeks, and adults in 18 weeks. Maintenance phase: monthly injections of highest concentration (1 ml of 0.20% vaccine).	No. of subjects at start: 72 Dropouts/withdrawals: 3 excluded because of lack of symptom, and 3 "defaulted" during weekly course leaving 66 patients for initial evaluation (33A, 33P). 16 pts. excluded from maintenance course (10A, 6P). 7 defaulted or left country (3A, 4P), 6 enrolled late did not complete monthly course (5A, 1P), 3 withdrawn (2A, 1P) for moderately severe reactions. No. of subjects at end: 50 (23A, 27P). Inclusion criteria: Chinese; age ≥ 8; history of seasonal or perenial rhinitis for 3+ consecutive years, characterized by sneeze, nasal obstruction and discharge, ± asthma; positive skin test to *D. pter.;* positive nasal challenge to	1) Patient-assessed symptom severity: sneezing, nasal obstruction, nasal discharge, and asthma graded daily on 4-point scale (none, mild, moderate, severe) 2) Investigator-assessed symptom severity 3) Skin reactivity 4) Nasal reactivity 5) Allergen-specific IgE and IgG antibody levels 6) Eosinophil counts 7) Adverse reactions	1) Patient-assessed symptom severity: Symptom Improvement after weekly course-% of pts. improved (Active v Placebo) Sneezing 50 v 32 NS Obstruction 24 v 24 NS Discharge 32 v 31 NS All symptoms 27 v 21 NS Symptom imrovement after 12 month maintenance course-% pts. improved (Active v Placebo) Sneezing 55 v 36 Obstruction 69 v 18 Discharge 75 v 43 All symptoms 55 v 19 (p = 0.02) 2) Investigator-assessed symptom severity: Not abstracted 3) Skin reactivity: Not abstracted 4) Nasal reactivity: Not abstracted 5) Allergen-specific IgE and IgG levels:	Quality Scoring: Population similar: No Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: No Notes: *(continued on next page)*

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
		D. pter.		Not abstracted	
	2) Placebo vaccine (saline only) (n = 35) Duration of study treatment: 1 year No description of symptomatic medication permitted (if any) Dates: 5/73-3/74 Location: Hong Kong Setting: Hospital-based chest clinic Type(s) of providers: Specialists	Exclusion criteria: Current use of corticosteroids or nasal cromoglycate Age: 11 patients under age 12 Sex: 34 F Race: 100% Asian Other: 22 subjects in each group reported a history of asthma symptoms. Only 6/66 monosensitized to *D. pter.*		6) Eosinophil counts: Not abstracted 7) Adverse reactions: Weekly course: One or more reactions in 91% of active group and 33% of placebo group. Average 9.2/pt active and 0.9/pt placebo. Breakdown by group % (active v placebo) Cutaneous local 91 v 33 Cutaneous general 6 v 3 Rhinitis 9 v 6 Wheezing/asthma 6 v 6 Anaphylaxis 3 v 0 Other 9 v 9 (not specified) Maintenance course: 95% of active group and 11% of placebo group. 7.2/pt active and 0.1/pt placebo. Breakdown by group % (active v placebo) Cutaneous local 96 v 11 Cutaneous general 0 v 0 Asthma 12 v 0	

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Grammer, Shaughnessy, Bernhard, et al., 1987	Design: RCT, parallel-group (matched-pairs design) Interventions: 1) Polymerized ragweed (PRW) prepared by a professional lab (n = 35). Short and giant ragweed pollens extracted, precipitated, and fractionated, then polymerized with glutaraldehyde. Injections given weekly for 15 weeks. AU and PNU delivered gradually increased from 2.5 to 62.5 and from 30 to 746, respectively, over the course of the first 5 injections. The last 10 injections were of a constant dose (125 AU, 1492 PNU). Cumulative totals were 1359 AU and 16,218 PNU. 2) Placebo (carmelized glucose and histamine phosphate, 20 µg/ml) (n = 35). Identical to active treatment in terms of volume injected. Duration of study treatment: Treatment lasted 15 weeks; outcomes assessed for 6 months Symptomatic medication permitted: Not described Dates: 1985 ragweed season Location: Chicago, IL Setting: University allergy practice	No. of subjects at start: 81 subjects who ultimately formed 35 pairs (no discussion of 11 unpaired subjects) Dropouts/withdrawals: 15 pairs (5 pairs lost to followup) No. of subjects at end: 10 "new" pairs formed under blinded status. Presumably 30 pairs were analyzed at end. Inclusion criteria: History compatible with AR caused by ragweed for previous 2+ years; positive skin test to ragweed; no IT for 3 years prior; healthy by H,x, PE and lab evaluation Exclusion criteria: None specified Age: 21-60 Sex: NR Race: NR Other: 12 patients with mild asthma	1) Adverse reactions: Recorded during clinic visits and by patients on reporting forms at specified intervals up to 48 hours after each injection; also reported to treatment nurse before next injection 2) Laboratory studies (urinalysis, CBC, etc.) 3) Total serum AgE-binding capacity and AgE binding by IgE 4) Patient-assessed symptom severity and medication use (combined in a single measure): nasal congestion, nasal discharge, sneezing, ocular pruritus, cough, and wheeze graded 3 times daily during pollen season on scale of 0-3 (not described); use of symptomatic medication recorded in study diaries daily during pollen season	1) Adverse reactions: 19/37 placebo pt with immediate local reaction (51%). 26 of 36 active group patients with immediate local reaction (72%). No systemic allergic reactions in either group. 2) Laboratory studies: Not abstracted 3) Total serum AgE-binding capacity and AgE binding by IgE: Not abstracted 4) Patient-assessed symptom severity and medication use (combined in a single measure): Absolute values not given, but scores significantly favored active treatment at all time points from week 1 until week 5. Week 1 p = 0.008 Week 2 p = 0.035 Week 3 p = 0.013 Week 4 p = 0.004 Week 5 p = 0.05 Primary season (Week 2-4) p = 0.005 Secondary season (Week 1-5) p = 0.02 Results obtained from 68 patients. No data on other patients.	Quality Scoring: Population similar: Not adequately described Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: No Intention-to-treat: No Notes:

(continued on next page)

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	Type(s) of providers: Specialists				
Grammer, Shaughnessy, Shaughnessy, et al., 1987	Design: RCT, parallel-group Interventions: 1) Polymerized ragweed (PRW) (n = 19). 15 weekly injections supplying 50,000 PNU of ragweed, equivalent to 1200 µg antigen E. No further details provided. 2) Placebo (carmelized glucose and histamine) (n = 19) 3) No treatment (n = 19) Duration of study treatment: Treatment lasted 15 weeks; outcomes assessed through ragweed pollen season (1st week in August through 1st week in October) Symptomatic medication permitted: Antihistamines and decongestants; patients with asthma permitted to continue with their regular asthma meds Dates: NR Location: Chicago, IL Setting: Univ allergy practice Type(s) of providers: Specialists	No. of subjects at start: 57 Dropouts/withdrawals: NR No. of subjects at end: NR, but only 50 of 57 patients reported clinical response data Inclusion criteria: Symptoms of allergic rhinitis during ragweed season Exclusion criteria: None specified Age (means): Untreated no asthma 29 Untreated asthma 33 Treated no asthma 32 Untreated asthma 34 Sex: 14 F Race: NR Other: 23 patients had diagnosis of asthma at enrollment.	1) Patient-assessed symptom severity and medication use (combined in a single measure): nasal congestion and sneezing graded 3 times daily during pollen season on scale of 0-3 (not described); number of antihistamine or decongestant tablets taken recorded in study diaries daily during pollen season 2) Total serum AgE-binding capacity and AgE binding by IgE	1) Patient-assessed symptom severity and medication use (combined in a single measure): 50 of 57 patients completed diary. Allocation across groups not given. Primary outcome was a comparison of cumulative symptom score in treated and untreated asthmatics and treated and untreated non asthmatics. Treated asthmatics had significantly lower scores (p = 0.01) and treated non-asthmatics had significantly lower scores (p = 0.04). 3) Total serum AgE-binding capacity and AgE binding by IgE: Not abstracted	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: No Dropouts described: No Intention-to-treat: No Notes: Initially 3 groups were defined: treated, placebo and untreated. Analysis was performed on combination of placebo and untreated group. Not possible to determine if treatment group improved from baseline. All we can determine is that cumulative score was lower.

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Grammer, Shaughnessy, Suszko, et al., 1983	Design: RCT, parallel-group Interventions: 1) Multiple (either five or six) grass-pollen polymer mixtures (n = 10). Treatment started in February. 12 weekly injections given, ranging in dose from 90 PNU (week 1) to 7200 PNU (weeks 8-12). Dose repeated in event of large local reaction (in which case additional injections given to reach target total dose, approximately 48,000 PNU). 2) Placebo (caramelized glucose histamine) (n = 13) Duration of study treatment: Injections given over 12 weeks (Feb-Apr); outcomes assessed through pollen season (early July) Symptomatic medication permitted: Not specified, but implied that antihistamines could be taken Dates: Feb-Jul 1982 Location: Chicago, IL Setting: Allergy clinic Type(s) of providers: Allergists	No. of subjects at start: 26 Dropouts/withdrawals: 3 No. of subjects at end: 23 Inclusion criteria: History typical of grass pollinosis; 4+ prick test to at least 1 grass pollen extract (1/20 wt/vol) of rye, timothy, redtop, June, orchard or Bermuda (ALO, Columbus, OH) Exclusion criteria: Immunotherapy within 5 years; abnormal ESR, CBC, UA Age: Range 21 to 65 years Sex: NR Race: NR Other:	1) Adverse reactions 2) Immunologic studies (total serum antibody against rye grass group I [RGGI], IgE against RGGI) 3) Patient-assessed symptom severity and medication use (combined in a single measure): symptoms (e.g., sneezing, nasal discharge, pruritus, cough) graded 3 times per day during pollen season (May - early July) on scale of 0-3 (not described); names of medication and numbers of pills taken also recorded 4) Patient global evaluation of efficacy of treatment: patients asked whether or not their symptoms were significantly improved (yes/no) 5) Lab tests (CBC with differential leukocyte count, erythrocyte sedimentation rate, urinalysis)	1) Adverse reactions: IT 2/10 pts had at least 1 immediate local reaction (erythema and induration); 1/10 had erythema alone; 1/10 had large late local reaction; no systemic reactions Placebo: 2/13 had at least one immediate local reaction; 3/13 had erythema alone; 1/13 had large local reaction 2) Immunologic studies: Not abstracted 3) Patient-assessed symptom severity and medication use (combined in a single measure): IT significantly lower than placebo ($p = 0.02$) (Fig. 5 interpolated figures IT 210 ± 75 [mean ± SEM]; placebo 500 ± 115) 4) Patient global evaluation of efficacy of treatment: IT 9/10 improved Placebo 3/13 improved $P < 0.01$ 5) Lab tests: Not abstracted	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: No Notes:

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Grammer, Zeiss, Suszko, et al., 1982	Design: RCT, parallel-group Interventions: 1) Polymerized ragweed (PRW) (n = 21). 15 weekly injections given. Doses for injections 1-5 were as follows (PNU per injection): 125; 312; 625; 1,250; 3,125. Dose for injections 6-15 was 6,250 PNU. Total dose approximately 50,000 PNU of ragweed, equivalent to 1,200 µg antigen E. Schedule modified in event of large local reaction. 2) Placebo (carmelized glucose and histamine) (n = 19) 3) No treatment (n = 15) Duration of study treatment: Injections given over 15 weeks; outcomes measured during one allergy season (Aug-Oct) Symptomatic medication permitted: Not described Dates: Treatment prior to 1981 ragweed pollen season Location: Chicago, IL Setting: University practice Type(s) of providers: Specialists	No. of subjects at start: 42 study patients + 15 no-treatment controls Dropouts/withdrawals: 2 No. of subjects at end: 40 study patients + 15 no-treatment controls Inclusion criteria: Symptoms of ragweed hay fever; positive prick skin test to ragweed pollen Exclusion criteria: NR Age: 21-65 Sex: NR Race: NR Other: None had received immunotherapy within previous 5 years	1) Adverse reactions 2) Antibody levels (IgE against AgE) 3) Patient-assessed symptom severity: sneezing, nasal discharge, nasal congestion, pruritus, and wheezing graded 3 times per day during allergy season on scale of 0 to 3 (not described)	1) Adverse reactions: 3/21 active treatment with local reaction. 7/21 had large reactions requiring additional dosing. No systemic reactions. 2/19 placebo subjects with local reactions. 1/19 with large local reaction requiring additional dosing. 2) Antibody levels (IgE against AgE): Not abstracted 3) Patient-assessed symptom severity: Average daily symptom scores plotted on graph with score vs. time. All values except final 2 weeks statistically significant. Also, total symptom scores shown on a graph, with significant differences between treatment vs. no-treatment control group (p = 0.0107) and between treatment and placebo (p = 0.0224).	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: No Intention-to-treat: No Notes:

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Hirsch, Kalbfleisch, and Cohen, 1982	Design: RCT, parallel-group (matched-pairs design) (see Notes) Interventions: 1) Standard immunotherapy using glycerinated aqueous ragweed extract (n = 20). Weekly injections given from early March through late April, then twice weekly through mid-August. Maintenance injections (schedule not described) given through 1st week of October. Dose increased to tolerance, limited only by local reactions. Mean cumulative dose 5,391 PNU (20.1 µg of antigen E). 2) Placebo (glycerinated caramelized histamine) (n = 14) Duration of study treatment: 7 months (early March to early October) Symptomatic medication permitted: Not described Dates: 1980 Location: Milwaukee, WI Setting: University-based clinic Type(s) of providers: Specialist	No. of subjects at start: 34 Dropouts/withdrawals: Variable number of subjects at weekly assessment shown in primary data table. No. of subjects at end: 32 Inclusion criteria: History of allergic nasal and ocular symptoms of allergic rhinitis without asthma during August and September for 2+ years; positive skin test Exclusion criteria: Immuno-therapy during last 2 years, except for subjects who participated in a previous trial in 1979; positive mold skin test; positive dust mite skin tests Age: Active 26-64 mean 40.7 Placebo 17-64 mean 38.6 Sex: Active 13M/7F Placebo 9M/5F Race: NR Other: Several patients in the trial participated in an IT trial in the prior year. These subjects were not re-randomized in this trial but received active treatment or placebo according to what was received in the previous trial.	1) Adverse reactions 2) Patient-assessed symptom severity: unidentified symptoms recorded daily “for several weeks before, during, and after” pollen season 3) Use of symptomatic medication: recorded daily “for several weeks before, during, and after” pollen season 4) Physical exam score 5) Allergen-specific IgE antibody levels	1) Adverse reactions: 10% of subjects in each group experienced local reactions. No systemic reactions. Two subjects in placebo group had flushing and palpitations for 10-15 minutes after the injection. 2) Patient-assessed symptom severity: Mean weekly symptom scores for the 6 weeks in which pollen was present were significantly lower in the treatment group during 5 of 6 weeks (active vs. placebo): Week 1) 12.6 ± 16.0 vs. 30.9 ± 23.5; $p < 0.02$ Week 2) 34.9 ± 22.6 vs. 51.6 ± 28.3; ns Week 3) 37.8 ± 21.8 vs. 62.7 ± 23.7; $p < 0.01$ Week 4) 33.0 ± 18.5 vs. 59.4 ± 33.4; $p < 0.02$ Week 5) 18.1 ± 16.1 vs. 39.2 ± 22.3; $p < 0.01$ Week 6) 17.4 ± 18.9 vs. 34.4 ± 19.3; $p < 0.025$ Mean symptoms (6 weeks of exposure): Active 24.8 ± 15.1; placebo 45.9 ± 18.6; $p < 0.005$ 3) Use of symptomatic medication: Medication scores were significantly different during 2 of the 6 exposure weeks. Data presented as mean weekly scores with SD. 4) Physical exam score: Not abstracted 5) Allergen-specific IgE antibody levels: Not abstracted	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: No Double-blind: Yes Blinding adequate: Yes Dropouts described: No Intention-to-treat: No Note: 8/20 patients in the ragweed group and 8/14 in the placebo group had participated in an earlier controlled trial of ragweed vs. placebo (Hirsch, Kalbfleisch, Golbert, et al., 1981 [status?; patients were from Milwaukee 1979 ragweed trial]). These patients continued to receive extracts of same allergen as before (ragweed or placebo), though using a different protocol. Newly recruited patients (n = 18) were randomized to treatment. Results abstracted here for 1980 trial only (SIT [Tr] vs. placebo), and not for SIT vs. RIT comparisons (1980 vs. 1979).

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Hirsch, Kalbfleisch, Golbert, et al., 1981	Design: RCT (?), parallel-group (matched-pairs design) Interventions: 1) Rinkel injection therapy using glycerinated aqueous ragweed, grass, or mountain cedar pollen extracts (n = 81). "Optimal dose" determined for each patient based on skin test by serial dilution titration and patient's clinical status. Optimal dose usually reached in 6-8 injections given at weekly intervals; maintenance injections then given weekly. Total mean cumulative dose 18.6 PNU. 2) Placebo (glycerinated caramelized histamine) (n = 74) Duration of study treatment: Each treatment seems to have been given "for several weeks before, during, and after" a single pollen season during 1978 and/or 1979 Symptomatic medication permitted: Not described Dates: 1978-79 Location: Multiple centers in US (Milwaukee; Yonkers, NY; Denver; Charleston; Washington, DC; San Antonio) Setting: Private allergy practices	No. of subjects at start: NR Dropouts/withdrawals: NR No. of subjects at end: 155 Inclusion criteria: 15+ years of age; two successive seasons of allergic rhinitis; no immunotherapy in previous 2 years Exclusion criteria: History suggestive of mold, house dust, or food allergies Age: Active 19-70 mean 38.2 Placebo 14-63 mean 35.6 Sex: Active 44M/37F Placebo 44M/30F Race: NR Other:	1) Patient-assessed symptom severity: unidentified symptoms recorded daily "for several weeks before, during, and after" pollen season 2) Use of symptomatic medication: recorded daily "for several weeks before, during, and after" pollen season 3) Physical exam score 4) Allergen-specific IgE antibody levels	Results were reported separately for multiple sites, seasons, and allergens; results summarized below are pooled results for all sites/seasons/allergens. 1) Patient-assessed symptom severity: Dot plots comparing active and placebo treatments are shown with lines designating mean and median symptom scores. Text describes differences as not significant. 2) Use of symptomatic medication: Dot plots comparing active and placebo treatments are shown with lines designating mean and median medication scores. Text describes differences as not significant. 3) Physical exam score: Not abstracted 4) Allergen-specific IgE antibody levels: Not abstracted	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: No Allocation concealed: Yes Double-blind: Yes Blinding adequate: Yes Dropouts described: No Intention-to-treat: Can't determine Notes: Not absolutely clear whether randomized or not.

(continued on next page)

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	Type(s) of providers: Specialists				
Horst, Hejjaoui, Horst, et al., 1990	Design: RCT, parallel-group Interventions: 1) Lyophilized and standardized mold (*Alternaria*) extract (n = 13). Two-day rush protocol used to initiate therapy (6 injections increasing from 40 to 2,000 BU and from 1/10,000 to 1/1,000 weight-by-volume). Maintenance injections of 2,000 BU each given every week for first 6 weeks after rush protocol, then every 2 weeks for 1 year. 2) Placebo (0.9% NaCl, 0.4% phenol, and 0.5 to 0.05 mg histamine dihydrochloride) (n = 11) Duration of study treatment: 1 year Symptomatic medication permitted: For asthma: inhaled and oral sympathomimetics, theophylline, bronchial disodium cromoglycate, ketotifen, and inhaled and system corticosteroids. For rhinoconjunctivitis: nasal and ocular disodium cromoglycate, beclomethasone, terfenadine, ketotifen, and oral steroids. Dates: Oct-Dec, 1986 Location: France	No. of subjects at start: 24 Dropouts/withdrawals: 2 placebo patients dropped out after 6 and 8 months. One for social reasons, one for lack of efficacy. No. of subjects at end: 22 Inclusion criteria: Clinical history of rhinitis ± asthma; perennial symptoms with possible seasonal exacerbation in summer and autumn; positive prick skin test to *Alternaria*; positive RAST to *Alternaria*; no other perennial allergy; negative skin tests and RAST to dust mite; exclusive mold sensitivity Exclusion criteria: Prior immunotherapy Age: 5-56 years Sex: Active 9M/4F Placebo 8M/3F Race: NR Other: 38-45% with asthma	1) Adverse reactions 2) Patient global assessment of efficacy: At end of 1st year, patients asked to grade efficacy of treatment on visual analog scale from 0% (complete failure) to 100% (total success) 3) Patient-assessed symptom severity and use of symptomatic medication (combined in a single measure): patients graded asthma and rhinoconjunctivitis symptoms and medication daily on scale of 0-3 4) Skin reactivity 5) Nasal reactivity 6) Allergen-specific IgE and IgG antibody levels	1) Adverse reactions: 2 patients with asthma exacerbation in active group. No systemic reactions in placebo group. 2) Patient global assessment of efficacy: Active 76.5 ± 27.9% Placebo 39.5 ± 30.4% p < .001 3) Patient-assessed symptom severity and use of symptomatic medication (combined in a single measure): 3 patients in active and 1 in placebo group did not complete symptom diary Global symptoms: active 0.84 ± 0.93 vs. placebo 3.55 ± 2.00 (p < 0.005) Rhinitis: active 0.64 ± 0.83 vs. placebo 2.65 ± 1.89 (p < 0.005) 4) Skin reactivity: Not abstracted 5) Nasal reactivity: Not abstracted 6) Allergen-specific IgE and IgG antibody levels: Not abstracted	Quality Scoring: Population similar: Not adequately described Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: No Note: Because most subjects were sensitized to multiple perennial allergens, the authors note that 6,000 subjects were screened to identify 50 potential subjects. Significant for generalizability.

(continued on next page)

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	Setting: Hospital-based pulmonary clinic Type(s) of providers: Specialists				
Iliopoulos, Proud, Adkinson, et al., 1991	Design: RCT, parallel-group (matched-pairs design) Interventions: 1) Short ragweed extract prepared by professional lab (n = 21). Initial dose equivalent to 0.0024 µg Amb a 1 (antigen E). Injections of gradually increasing strength given weekly until maintenance dose (equivalent to 1.92 µg Amb a 1) achieved (3 months). Maintenance injections then administered biweekly through final nasal challenge test (2 months after end of 1986 pollen season). Cumulative dose approximately 24 µg Amb a 1. 2) Placebo (vehicle + histamine) (n = 20). Increasing doses of histamine administered to simulate local reactions in treated group. Duration of study treatment: ~10 months; immunotherapy started Feb 1986 and continued until 2 months after end of pollen season Symptomatic medication permitted: Not described Dates: 1986 ragweed season	No. of subjects at start: 41 Dropouts/withdrawals: NR No. of subjects at end: Presumably 41 Inclusion criteria: Ragweed hay fever history; positive skin test to ragweed Exclusion criteria: None specified Age: NR Sex: NR Race: NR Other:	1) Patient-assessed symptom severity and medication use (combined in single measure): unspecified symptoms and medication use recorded in study diaries during pollen season (mid-Aug to mid-Oct); scoring system used not described 2) Allergen-specific IgE and IgG antibodies 3) Adverse reactions 4) Nasal reactivity 5) Skin reactivity	1) Patient-assessed symptom severity and medication use (combined in single measure): Significantly less symptoms in treated group ($p < 0.04$). Data not given. No baseline differences (data not shown). 2) Allergen-specific IgE and IgG antibodies: Not abstracted 3) Adverse reactions: 6/21 systemic reaction with wheezing, coughing, hives, stuffy/runny nose. 4/6 required epinephrine. One subject had lip swelling. 4) Nasal reactivity: Not abstracted 5) Skin reactivity: Not abstracted	Quality Scoring: Population similar: Not adequately described Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 1b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: Yes Notes:

(continued on next page)

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	Location: Baltimore, MD Setting: Univ allergy practice Type(s) of providers: Specialists				
Juniper, Kline, Ramsdale, et al., 1990	Design: RCT, parallel-group (matched-pairs design) Interventions: 1) Modified ragweed tyrosine adsorbate (Pollinex®-R), an aqueous extract of short ragweed pollen (n = 30). Four 0.5-ml injections of increasing strength (110, 250, 710, and 2100 PNU/0.5 ml) given during the 6 weeks before the start of the ragweed pollen season. 2) Budesonide aqueous nasal spray (n = 30). 100 µg given twice daily into each nostril beginning 1 week before the start of ragweed pollen season and continuing for a total of 7 weeks (encompassing entire pollen season). Duration of study treatment: 12 weeks: 6 weeks of pre-season immunotherapy overlapping at end with 1st week of nasal spray, plus 6 additional weeks of nasal spray Symptomatic medication permitted: Terfenadine 60 mg, up to 240 mg per day;	No. of subjects at start: 60 Dropouts/withdrawals: After randomization, 3 withdrew (one joined military, one with chicken pox, one with severe asthma exacerbation requiring corticosteroids) 1 IT subject withdrew after 1st dose because of systemic reaction, 5 in IT group withdrew after 1st injection, 1 after 2nd injection and 7 after 3rd dose because of large local reactions. Seven patients completed all 4 injections. 1 patient in med group had systemic symptoms after 2nd injection and withdrew. 8 from IT group withdrew during pollen season. All for uncontrolled symptoms. No. of subjects at end: Not clear. 30 med and 27 IT analyzed. Inclusion criteria: Moderate to severe rhinoconjunctivitis during ragweed season for at least 2 years; positive skin test to ragweed; no more mild skin test reactivity to fungal spores Exclusion criteria: Perennial rhinitis; polyps; chronic nasal obstruction; serious illness; inhaled or oral corticosteroids for	1) Patient-assessed symptom severity: severity and duration of sneezing, stuffy nose, runny nose, itchy nose, and eye symptoms graded daily on scale of 0 (none) to 3 (severe/ continuous) 2) Use of symptomatic medication: amount of terfenadine and eye drops used recorded daily 3) Adverse reactions: recorded during clinic visits at 1, 3, and 7 weeks after starting nasal spray	1) Patient-assessed symptom severity: Mean daily symptom scores significantly better in med group vs IT group: Sneezing $p < 0.0001$, stuffy nose $p < 0.0001$, runny nose $p = 0.0004$, itchy nose $p = 0.0008$. Numbers not given. Eye symptoms: no difference 2) Use of symptomatic medication: Terfenadine use higher in IT group: $p < 0.0001$ Eye drop use: no difference 3) Adverse reactions: Number of subjects (IT v Med): Headache 6 v 9 Nasal irritation 4 v 4 Drowsiness/fatigue 1 v 2 Injection reaction leading to withdrawal 13 v 1	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 1b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: Yes Note: Double-dummy blinding technique employed.

(continued on next page)

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	naphazoline HCl with pheniramine maleate eye drops, one drop in each eye, up to 4 times per day; salbutamol inhaler, 200 µg, up to 800 µg daily Dates: 1988 ragweed season Location: Hamilton, Ontario Setting: Univ hospital clinic Type(s) of providers: Specialists	1 month prior to enrollment; IT in prior 12 months; pregnant or lactating women Age: Mean 43.5 IT, 45.8 med Sex: 14 F/30 IT, 16 F/30 med Race: NR Other:			
Krouse and Krouse, 2000	Design: RCT, parallel-group (matched-pairs design) Interventions: 1) Experimental group: twice weekly immunotherapy injections in an accelerated protocol over 6 months (n = 5). Injections consisted of active serum containing all specific positive antigens identified in pre-study skin end-point titration, including all of the 3 study antigens (oak, short ragweed, and *D. pteronyssinus* [house dust mite]) to which they tested positive. 2) Control group: twice weekly immunotherapy injections in an accelerated protocol over 6 months (n = 5). Injections consisted of active serum containing all specific positive antigens identified in pre-study skin end-point titration, *except for*	No. of subjects at start: 18 Dropouts/withdrawals: 8 failed to complete 6-month study No. of subjects at end: 10 (5 each group) Inclusion criteria: Symptoms of rhinosinusitis; positive skin prick test to short ragweed and oak or *D. pteronyssinus* Exclusion criteria: ?? Age: 42.4 A, 57.8 P Sex: NR Race: NR Other:	1) Patient-assessed disability: assessed using the Rhinosinusitis Disability Index (RSDI) and the Sino-Nasal Outcome Test-16 (SNOT-16), completed before and after treatment 2) Patient-assessed symptom severity: assessed using the Sinus Symptom Questionnaire (SSQ), completed before and after treatment 3) Nasal endoscopy (purulent rhinorrhea, mucosal erythema nasal obstruction, and nasal edema) 4) Nasal reactivity	1) Patient-assessed disability: Significant difference in Emotional Scale Score of RSDI 2) Patient-assessed symptom severity: Not significant. 3) Nasal endoscopy: Not abstracted 4) Nasal reactivity: Not abstracted	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: Yes Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: No Notes: No outcomes based on daily recording of symptoms. No standardization of experimental intervention. No restrictions on concomitant use of other medications, *(continued on next page)*

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	the 3 study antigens (oak, short ragweed, and *D. pteronyssinus* [house dust mite]). Duration of study treatment: 6 months Symptomatic medication permitted: Patients "able to use whatever adjuvant therapies they chose to assist them with managing their symptoms" Dates: NR Location: Florida Setting: Community ENT practice Type(s) of providers: Specialist-ENT				including steroids, which could have a substantial effect on symptoms.
Leynadier, Banoun, Dollois, et al., 2001	Design: RCT, parallel-group Interventions: 1) Purified, standardized, calcium phosphate-adsorbed allergen extract composed of equal parts of five grass pollens (orchard, meadow, rye, sweet vernal, and timothy) (n = 16). Build-up phase: 16 weekly injections given in increasing doses (0.01 IR to 30 IR). Maintenance phase: injections given once every 2 weeks before the beginning of pollen season, then once a month during pollen season (with a 50% reduction in	No. of subjects at start: 29 Dropouts/withdrawals: 2 No. of subjects at end: 27 Inclusion criteria: Allergy to grass pollen; typical symptoms of rhinoconjunctivitis during the grass pollen season from May to July; positive skin prick test to 5 grass pollen extracts (wheal > 5 mm); serum grass pollen specific IgE antibody levels > class 2, as determined by RAST; positive grass pollen nasal provocation test Exclusion criteria: Specific	1) Patient-assessed symptom severity: sneezing, blocked nose, running nose, itching nose, red eyes, itching eyes, tearing eyes, coughing, wheezing, and breathlessness graded daily during allergy season on scale of 0-3 (not described) 2) Use of symptomatic medication: scored daily during allergy season, as follows: Each levocabastine eye drop or puff of salbutamol or beclomethasone: 1	1) Patient-assessed symptom severity (area under curve): Total symptoms: IT 49.5 Placebo 56 Difference 6.4 (-18.6 to 31.5; p = NS) Nose: IT 33.5 Placebo 38.6 Difference 5.1 (-12.7 to 23.1; p = NS) Eyes: IT 16.0 Placebo 17.3 Difference 1.2 (-8.6 to 11.2; p = NS) 2) Use of symptomatic medication: IT: 11.1	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: Not adequately described Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Not described Dropouts described: Yes Intention-to-treat: No *(continued on next page)*

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	volume of solution injected). Dose/schedule modifications "allowed for medical indications according to the routine specific immunotherapy procedure." 2) Placebo (diluent, no histamine) (n = 13). Duration of study treatment: 1 year Symptomatic medication permitted: Antihistamines (levocabastine eye drops and cetirizine 10 mg tablets) and inhaled ß-agonist (salbutamol) permitted on regular basis; max of 2 short courses of betamethasone (0.5 mg) could be prescribed during pollen season if symptoms not controlled by antihistamines; inhaled beclomethasone (250 µg) permitted in case of severe asthma Dates: Sep 1997 to Sep 1998 Location: France Setting: NR Type(s) of providers: NR, but presumably allergists	immunotherapy during last 5 years; perennial rhinitis; severe seasonal asthma; patients receiving systemic corticosteroids; contraindications to immunotherapy Age: 30 (range 18-44 years) Sex: 15 women; 14 men Race: NR Other:	Each cetirizine tablet: 2 Each betamethasone tablet: 3 3) Nasal reactivity 4) Skin reactivity 5) Specific IgE and IgG4 levels 6) Adverse reactions	Placebo: 40.8 Difference 29.6 (6.5 to 52.7; p = 0.005) 3) Nasal reactivity: Not abstracted 4) Skin reactivity: Not abstracted 5) Specific IgE and IgG4 levels: Not abstracted 6) Adverse reactions: Local reactions (swelling and erythema > 5 cm at injection site): IT 6/16 Placebo 0/13 Systemic reactions (mild exacerbations of rhinoconjunctivitis and urticaria): IT 7/16 Placebo 2/13	Notes:

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Leynadier, Herman, Vervloet, et al., 2000	Design: RCT, parallel-group Interventions: 1) Standardized natural rubber latex extract (n = 9). Treatment started with a 2-day course of rush immunotherapy in hospital (doses progressing from 0.001 IR to 2 IR). First month thereafter, weekly injections of gradually increasing doses given. Maximum tolerated dose achieved within 2 months, with maintenance doses given every month thereafter. 2) Placebo (no histamine) (n = 8) Duration of study treatment: 1 year Symptomatic medication permitted: antihistamines, cromones, short-acting ß$_2$-agonists, or inhaled cortiocosteroids Dates: Enrollment 1995-1997 Location: France Setting: Hospital-based clinics Type(s) of providers: Specialists	No. of subjects at start: 17 Dropouts/withdrawals: 3 in placebo group: 1 underwent surgery, 1 withdrew consent, 1 lost to followup. No. of subjects at end: 14 Inclusion criteria: Rhinitis and cutaneous allergy to latex demonstrated by skin test and specific IgE Exclusion criteria: Clinically significant dust mite allergy; animal allergy if pet lived in home; severe asthma; immunotherapy for another allergen Age: 22-41 years Sex: 1M/16F Race: NR Other:	1) Patient-assessed symptom severity: symptoms of rhinitis (rhinorrhea, nasal itching, nasal blockage, sneezing), conjunctivitis (tearing, itching, edema, erythema), and cutaneous signs (pruritus, urticaria, eczema) graded weekly on scale of 0 (absent) to 3 (intolerable); asthma symptoms also graded weekly on scale of 0 (absent) to 3 (asthma attack making patient unable to perform everyday activities) 2) Use of symptomatic medication: quantities consumed each week recorded ; doses scored as follows: 1 point: local antiallergic treatment or puff of ß$_2$-agonist; 2 points: antihistamine tablet; 2.5 points: inhaled corticosteroid equivalent to 250 µg beclo-methasone; 18 points: corticosteroid tablet equivalent to 20 mg prednisolone 3) Conjunctival reactivity 4) Adverse reactions	1) Patient-assessed symptom severity: Rhinitis scores: Baseline (active vs. placebo) 2.8 ± 2.15 vs. 4.8 ± 1.85 6 months (active vs. placebo) 1.6 ± 2.9 vs. 4.0 ± 2.11 ($p < 0.04$) 12 months (active vs. placebo) 0.9 ± 1.22 vs. 2.9 ± 2.26 2) Use of symptomatic medication: Line graph shown. Calculated area under the curve showed ratio of active to placebo of 21%, indicating 79% improvement. 3) Conjunctival reactivity: Not abstracted 4) Adverse reactions: Half of patients in active group with local reaction. Active vs. placebo (%) Rhinitis: 15.2 vs. 5.6 Conjunctivitis: 10.4 vs. 2.0 Asthma attack: 2.7 vs. 0.8 Pharyngeal edema: 1.2 vs. 0 Giant urticaria: 1.2 vs. 0 Angioedema: 0.6 vs. 0 Hypotension: 0.3 vs. 0.4 Other 14.9 vs. 4.4	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: No Note: No histamine in placebo injections.

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Lichtenstein, Norman, and Winkenwerder, 1968	Design: RCT, parallel-group (matched-pairs design) (see Notes) Interventions: 1) Immunotherapy using ragweed antigen E (n = 24 at start; 22 included in analysis). Injections given weekly for 14 weeks. Dosage "based on the patient's tolerance to the injections;" total dose ranged from 16.9 to 800 µg antigen E (mean: 285.5 µg). 2) Placebo (dilutions of buffer containing 0.5 mg histamine/ml (n = 24 at start; 18 included in analysis). Duration of study treatment: Injections given over 14 weeks; symptoms monitored for one allergy season (early Aug to early Oct) Symptomatic medication permitted: Chlorpheniramine 4 mg or tripellenamine 50 mg; no corticosteroid therapy required Dates: 1965-66 Location: Baltimore, MD Setting: Academic allergy clinic Type(s) of providers: Specialists	No. of subjects at start: 48 Dropouts/withdrawals: 2 dropouts and incomplete clinical data on 6 others No. of subjects at end: 40 Inclusion criteria: Hay fever symptoms during ragweed season Exclusion criteria: NR Age: NR Sex: NR Race: NR Other:	1) Blocking antibody levels 2) Cell sensitivity (amount of antigen E required to evoke a 50% response from leukocytes) 3) Patient-assessed symptom severity and use of symptomatic medication (combined in a single measure): sneezing, stuffy/runny nose, red/itchy eyes, and coughing graded daily during allergy season on scale of 0 to 3 (not described); number of antihistamine tablets taken recorded daily and "added to the symptom score" 4) Investigator-assessed symptom severity 5) Adverse reactions	1) Blocking antibody levels: Not abstracted 2) Cell sensitivity: Not abstracted 3) Patient-assessed symptom severity and use of symptomatic medication (combined in a single measure): Average symptom score 7.2 active vs. 9.8 placebo. Table presents symptom scores for matched pairs. Average peak season symptom in active group 6.5 vs. placebo group 9.8 ($p < 0.01$ Wilcoxon signed rank test) 4) Investigator-assessed symptom severity: Not abstracted 5) Adverse reactions: 11 experienced local reactions in active group; 1 with systemic reaction of hives and wheezing.	Quality Scoring: Population similar: Not adequately described Intervention(s) described: No Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: No Blinding adequate: Not applicable Dropouts described: Yes Intention-to-treat: No Notes: 10/24 patients in the antigen-E group and 10/24 in the placebo group were recruited from a previous trial (Lichtenstein, Norman, Winkenwerder, et al., 1966, below). All continued with the therapy to which they were assigned in the earlier trial, except two patients who had been receiving crude ragweed extract, who were assigned to the antigen-E group. Only newly acquired patients (n = 28) were randomized to treatment.

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Lichtenstein, Norman, and Winkenwerder, 1971	Design: RCT, parallel-group Interventions: 1) Whole or crude ragweed pollen extract, supplied as a lyophilized powder for reconstitution (n = 19). Initial dose 0.012 µg (0.2 PNU). Further dosing schedule described below. Mean cumulative dose 0.55 mg protein (8800 PNU) in 26.7 injections. 2) Antigen E, prepared by professional lab (n = 18). Initial dose 0.02 µg protein. Further dosing schedule described below. Mean cumulative dose 1.0 mg in 23.1 injections. 3) Antigens E + K (in 2:1 ratio), prepared by professional lab (n = 21). Initial dose 0.02 µg protein. Further dosing schedule described below. Mean cumulative dose 1.4 mg in 23.7 injections. 4) Placebo (diluent with histamine) (n = 21). Dilutions prepared from 0.5 mg/ml histamine base, so that graded increase in local reaction was attained as dose was increased. All treatments: Injections given every week beginning Mar 6. Doses doubled each week, unless local or systemic reactions warranted a slower	No. of subjects at start: NR Dropouts/withdrawals: "Few" (actual numbers NR) No. of subjects at end: 88 Inclusion criteria: Questionnaire data suggesting allergic rhinitis Exclusion criteria: NR Age: NR Sex: NR Race: NR Other:	1) Adverse reactions 2) Patient-assessed symptom severity: unspecified symptoms recorded daily in study diaries during ragweed season; method of scoring not described 3) Blocking antibody levels 4) Leukocyte histamine release	1) Adverse reactions: One moderate to severe local reaction per patient. Systemic reactions 1.6 per patient with crude extract vs. 0.4 per patient with purified. 2) Patient-assessed symptom severity: Treatment groups had symptom scores 35-40% lower than placebo. No mean given. Average seasonal symptom scores estimated at 11 for placebo group and 7-7.5 for treatment groups. Scatter-gram given with means. $P < 0.01$ 3) Blocking antibody levels: Not abstracted 4) Leukocyte histamine release: Not abstracted	Quality Scoring: Population similar: Not adequately described Intervention(s) described: No Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: No Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: No Blinding adequate: Not applicable Dropouts described: No Intention-to-treat: No Note: Apparently only single-blinding.

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	increase. Near end of injection period (1st week of Aug), patients who had fallen behind in dosage because of adverse reactions received injections twice per week to increase total dose. Duration of study treatment: Approximately 8 months; injections given Mar 6 - 1st week of Aug; outcomes monitored through ragweed season (mid-Aug through mid-Oct) Symptomatic medication permitted: Not described Dates: 1968 ragweed season Location: Baltimore, MD Setting: Academic hospital allergy practice Type(s) of providers: Specialists				

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Lichtenstein, Norman, Winkenwerder, et al., 1966	Design: RCT, parallel-group (matched-pairs design) (see Notes) Interventions: 1) Crude ragweed pollen extract (n = 15). Given as 15 weekly injections. First injection 0.001 µg protein N; dose doubled every week provided previous dose had produced no reaction. Total dose ranged from 0.39 to 28.8 µg protein N, containing 0.15 to 11 µg antigen E (0.026 to 1.84 µg protein N). 2) Ragweed antigen E (n = 11). Given as 15 weekly injections. First injection 0.0003 µg protein N; dose doubled every week provided previous dose had produced no reaction. Total dose ranged from 4.0 to 61.7 µg antigen E (0.7 to 11.2 µg protein N). 3) Placebo (saline) (n = 15). Duration of study treatment: Injections given over 15 weeks; symptoms monitored for one allergy season (early August to late September) Symptomatic medication permitted: Dexchlor-pheniramine maleate 2 mg Dates: 1964 Location: Baltimore, MD	No. of subjects at start: 41 Dropouts/withdrawals: 7 Crude antigen group: 3 Antigen E group: 1 Control (placebo): 3 Only reason given was "various technical reasons". No. of subjects at end: 34 Inclusion criteria: Hay fever symptoms restricted generally to ragweed pollen season; "adequate" in vitro histamine release to ragweed antigen Exclusion criteria: Asthma Age: NR Sex: NR Race: NR Other:	1) Cell sensitivity (amount of antigen E required to evoke a 50% response from leukocytes) 2) Patient-assessed symptom severity and use of symptomatic medication (combined in a single measure): sneezing, stuffy/runny nose, red/itchy eyes, and coughing graded twice daily during allergy season on scale of 0 (no symptoms) to 3 (symptoms lasting more than 2 hours); number of antihistamine tablets taken recorded daily and added to the symptom score 3) Investigator-assessed symptom severity 4) Adverse reactions	1) Cell sensitivity: Not abstracted 2) Patient-assessed symptom severity and use of symptomatic medication (combined in a single measure): Graph showing symptom score vs. time given for each treatment group. Table with average daily symptom scores given. Differences not significant Control 3.7 (0.3-11.8) Crude antigen 3.0 (0.9-6.5) Antigen E 3.4 (1.1-7.3) 3) Investigator-assessed symptom severity: Not abstracted 4) Adverse reactions: 2/15 patients completed the full dose escalation for crude ragweed allergen. Doses limited by local injection site reactions. 4 subjects had systemic reactions (hives). 5/10 patients receiving antigen E achieved the highest dose level. 4 patients had local reactions and 1 patient had a systemic reaction. No data are given for AEs in the control group.	Quality Scoring: Population similar: Not adequately described Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Yes Double-blind: No Blinding adequate: Not applicable Dropouts described: Yes Intention-to-treat: No Notes: Patients were drawn from a larger trial (no publication cited). 11/41 had been receiving antigen E and continued with this therapy. Remaining 30 patients were randomly divided between crude ragweed and placebo groups.

(continued on next page)

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	Setting: Academic allergy practice Type(s) of providers: Specialists				
Lowell and Franklin, 1965	Design: RCT, parallel-group (matched-pairs design) Interventions: Recruited patients had all been receiving injections of "ragweed and other pollen extracts" for an unspecified period of time before the study started. Were then randomized to: 1) Continued treatment with same mixture of extracts (n = ?); or 2) Continued treatment with previous mixture of extracts *minus* ragweed-pollen extract (n = ?). Duration of study treatment: 8 months (early March to end of October) Symptomatic medication permitted: Not described Dates: 1963 Location: Boston, MA Setting: Hospital Allergy Clinic Type(s) of providers: Specialists	No. of subjects at start: 27 Dropouts/withdrawals: 3 No. of subjects at end: 24 Inclusion criteria: Symptoms of allergic rhinitis coinciding with 1962 ragweed pollen season ± prior or ongoing immunotherapy; absence of symptoms of AR at other times of the year Exclusion criteria: Pregnancy Age: NR Sex: NR Race: NR Other:	1) Patient- and investigator-assessed symptom severity: symptoms recorded daily by patients; these records reviewed and discussed with patient at each clinic visit, and consensus scores for duration and severity of symptoms reached by patient and investigator; sev erity of symptoms graded on numerical scale from 0 (none) to 100 (incapacitating) 2) Use of symptomatic medication: recorded daily by patients in study diaries 3) Total symptom-medication scores: combines above two measures	1) Patient- and investigator-assessed symptom severity: This is a joint score negotiated based upon discussion between patient and physician. Data presented as graph of symptoms over time. Data also presented as a Table with symptom scores compared between treated and untreated subjects each week. All values for symptom scores favored the treated group. Values were significant during the weeks corresponding to ragweed pollen exposure. 2) Use of symptomatic medication: Data presented as graph of medication score over time. Data also presented as a Table with medication scores compared between treated and untreated subjects each week. All values for medication scores favored the treated group. Values were significant during the weeks corresponding to ragweed pollen exposure. 3) Total symptom-medication scores: Data from symptom and medication scores merged. Week-by-week analysis shows statistical significance during weeks of presumed ragweed pollen exposure.	Quality Scoring: Population similar: Not adequately described Intervention(s) described: No Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: No Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Yes Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: No Notes: This is actually a withdrawal of therapy study. Pollen counts not performed during experimental period. Of a clinic population of 500 patients, only 27 met entry criteria.

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
McAllen, 1969	Design: RCT, parallel-group Interventions: 1) Alum-precipitated extract of pollens of 5 grasses (Allpyral G®) (n = 47). Given in nine weekly injections, with dose gradually increasing from 50 to 10,000 PNU. 2) Depot emulsion extract of pollens of 12 grasses (D-Vac®) (n = 40). Three injections of 750; 3,500; and 7,500 Noon units given at 4-week intervals. 3) Placebo (normal saline) (n = 23). Given in three injections at 4-week intervals. Duration of study treatment: Injections given over 9 or 12 weeks; outcomes measured during single pollen season Symptomatic medication permitted: "Tablets" and nasal decongestants Dates: Nov 1966 - Feb 1967 Location: London, UK Setting: Allergy clinic Type(s) of providers: Allergists	No. of subjects at start: 110 Dropouts/withdrawals: 19 No. of subjects at end: 91 Inclusion criteria: Symptoms of hay fever for at least 2 previous years; positive skin prick test to grass pollen extract Exclusion criteria: Age < 12 or > 60; symptoms outside months of May-July; perennial rhinitis; systemic corticosteroids; previous satisfactory response to antihistamine drugs Age: 26 years Sex: 60 women; 50 men Race: NR Other:	1) Patient global evaluation of efficacy: at end of pollen season, patients graded treatment as "satisfactory" or "unsatisfactory" 2) Patient-assessed symptom severity: unspecified symptoms graded daily during pollen season on scale of 0 (clear of symptoms all day) to 3 (severe symptoms which were not controlled by tablets or nasal decongestants) 3) Adverse reactions	1) Patient global evaluation of efficacy: ITT Completers alum extract: 30/47 30/41 depot emul: 21/40 21/30 placebo: 7/23 7/20 alum vs. placebo; p = 0.01 depot vs. placebo; p = 0.046 (chi-square test) 2) Patient-assessed symptom severity: Symptom-free days Alum: 35 Depot: 38.5 Placebo: 28.5 Alum vs. placebo: p = 0.087 Depot vs placebo: p = 0.038 Mean points count Alum: 54 Depot: 49 Placebo: 72 Alum vs. placebo: p = 0.074 Depot vs. placebo: p = 0.054 3) Adverse reactions: Generalized urticaria within 1 hour Alum 1 pt; depot 2 pts Asthma and rhinitis after 12 hours Alum 8 pt; depot 1 pt Small persistent nodules at injection site Depot 10 pts	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: No Dropouts described: Yes Intention-to-treat: Yes Notes: Placebo was normal saline rather than weak histamine solution; local reactions not reported, but this could have unblinded placebo patients.

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
McHugh and Ewan, 1992	Design: RCT, parallel-group Interventions: 1) House dust mite (*Dermatophagoides pteronyssinus*) extract (Pharmalgen®) (n = 30). Administered according to protocol described in Ewan, Alexander, Snape, et al., 1988 (above), and McHugh, Lavelle, Kemeny, et al., 1990 2) House dust mite extract (Allpyral®) (n = 20). Administered according to protocol described in McHugh, Lavelle, Kemeny, et al., 1990 3) Placebo (histamine dihydrochloride) (n = 30) Duration of study treatment: 12 months Symptomatic medication permitted: beclomethasone nasal spray, terfenadine, chlorpheniramine Dates: NR Location: Cambridge, UK Setting: Academic allergy unit Type(s) of providers: Specialists	No. of subjects at start: 80 (20 of 80 enrolled in single blind trial of an alternate agent) Dropouts/withdrawals: 2 in Pharmalgen group 1 in placebo 3 in Allpyral group Reasons not given No. of subjects at end: 74 Inclusion criteria: Described in prior publication. Patients had known allergy to dust mite with positive prick skin tests and nasal challenge studies. Exclusion criteria: NR Age: 15-72 Sex: 44M/36F Race: NR Other:	1) "Clinical index": composite measure derived from: a) visual analog symptom score; b) diary card symptom score; c) nasal challenge results; d) skin prick test results; e) medication score 2) Patient-assessed symptom severity: rhinitis symptoms (sneezing, discharge, and obstruction) graded a) daily (?) on visual analog score where 0% = asymptomatic and 100% = very severe; and b) twice daily on categorical scale of 0-3 (not described) 3) Nasal reactivity 4) Skin reactivity 5) Use of symptomatic medication: recorded daily on study diary cards	1) "Clinical index": Scores are baseline, 3 mo, 12 mo. Pharmalgen: 27.0, 42.5, 49.5 Placebo: 27.0, 32.5, 32.0 Allpyral: 27.0, 36.5, 38.0 Pharmalgen vs. placebo ($p < 0.002$ and $p < 0.001$ at 3 and 12 months) Allpyral vs. placebo ($p = 0.15$) Pharmalgen vs. Allpyral ($p < 0.006$) favoring Pharmalgen 2) Patient-assessed symptom severity: Comparison of baseline vs. 12 mo. SE shown Pharmalgen: 30.9 ± 4.0, 16.0 ± 2.7 Allpyral: 14.7 ± 4.1, 14.5 ± 3.2 Placebo: 28.8 ± 3.5, 22.4 ± 2.4 3) Nasal reactivity: Not abstracted 4) Skin reactivity: Not abstracted 5) Use of symptomatic medication: Comparison is 0 and 12 months. SE shown Pharmalgen: 1.42 ± 0.42, 0.19 ± 0.12 Allpyral: 0.94 ± 0.29, 1.05 ± 0.57 Placebo: 1.28 ± 0.55, 0.96 ± 0.37	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: No Allocation concealed: Not described Double-blind: No Blinding adequate: Not applicable Dropouts described: Yes Intention-to-treat: No Notes: Interim results for some patients (n = 38) in this trial reported in Ewan, Alexander, Snape, et al., 1988 (above).

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Mischler, O'Brien, Rugloski, et al., 1981	Design: RCT, parallel-group Interventions: 1) Gluteraldehyde-modified ragweed pollen tyrosine adsorbate (MRTA) (n = 177). Four weekly injections given in doses of 300; 700; 2,000; and 6,000 NU/0.5 ml. 2) Placebo (tyrosine suspension) (n = 189). Duration of study treatment: Injections given over 4 weeks; outcomes assessed for one allergy season. Symptomatic medication permitted: Chlorpheniramine maleate 4 mg supplied; however, "many patients also took medication on their own, without consent of their physician" Dates: 1976 Location: Eastern Canada Setting: Multicenter (presumably) allergy practices Type(s) of providers: Specialists (presumed)	No. of subjects at start: 366 (177 active, 189 placebo) Dropouts/withdrawals: 119 active 103 placebo No. of subjects at end: Completing injections and diary data: 58 active 86 placebo Inclusion criteria: Seasonal AR for 2+ years; positive skin test to ragweed Exclusion criteria: Pregnancy; chronic asthma or other respiratory disease; immunotherapy within 12 months Age: 266 adults (15-73, mean 32.8) 100 children (5-16, mean 11.2) Sex: 195M/171F Race: NR Other:	1) Patient-assessed symptom severity: sneezing, stuffy and/or runny nose, itchy eyes, and cough graded twice daily on scale of 0 (none) to 3 (lasted more than 2 hours) 2) Use of symptomatic medication: use of investigator-supplied antihistamine and (separately) other symptomatic meds recorded by patients in study diaries 3) Total symptom-and-medication score (combination of above measures, called "combined efficacy score" by investigators) 4) Allergen-specific IgE and IgG antibody levels 5) Adverse reactions	1) Patient-assessed symptom severity: Active vs. placebo Sneeze: 27.8 vs. 38.6 (ns) Nose: 40.7 vs. 56.9 (ns) Eye: 21.1 vs. 39.4 (p = 0.0183) Cough 4.3 vs. 8.1 (ns) 2) Use of symptomatic medication: Antihistamine: Active 9.9 vs. placebo 22.0 (p = 0.0352) Other medications: Active 71.3 vs. placebo 151.2 (p = 0.0646) 3) Total symptom-and-medication score (combination of above measures, called "combined efficacy score" by investigators): Active 181.1 vs. placebo 318.3 (p = 0.0154) 4) Allergen-specific IgE and IgG antibody levels: Not abstracted 5) Adverse reactions: 13% overall discontinued therapy because of late local reactions or sneezing and wheezing (n = 1).	Quality Scoring: Population similar: No Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 1b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: No Notes: Patients who participated in RCT phase (1st year) given opportunity to receive MRTA (in open fashion) during 2nd year. Symptom data reported for only 5/8 centers in 1976 phase of study. Data abstracted from from RCT phase (1976) only. High dropout rate.

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Movérare, Vesterinen, Metso, et al., 2001	Design: RCT, parallel-group Interventions: 1) Immunotherapy using extracts of birch (n = 26) or timothy (n = 4) pollen. Initial rush phase with standardized aqueous extracts (Aquagen®). Three injections given daily using gradually increasing doses up to highest tolerated dose at end of 1st week (target dose: 10,000 SQ). Treatment then continued with standardized depot preparations (Alutard®), given every 3 weeks in increasing doses until individual maintenance dose reached (target: 60,000 to 100,000 SQ). Maintenance dose continued every 3 weeks for 3 years. 2) No immunotherapy (n = 16). Duration of study treatment: 3 years (active treatment; see Notes) Symptomatic medication permitted: Not specified Dates: NR Location: Helsinki, Finland Setting: Allergology clinic Type(s) of providers:	No. of subjects at start: 46 Dropouts/withdrawals: 7 No. of subjects at end: 39 Inclusion criteria: History of birch- or timothy-pollen allergy; rhinitis or conjunctivitis during at least 3 pollen seasons; positive skin prick test to birch- or timothy pollen; specific serum IgE to birch or timothy pollen Exclusion criteria: NR Age: 20 years Sex: 21 women; 25 men Race: NR Other: 41 birch pollen 5 timothy grass pollen	1) Total IgE and allergen-specific IgE, IgG, and IgG4 antibody levels 2) Patient-assessed symptom severity: symptoms graded once per allergy season (pretreatment, 1st year, and 3rd year) on visual analog scale from 0 to 100 (not described) 3) Use of symptomatic medication: assessed two ways: a) graded once per allergy season (pretreatment, 1st year, and 3rd year) on visual analog scale from 0 to 100 (not described); and b) graded once every month from March to October of 1st year on scale of 0 (no use of medication) to 2 (regular use of medication) ("monthly medication index") 4) Adverse reactions	1) Total IgE and allergen-specific IgE, IgG, and IgG4 antibody levels: Not abstracted 2) Patient-assessed symptom severity: RIT 21.2 ± 19.5; n = 24 Control 39.0 ± 15.1; n = 11 P = 0.002 3) Use of symptomatic medication: a) Medication scores Year 1 RIT 20.4 ± 19.9; n = 24 Control 45.4 ± 23.3; n = 11 P = 0.0077 b) Average monthly med index RIT 1.59 ± 1.82 control 3.29 ± 1.77 p < 0.05 4) Adverse reactions: RIT – systemic reaction (fever after injection) 1 case; generalized urticaria 3 cases; mild asthmatic symptoms 1 case (all pts continued RIT at decreased dose)	Quality Scoring: Population similar: Not adequately described Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: No Blinding adequate: Not applicable Dropouts described: Yes Intention-to-treat: Can't determine Notes: No attempt at blinding. No outcomes based on daily recording of symptoms or medication use. Control patients offered active treatment after 1 year; those who accepted left the study. Five control patients followed up for 3 years. Imbalance in conjunctivitis symptoms at baseline. Year 3 data compromised by > 50% dropout rate in control group.

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Naclerio, Proud, Moylan, et al., 1997	Design: RCT, parallel-group Interventions: All included patients had been receiving maintenance immunotherapy with aqueous ragweed extract at a dose of approximately 12 µg of Amb a 1 (5000 AU) every 2 weeks for a minimum of 3 years when they entered trial. Then randomized to receive either: 1) Continued maintenance therapy (as above) (n = 10); or 2) Placebo maintenance therapy (saline mixed with histamine) (n = 10). Duration of study treatment: 1 year Baseline measurements taken during ragweed season before randomization (symptoms and antibody levels) and in December or early January immediately before randomization (nasal reactivity) Symptomatic medication permitted: Not described Dates: Year not given. Included one ragweed season. Location: Baltimore, MD Setting: Academic hospital clinic Type(s) of providers:	No. of subjects at start: 20 Dropouts/withdrawals: 0 No. of subjects at end: 20 Inclusion criteria: Receiving ragweed IT for 3+ years Exclusion criteria: Significant nasal abnormalities or pathology Age: NR Sex: NR Race: NR Other:	1) Nasal reactivity 2) Patient-assessed symptom severity and medication use (combined in a single measure): unspecified rhinitis symptoms and medication use recorded in daily diaries during ragweed season; scoring system not described 3) Allergen-specific IgE and IgG antibodies	1) Nasal reactivity: Not abstracted 2) Patient-assessed symptom severity and medication use (combined in a single measure): Data available for 16/20 (8 per group). No significant difference. Data could be interpreted from graph. Determined that study power would have allowed 90% chance to miss significant difference. 3) Allergen-specific IgE and IgG antibodies: Not abstracted	Quality Scoring: Population similar: Not adequately described Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate Yes Dropouts described: Yes Intention-to-treat: Yes Note: Does not provide efficacy data, since this was a withdrawal of therapy study with pre-determined laboratory endpoints.

(continued on next page)

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	Specialists				
Norman, Lichtenstein, Kagey-Sobotka, et al., 1982	Design: RCT, parallel-group (matched triplets) Interventions: Patients in all 3 treatment groups divided into "average" and higher-than-average" sensitivity groups. 1) Ragweed allergoid administered in a clustered regimen (n = 22 at start; 16 completed). "Average" sensitivity patients: 5 clinic visits totaling 11 injections. 1st visit, three injections at 30-min intervals in doses of 5, 10, and 20 allergoid units. Two injections given at each subsequent visit for cumulative projected dose of 1,925 units (168,000 PNU). Approximately 3 weeks between 1st and 2nd visit; 2-3 weeks between subsequent visits. "Higher-than-average" sensitivity patients: 6 clinic visits totaling 13 injections. 1st visit, three injections at 30-min intervals in doses of 0.5, 2, and 3 allergoid units. Two injections given at each subsequent visit for cumulative projected dose of 1,175.5 units (103,000 PNU). Approximately 3 weeks between 1st and 2nd visit; 2-3 weeks between subsequent visits. Mean cumulative dose actually administered 727 units (364µg AgE; 63,600 PNU).	No. of subjects at start: 66 Dropouts/withdrawals: 2 dropouts before completion of screening; then: 2 dropouts allergen group 6 dropouts allergoid group 5 dropouts placebo group No. of subjects at end: 53 completed first year Inclusion criteria: 3+ years of seasonal rhinitis; positive intradermal skin test to ragweed antigen Exclusion criteria: NR Age: NR Sex: NR Race: NR Other:	1) Adverse reactions 2) Patient-assessed symptom severity and use of symptomatic medication (combined in a single measure): duration of sneezing, rhinitis, conjunctivitis, and cough, and use of symptomatic medication recorded twice daily during allergy season 3) Cell sensitivity (amount of antigen E required to evoke a 50% response from leukocytes) 4) Total and allergen-specific IgE, and IgG-against-AgE antibody levels	1) Adverse reactions: Allergen group: All patients had at least one local reaction and "most" had multiple reactions. Large local reactions in 5 patients. Nine systemic reactions occurred in 8 patients who completed the injection series. Allergoid group: 11 systemic reactions in 5 patients. Similar incidence of large local reactions compared to allergen group. 2) Patient-assessed symptom severity and use of symptomatic medication (combined in a single measure): Analyzable data reported on 16 allergen, 16 allergoid and 20 placebo patients Mean score: Allergen 5.3 Allergoid 5.1 Placebo 8.8 Active vs. placebo ($p < 0.01$) 3) Cell sensitivity (amount of antigen E required to evoke a 50% response from leukocytes): Not abstracted 4) Total and allergen-specific IgE, and IgG-against-AgE antibody levels: Not abstracted	Quality Scoring: Population similar: Not adequately described Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: No Allocation concealed: Not described Double-blind: No Blinding adequate: Not applicable Dropouts described: Yes Intention-to-treat: No Notes: Assignment not described; may not have been random. Also, blinding not described. At end of initial trial, patients in allergoid and extract groups invited to continue with booster injections of same materials; results reported for this open follow-up.

(continued on next page)

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	2) Unaltered ragweed extract (glycerinated extract of short ragweed pollen) administered in a weekly regimen (n = 22 at start; 20 completed). "Average" sensitivity patients: 17 weekly injections, starting at 1.0 allergen unit and progressing to 500 units (1,200 PNU, for a projected cumulative dose of 2,083 units (5,000 PNU). "Higher-than-average" sensitivity patients: 20 weekly injections, starting at 0.1 allergen unit and progressing to 500 units, for a projected cumulative dose of 2,084 units. Mean cumulative dose actually administered 856 units (8.56 µg AgE; 2,000 PNU). 3) Placebo administered in a clustered regimen (n = 22 at start; 17 completed). Duration of study treatment: Varied, depending on treatment (see above); outcomes assessed during a single allergy season Symptomatic medication permitted: Antihistamine "and other medication" Dates: 1978 Location: Baltimore, MD Setting: University allergy clinic Type(s) of providers: Specialists				

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Ortolani, Pastorello, Incorvaia, et al., 1994	Design: RCT, parallel-group Interventions: 1) Alginate-conjugated extract of *Parietaria judaica* (wall pellitory) pollen (Conjuvac®-*Parietaria*) (n = 18). Extract used was biologically standardized and partially purified; 1 U of preparation represented 61.2 µg of pollen. Build-up phase: 12 weekly injections of increasing dose (1, 2, 4, 8, 10, 20, 40, 80, 100, 200, 400, and 800 U). Maintenance phase: top dose or maximum tolerated dose given at monthly intervals. 2) Placebo (lyophilized sodium alginate ± 5 µg histamine dihydrochloride) (n = 17) Duration of study treatment: 1 year Symptomatic medication permitted: Terfenadine tablets and salbutamol spray Dates: NR Location: Milan, Italy Setting: Academic internal medicine department Type(s) of providers: NR	No. of subjects at start: 35 (18 active, 17 placebo) Dropouts/withdrawals: 4 No. of subjects at end: 31 Inclusion criteria: Severe rhinoconjunctivitis ± asthma during *Parietaria* season for 2+ years; positive prick skin test to *Parietaria*; negative skin tests to grass, tree, weed, mite, mold, and pet allergens; positive RAST to *Parietaria* Exclusion criteria: Prior IT for *Parietaria;* other active respiratory diseases; nasal polyps; systemic corticosteroid use; pregnancy Age: Range, 14-59; mean, 41 Sex: 20 F Race: NR Other:	1) Patient-assessed symptom severity and medication use (combined in a single measure): eye (itching, redness, or weeping), nasal (sneezing, rhinorrhea, or blockage), and lung (cough, dyspnea, or asthma) symptoms graded daily on scale of 0-3 (not described); use of symptomatic medication recorded daily in study diaries 2) Nasal, conjunctival, and skin reactivity 3) Adverse reactions: recorded and described as local vs. systemic and immediate (within 30 minutes) vs. late 4) Allergen-specific IgE, IgG, IgG1, and IgG4 antibody levels	1) Patient-assessed symptom severity and medication use (combined in a single measure): Complete assessment on 17 active and 14 placebo patients who submitted diaries. Significantly lower S-M scores in active vs. treatment group ($p < 0.05$). Sub-symptom analysis showed significance for runny nose ($p = 0.0087$), sneezing ($p = 0.0488$), but not nasal blockage. No means or SDs given. 2) Nasal, conjunctival, and skin reactivity: Not abstracted 3) Adverse reactions: 16/18 active and 1/17 placebo patients had local reactions. 5/18 active and 2/17 placebo had systemic reactions. 5 rhinitis and 1 urticaria in active group. 2 rhinitis in placebo group. All but one reaction immediate. 4) Allergen-specific IgE, IgG, IgG1, and IgG4 levels: Not abstracted	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 1b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: No Intention-to-treat: No Notes:

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Parker, Whisman, Apaliski, et al., 1989	Design: RCT, parallel-group (matched-pairs design) Interventions: 1) Extract of *Juniperus ashei* (mountain cedar) pollen (n = 26). Extract prepared in a single lot by lab in Spokane, WA. "Conventional high-dose" protocol used, beginning with 0.1 ml of 1:50,000 wt/vol dilution and progressing by 0.05- to 0.1-ml increments until 0.5 ml was reached. A 10-fold higher concentration then administered in the same dosing increments until the highest tolerated dose or 0.5 ml of 1:50 wt/vol was reached. 1-3 injections per week given during build-up phase; weekly injections given during maintenance phase. 2) Placebo (carmelized glucose, HSA, and histamine phosphate) (n = 25) Duration of study treatment: NR No description of symptomatic medication permitted (if any) Dates: Jan-July 1987 Location: Lackland AFB, Tx Setting: Military hospital allergy clinic Type(s) of providers: Specialists	No. of subjects at start: NR Dropouts/withdrawals: NR No. of subjects at end: 51 Inclusion criteria: History consistent with *Juniperis* rhinoconjunctivitis; positive skin prick test to *Juniperis* Exclusion criteria: Age < 18; pregnancy; use of ß-blocker; IT within prior 5 years Age: 22-75 (mean 43.4 active, 47.1 placebo) Sex: 26 F Race: NR Other:	1) Patient-assessed symptom severity and medication use (combined in a single measure): itchy nose, nasal congestion, sneezing, nose blowing, itchy eyes or throat, wheezing, shortness of breath, chest tightness, and cough graded daily during the pollen season on scale of 1 to 5 (not described); use of symptomatic medication recorded daily in study diaries (scored as 1 point per standard dose) 2) Skin reactivity 3) Allergen-specific IgE, IgG1, and IgG4 antibody levels	1) Patient-assessed symptom severity and medication use (combined in a single measure): Mean score 57.0 active, 129.9 placebo (p = 0.0001). Individual data provided. 2) Skin reactivity: Not abstracted 3) Allergen-specific IgE, IgG1, and IgG4 levels: Not abstracted	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: No Blinding adequate: Not applicable Dropouts described: No Intention-to-treat: No Notes:

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Pastorello, Pravettoni, Incorvaia, et al., 1992	Design: RCT, parallel-group Interventions: 1) Alum-absorbed grass allergoid obtained by mild formalinization of a mixed grass-pollen extract (six grasses: *Dactylis glomerata, Festuca elatior, Holcus lanatus, Phleum pratense, Lolium perenne, Poa pratensis*) (n = 10). Treatment started in January. Weekly injections of increasing doses given to a top dose of 20,000 PNU or maximum tolerated dose. Weekly doses administered until mid-April, after which a 50% equivalent dose was given every 3 weeks as maintenance. Mean pre-seasonal cumulative dose 46,050 PNU (range, 20,700 to 54,500). Mean maximum dose administered in a single injection 16,250 PNU (range, 4500 to 20,000). 2) Placebo (caramel NF acid solution ± histamine hydrochloride [randomly added to approximately 50% of vials]) (n = 9) Duration of study treatment: 1 year Symptomatic medication permitted: Xylometazolin, terfenadine, and salbutamol Dates: Jan 1986 – Jun 1986 Location: Milan, Italy	No. of subjects at start: 19 Dropouts/withdrawals: NR No. of subjects at end: NR Inclusion criteria: Seasonal rhinoconjunctivitis for at least 3 years; positive skin prick test for a mix of grass pollen extracts with wheal at least twice area of wheal induced by 1 mg/ml histamine; negative SPT for other pollens (birch, hazel, alder, mugwort, and wall pellitory; positive RAST for grass pollen (at least class 3) Exclusion criteria: Previous specific IT with grass pollen extracts Age: 27.4 years (range 18-56) Sex: 12 women; 5 men Race: NR Other:	1) Adverse reactions 2) Patient-assessed symptom severity and medication use (combined in a single measure): unspecified nasal, conjunctival, and bronchial symptoms graded daily during pollen season on scale of 0-3 (not described); use of symptomatic medication scored daily during pollen season as follows: Nasal vasoconstrictor: 1 per drop Antihistamine: 1 per tablet ß-2-agonist: 1 per puff 3) Skin reactivity 4) Nasal reactivity 5) Allergen-specific IgE and IgG	1) Adverse reactions: IT group: Late local reactions 3/10 pts Late systemic reactions 1/10 pt Placebo group: No adverse reactions 2) Patient-assessed symptom severity and medication use (combined in a single measure): IT patient had significantly lower symptom and medication scores ($p < 0.01$). Data shown in figure of scores over time. 3) Skin reactivity: Not abstracted 4) Nasal reactivity: Not abstracted 5) Allergen-specific IgE and IgG: Not abstracted	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Not described Dropouts described: No Intention-to-treat: Can't determine Notes:

(continued on next page)

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	Setting: Allergy clinic Type(s) of providers: Allergists				
Pence, Mitchell, Greely, et al., 1976	Design: RCT, parallel-group Interventions: 1) Aqueous extract of *Juniperus sabinoides* (mountain cedar) pollen (n = 17). Extract prepared in a single lot by lab in Lenoir, NC. Build-up phase: gradually increasing doses given twice weekly, beginning with thousand-fold dilution of the full-strength concentration, until maintenance dose was reached. Maintenance phase: maintenance dose (6 mg of extracted pollen) given weekly. Total dose given ranged from 1 mg to 157 mg of extracted pollen, with mean dose of 58 mg. 2) Placebo (caramelized glucose with histamine added) (n = 15) Duration of study treatment: 1 year Symptomatic medication permitted: Antihistamines or antihistamine-decongestant combinations Dates: 1974-75 mountain cedar pollen season Location: Texas	No. of subjects at start: 40 Dropouts/withdrawals: 8 No. of subjects at end: 32 Inclusion criteria: History of seasonal hay fever or asthma during Nov-March; strongly positive intradermal skin test to mountain cedar pollen; not currently on IT Exclusion criteria: None specified Age: Active group 15-78, mean 37; placebo group 27-62, mean 44 Sex: Active 10 F/17 M, placebo 9 F/15 M Race: NR Other: 8 patients with prior IT. None to mountain cedar.	1) Patient-assessed symptom severity and medication use (combined in a single measure): presence and duration of stuffy/runny nose, sneezing, itchy/watery eyes, cough, and shortness of breath/wheezing recorded twice daily (persisted for ½ hour, ½ to 2 hours, or > 2 hours); use of symptomatic medication recorded daily in study diaries 2) Skin sensitivity 3) Allergen-specific IgE antibody levels	1) Patient-assessed symptom severity and medication use (combined in a single measure): Mean daily symptom-medication scores (± SD) were lower for treated patients (5.46 ± 3.22) than for control patients (8.83 ± 3.15) ($p < 0.01$) 2) Skin sensitivity: Not abstracted 3) Allergen-specific IgE levels: Not abstracted	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 1b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: No Note: SDs calculated from raw data presented in paper.

(continued on next page)

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	Setting: Military hospital allergy clinic Type(s) of providers: Specialists				
Pichler, Marquardsen, Sparholt, et al., 1997	Design: RCT, parallel-group Interventions: 1) Standardized extract of *Dermatophagoides pteronyssinus* and *D. farinae* (house dust mite) adsorbed to aluminum hydroxide (Alutard®) (n = 16). "Clustered rush protocol" used: 2-3 injections given at 30-min intervals during weekly visits until maintenance dose (100,00 SQ Units) reached; maintenance dose given every 8 weeks thereafter. 2) Placebo extract (n = 14) Duration of study treatment: 1 year (RCT phase); trial followed by 1-year period during which some (but not all) patients in the placebo group elected to receive active treatment Symptomatic medication permitted: Antihistamine-containing eye drops or nasal spray (levocabastine) and topical steroids (budesonide) for nasal or bronchial use were allowed freely Dates: Not given	No. of subjects at start: 33 Dropouts/withdrawals: 3 (non-compliance or pregnancy) No. of subjects at end: 30 Inclusion criteria: Typical history of perennial rhinopathy and/or asthma; positive prick ST to *D. pteronyssinus* and/or *D. farinae;* positive test for specific IgE to *D. pteronyssinus* and/or *D. farinae;* positive conjunctival or nasal provocation test with mixture of *D. pteronyssinus* and/or *D. farinae;* FEV1 >80% predicted Exclusion criteria: Immunologic or cardiovascular diseases; pregnancy; poor compliance; severe asthma (defined as requiring emergency treatment in last 3 years, nocturnal symptoms despite treatment in past 3 months, need for oral corticosteroids, asthma associated with aspirin or bisulfites); allergy to animal dander if exposed to animals Age: Active, 20-46 (mean 28.8); placebo, 20-42 (mean 31.7) Sex: Active, 5 F/10 M; placebo, 4 F/10 M	1) Adverse reactions 2) Skin reactivity 3) Conjunctival reactivity 4) Patient-assessed symptom severity: rhinitis and bronchial asthma "complaints" recorded daily during two 4-week periods and quantified on a visual analog scale, of which the length was measured 5) Bronchial hyperreactivity to methacholine 6) Use of symptomatic medication: recorded daily during two 4-week periods	1) Adverse reactions: 2 patients with local swelling > 8 cm. 3 patients with mild systemic reaction (rhinorrhea, broncho-spasm), 1 with late exacerbation of rhinoconjunctivitis, 2 with late increase in asthma symptoms. 1 with systemic symptoms requiring epinephrine. 2) Skin reactivity: Not abstracted 3) Conjunctival reactivity: Not abstracted 4) Patient-assessed symptom severity: Values based upon analysis of data from 30 patients because of missing data points. Rhinitis symptoms: Active: 22 before and 9 after (p = 0.0064) Placebo: 39.5 before and 28 after (p = 0.5762) Active vs. placebo before p = 0.1972 Active vs. placebo after p = 0.0383 Asthma symptoms: Active: 5.5 before and 3.5 after (p = 0.0140) Placebo: 13 before and 7 after (p = 0.8467) Active vs. placebo before p = 0.4551 Active vs. placebo after p = 0.0903 5) Bronchial hyperreactivity to methacholine: Not abstracted	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 1b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: No Intention-to-treat: No Notes:

(continued on next page)

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	Location: Switzerland Setting: Hospital allergy practice Type(s) of providers: Specialists	Race: NR Other: 10 asthmatics in active group and 8 in placebo group		6) Use of symptomatic medication: Use of b-agonists/inhaled corticosteroids (baseline v 1 year): Active: 8/11 v 4/8 Placebo: 4/9 v 2/6 Use of nasal corticosteroids (baseline v 1 year): Active: 5 v 2 Placebo: 2 v 2	
Radcliffe, Lampe, and Brostoff, 1996	Design: RCT, crossover Interventions: 1) Allergen-specific, low-dose immunotherapy using the maximum intradermally tolerated dose (MITD). MITD determined individually for each allergen and defined as 0.05 ml of the strongest concentration in a 1:5 dilution series that did not produce a positive intradermal wheal (positive = mean diameter ≥ 3 mm or more than 2 mm larger than wheal occurring with negative control). Skin-prick testing done to establish MITD for following allergens: house dust, house dust mite, mixed mold spores, cat dander, dog dander, mixed feathers, mixed grass pollen, histamine (positive control), and phenol + glycerin (negative control). Multiple-dose, multiple-allergen MITD injection solution prepared for each patient. Treatment consisted of daily self-administered subcutaneous injection of 0.2 ml of the solution.	No. of subjects at start: 39 Dropouts/withdrawals: 3 No. of subjects at end: 36 Inclusion criteria: Symptoms of perennial allergic rhinitis Exclusion criteria: Positive response to the negative control skin test; well controlled on drug therapy; lack of positive skin test to relevant allergen; nasal polyps Age: 16-66 mean 38.78 Sex: 16M/20F Race: NR Other:	1) Patient preference: patients asked at end of trial whether they had a preference for one treatment over another based on overall symptom improvement 2) Patient-assessed rhinitis symptom severity: nasal blockage, nasal discharge, postnasal drip, sneezing, and anosmia graded daily on scale of 0 (none) to 4 (severe) 3) Patient-assessed *non*-rhinitis symptom severity: assortment of CNS, respiratory, gut, musculo-skeletal, and skin symptoms also graded daily on scale of 0 (none) to 4 (severe) 4) Use of symptomatic medication: recorded daily in study diaries	1) Patient preference: 78% preferred active treatment (p = 0.006) 2) Patient-assessed rhinitis symptom severity: Total (active period vs. placebo period) Total symptoms: -6.81 vs. 1.03 p = 0.006 Nasal blockage -2.31 vs. 0.19 p = 0.02 Nasal discharge -1.86 vs. 0.47 p = 0.006 Postnasal drip -1.42 vs. 0.75 p = 0.02 Sneezing: -0.28 vs. -0.28 p = 1.00 Anosmia -0.94 vs. -0.11 p = 0.02 3) Patient-assessed *non*-rhinitis symptom severity: No data given 4) Use of symptomatic medication: No data given, as concurrent medication use minimal.	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Yes Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: No Note: This is a crossover study with intervention periods of 2 weeks. Carry-over effect very likely. Also, adequacy of blinding is an issue, with no histamine in the placebo vaccine.

(continued on next page)

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	2) Placebo (diluent [benzyl alcohol + saline] alone) Duration of study treatment: 2 weeks per treatment period (2-week run-in / 2 weeks treatment A / 2-week wash-out / 2 weeks treatment B) Symptomatic medication permitted: "mainly" oral antihistamines and nasal steroids; patients instructed to keep doses to minimum compatible with reasonable comfort Dates: NR Location: England Setting: University Clinic Type(s) of providers: NR				

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Rak, Heinrich, Jacobsen, et al., 2001	Design: RCT, parallel-group Interventions: 1) Standardized depot preparation of birch pollen allergen extract (Alutard® SQ) (n = 21). Treatment given before start of pollen season. Dosage schedule described in Nielsen et al. All patients reached the maintenance dose of 1 ml of 100,000 SQ and received a total of 120-150 µg of allergen before the start of the pollen season. 2) Budesonide nasal spray 200 µg in each nostril once daily in the morning (n = 20). Treatment started 2 weeks before the predicted start of birch pollen season and continued throughout the entire season (mid-April to end of May = 6 weeks). Duration of study treatment: Unclear for immunotherapy (1 pre-season); 6 weeks for nasal steroid; outcomes assessed just before and during one birch pollen season Symptomatic medication permitted: decongestant drops, local antihistamine drops (levocabastine), antihistamine tablets (acrivastine), and for asthmatics, salbutamol Dates: 1992-93	No. of subjects at start: 41 Dropouts/withdrawals: 0 No. of subjects at end: 41 Inclusion criteria: Rhino-conjunctivitis symptoms during birch pollen season; positive prick skin test to birch allergen; specific IgE antibody to birch pollen; if designated asthmatic, positive methacholine challenge test Exclusion criteria: Daily contact with animals in animal allergic subjects; patients with perennial rhinitis symptoms and/or positive skin test response to mites and molds Age: 19-42 mean 29 Sex: 22M/19F Race: NR Other:	1) Patient-assessed symptom severity: eye and nose symptoms graded on scale of 0 (no symptoms) to 3 (severe); recorded daily during three 1-week periods (winter [baseline], just before start of pollen season, and during pollen season) 2) Spirometry (morning and evening peak flow rates) 3) Use of symptomatic medication: recorded daily during three 1-week periods (winter [baseline], just before start of pollen season, and during pollen season); anti-rhinitis drugs scored as follows: decongestant drops, 0.5; acrivastine, 1; and levoca-bastine, 1.5; use of salbutamol assessed separately 4) Bronchial reactivity 5) Eosinophil measures (count, cationic protein, chemotactic activity)	1) Patient-assessed symptom severity: Mean daily symptom scores for combined eyes and nose shown on graph for each of the 6 weeks of pollen season. Numeric values not given. Values were significantly different favoring nasal steroids during weeks 5 and 6 ($p < 0.03$ and $p < 0.04$, respectively). 2) Spirometry: Not abstracted 3) Use of symptomatic medication: Composite medication scores shown on a graph. No significant differences between groups at any time point. 4) Bronchial reactivity: Not abstracted 5) Eosinophil measures: Not abstracted	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: Yes Note: Double-dummy blinding technique employed.

(continued on next page)

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	Location: Sweden Setting: ENT clinic in county hospital Type(s) of providers: Specialists				
Tari, Mancino, Ghezzi, et al., 1997	Design: RCT, parallel-group Interventions: 1) Alum-adsorbed *Parietaria judaica* (wall pellitory) pollen allergoid (Allergovit®) (n = 20). Pollen extracts standardized against a well-characterized, biologically standardized reference extract. Build-up phase: weekly injections of 0.1, 0.2, 0.4, and 0.8 ml of strength A preparation (1,000 TU/ml) (with slight variations for individual patients), followed by weekly injections of increasing concentrations of strength B preparation (10,000 TU/ml), to a maximum of 1.0 ml (mean cumulative dose of 24,500 TU). Maintenance phase: injections of half the maximum dose administered every 3-4 weeks. 2) Placebo (alum suspension colored with caramel NF acid) (n = 20) Duration of study treatment: 1 year (RCT phase); trial followed by 1-year open study during which all patients received active treatment No description of symptomatic	No. of subjects at start: 40 Dropouts/withdrawals: 1 placebo subject (noncompliance) No. of subjects at end: 39 Inclusion criteria: Clinical history of rhinitis to *Parietaria* ± asthma for 3+ consecutive years; positive prick ST to *Parietaria;* positive nasal provocation with *Parietaria;* positive *Parietaria*-specific IgE test Exclusion criteria: IT in previous 3 years; acute or chronic respiratory infections; active immunologic or systemic disease Age: Active, 20-46 (mean 33.65); placebo, 13-50 (mean 31.65) Sex: Active, 10 F/10 M; placebo, 10 F/10 M Race: NR Other: Asthma present in 14 active and 10 placebo patients	1) Patient-assessed symptom severity and medication use (combined in a single measure): nasal, conjunctival, and bronchial symptoms graded daily on 4-point severity scale (not described); "corresponding scores" compiled for medication use 2) Peak flow rates 3) Adverse reactions: all possible adverse reactions (immediate and late reactions, and systemic responses) were recorded by investigators and graded as mild, moderate, or severe 4) Nasal reactivity 5) Skin reactivity 6) Total IgE and allergen-specific IgE, IgG, IgG1, and IgG4 antibody levels 7) Lymphocyte populations	1) Patient-assessed symptom severity and medication use (combined in a single measure): Described as significant ($p \leq 0.05$) improvement in symptom score for active treatment group. No means or statistics given. 2) Peak flow rates: Not abstracted 3) Adverse reactions: Active: 9 immediate local reactions in 6 patients, and 9 late local reactions in 5 patients. 3 late systemic reactions in 2 patients. No anaphylaxis. Placebo: No local, systemic or anaphylactic reactions 4) Specific nasal reactivity: Not abstracted 5) Skin prick test: Not abstracted 6) Total IgE and allergen-specific IgE, IgG, IgG1, and IgG4: Not abstracted 7) Lymphocyte populations: Not abstracted	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 1b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: No Notes:

(continued on next page)

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	medication permitted (if any) Dates: 1989-90 Location: Italy Setting: Academic hospital allergy practice Type(s) of providers: Specialists				
Van Metre, Adkinson, Amodio, et al., 1980	Design: RCT, parallel-group Interventions: 1) Ragweed pollen extract, administered according to standard immunotherapy schedule (n = 15). 24 weekly injections given in gradually increasing doses (from 0.15 ml of a 1:312,500 concentration to 0.5 ml of a 1:20 concentration), as tolerated. Maintenance dose then given (?) through pollen season. 2) Ragweed pollen extract, administered by the Rinkel method (n = 23). "Optimal dose" determined for each patient based on skin test by serial dilution titration and patient's clinical status. This dose (normally 0.5 ml of the end-point dilution) achieved via a series of weekly injections of gradually increasing strength given from February 27 to August 31; maintenance injections then given weekly during ragweed season. Median cumulative	No. of subjects at start: 52 Dropouts/withdrawals: Text states that 15 patients randomized to placebo group which would have totaled 53 patients. However all data discuss 14 patients in placebo group. Possible typographic error in methods section? No. of subjects at end: 52 Inclusion criteria: History of seasonal rhinitis in Aug/Sept for 2 preceding years; positive skin test response to ragweed pollen extract and ragweed antigen E; positive in vitro leukocyte histamine release to ragweed pollen extract Exclusion criteria: Major rhinitis symptoms during mold season of July and Oct/Nov Age: 18-50 Sex: 39M/13F Race: NR	1) Patient-assessed symptom severity and medication use (combined in a single measure): calculated based on daily diary recordings, but symptoms recorded and method of scoring not described 2) Total IgE and allergen-specific IgE and IgG antibody levels 3) Patient global evaluation of efficacy of treatment: at end of trial, symptoms graded in comparison with those of previous year as "less severe," "same," or "more severe" 4) Adverse reactions	1) Patient-assessed symptom severity and medication use (combined in a single measure): Graph of symptom-medication score vs. time given. Mean daily scores reported as significantly lower in the standard treatment group compared to placebo or Rinkel method ($p < 0.01$). No significant difference in comparing Rinkel vs. placebo groups ($p = 0.3$). Data also presented as dot plot with median values given. No numeric data given. 2) Total IgE and allergen-specific IgE and IgG antibody levels: Not abstracted 3) Patient global evaluation of efficacy of treatment: Patients reporting "hay fever symptoms less severe in 1979" Less severe, same, more severe: Standard: 15, 0, 0 Placebo: 9, 2, 1 Rinkel 1979: 11, 2, 1 Rinkel 1978/79: 9, 0, 0 4) Adverse reactions:	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: No Intention-to-treat: No Note: 9/23 pts in the Rinkel-method group were continuing treatment started in the course of an earlier RCT. Results were reported separately for this group.

(continued on next page)

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	dose approx. 0.0285 µg AgE; range, 0.005 to 0.827. 3) Placebo (histamine caramelized glucose), administered according to Rinkel schedule (n = 14). Duration of study treatment: February 27-October 8 Symptomatic medication permitted: Chlorpheniramine maleate 4 mg or carbinoxamine maleate 4 mg + pseudoephedrine 60 mg, every 4 hours, as needed Dates: 1979 Location: Baltimore, MD Setting: University allergy practice Type(s) of providers: Specialist	Other:		One local and no systemic reactions in Rinkel groups or placebo group. 7/15 patients in standard group had 1+ systemic reactions: 6 moderate treated with epinephrine, 3 mild treated with antihistamine, and 10 very mild requiring no medication. 5 local reactions occurred in 4 subjects in standard therapy group.	

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Van Metre, Adkinson, Amodio, et al., 1982	Design: RCT, parallel-group (matched-pairs design) Interventions: 1) Short ragweed pollen extract concentrate (187 µg AgE/ml), weekly injections (n = 15). Initial dose 0.1 ml of 1:10,000 dilution. Dose increased every week over 21 weeks to maximum tolerated or maintenance dose (0.1 ml of concentrate). Maintenance injections given every 1-3 weeks thereafter. Median cumulative dose 70 µg of AgE (range, 16.4 to 252). 2) Short ragweed pollen extract concentrate (187 µg AgE/ml), clustered injections (n = 18). Injections (3, 2, or 1) given every 3 weeks. Initial treatment 3 doses (0.1, 0.5, and 0.9 ml) of 1:10,000 dilution. Doses increased every 3 weeks over 19 weeks to maximum tolerated or maintenance dose (0.1 ml of concentrate). Maintenance injections given approximately every 3 weeks thereafter. Median cumulative dose 17.5 µg of AgE (range, 2.2 to 147). 3) Placebo extract with histamine, weekly injections, gradually escalating to include 0.014 mg of histamine phosphate (n = 5). 4) Placebo extract with histamine, clustered injections, gradually escalating	No. of subjects at start: 44 Dropouts/withdrawals: 0 No. of subjects at end: 44 Inclusion criteria: History of seasonal rhinitis in late Aug and Sep for 2+ preceding years; positive prick ST to ragweed Exclusion criteria: Major rhinitis symptoms in mold-dominated seasons Age: 27 pts age 18-35 and 17 patients age 36-50 Sex: 14 F Race: NR Other: 11 patients had prior ragweed IT but none in last 6 years. Preferentially recruited patients with negative mold ST responses.	1) Adverse reactions 2) Patient-assessed symptom severity and medication use (combined in single measure): unspecified symptoms and medication use recorded in study diaries from June 16 to Oct 6; scoring system used not described 3) Total IgE and allergen-specific IgE and IgG antibody levels 4) Skin reactivity 5) Patient global evaluation of efficacy: At end of study, patients compared symptoms experienced during study pollen season with those experienced during previous year's pollen season ("less severe," "same," "more severe")	1) Adverse reactions: No large local or systemic reactions in placebo group. Active group: Large local: 33 reactions in 13 subjects (weekly); 15 reactions in 9 subjects (cluster) Systemic: 13 reactions in 7 subjects (weekly); 19 reactions in 10 subjects (cluster) 2) Patient-assessed symptom severity and medication use (combined in single measure): Mean daily symptom-medication scores in both treatment groups significantly lower than placebo ($p < 0.01$). Score: weekly 3.79, cluster 2.21, placebo 11.14 3) Total IgE and allergen-specific IgE and IgG antibody levels: Not abstracted 4) Skin reactivity: Not abstracted 5) Patient global evaluation of efficacy: Less severe, same, more severe: Active weekly: 14, 1, 0 Active cluster: 16, 1, 1 Placebo weekly: 4, 1, 0 Placebo cluster: 4, 1, 1	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: No Randomized: Yes Allocation concealed: No Double-blind: No Blinding adequate: Not applicable Dropouts described: Yes Intention-to-treat: Yes Note: Two placebo groups combined for purposes of analysis.

(continued on next page)

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	to include 0.014 mg of histamine phosphate (n = 6). Duration of study treatment: 7+ months (injections given between Feb 25 and Oct 6) Symptomatic medication permitted: Chlorpheniramine maleate 4 mg or carbinoxamine maleate 4 mg + pseudo-ephedrine 60 mg every 4 hours as needed Dates: 1980 ragweed season Location: Baltimore, MD Setting: Academic hospital based allergy practice Type(s) of providers: Specialists				
Varney, Gaga, Frew, et al., 1991 **and** **Durham, Varney, Gaga, et al., 1991**	Design: RCT, parallel-group Interventions: 1) Partially purified, standardized, alum-adsorbed grass pollen (*Phleum pratense*) extract (Alutard® SQ) (n = 21). Treatment started in April. Build-up phase: Twice weekly injections of gradually increasing doses, from 0.1 ml x 100 SQ/ml (injection 1) to 1.0 ml x 100,000 SQ/ml (injection 15). Adjustments in schedule made on an individual basis, with no further increases after May 28. Maintenance doses (volume reduced by 40%) given	No. of subjects at start: 40 Dropouts/withdrawals: 3 No. of subjects at end: 37 Inclusion criteria: History of severe summer hay fever; poor symptom control despite symptomatic treatment; positive skin prick test (wheal > 5 mm) to timothy grass pollen extract Exclusion criteria: Appreciable clinical history of other allergies; previous IT in 5 years; chronic asthma Age: 35 years (range 19 to 52)	1) Patient-assessed symptom severity (daily diary): breathlessness, coughing, wheezing, chest tightness, sneezing, blocked nose, running nose, itching eyes, red eyes, streaming eyes, swollen eyes, and itching and dryness of mouth and throat graded daily from April to October on visual analog scale of 0-3 (not described) 2) Use of symptomatic medication: scored daily from April to October as follows: Each eye drop, nasal	1) Patient-assessed symptom severity (daily diary): IT 360 Placebo 928 Difference 522 (238 to 825) P = 0.001 2) Use of symptomatic medication: IT 129 Placebo 627 Difference 335 (178 to 574) P = 0.002 3) Patient-assessed symptom severity (every 2 weeks): 19 June analysis: IT 2.2 Placebo 5.5 Difference -3 (-4.8 to -0.5)	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: Not adequately described Level of evidence: 2b Randomized: Yes Allocation concealed: yes Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: Can't determine Notes: *(continued on next page)*

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	monthly. 2) Placebo ± histamine ("intermittently 'spiked' with histamine") (n = 16) Duration of study treatment: 8 months (April-November) Symptomatic medication permitted: Sodium cromoglycate eye drops and nasal spray, acrivastine, and salbutamol permitted as required; 7-day course of oral prednisolone could be prescribed if these failed to control symptoms Dates: Location: London, UK Setting: Allergy clinic Type(s) of providers: Allergists	Sex: 18 women; 22 men Race: NR Other:	spray, or salbutamol inhalation: 1 Each acrivastine or prednisolone: 2 3) Patient-assessed symptom severity (every 2 weeks): During pollen season, patients asked to grade their overall symptoms every 2 weeks on a visual analog scale from 0-10 4) Conjunctival reactivity 5) Skin reactivity 6) Patient global assessment of efficacy of treatment: At end of pollen season, patients asked to assess the severity of their hay fever in comparison to previous years on scale of +3 (much better) to -3 (a lot worse) 7) Investigator global assessment of efficacy of treatment 8) Adverse reactions	3 July analysis: IT 1.7 Placebo 4.0 Difference -2.3 (-5 to -1) Symptom-free days: IT 29 days Placebo 8 days Diff 21 d (-26 to -1) p = 0.04 4) Conjunctival reactivity: Not abstracted 5) Skin reactivity: Not abstracted 6) Patient global assessment of efficacy of treatment: IT +3 median Placebo +1 P < 0.001 (Mann-Whitney U test) 7) Investigator global assessment of efficacy of treatment: Not abstracted 8) Adverse reactions: 22 delayed local reactions (swelling < 8 cm diameter) 2 systemic reactions (chest tightness and flushing at 10 min; 1 case of delayed urticaria)	

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Walker, Pajno, Lima, et al., 2001 **and** **Wilson, Nouri-Aria, Walker, et al., 2001**	Design: RCT, parallel-group Interventions: 1) Partially purified, standardized, alum-adsorbed grass pollen (*Phleum pratense*) extract (Alutard® SQ) (n = 22). Treatment started in October. Modified "cluster" regimen used: twice-weekly injections given of gradually increasing doses (from 0.1 ml x 100 SQ/ml to 1.0 ml x 100,000 SQ/ml) over 4 weeks. Adjustments in doses made on an individual basis, "according to published guidelines." Maintenance injections given monthly for further 2 years (dose reduced up to 40% during pollen season). 2) Placebo containing 0.01 mg/ml histamine acid phosphate in diluent (n = 22) Duration of study treatment: Approximately 26-27 months (October 1996-December 1998); patients kept pre-trial symptom and medication diaries from May to August 1996 Symptomatic medication permitted: Sodium cromoglycate eye drops and nasal spray, acrivastine, and salbutamol permitted as required; 7-day course of oral prednisolone could be prescribed if these failed to control symptoms	No. of subjects at start: 44 Dropouts/withdrawals: 7 No. of subjects at end: 37 Inclusion criteria: History of severe hay fever uncontrolled by conventional symptomatic treatment; positive skin prick test (wheal > 5 mm) to grass pollen Exclusion criteria: History of multiple allergies; IT in past 5 years; methacholine PC_{20} (concentration of inhaled methacholine that caused a 20% decrease in FEV_1) < 2 mg/mL (normal range > 16 mg/mL) Age: 32 years (range 22 to 64) Sex: 21 women; 23 men Race: NR Other:	1) Patient-assessed symptom severity: breathlessness, cough, wheezing, chest tightness, sneezing, nasal blockage, running nose, itching eyes, red eyes, streaming eyes, swollen eyes, and itching and dryness of mouth and throat graded daily from May to August on visual analog scale of 0-3 (not described) 2) Use of symptomatic medication: scored daily from May to August as follows: Each eye drop, nasal spray, or salbutamol inhalation: 1 Each acrivastine or prednisolone tablet: 2 3) Bronchial reactivity 4) Skin reactivity 5) Eosinophils, T cells, and IL-5 6) Quality of life: assessed using the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ); completed at baseline and during allergy season 7) Adverse reactions	1) Patient-assessed symptom severity: Difference IT vs. placebo 1186.5 (241.5 to 1928.6; p = 0.01) 2) Use of symptomatic medication: Difference IT vs. placebo 1043.0 (332.0 to 2667.1; p = 0.007) 3) Bronchial reactivity: Not abstracted 4) Skin reactivity: Not abstracted 5) Eosinophils, T cells, and IL-5: Not abstracted 6) Quality of life (overall): Difference IT vs. placebo 0.8 (0.18 to 1.5; p = 0.02) 7) Adverse reactions: No immediate (within 1 hr) systemic reactions or large local reactions observed during induction or maintenance. 9 delayed mild systemic reactions during induction period 4 IT group 5 placebo group 3 delayed mild systemic reactions during maintenance period 3 IT group 0 placebo group	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: Yes Level of evidence: 1b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: No Notes:

(continued on next page)

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	Dates: 1996 to 1998 Location: London, UK Setting: Allergy clinic Type(s) of providers: Allergists				
Weyer, Donat, L'Heritier, et al., 1981	Design: RCT, parallel-group Interventions: 1) Crude extract of the pollen of four grasses (*Dactylis glomerata, Lolium perenne, Secale cereale,* and *Phelum pratense*) (n = 17). Five weekly injections of diluted aqueous extract given in increasing doses (from 0.0025 to 0.05 µg protein contained in 0.2 ml). Then 12 (weekly?) injections of $Al(OH)_3$-adsorbed extract given in gradually increasing doses (1-6.25 µg protein in 0.2 ml of solution). Previous dose repeated in event of strong local or general reaction. Mean dose administered 19.3 ± 3.4 µg protein. 2) Placebo (saline-phenol diluent) (n = 16) Duration of study treatment: 5 months (Nov 1978-Apr 1979); outcomes recorded in study diaries from May 15 to June 30, 1979 Symptomatic medication permitted: Antihistamine	No. of subjects at start: 33 Dropouts/withdrawals: 1 No. of subjects at end: 32 Inclusion criteria: Symptoms of seasonal allergic rhinitis with worsening or symptoms from April to July in previous 2 years; positive skin prick test (wheal at least 8 mm) to four-grass pollen extract; Exclusion criteria: Previous IT treatment with grass pollen extracts; history of corticosteroid treatment during grass pollen season; very severe symptoms Age: 26 years (range 9 to 46) Sex: 17 women; 16 men Race: NR Other: Patients with "very severe symptoms" were excluded "for ethical reasons"	1) Patient-assessed symptom severity: sneezing, stuffy nose, running nose, itchy eyes, watery eyes, red eyes, chest tightness, and asthma graded daily during the pollen season on scale of 0 (no symptoms) to 2 (strong symptoms) 2) Use of symptomatic medication: Meds taken recorded daily (with dose) during the pollen season in study diaries; scored by investigators as follows: No meds taken: 0 Mean of 2 tabs of antihistamine per day: 10 Mean of 3 doses of sodium cromoglycate per day: 20 Mean of 2 inhalations of salbutamol per day: 20 1-week prednisone course: 25 3) Patient-assessed symptom severity and medication use (combined in a single measure)	1) Patient-assessed symptom severity: IT 16 ± 10 Placebo 24 ± 8 P < 0.09 2) Use of symptomatic medication: IT 3 ± 5 Placebo 11± 13 P < 0.07 3) Patient-assessed symptom severity and medication use (combined in a single measure): IT 10 ± 7 Placebo 18 ± 15 P < 0.03 4) Adverse reactions: No quantitative data given "Very few reactions were observed" "A few patients had symptoms, both in the treated and in the placebo group."	Quality Scoring: Population similar: Not adequately described Intervention(s) described: No Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: No Dropouts described: No Intention-to-treat: Can't determine Notes:

(continued on next page)

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	(Mequitazine®), up to 2 tablets per day, at first sign of symptoms; if not sufficient, then sodium cromoglycate nasal spray, up to 4 nebulized doses per day; if still not sufficient and pulmonary symptoms present, then salbutamol, 2 inhalations per day; if still not sufficient, then 6-day course of prednisone given Dates: Nov 1978 – Apr 1979 Location: Paris, France Setting: Allergy clinics Type(s) of providers: Allergists		4) Adverse reactions		
Winther, Malling, Moseholm, et al., 2000	Design: RCT (see Note), parallel-group Interventions: 1) Aluminum-adsorbed birch pollen (*Betula verrucosa*) extract (Alutard® SQ) (n = 26). Clustered regimen given, with gradually increasing doses (from 10 to 100,000 SQ-U) given weekly for 6 weeks. Dose/schedule adjusted in event of adverse reactions. Interval between maintenance injections gradually increased to 2 months. Median cumulative dose 613,110 SQ-U (range, 266,210-645,110). 2) Aluminum-adsorbed grass pollen (*Phleum pratense*) extract (Alutard® SQ) (n = 26).	No. of subjects at start: 52 Dropouts/withdrawals: 3/7/2 in years 1/2/3 No. of subjects at end: 40 Inclusion criteria: History of severe allergy to birch and grass pollen with symptoms in Apr-Jul; positive skin prick (wheal area > 7 mm2) to birch and grass pollen; positive RAST for specific IgE (class 2 or greater) to birch and grass pollen Exclusion criteria: Perennial rhinitis; clinical allergy to animal dander with contact at least weekly; IT wthin previous 5 years Age: 26 years (range 18 to 52)	1) Patient-assessed symptom severity: sneezing, rhinorrhea, nasal congestion, itchy nose and/or throat, and itchy eyes graded once daily from April to August on scale of 0 (no symptoms) to 3 (severe symptoms) 2) Use of rescue medication: intake recorded daily from April to August	1) Patient-assessed symptom severity: Year 1 Birch group had fewer symptoms than untreated group (p = 0.015) Grass group had similar symptoms as untreated group (p = 0.355) 2) Use of rescue medication: Year 1 Birch group had less medication use than untreated group (antihistamine tablets p = 0.015; eye-drops, p = 0.001; mg prednisolone, p = 0.002) Grass group had less use of antihistamine, but similar use of other medications as untreated group (antihistamine tablets, p = 0.001; eye-drops, p = 0.345; mg prednisolone, p-0.873)	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Unclear (see Note) Allocation concealed: Not described Double-blind: Yes Blinding adequate: Not described Dropouts described: Yes Intention-to-treat: Can't determine

(continued on next page)

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	Protocol as above. Median cumulative dose 724,110 SQ-U (range, 68,110-6948,110). Duration of study treatment: 1 year (RCT phase); trial preceded by 1-year observation (no treatment) period and followed by a 1-year period during which all patients received treatment with *both* grass and birch pollen extracts Symptomatic medication permitted: Acrivastine and antazoline-naphazoline eye drops; if symptoms inadequately controlled, course of prednisolone could be prescribed Dates: 1992-1994 Location: Copenhagen, Denmark Setting: Allergy clinic Type(s) of providers: Allergist	Sex: 24 women; 28 men Race: NR Other:			Notes: Though study not explicitly described as "randomized," likely to be RCT.

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Zenner, Baum-garten, Rasp, et al., 1997	Design: RCT, parallel-group Interventions: 1) Short-term immunotherapy using a partially purified, standardized, and aluminum hydroxide adsorbed extract containing equal parts of six grasses (*Dactylis glomerata, Lolium perenne, Avena elatior, Phleum pratense, Poa pratensis, and Festuca pratensis*) and rye (*Secale cereale*) (n = 45). Seven weekly injections given in increasing doses (from 3 to 1,000 SE [1,000 SE contains between 1.0 and 2.0 µg of individual grasses]). Dose/schedule modifications made "for medical indications according to the routine procedure of specific immunotherapy." 2) Placebo containing increasing doses of histamine dihydrochloride (n = 41) Duration of study treatment: 7 weeks before start of allergy season Symptomatic medication permitted: Disodium cromoglycate eyedrops and nasal spray, local and systemic antihistamines, sympatho-mimetics and local glucocorticosteroids all permitted Dates: NR	No. of subjects at start: 87 Dropouts/withdrawals: 6 No. of subjects at end: 81 Inclusion criteria: Allergic rhinitis history; positive skin prick (wheal at least 5 mm diameter) to grass and/or rye pollen Exclusion criteria: need for treatment for allergic asthma, perennial rhinitis, or acute infected nasal mucosa; current use of systemic corticosteroids; IT in past 3 years Age: 28.5 (range 16 to 53) Sex: 27 women; 59 men Race: NR Other:	1) Patient-assessed symptom severity: nasal, conjunctival, and bronchial symptoms scored daily during allergy season on scale of 0 (no symptoms) to 3 (severe symptoms) 2) Use of symptomatic medication: graded daily during the allergy season as follows: No drugs: 0 Disodium cromoglycate: 1 Topical corticosteroids or antihistamines: 2 Nasal decongestants: 3 3) Skin reactivity 4) Specific IgE and IgG4 5) Adverse reactions	1) Patient-assessed symptom severity: Overall: STI 82.2 ± 10.1 (mean ± SD) 54 (39-96) median, CI Placebo 116.0 ± 13.2 97.5 (81-117) P = 0.02 (one-tailed Mann-Whitney U test) 2) Use of symptomatic medication: STI 26% of 70 days Placebo 33% P = 0.296 3) Skin reactivity: Not abstracted 4) Specific IgE and IgG4: Not abstracted 5) Adverse reactions: Local reactions (swelling, erythema > 5 cm diameter at injection site): STI 30/309 injections Placebo 6/284 injections Systemic reactions (moderate exacerbations of rhinoconjunctivitis, urticaria, edema of eyelid): STI 9 pts (12 injections) Placebo 5 pts (7 injections) No severe systemic reactions	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: No Intention-to-treat: No Notes:

(continued on next page)

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	Location: Germany Setting: NR Type(s) of providers: Allergists				

[†] Quality scoring criteria were as follows:
Population similar: Was the study population described and reasonably similar to an adult working US population? (Yes [described and similar], No [described, but not similar], Not adequately described)
Intervention(s) described: Were the intervention protocols referenced or described in sufficient detail to replicate? (Yes, No)
Comorbidities described: Was the presence of comorbid asthma (or other upper respiratory conditions) described in the study population? (Yes, No)
Diagnosis by MD: Was the diagnosis of allergic rhinitis based on physician diagnosis? (Yes, No, Not applicable [asthma patients only])
Objectively confirmed: If physician-diagnosed, was the diagnosis supported by objective evidence of allergy (e.g., skin prick or serum IgE antibody testing)? (Yes, No, Not applicable)
Outcome measures valid: Were the main outcomes of interest to us measured in a way that has been demonstrated empirically to be valid and reliable (e.g., using a standardized scale such the RQLQ or SF-36)? (Yes, No, Not adequately described)
Level of evidence: Based on Oxford Center for Evidence-Based Medicine Levels of Evidence (1a, 1b, 1c, 2a, 2b, 2c, 3a, 3b, 4, 5)
Randomized: Was the study described as "randomized"? (Yes, No)
Allocation concealed: If the method for concealing allocation from the investigators was described, was it *adequate* (table of random numbers, computer-generated, coin tossing, etc.) or *inadequate* (alternating, date of birth, hospital number, etc.)? (Not described, Yes [described and adequate], No [described, but inadequate])
Double-blind: Was the study described as "double-blind"? (Yes, No)
Blinding adequate: If the method of double-blinding was described, was it *adequate* (e.g., identical placebo, active placebo, injection vs. tablet with double dummy) or *inadequate* (e.g., tablet vs. injection with no double dummy)? (Not described, Yes [described and adequate], No [described, but inadequate])
Dropouts described: Did the study describe dropouts and withdrawals so that all patients entering the trial could be accounted for? (Yes, No)
Intention-to-treat: Was the analysis performed according to the intention-to-treat principle? (Yes, No, Can't determine)

Evidence Table 4: Combined Treatments

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Andri, Senna, Betteli, et al., 1992	Design: RCT, parallel-group Interventions: 1) Terfenadine 60 mg bid + nimesulide (NSAID) 100 mg bid (n = 15) 2) Terfenadine 60 mg bid + placebo (n = 15) Duration of study treatment: 30 days No other drugs "likely to affect hay fever" permitted No pre-trial washout period described Dates: 5/2/89 - 5/30/89 Location: Italy Setting: Outpatient allergy clinic Type(s) of providers: Allergist	No. of subjects at start: 30 Dropouts/withdrawals: 2 (left area during pollen season) No. of subjects at end: 28 Inclusion criteria: History of parietaria pollen AR; positive skin test; RAST positivity; positive nasal provocation Exclusion criteria: "Other major disease;" ASA sensitivity Age: 18-48 (mean 32.1, SD 8.9) Sex: 18 M, 12 F Race: NR Other:	1) Investigator-assessed symptom severity 2) Patient-assessed symptom severity: nasal itching, nasal obstruction, sneezing, running nose, eye irritation, and eye watering graded daily by patients scale of 0 (none) to 3 (severe) 3) Patient global assessment of efficacy: recorded once at end of trial – categorical scale keyed to perceived degree of improvement in symptoms (< 50%, 50-80%, > 80%) 4) Adverse events: Not clear how reported/ recorded	1) Investigator-assessed symptom severity: Not abstracted 2) Patient-assessed symptom severity: Mean symptom score shown Figure 2, $P \leq 0.005$ terfenadine + nimesulide vs. terfenadine + placebo Table 2: Average symptom score (no SD reported): Terfenadine + nimesulide: Day 1, 8.4; day 15, 2.9; day 30, 1.1 Terfenadine + placebo: Day 1, 7.4; day 15, 3.6; day 30, 2.6 $P \leq 0.001$ at days 15 and 30 3) Patient global assessment of efficacy: Terfenadine + nimesulide: Recovering n = 10, good improvement 2, no or slight improvement 2 Terfenadine + placebo: Recovering 5, good improvement 2, no to slight improvement 7 $0.1 < P \leq 0.12$, by Chi-square 4) Adverse events: 3 terfenadine + nimesulide, 2 terfenadine + placebo reported occasional sleepiness and sedation (5 total, with no withdrawal)	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: No Blinding adequate: Not applicable Dropouts described: Yes Intention-to-treat: Can't determine Notes: Local pollen counts conducted daily during trial. No sample size or power calculation.

Evidence Table 4: Combined Treatments (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Backhouse, Finnamore, and Gosden, 1986	Design: RCT, parallel-group Interventions: 1) Terfenadine 60 mg bid + flunisolide (two 25-mcg spray to each nostril bid) (T+F) (n = 49) 2) Terfenadine 60 mg bid (T) (n = 50) Duration of study treatment: 11 weeks No mention of rescue med No pre-trial washout period described; patients who had received systemic steroid therapy within previous 3 months or anti-allergic treatment within previous 2 weeks were excluded Dates: May and Aug (1985?) Location: England Setting: Outpatient Type(s) of providers: Specialist	No. of subjects at start: 99 Dropouts/withdrawals: 22 total 17 from T group (10 poor symptom control, 1 headache, 1 pregnancy, 1 glandular fever, 2 lack of symptoms, 1 personal reasons, 1 lost to follow-up) 5 from T+F group (2 poor symptoms control, 2 personal reasons, 1 left country) P < 0.005 No. of subjects at end: 75 Inclusion criteria: 2-year history of moderate-severe seasonal allergic rhinitis Exclusion criteria: Pregnant, lactating, URI, nasal obstruction abnormalities, systemic steroids within 3 months, allergy treatment within 2 weeks Age: 13-65, mean age Sex: 51 M, 48 F Race: NR Other:	1) Investigator-assessed symptom severity 2) Patient-assessed symptom severity: sneezing, runny nose, blocked nose, and eye symptoms assessed on scale of 1-4 by patients in daily diary recordings and at clinic visits at 3,7, and 11 weeks 3) Investigator-and-patient global assessment: overall effect of treatment rated ("by both the doctor and the patient") as excellent, good, poor, none, or symptoms worse at clinic visits at 3, 7, and 11 weeks 4) Adverse events: Not clear how reported/ recorded	1) Investigator-assessed symptom severity: Not abstracted 2) Patient-assessed symptom severity: (see Table 2 for w eek 3 and 7 results) Week 11 mean scores (SD): Sneezing: T group 1.3 (0.6), T+F group 1.0 (0.2), P = 0.12 Nose blowing: T group 1.3 (0.8), T+F group 1.0 (0.2), P = 0.15 Runny nose: T group 1.4 (0.8), T+F group 1.2 (0.5), P = 0.03 Stuffy nose: T group 1.3 (0.7), T+F group 1.2 (0.5), P = 0.28 Eye symptoms: T group 1.4 (0.8), T+F group 1.1 (0.3), P = 0.18 Note: significant p-values mostly at week 7, when pollen count was high 3) Investigator-and-patient global assessment: Week 7, good or excellent response 96% T&F group, 62% T group, P = 0.001 Not reported for Week 11 4) Adverse events: 29 pts T group (9 drowsiness, 5 nausea/vomiting, 3 headache, 2 loss of concentration, 1 loss of balance, 1 depression, 8 other), only 12 felt to be due to study drug 35 pts T+F group (10 nasal/throat irritation, 7 drowsiness, 2 headache, 2 hangover, 1 irritation, 1 husky voice, 3 dry throat, 9 other), only 21 felt to be due to study drug	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: No Objectively confirmed: No Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: No Blinding adequate: No Dropouts described: Yes Intention-to-treat: Can't determine Notes: Single-blind trial. Local pollen counts recorded during weeks 3-9 of study.

Evidence Table 4: Combined Treatments (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Benincasa and Lloyd, 1994	Design: RCT, parallel-group Interventions: 1) Fluticasone propionate nasal spray 200 µg (2 actuations per nostril) + oral cetirizine 10 mg, once per day (n = 227) (Combo group) 2) Fluticasone propionate nasal spray 200 µg once per day (n = 227) (FPANS group) Duration of study treatment: 8 weeks Patients provided with eye drops containing a mixture of antazoline and xylometazoline (Otrivine-Antistin®) to be used "if eye symptoms became troublesome" No pre-trial washout period described; patients who had taken following drugs, in time frames indicated, were excluded: intranasal or oral corticosteroids, ketotifen, or sodium cromoglycate (4 weeks); astemizole (6 weeks); depot corticosteroids (8 weeks); immunotherapy injections (grass pollen) (6 months) Dates: Start date 5/14/90, end date 8 weeks later Location: UK Setting: 64 general practice clinics	No. of subjects at start: 455 screened, 454 randomized (227 per group) Dropouts/withdrawals: 68 (1 withdrew prior to randomization, 37 from FPANS group, 30 from Combo group). No. of subjects at end: 387 Inclusion criteria: Required treatment for hay fever symptoms during June in previous 2 years; at least 2 of following symptoms (1 nasal symptom): sneezing, nasal itching, runny nose, or nasal congestion, eye watering/irritation, or headache. Patients with asthma included if unlikely to require change in medication over 8-week study period. Exclusion criteria: Prescription med for respiratory infection in past 2 weeks; treatment for allergic rhinitis in past week; intranasal or oral corticosteroids, ketotifen or sodium cromoglycate in past 4 weeks; astemizole in past 6 weeks, depot steroids in past 8 weeks, or immunotherapy to grass pollen in past 6 months; nasal surgery past 2 months, nasal pathology (polyp, turbinate hypertrophy, septal deviation), chronic sinusitis; recurrent conjunctivitis, or soft contact lens use; pregnant or lactating Age: FPANS group: mean 31 (range 12-80); Combo group: mean 30 (12-66)	1) Patient-assessed symptom severity: nasal symptoms, eye symptoms, and headache graded daily on scale of 0 (no symptoms) to 7-9 (severe symptoms). Diaries used weeks 3-8. 2) Use of rescue med (eye drops): recorded daily in study diaries 3) Patient global evaluation of efficacy of treatment: patients asked at end of study whether treatment had adequately controlled their nasal, eye, and headache symptoms (yes/no) 4) Investigator global evaluation of efficacy 5) Adverse events: not clear how reported/ recorded; all AEs recorded regardless of possible relationship to study drugs	1) Patient-assessed symptom severity: no significant differences in any symptoms or symptom-free days Symptom scores (mean [SD]): Nasal: 1.5 (1.4) FPANS, 1.5 (1.6) Combo Eye: 1.3 (1.3) FPANS, 1.1 (1.3) Combo Headache: 0.4 (0.9) FPANS, 0.4 (0.7) Combo Proportion symptom-free days (mean [SD]): Nasal: 0.45 (0.38) FPANS, 0.46 (0.4) Combo Eye: 0.56 (0.36) FPANS, 0.57 (0.36) Combo Headache: 0.86 (0.22) FPANS, 0.85 (0.25) Combo 2) Use of rescue medication: No significant difference Proportion of dayswithout rescue medication, mean (SD): FPANS: 0.81 (0.29) Combo: 0.82 (0.26) 3) Patient global evaluation of efficacy of treatment: Percentage reporting adequate control: Nasal: 88% FPANS, 89% Combo Eye: 75% FPANS, 82% Combo Headache: 83% FPANS, 86% Combo 4) Investigator global evaluation of efficacy: Not abstracted 5) Adverse events: Serious AEs: 12 pts (5%) FPANS group, 10 pts (4%) Combo group Highest reported serious AE was drowsiness: 2 FPANS, 3 Combo. Only 1 SAE in FPANS group and 4 serious	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: No Outcome measures valid: No Level of evidence: 1b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: Yes Note: No sample size calculation reported.

(continued on next page)

Evidence Table 4: Combined Treatments (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	Type(s) of providers: Primary care	Sex: 194 M (95 FPANS, 99 Combo); 260 F (132 FPANS, 128 Combo) Race: NR Other:		AEs in Combo group were judged to be related to study medication. Minor AEs: 295 events from 124 pts (55%) FPANS group; 286 events from 133 pts (59%) Combo group. Most AEs were symptoms of seasonal allergic rhinitis (highest reported AE was headache, 28% of FPANS group, 22% of Combo group). Only 14 (5%) of reports in FPANS group and 17 (6%) in Combo group were considered by MD to be related to study treatment.	
Berger, Fineman, Lieberman, et al., 1999	Design: RCT, parallel-group Interventions: 1) Azelastine nasal spray, 2 sprays per nostril bid (1.1 mg/day) + placebo capsule once per day (AZ) (n = 538) 2) Intranasal beclomethasone dipropionate monohydrate, 2 sprays per nostril bid (336 µg/day) + loratadine 10 mg once per day (BEC+LOR) (n = 532) Duration of study treatment: 7 days Rescue med: chlorphenir-amine maleate 4 mg prn during washout, but not 48 hrs prior to randomization Trial preceded by 1- to 2-week washout period (1 week for pts on oral antihistamine, 2 weeks for pts on nasal steroid) Dates: 1998 spring allergy season	No. of subjects at start: 1070 from 3 separate studies Dropouts/withdrawals: 15 total 10 pts in AZ group: 1 intercurrent illness, 4 protocol violation, 1 withdrew consent, 1 treatment failure, and 3 pts discontinued due to AEs (1 sinusitis, 1 sneezing, 1 upper respiratory infection) 5 pts in BEC+LOR group: 2 intercurrent illness, 1 protocol violation, 2 discontinued due to AEs (1 vertigo/N/CP, 1 nasal burning) No. of subjects at end: 1055 Inclusion criteria: Age ≥ 12; documented seasonal allergic rhinitis; on monotherapy with either oral antihistamine or nasal steroid; MD-determined candidate for combination therapy due to lack of adequate symptom control; symptoms rating score ≥ 18 (range 0-50), with at least 3 symptoms of moderate or greater intensity	1) Investigator global assessment 2) Patient global assessment: Patients asked to compare how they felt on last day of treatment (day 7) with how they felt prior to treatment on scale ranging from +2 (much better, near complete or complete symptom relief) to -2 (much worse, marked deterioration of symptoms), assessment of +1 or +2 considered improvements 3) Adverse events: Not clear how reported/ recorded	1) Investigator global assessment: Not abstracted 2) Patient global assessment: Improved Study 1: AZ 80%, BEC+LOR 90% Improved Study 2: AZ 77%, BEC+LOR 86% Improved Study 3: AZ 84%, BEC+LOR 85% 3) Adverse events: AZ group: 8% aftertaste, 5% headache, 3% rhinitis, 2% somnolence BEC+LOR group: 1% aftertaste, 6% headache, 1% rhinitis, 1% somnolence	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: No Outcome measures valid: No Level of evidence: 1b Randomized: Yes Allocation concealed: Yes Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: Yes Notes: Bottles of nasal steroid looked different. Reports results of 3 separate RCTs. Treatment lasted only 7 days.

(continued on next page)

Evidence Table 4: Combined Treatments (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	Location: US Setting: 71 outpatient allergy/ENT centers Type(s) of providers: Specialist	Exclusion criteria: Unable to use/tolerate nasal spray; asthma; investigational drug w/in 30 days; use of antidepressants; upper respiratory infection within 30 days; any clinically significant acute/chronic illness Age: Mean 35 (range 12-80) Sex: 57-63% F, 37-43% M Race: 81-90% white			
Bertrand, Jamart, Marchal, et al., 1996	Design: RCT, parallel-group Interventions: 1) Pseudoephedrine 120 mg (extended-release) bid + cetirizine 5 mg bid (n = 70) (COM group) 2) Pseudoephedrine 120 mg (extended-released) bid (n = 70) (PER group) 3) Cetirizine 5 mg bid (n = 70) (CTZ group) Duration of study treatment: 3 weeks No mention of rescue med Pre-trial washout period ranged from 2 days to 6 weeks, depending on pre-trial medication Dates: NR Location: 8 centers in Belgium and Luxembourg	No. of subjects at start: 210 Dropouts/withdrawals: 39 total 7 CTZ group (1 inefficacy, 2 AEs, 4 protocol violation/personal reasons); 19 PER group (2 inefficacy, 9 AEs, 8 protocol violation/personal reasons); 13 COM group (4 AEs, 9 protocol violation/personal reasons) No. of subjects at end: 210 included in analysis Inclusion criteria: Perennial allergic rhinitis of at least 1 year duration; positive skin or RAST allergy test; presence of nasal obstruction, sneezing, and rhinorrhea Exclusion criteria: Pollen-sensitive patients excluded during pollen season; infectious rhinitis; nasal polyposis; nasal septal deviation; dermatitis; infections requiring antibiotic treatment; pregnancy; childbearing potential; breastfeeding	1) Investigator-assessed symptom severity 2) Patient-assessed symptom severity: blocked nose, sneezing, runny nose, itchy nose, and itchy eyes graded on scale of 0 (no symptoms) to 4 (severe symptom interfering with daily activities and/or sleep) at end of every day throughout trial 3) Investigator global assessment 4) Adverse events: Not clear how reported/ recorded	1) Investigator-assessed symptom severity: Not abstracted 2) Patient-assessed symptom severity: Figures 1-5, daily symptom scores per group: Nasal obstruction: P < 0.0001, COM vs. CTZ; P = 0.004, COM vs. PER; P = 0.128, CTZ vs. PER Rhinorrhea: P = 0.174, COM vs. CTZ; P = 0.001, COM vs. PER; P = 0.072, CTZ vs. PER Sneezing: P = 0.790, COM vs. CTZ; P = 0.021, COM vs. PER; P = 0.012, CTZ vs. PER Nasal itching: P = 0.384, COM vs. CTZ; P = 0.158, COM vs. PER; P = 0.018, CTZ vs. PER Eye itching: P = 0.204, COM vs. CTZ; P = 0.080, COM vs. PER; P = 0.006, CTZ vs. PER 3) Investigator global assessment: Not abstracted 4) Adverse events: 31 CTZ (6 somnolence, 4 bronchitis, 3 headache, 2 asthenia, 1 each insomnia and nervousness) 38 PER (7 insomnia, 6 dry mouth, 6	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 1b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: Yes Note: Double-dummy blinding technique employed.

(continued on next page)

Evidence Table 4: Combined Treatments (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	Setting: Outpatient Type(s) of providers: Otolaryngologist	Age: 12-65 Sex: 97 M, 113 F Race: NR Other:		nausea, 5 headache, 4 asthenia, 3 somnolence, 1 nervousness) 35 COM (9 somnolence, 8 headache, 4 each asthenia, dry mouth, nervousness, and insomnia)	
Bronsky, Boggs, Findlay, et al., 1995	Design: RCT, parallel-group Interventions: 1) Loratadine 10 mg + pseudoephedrine 240 mg (extended-release) once per day (Combo group) (n = 212) 2) Loratadine 10 mg once per day (LOR group) (n = 212) 3) Pseudoephedrine 120 mg (extended-release) bid (PSE group) (n = 211) 4) Placebo (n = 212) Duration of study treatment: 2 weeks No mention of rescue med Trial preceded by washout period ranging from 1 day to 1 month (depending on pre-trial medication) and a 4- to 7-day placebo run-in phase (baseline) Dates: Fall allergy season, 1989 Location: US Setting: 14 outpatient allergy centers	No. of subjects at start: 879 Dropouts/withdrawals: 5 dropouts prior to treatment 54 total discontinuations 11 Combo group (5 treatment failure, 4 AEs, 1 noncompliance, 1 lost to follow-up) 17 LOR group (12 treatment failure, 1 AEs, 4 noncompliance) 13 PSE group (4 treatment failure, 9 AEs) 13 placebo group (11 treatment failure, 2 AEs) No. of subjects at end: 874 included in safety analysis, 847 in efficacy analysis (27 protocol violations) Inclusion criteria: Seasonal allergic rhinitis for at least 1 year, confirmed by skin test to ragweed or other prevalent seasonal allergens; total symptom score ≥ 11 on 50% of days during placebo phase; ≥ 80% compliance with placebo phase drug Exclusion criteria: Immuno-therapy within 6 months; asthma requiring steroids; multiple drug allergies; nonresponders or previous reaction to anti-histamines; upper respiratory infection, investigational drug	1) Investigator-assessed symptom severity: rhinor-rhea, nasal stuffiness, nasal itching, sneezing, burning or itching eyes, watering eyes, red eyes, and itching of the ears or palate graded on scale of 0 (none) to 3 (severe) during clinic visits on days 4, 8, and 15 of the treatment period. 2) Patient-assessed symptom severity: Patients kept daily diary of symptom severity (presumably using same scale as above, though this is not stated). 3) Investigator global assessment of response to treatment 4) Patient global assessment of response to treatment: graded on scale of 1 (excellent) to 5 (treatment failure) during clinic visits on days 4, 8, and 15 of the treatment period. 5) Adverse events: Not clear how reported/	1) Investigator-assessed symptom severity: Not abstracted 2) Patient-assessed symptom severity: No quantitative data reported. Results described as "similar" to those of investigator assessment of symptom severity. Total symptom score reduction significantly greater ($P \leq 0.05$) in Combo group than in other three treatment groups. Total symptom score reduction also greater in LOR group than in placebo group ($P = 0.04$). Repeated measures analysis $P \leq 0.01$ in Combo and LOR groups compared to placebo (plus Combo vs. PSE group). Similar results for nasal and nonnasal symptom scores. 3) Investigator global assessment of response to treatment: Not abstracted 4) Patient global assessment of response to treatment: Excellent or good response 125 (61%) Combo, 106 (52%) PSE, 95 (47%) LOR, 73 (35%) placebo 5) Adverse events: 124 Combo (55 headache, 17 dry mouth, 14 pharyngitis, 13 somnolence, 12 insomnia, 11 nervousness) 102 LOR group (50 headache, 18	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 1b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: No Notes: Double-dummy blinding technique employed. Pollen counts determined twice weekly during trial at all study sites.

(continued on next page)

Evidence Table 4: Combined Treatments (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	Type(s) of providers: Allergists	within 1 month; pregnancy/ lactation; significant medical condition Age: Range 12-82, median 28-30 Sex: Of 847 pts, 395 (47%) male, 452 (53%) female Race: Of 847 pts, 747 (88%) white, 43 (5%) black, 57 (7%) other Other:	recorded	pharyngitis, 9 somnolence, 7 dry mouth, 1 each insomnia and nervousness) 133 PSE group (57 headache, 19 insomnia, 16 dry mouth, 11 pharyngitis, 10 somnolence, 8 nervousness) 100 placebo group (60 headache, 15, pharyngitis, 8 somnolence, 6 dry mouth, 1 nervousness) More AEs in Combo and PSE groups than in placebo group, $P \leq 0.05$ Hyperkinesia higher in PSE group compared to placebo or loratadine.	
Brooks, Francom, Peel, et al., 1996	Design: RCT, parallel-group Interventions: 1) Loratadine 10 mg once per day + beclomethasone nasal spray, 2 sprays (about 84 µg) in each nostril twice a day (LOR+BEC) (n = 20) 2) Loratadine 10 mg once per day (LOR) (n = 20) 3) Beclomethasone nasal spray, 2 sprays (about 84 µg) in each nostril twice a day (BEC) (n = 20) Duration of study treatment: 9 days (2-week study period included 5-day no-treatment run-in period) Patients instructed not to take any other drugs that might affect their hay fever during study period Trial preceded by 5-day no-	No. of subjects at start: 60 Dropouts/withdrawals: NR No. of subjects at end: 60 Inclusion criteria: History of ragweed seasonal allergic rhinitis with strongly positive skin tests Exclusion criteria: Evidence of significant complicating disease on history, physical, or laboratory testing; pregnancy Age: Reported as "roughly comparable" Sex: 10M/10F LOR 7M/13F BEC 7M/13F LOR+BEC group Race: NR Other:	1) Patient-assessed symptom severity: congestion, running/ blowing, sneezing, itching, and eye symptoms graded twice daily on scale of 1 (no symptoms) to 5 (maximum symptoms) 2) Patient global evaluation of efficacy of treatment: on last day of study, patients asked to grade overall effectiveness of treatment as "excellent," "good," "fair," or "poor'	1) Patient-assessed symptom severity: Mean changes shown in Figures 1-5 for 3 segments (days 2-3, days 5-7, days 8-10). Overall similar improvement with BEC and LOR+BEC for congestion, eye symptoms, and runny nose. LOR+BEC better than BEC alone for itching ($p = 0.13$) and sneezing ($p = 0.589$), but was not statistically significant. LOR+BEC was significantly better than LOR alone ($p < 0.001$) for all symptoms. 2) Patient global evaluation of efficacy of treatment: LOR+BEC superior to BEC alone ($p = 0.042$), and to LOR alone ($p = 0.001$). No difference between BEC and LOR alone ($p = 0.122$). Excellent: 6 BEC, 4 LOR, 11 LOR+BEC Good: 9 BEC, 5 LOR, 8 LOR+BEC Fair: 4 BEC, 9 LOR, 1 LOR+BEC Poor: 1 BEC, 2 LOR, 0 LOR+BEC	Quality Scoring: Population similar: Not adequately described Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: No Blinding adequate: Not applicable Dropouts described: Yes Intention-to-treat: Can't determine Notes: Double-dummy blinding technique employed. No sample size estimate or adverse events reported.

(continued on next page)

Evidence Table 4: Combined Treatments (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	treatment run-in period Dates: Aug 18 - Sept 1 (year unknown) Location: US (Kalamazoo, MI) Setting: Pharmaceutical (Upjohn) research clinic Type(s) of providers: NR				
Brooks and Karl, 1988	Design: RCT, parallel-group Interventions: 1) Terfenadine 60 mg bid + flurbiprofen 100 mg tid (n = 14) 2) Terfenadine 60 mg bid (n = 14) Duration of study treatment: 1 week No mention of rescue med Trial preceded by 1-week run-in period, during which patients first took the symptomatic treatment of their choice (first ½ of run-in week), then terfenadine 60 mg bid (second ½ of run-in week) Dates: NR Location: Bronson Clinical Research Unit, Kalamazoo MI Setting: Outpatient **Type(s) of providers: NR**	No. of subjects at start: 28 Dropouts/withdrawals: 1 No. of subjects at end: 27 Inclusion criteria: "Credible" history of seasonal rhinitis and positive skin test Exclusion criteria: Significant complicating disease; aspirin sensitivity Age: Terfenadine + flurbiprofen: mean 36.8 (SD 10.3) Terfenadine alone: 37.9 (SD 9.7) Sex: Terfenadine + flurbiprofen: 5M/9F Terfenadine alone: 9M/5F Race: NR	1) Patient-assessed symptom severity: discrete symptoms graded 4 times per day on different scales, with 0 always indicating no symptoms and highest number always indicating maximum symptoms; symptoms graded were: congestion (0-8); drainage/postnasal drip (0-3); running nose/ blowing (0-4); sneezing in last ½ hour (0-4); hay fever-related itching (0-4); hay fever-related eye symptoms (0-4) 2) Adverse events: not clear how reported/ recorded	1) Patient-assessed symptom severity: Mean daily symptoms scores show in Figures 1-4. No values reported. P-values are based on comparison of mean daily totals. P-values significant (< 0.05) on day 3 (congestion, P = 0.043; sneeze score, P = 0.026) and day 4 (running/blowing nose, P = 0.006) 2) Adverse events: Several volunteers reported side effects, mostly moderate gastrointestinal symptoms. Not quantified further. One dropout after day 1 after experiencing cramps & nausea (received terfenadine + flurbiprofen).	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: No Blinding adequate: Not applicable Dropouts described: Yes Intention-to-treat: Yes Notes: Patients assigned to 1 of 4 strata based on total symptom score, then randomized. P-values are based on comparison of mean daily totals. No overall assessment of treatment (e.g., pre- and post-treatment summary scores). Analysis is incorrect. Time period of treatment may be too short.

Evidence Table 4: Combined Treatments (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Bukstein, Biondi, Blumenthal, et al., 1996	Design: RCT, parallel-group Interventions: 1) Nedocromil sodium 1% nasal spray (1 spray per nostril, 4 times per day) + astemizole (one 30-mg dose on Day 1, one 20-mg dose on Day 2, and one 10-mg dose per day thereafter) (n = 147) 2) Astemizole (as above) + placebo nasal spray (n = 150) 3) Double-dummy placebo (n = 74) Duration of study treatment: 4 weeks Pseudoephedrine and artificial tears permitted "for relief of intolerable symptoms" Trial preceded by washout period ranging from 16 hours to 4 weeks (depending on pre-trial medication) and 1-week baseline period timed to coincide with start of local ragweed pollen season Dates: Local ragweed season Location: US Setting: 13 outpatient sites Type(s) of providers: Allergists	No. of subjects at start: 371 Dropouts/withdrawals: 20 dropouts from treatment failure (12), protocol violation/ noncompliance (6), other (2) 6 not included in analysis (4 withdrawn from poor use of treatment, 1 upper respiratory infection, 1 travel out of pollen area) No. of subjects at end: 365 Inclusion criteria: Seasonal allergic rhinitis to ragweed for 2 years requiring continuous treatment; positive skin test Exclusion criteria: Women of childbearing potential; sinusitis; polyposis; immunotherapy; recent astemizole, corticosteroids, cromolyn sodium, short-acting antihistamines, decongestants, vasoconstrictors, or theophylline Age: 12-64; means 33.9 (nedocromil + astemizole), 35.1 (astemizole), and 31.8 (placebo) Sex: 279 (76%) male; 86 (44%) female Race: NR Other:	1) Patient-assessed symptom severity: stuffy nose, runny nose, itchy nose, sneezing, and overall nasal symptoms graded daily on scale of 0 (none) to 4 (very severe) 2) Patient-assessed sleep disturbance due to rhinitis: graded daily on scale of 0 to 2 (not described) 3) Use of rescue med (recorded by patients in daily diaries) 4) Investigator assessment of clinical signs of rhinitis 5) Investigator global assessment of treatment efficacy 6) Patient global assessment of treatment efficacy: graded as "good" (symptoms fully or mostly controlled), "fair" (symptoms fairly well controlled), or "poor" (symptoms controlled poorly or not at all) during clinic visits at 1 and 4 weeks 7) Adverse events: Not clear how reported/ recorded	1) Patient-assessed symptom severity: Symptom summary mean (SD): Nedocromil + astemizole: 1.02 (0.78), $p < 0.001$ vs. placebo, $p < 0.01$ vs. astemizole Astemizole: 1.21 (0.84), $p < 0.001$ vs. placebo Placebo: 1.49 (0.90) Mean change from baseline (SD): Nedocromil + astemizole: -0.39 (0.76), $p < 0.001$ vs. placebo, $p < 0.01$ vs. astemizole Astemizole: -0.22 (0.68), $p < 0.001$ vs. placebo Placebo: +0.21 (0.77) 2) Patient-assessed sleep disturbance due to rhinitis: Nedocromil + astemizole 0.58 (0.63), $p = 0.11$ vs. placebo Astemizole 0.69 (0.62), $p < 0.18$ vs. placebo Placebo 0.73 (0.61) 3) Use of rescue med (pseudo-ephedrine) (tabs/day): Nedocromil + astemizole 0.34 (0.86), $p = 0.02$ vs. astemizole Astemizole 0.55 (1.03) Placebo 0.68 (1.15) 4) Investigator assessment of clinical signs of rhinitis: Not abstracted 5) Investigator global assessment of treatment efficacy: Not abstracted 6) Patient global assessment of treatment efficacy: Symptoms controlled fully/mostly: Nedocromil + astemizole: 64%, $p < 0.001$ vs. placebo, $p < 0.01$ vs. astemizole alone	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 1b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: Yes Note: Pollen counts measured daily at each site.

(continued on next page)

Evidence Table 4: Combined Treatments (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
				Astemizole: 47%, p < 0.01 vs. placebo Placebo: 28% 7) Adverse events: 63 (43%) Nedocromil + astemizole 52 (35%) Astemizole 20 (27%) Placebo Trend towards more headache in combo group (p = 0.058)	
Busse, Janssens, and Eisen, 1996	Design: RCT, parallel-group Interventions: 1) Nasal spray containing levocabastine (0.5 mg/ml) and oxymetazoline (0.5 mg/ml), 2 sprays per nostril twice per day (n = 251) 2) Levocabastine nasal spray, 2 sprays per nostril twice per day (n = 255) 3) Oxymetazoline nasal spray, 2 sprays per nostril twice per day (n = 252) 4) Placebo nasal spray (n = 257) Duration of study treatment: 1 week No mention of rescue med No pre-trial washout period described; patients who had taken following drugs, in time frames indicated, were excluded: systemic cortico-steroids (1 month); topical corticosteroids or sodium cromoglycate (2 weeks);	No. of subjects at start: 1015 Dropouts/withdrawals: 38 (7 levocabastine, 5 levocabastine-D, 12 oxymetazoline, 14 placebo No. of subjects at end: 977 Inclusion criteria: Age 18-60 with 1-year history of seasonal allergic rhinitis; positive skin test to ragweed allergen (= 3 mm); moderate-severe nasal congestion and at least one other moderate-severe nasal symptom Exclusion criteria: Other forms of rhinitis or sinusitis; moderate-severe asthma; serious comorbid disease; systemic steroids within 1 month; topical steroids or sodium cromoglycate within 2 weeks; decongestants or antihistamines within 3 days; astemizole within 6 weeks; any use of tricyclic antidepressants, MAOI, other CNS depressants; antihypertensive drugs; change in immunotherapy in past 6 months; pregnant or lactating; investigational drug within 30 days; hypersensitivity to antihistamines; travel outside of	1) Patient-assessed symptom severity: nasal congestion, rhinorrhea, nasal itching, sneezing, itching eyes, lacrimation, and redness of eyes graded daily using scale of 0 (absent) to 3 (severe) 2) Investigator-assessed symptom severity 3) Patient global evaluation of efficacy: effect of treatment on overall severity of rhinitis graded at end of trial as "excellent," "good," "fair," "poor," or "worse" 4) Investigator global evaluation of efficacy 5) Adverse events: spontaneously reported during clinic visits (after 3 days of treatment and at end of week)	1) Patient-assessed symptom severity: Reported mean change in Area Under Curve (AUC) from baseline. Statistical significance calculated versus placebo. Total all symptoms (mean change AUC): -1.7 placebo -3.3 levocabastine-D *** -3.5 levocabastine *** -1.8 oxymetazoline *** P = 0.001 compared to placebo 2) Investigator-assessed symptom severity: Not abstracted 3) Patient global evaluation of efficacy: Report of excellent or good: 26% placebo 52% levocabastine-D 44% levocabastine 39% oxymetazoline 4) Investigator global evaluation of efficacy: Not abstracted 5) Adverse events: 32% placebo 40% levocabastine-D 30% levocabastine 40% oxymetazoline Headache and application site	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 1b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: Yes Note: Data pooled from 3 RCTs sharing a common protocol.

(continued on next page)

Evidence Table 4: Combined Treatments (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	astemizole (6 weeks); other decongestants or anti-histamines (3 days) Dates: 1990 fall ragweed pollen season Location: US and Canada Setting: Outpatient Type(s) of providers: specialists	pollen area for longer than 1 day Age: Eligible 18-60; mean (yrs) reported per group 36.5 placebo 35.8 levocabastine-D 36.5 levocabastine 35.7 oxymetazoline Sex: 167M/90F placebo 173M/78F levocabastine-D 168M/87F levocabastine 161M/91F oxymetazoline Race: NR Other:		reactions most frequently reported A Es Headache: 31 placebo 26 levocabastine-D 15 levocabastine 31 oxymetazoline Application site reactions: 15 placebo 23 levocabastine-D 17 levocabastine 34 oxymetazoline	
Diamond, Gerson, Cato, et al., 1981	Design: RCT, parallel-group Interventions: (34-40 pts per group) 1) Triprolidine 2.5 mg + pseudoephedrine 60 mg, given in a single tablet 3 times per day (n = NR) 2) Triprolidine 2.5 mg, 3 times per day (n = NR) 3) Pseudoephedrine 60 mg, 3 times per day (n = NR) 4) Placebo, 3 times per day (n = NR) Duration of study treatment: 1 day, from 10:00 AM to 6:00 PM (drugs administered and outcomes measured on-site) No mention of rescue med	No. of subjects at start: NR Dropouts/withdrawals: NR No. of subjects at end: 151 Inclusion criteria: Allergic rhinitis by symptoms, scratch test, and nasal airway resistance Exclusion criteria: Nasal defect or pathology Age: 18 or older Sex: 100 M, 51 F Race: NR Other:	1) Nasal airway resistance: measured every hour using two Validyne MP45 transducers and an oscilloscope 2) Patient-assessed symptom severity: nasal congestion, sneezing, rhinorrhea, lacrimation, and itching of the eyes, nose, and throat graded on scale of 1-6 (with higher numbers indicating increasing severity) every hour, at time of NAR assessment 3) Adverse events: Patients queried every hour about the occurrence of adverse events in general and specifically about whether or not they	1) Nasal airway resistance: Not abstracted 2) Patient-assessed symptom severity: Nasal congestion: changes in mean scores shown in Figure 2; combination caused greater reduction than placebo at 6, 7, and 8 hours ($P \leq 0.025$), and greater reduction than tripolidine alone at 6 and 8 hours ($P \leq 0.025$) Symptom complex score: changes shown in Figure 3; combination ($P \leq 0.025$) and triprolidine had greatest reduction in mean scores 3) Adverse events: Drowsiness most frequently reported AE due to antihistamine; few reports of jitteriness due to decongestant	Quality Scoring: Population similar: Not adequately described Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: No Intention-to-treat: Can't determine Notes: Patients assessed for a total of 8 hours over the course of a single day.

(continued on next page)

Evidence Table 4: Combined Treatments (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	Patients instructed to refrain from antihistamines for 48 hours and nasal decongestants for 16 hours before reporting for treatment Dates: Grass and ragweed season (Apr-Jun and Aug-Oct) Location: US, Kentucky Setting: Outpatient (academic medical center) Type(s) of providers: NR		had experienced dizziness, drowsiness, nervousness, or nausea		Number of patients in each treatment group not reported; stated only that there were 34-40 per group.
Dockhorn, Aaronson, Bronsky, et al., 1999	Design: RCT, parallel-group, nonallergic and allergic patients stratified separately Interventions: 1) Ipratropium bromide nasal spray 0.03% (42 µg per nostril tid) + beclomethasone dipropionate nasal spray (84 µg per nostril bid) (n = 207) 2) Ipratropium bromide nasal spray 0.03% (42 µg per nostril tid) (n = 103) 3) Beclomethasone dipropionate nasal spray (84 µg per nostril bid) (n = 109) 4) Placebo nasal sprays (n = 106) Duration of study treatment: 2 weeks (Phase III of trial, see Notes) No mention of rescue med	No. of subjects at start: 553 (279 allergic, 274 nonallergic) Dropouts/withdrawals: 43 total 525 completed Part II 510 completed Part III 17 (3%) dropouts due to AEs 18 (3%) dropouts due to administrative reasons 3 protocol violations 5 lack of efficacy No. of subjects at end: 510 Inclusion criteria: Allergic rhinitis (positive skin test and history) or nonallergic rhinitis (negative skin test) Exclusion criteria: Complete nasal obstruction; abnormal sinus film; upper respiratory infection; rhinitis medicamentosa; glaucoma; BPH Age: 8-75 (mean 36.7, SD 16.7, 18% age 8-18)	1) Patient-assessed symptom severity: rhinorrhea, congestion, and sneezing graded daily on scale of 1 (none) to 5 (unbearable); duration of rhinorrhea assessed by having patient record each day the number of hours nose ran between 8 AM and 8 PM 2) Investigator global assessment of efficacy 3) Patient global assessment of efficacy: graded on weekly basis using scale of 1 (no symptom control) to 4 (excellent symptom control); separate assessments for rhinorrhea, nasal congestion, and sneezing 4) Quality of life: Assessed using the SF-36	1) Patient-assessed symptom severity: Mean rhinorrhea severity and duration reduced in all three treatment groups compared to placebo (values shown in figures, $P < 0.05$). Combination therapy caused 45% reduction in rhinorrhea severity and 47% reduction in duration from baseline. Subgroup analysis of patients with substantial reduction: Rhinorrhea severity reduction: 74% combination, 57% ipratropium, 64% beclomethasone, 47% placebo. Rhinorrhea duration reduction: 66% combination, 50% ipratropium, 54% beclomethasone, and 38% placebo. Combination more effective than ipratropium or placebo in reducing severity of nasal congestion or sneezing, $P < 0.05$. Nasal congestion reduction: 31% combination, 23% ipratropium, and 23% placebo. Sneezing reduction: 37% combination,	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: Yes Level of evidence: 1b Randomized: Yes Allocation concealed: Yes Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: Can't determine Notes: Trial had 4 phases: Phase I: 1-week run-in period during which patients took no medication (baseline values from this period); Phase II: 2-week RCT comparing monotherapies (ipratropium vs. beclomethasone vs. placebo); *(continued on next page)*

Evidence Table 4: Combined Treatments (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	Multiple-phase trial – see Notes Dates: NR Location: US Setting: 10 outpatient clinics Type(s) of providers: Allergy specialists and general practitioners	Sex: 63% F, 37% Race: 90% white, 2% black, 8% other Other:	Health Survey and the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ), administered at baseline and at end of treatment (2 weeks) 5) Adverse events: Patients queried about adverse events at each clinic visit; AEs recorded regardless of possible relation to treatment	26% ipratropium, and 26% placebo. 2) Investigator global assessment of efficacy: Not abstracted 3) Patient global assessment of efficacy: Good or excellent control of rhinorrhea: 73% combination, 65% ipratropium, 68% beclomethasone, 51% placebo All three active treatments rated as more effective than placebo for nasal congestion, $P < 0.05$. Combination more effective than placebo for control of sneezing, $P < 0.05$. 4) Quality of life: RQLQ scores improved for all 4 treatments compared to baseline, $P < 0.05$, combined > ipratropium or placebo. SF-36 less able to discriminate between treatment groups, although combination treatment superior to ipratropium for 3 domains (role functioning, vitality, health transition) 5) Adverse events: 56 (27%) combined (33 possibly drug-related) 31 (30%) ipratropium (10 possibly drug-related) 27 (25%) beclomethasone (10 possibly drug-related) 32 (30%) placebo (9 possibly drug-related) Most common AEs were pain, headache, nasal dryness, and epistaxis	Phase III: 2-week RCT comparing combination therapy vs. monotherapies vs. placebo (described here); Phase IV: 1-week washout period, during which patients were monitored for signs of rebound of nasal symptoms. Double-dummy blinding technique employed.

Evidence Table 4: Combined Treatments (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Dockhorn, Williams, and Sanders, 1996	Design: RCT, parallel-group Interventions: 1) Acrivastine 8 mg + pseudoephedrine 60 mg, given in one capsule, 4 times per day (n = 176) 2) Acrivastine 8 mg, 4 times per day (n = 175) 3) Pseudoephedrine 60 mg, 4 times per day (n = 177) 4) Placebo (n = 174) Duration of study treatment: 2 weeks No mention of rescue med No pre-trial washout period described (1-day baseline phase); individuals taking antihistamines, nasal decongestants, MAOIs, cromolyn sodium, or corticosteroids within specified times prior to study (based on half-lives of respective drugs) were excluded Dates: NR (during ragweed season) Location: US Setting: 13 outpatient clinics Type(s) of providers: NR	No. of subjects at start: 702 Dropouts/withdrawals: 56 total 5% combination, 10% placebo 20 due to AEs 19 due to worsening allergy symptoms (9 placebo, 5 acrivastine, 4 pseudoephedrine, 1 combination) 7 protocol violations 6 lost to follow-up 4 withdrew consent No. of subjects at end: 646 Inclusion criteria: Seasonal allergic rhinitis (2-year history), positive skin test to ragweed, Exclusion criteria: Anatomic nasal obstruction; vasomotor rhinitis; women of childbearing potential not on birth control; use of antihistamines/nasal decongestants/MAOIs, cromolyn sodium, or steroids Age: 11-73, mean age 32 Sex: 53-60% female Race: 86-90% white Other:	1) Patient-assessed symptom severity: runny nose; sneezing; itchy nose/throat; tearing, itching, or redness of eyes; nasal congestion; and mouth breathing graded 3 times per day on scale of 0 (absent) to 5 (very severe) 2) Investigator global assessment of efficacy 3) Adverse events: Evaluated by spontaneous reports of AEs and changes in vital signs	1) Patient-assessed symptom severity: Mean diary symptom score (no SD): 10.3 combination, 12.3 acrivastine, 11.8 pseudoephedrine, 13.4 placebo P < 0.001 combo vs. acrivastine P = 0.002 combo vs. pseudoephedrine P < 0.001 combo vs. placebo Mean nasal congestion score (no SD): 3.8 combination, 4.7 acrivastine, 4.1 pseudoephedrine, 4.9 placebo P < 0.001 combo vs. acrivastine Mean allergy symptoms score (no SD): 6.5 combination, 7.6 acrivastine, 7.6 pseudoephedrine, 8.6 placebo P < 0.001 combo vs. pseudoephedrine 2) Investigator global assessment of efficacy: Not abstracted 3) Adverse events: Combination therapy: 9% dry mouth, 7% somnolence, 4% nervousness, 4% insomnia 20 dropouts due to AEs (6 combination, 5 acrivastine, 6 pseudoephedrine, 3 placebo)	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 1b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: No Notes:

Evidence Table 4: Combined Treatments (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Drouin, Yang, Horak, et al., 1995	Design: RCT, parallel-group Interventions: 1) Beclomethasone dipropionate nasal spray (100 µg in each nostril twice daily) + loratadine 10 mg once per day (Combo) (n = 76) 2) Beclomethasone dipropionate nasal spray (100 µg in each nostril twice daily) (BEC) (n = 78) Duration of study treatment: 1 week No mention of rescue med Trial preceded by washout period ranging from 24 hours to 1 month, as follows: topical or oral decongestants (24 hours); oral antihistamines (48 hours, except astemizole [1 month]); intranasal steroids (72 hours); cromolyn sodium (1 week); systemic or orally inhaled steroids (1 month) Dates: NR Location: Austria, Belgium, Canada, Germany, England Setting: 5 medical centers Type(s) of providers: specialists (2 allergy, 1 ENT, 1 unknown)	No. of subjects at start: 156 Dropouts/withdrawals: 2 (1 per group) failed to return for follow-up visit. No. of subjects at end: 154 Inclusion criteria: Moderately severe seasonal allergic rhinitis with positive skin test; patient on immunotherapy must be on stable dose for at least 1 month prior to study Exclusion criteria: Severe asthma or COPD; nasal polyps or other structural abnormality; pregnant, lactating or not on medically accepted birth control; significant comorbid disease that might interfere with treatment evaluation Age: 18-65 Mean 31 yrs Loratadine + Beclomethasone Mean 32 yrs Beclomethasone Sex: 48 M/33 F Loratadine + Beclomethasone 38 M/40 F Beclomethasone Note: Sex had significant treatment-by-center interaction (P = 0.03) but was determined to have no impact on overall efficacy comparison. Race: Noted to be comparable, actual % not reported Other:	1) Patient-/investigator-assessed symptom severity: nasal discharge, nasal stuffiness, nasal itching, sneezing, itching eyes, tearing, redness of eyes, and ear/palate itching graded daily (by patients) and on days 3 and 7 (by investigator) on scale of 0 (none) to 3 (severe, very disturbing most of the time) 2) Patient global evaluation of efficacy: graded on last day of treatment on scale of 1 (excellent) to 5 (treatment failure) 3) Investigator global evaluation of efficacy 4) Adverse events: recorded by patients in study diaries and elicited by investigators during clinic visits on days 3 and 7	1) Patient-/investigator-assessed symptom severity: Improvement in total symptom score ("improvement" not defined; mean scores not reported): Day 3: 54% Combo, 46% BEC alone (P = 0.08) Day 7: 68% Combo, 58% BEC alone (P < 0.05) 2) Patient global evaluation of efficacy: Combo: Excellent 39% Good 51% Fair 3% Poor or Failure 7% BEC alone: Excellent 19% Good 54% Fair 18% Poor or Failure 9% Good to excellent response, 90% Combo vs. 73% BEC, P < 0.05. 3) Investigator global evaluation of efficacy: Not abstracted 4) Adverse events: 23 pts (30%) Combo 20 pts (26%) BEC Most common AE was somnolence 5% in Combo group, 6% in BEC only group.	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 1b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: Yes Note: Not clear whether symptom data reported was assessed by patients or investigators.

Evidence Table 4: Combined Treatments (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Falliers and Redding, 1980 **Study 1 (seasonal allergic rhinitis)**	Design: RCT, parallel-group Interventions: 1) Azatadine maleate 1 mg + pseudoephedrine 120 mg, combined in one repeat-action tablet; 3 doses over 2 days (n = 30) 2) Azatadine maleate 1 mg, 3 doses over 2 days (n = 30) 3) Pseudoephedrine 120 mg, in a repeat-action tablet (60 mg in coating and 60 mg in core), 3 doses over 2 days (n = 30) 4) Placebo, 3 doses over 2 days (n = 30) Duration of study treatment: 2 days (treatment given and patients assessed on-site) No mention of rescue med Patients abstained from antihistamines and decongestants for 12 hours and systemic steroids for at least 4 weeks before reporting for treatment Dates: Single pollen season, 1978 Location: Denver, CO Setting: Outpatient Type(s) of providers: NR	No. of subjects at start: 120 Dropouts/withdrawals: 3 No. of subjects at end: 117 Inclusion criteria: Seasonal allergic rhinitis based on history and positive skin test Exclusion criteria: Pregnant women; hypersensitivity to study drugs; illnesses that contraindicate antihistamine or sympathomimetic amine use Age: 18 or older Sex: No difference among groups, values not reported Race: NR Other:	1) Patient-assessed symptom severity: frequency of nose blowing and sneezing graded on scale of 1 (1) to 8 (more than 15); severity of runny nose, nasal stuffiness, watery eyes, and itching of eyes, nose, and throat graded on scale of 0 (none) to 3 (severe); scores recorded hourly from 8:00 AM to 4:00 PM (both days), then again from 6:00 to 10:00 PM (first day only) 2) Adverse events: Symptom scoring cards given to patients included questions about drowsiness, dizziness, jitteriness, nausea, and headache	1) Patient-assessed symptom severity: Active treatments superior to placebo, $P < 0.10$; combination treatment superior ($P < 0.05$) to both azatadine and placebo. Reductions in mean total symptom score: 70% combination 52% azatadine 43% pseudoephedrine 11% placebo Reductions in mean nasal congestion symptom score: 68% combination 35% azatadine 62% pseudoephedrine 11% placebo 2) Adverse events: Most common = drowsiness (mild-moderate severity) in 30 of 111 (27%), higher in azatadine (50%) and combination groups (30%), $P < 0.10$. Jitteriness higher in pseudoephedrine group ($P < 0.10$). Other reactions insomnia, dizziness, nervousness, dry nose, nausea, and headache. No withdrawals due to AEs.	Quality Scoring: Population similar: Not adequately described Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 1b Randomized: Yes Allocation concealed: Yes Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: No Notes:

Evidence Table 4: Combined Treatments (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Falliers and Redding, 1980 **Study 2 (perennial allergic rhinitis)**	Design: RCT, parallel-group Interventions: 1) Azatadine maleate 1 mg + pseudoephedrine 120 mg, combined in one repeat-action tablet, 2 times per day (n = 10) 2) Azatadine maleate 1 mg, 2 times per day (n = 10) 3) Pseudoephedrine 120 mg, in a repeat-action tablet (60 mg in coating and 60 mg in core), 2 times per day (n = 11) 4) Placebo, 2 times per day (n = 10) Duration of study treatment: 6 weeks No mention of rescue med No pre-trial washout period described Dates: Single pollen season 1978 Location: Denver, CO Setting: Outpatient Type(s) of providers: NR	No. of subjects at start: 41 Dropouts/withdrawals: 2 No. of subjects at end: 39 Inclusion criteria: Perennial allergic rhinitis (based on history) Exclusion criteria: Pregnant women; hypersensitivity to study drugs; illnesses that contraindicate antihistamine or sympathomimetic amine use Age: 18 or older Sex: No difference among groups, values not reported Race: NR Other:	1) Patient-assessed symptom severity: rhinorrhea, sneezing, itchy nose, itchy eyes, tearing, conjunctivitis, and nasal congestion graded by patients on scale of 0 (none) to 3 (severe) during clinic visits at baseline and weeks 2, 4, and 6 2) Investigator global assessment of efficacy 3) Patient global assessment of efficacy: Assessed at last clinic visit (6 weeks); method of assessment not described 4) Adverse events: Patients asked about AEs at each clinic visit (2, 4, and 6 weeks); physicians specifically asked to note presence/absence of drowsiness	1) Patient-assessed symptom severity: Active treatments superior to placebo, $P < 0.10$; combination treatment superior ($P < 0.05$) to both azatadine and placebo. Reductions in mean total symptom score: 82% combination 58% azatadine 55% pseudoephedrine 9% placebo Reductions in mean nasal congestion symptom score: 73% combination 27% azatadine 63% pseudoephedrine 10% placebo 2) Investigator global assessment of efficacy: Not abstracted 3) Patient global assessment of efficacy: Overall response, all active preparations superior to placebo, $P < 0.01$, in decreasing order of preference: combination therapy, azatadine, pseudoephedrine, placebo 4) Adverse events: Most common = drowsiness (mild-moderate severity) in 8 of 41 (20%), higher in azatadine (50%) and combination groups (30%), $P < 0.10$	Quality Scoring: Population similar: Not adequately described Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 1b Randomized: Yes Allocation concealed: Yes Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: No Notes:

Evidence Table 4: Combined Treatments (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Finn, Aaronson, Korenblat, et al., 1998	Design: RCT, crossover, allergic and nonallergic patients randomized separately Interventions: 1) Terfenadine (60 mg bid) + ipratropium bromide nasal spray 0.03% (42 µg per nostril tid) 2) Terfenadine (60 mg bid) + placebo nasal spray tid Duration of study treatment: 2 weeks for each treatment, with a 1-week washout period between periods 1-week run-in/baseline period; no anticholinergic agents, antihistamines, sympathomimetic decongestants, nasal/ocular cromolyn, prostaglandin inhibitors, tranquilizers with anticholinergic effects, or glucocorticosteroids permitted before or during study. Dates: NR Location: US Setting: 7 outpatient centers Type(s) of providers: Specialists	No. of subjects at start: 205 (114 allergic, 91 nonallergic) Dropouts/withdrawals: 16 excluded from efficacy analysis: 3 with seasonal allergic rhinitis 13 completed only 1st treatment period 15 noncompleters: 8 patients due to AEs 5 administrative reasons 2 protocol violations No. of subjects at end: 190 completed; 189 used in efficacy and safety evaluations Inclusion criteria: Perennial rhinitis (allergic or nonallergic) with clinically significant rhinorrhea; allergic rhinitis defined by positive skin tests; rhinorrhea severity score ≥ 2 for 2 hours per day Exclusion criteria: Complete nasal obstruction; sinusitis; abnormal radiograph; upper or lower respiratory infection; rhinitis medicamentosa; glaucoma; BPH; hypersensitivity to study meds Age: Range 18-75, mean 40.1 Sex: 59% F, 41% M Race: 90% white Other:	1) Patient-assessed symptom severity: rhinorrhea graded for severity once daily on a scale of 0 (none) to 5 (very severe) and for duration by the number of hours daily between 8 AM and 8 PM; severity of sneezing and congestion graded once daily on scale of 0-5 (as above) 2) Investigator global assessment of efficacy 3) Patient global assessment of efficacy: overall control of nasal symptoms graded at biweekly clinic visits on scale of 0 (none) to 3 (excellent) 4) Adverse events: Patients queried about AEs at each biweekly clinic visit; investigators instructed to record all AEs regardless of possible relationship to study drugs	1) Patient-assessed symptom severity: Rhinorrhea severity decreased from 2.85 at baseline to 1.78 (38% reduction) with combined therapy (P = 0.0001); 10% additional reduction over terfenadine + placebo. Rhinorrhea duration decreased from 6.04 at baseline to 1.78 (46% reduction) with combined therapy (P = 0.0001); 16% additional reduction over terfenadine + placebo. No statistical differences between treatment groups for congestion and sneezing. 2) Investigator global assessment of efficacy: Not abstracted 3) Patient global assessment of efficacy: Good to excellent control of rhinorrhea: 69% in combined therapy vs. 53% in terfenadine + placebo (P = 0.0008). Good to excellent control of sneezing: higher in combined therapy group, P = 0.0452. No difference in control of congestion. 4) Adverse events: N = 63 (32%) combined therapy (31 [16%] possibly drug-related) N = 31 (16%) terfenadine + placebo (14 [7%] possibly drug-related). Higher % of blood-tinged nasal mucus 6.6% vs. 0.5% (combined vs. terfenadine alone), epistaxis (5.1% vs. 1.5%), and nasal dryness (2.5% vs. 1.5%).	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 1b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: No Notes:

Evidence Table 4: Combined Treatments (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Grosclaude, Mees, Pinelli, et al., 1997	Design: RCT, parallel-group Interventions: 1) Pseudoephedrine 120 mg (extended-release) bid + cetirizine 5 mg bid (n = 230) 2) Pseudoephedrine 120 mg (extended-released) bid (n = 226) 3) Cetirizine 5 mg bid (n = 231) Duration of study treatment: 2 weeks No rescue med permitted No pre-trial washout period described; patients who had taken following drugs, in time frame indicated, were excluded: astemizole (6 weeks); systemic cortico-steroids, ketotifen, or MAOIs (2 weeks); topical cortico-steroids or sedative (1 week); nasal decongestants, anti-histamines, or nasal or ocular cromoglycate (2 days) Dates: Mar-Sept 1992 Location: France and Germany Setting: 43 centers (30 France, 13 Germany) Type(s) of providers: NR	No. of subjects at start: 687 Dropouts/withdrawals: 71 total n = 30 lack of efficacy n = 22 adverse events n = 19 unrelated to drug, mostly protocol violations No. of subjects at end: 616 completers Inclusion criteria: Pollen-associated allergic rhinitis of 1 year or more; positive skin or RAST tests to seasonal allergens Exclusion criteria: Asthma requiring change in treatment or systemic/inhaled steroids; atopic dermatitis requiring antihistamines or systemic/topic steroids; upper respiratory infection; nasal polyposis; septal deviation; infection requiring antibiotics; many comorbid illnesses; escalating doses of desensitization therapy; drug trial in previous 3 months Age: Range 9-66, mean 32 Sex: 48-53% M, 47-52% F Race: NR Other:	1) Patient-assessed symptom severity: nasal obstruction, sneezing, rhinorrhea, nasal pruritus, and ocular pruritus graded once per day on scale of 0 (absent) to 3 (severe/ hampering daily activities or sleep) 2) Investigator-assessed symptom severity 3) Investigator global assessment of efficacy 4) Adverse events: Not clear how reported/ recorded; all AEs recorded regardless of possible relationship to study drugs	1) Patient-assessed symptom severity: Median proportion of "comfortable" days (symptoms absent or mild): 53.3% combination, 30.8% cetirizine, 33.3% pseudoephedrine, P < 0.001 5-symptom mean score over total treatment: 0.85 combination, 1.03 cetirizine, and 1.14 pseudoephedrine, P < 0.001 for combo vs. cetirizine, P < 0.001 for combo vs. pseudoephedrine Results of 4-symptom score, excluding blocked nose, showed similar difference between combination vs. cetirizine or pseudoephedrine, P < 0.001. Individual symptom scores showed significant difference for combination vs. cetirizine (P ≤ 0.01) for all symptoms except itchy eyes, and vs. pseudoephedrine for all symptoms except nasal congestion. 2) Investigator-assessed symptom severity: Not abstracted 3) Investigator global assessment of efficacy: Not abstracted 4) Adverse events: 68 (29.6%) combination 68 (30.1%) pseudoephedrine 54 (23.4%) cetirizine Severe AEs: 17 (7.4%) combination 15 (6.6%) pseudoephedrine 7 (3%) cetirizine Withdrawals due to AEs: 9 (3.9%) combination 7 (3.1%) pseudoephedrine	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 1b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: No Notes:

(continued on next page)

Evidence Table 4: Combined Treatments (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
				6 (2.6%) cetirizine Common AEs: Combination: Headache, insomnia Cetirizine: Somnolence, headache, asthenia Pseudoephedrine: Insomnia, headache, dry mouth	
Henauer, Seppey, Huguenot, et al., 1991	Design: RCT, parallel-group Interventions: 1) Terfenadine 60 mg (rapid-release) + pseudoephedrine 120 mg (extended-release), combined in one tablet, taken twice per day (n = 25) 2) Terfenadine 60 mg (rapid-release) bid (n = 25) Duration of study treatment: 2 weeks No mention of rescue med No pre-trial washout period described Dates: NR Location: Switzerland Setting: Outpatient Type(s) of providers: Allergy specialist	No. of subjects at start: 50 Dropouts/withdrawals: 3 withdrew due to AEs (2 combo, 1 terfenadine) No. of subjects at end: Results reported on 50 patients Inclusion criteria: Perennial rhinitis Exclusion criteria: Allergy to animals; other relevant concomitant diseases and therapies Age: 35 (SD, 9) M; 27 (8) F Sex: 21 M, 29 F Race: NR Other:	1) Investigator global assessment of improvement 2) Investigator-assessed symptom severity 3) Patient-assessed symptom severity: nasal congestion, sneezing, rhinorrhea, itchy nose and/or throat, itchy eyes, watery eyes, and red eyes graded once daily on a scale of 0 (no symptom) to 3 (symptom very troublesome) 4) Adverse events: Assessed at clinic visits at 1 and 2 weeks using check list of potential AEs (drowsiness, nervousness, headache, insomnia, dry mouth, nausea, palpitation) 5) Rhinoscopy assessments (swelling and hyperemia of nasal mucosa, nasal secretion, and nasal obstruction) 6) Acceptability of treatment: Patients asked	1) Investigator global assessment of improvement: Not abstracted 2) Investigator-assessed symptom severity: Not abstracted 3) Patient-assessed symptom severity: All 7 symptoms improved according to patient ratings, appeared to favor combination, but differences between groups were not statistically significant (actual data not shown). 4) Adverse events: 20/25 patients in combination group 9/25 patients in terfenadine group P = 0.004 Frequent AEs: Insomnia (13 vs. 3), dry mouth (11 vs. 2), headache (8 vs. 4) 5) Rhinoscopy assessments: Not abstracted 6) Acceptability of treatment: 15 (65%) combination 18 (78%) terfenadine	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: No Objectively confirmed: No Outcome measures valid: No Level of evidence: 1b Randomized: Yes Allocation concealed: Yes Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: Yes Notes:

(continued on next page)

Evidence Table 4: Combined Treatments (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
			at final visit (2 weeks) if they would take the medication again		
Juniper, Kline, Hargreave, et al., 1989	Design: RCT, parallel-group; randomization stratified according to degree of sensitivity to ragweed Interventions: 1) Beclomethasone dipropionate aqueous nasal spray, 50 µg per nostril four times per day + astemizole 10 mg once per day (n = 30) 2) Beclomethasone dipropionate aqueous nasal spray, 50 µg per nostril four times per day (n = 30) 3) Astemizole 10 mg once per day (n = 30) Duration of study treatment: 6 weeks Patients instructed to take rescue med as follows if symptoms inadequately controlled by study med: for nasal symptoms, freon-propelled beclomethasone dipropionate nasal spray, one puff (50 µg) in each nostril, up to 4 times per day; for eye symptoms, naphazoline HCl and anatazoline ophthalmic drops, one drop in each eye, up to 4 times per day; sodium cromoglycate eye drops, up to 4 times per day, permitted if this treatment insufficient	No. of subjects at start: 90 Dropouts/withdrawals: 1 due to med noncompliance No. of subjects at end: 89 Inclusion criteria: Rhino-conjunctivitis requiring treatment during 2 previous ragweed-pollen seasons; positive skin test to ragweed-pollen Exclusion criteria: Pregnant; lactating; astemizole, steroid nasal spray, or oral steroid within 6 weeks Age: Mean 39.8-42.2 (SD 11.8-13.8) Sex: 46 M, 44 F Race: NR Other:	1) Patient-assessed symptom severity: severity and duration of sneezing, stuffy nose, runny nose, eye symptoms, and asthma graded twice per day on scale of 0 (absent) to 3 (severe/continuous) 2) Use of rescue med: recorded by patients at end of each day in study diaries 3) Adverse events: Patients asked at regular clinic visits (weeks 1, 3, and 6) to report all non-rhinoconjunctivitis symptoms experienced since the previous visit, regardless ofwhether they perceived them to be related to study treatment 4) Treatment compliance: assessed by weighing nasal spray bottles and counting unused tablets (at end of study or at each clinic visit?)	1) Patient-assessed symptom severity (mean daily scores): Sneezing: Astemizole 0.395 Beclomethasone 0.193 Combination 0.155 p < 0.05, BEC vs. astemizole p < 0.05, combination vs. astemizole p = ns, combination vs. BEC Stuffy nose: Astemizole 0.594 Beclomethasone 0.319 Combination 0.322 p < 0.05, BEC vs. astemizole p < 0.05, combination vs. astemizole p = ns, combination vs. BEC Runny nose: Astemizole 0.406 Beclomethasone 0.152 Combination 0.192 p < 0.05, BEC vs. astemizole p < 0.05, combination vs. astemizole p = ns, combination vs. BEC Eye symptoms: Astemizole 0.424 Beclomethasone 0.563 Combination 0.335 Asthma: Astemizole 0.030 Beclomethasone 0.015 Combination 0.048 2) Use of rescue med: Beclomethasone use: Astemizole 0.871 Beclomethasone 0.206	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 1b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: Yes Notes: Double-dummy blinding technique employed. Intermittent pollen counts made throughout the study.

(continued on next page)

Evidence Table 4: Combined Treatments (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	No astemizole, steroid nasal spray, or oral steroids permitted within 6 weeks prior to enrollment Dates: Ragweed season Location: Canada Setting: Outpatient Type(s) of providers: Allergy specialists			Combination 0.241 p < 0.05, BEC vs. astemizole p < 0.05, combination vs. astemizole p = ns, combination vs. BEC Eye drop use: Astemizole 0.707 Beclomethasone 1.016 Combination 0.354 Asthma aerosol use: Astemizole 0.195 Beclomethasone 0.049 Combination 0.113 3) Adverse events: 16 astemizole (9 drowsiness, 3 hunger, 3 dryness, 1 headache) 16 beclomethasone (4 drowsiness, 3 hunger, 2 dryness, 2 nasal bleeding, 1 headache, 2 thirst, 2 skin irritation) 20 combination (4 drowsiness, 4 hunger, 2 dryness, 3 nasal bleeding, 3 headache, 1 thirst, 1 skin irritation, 2 nausea) 4) Treatment compliance: No differences between groups: Astemizole 99.3% pills, 91.8% placebo spray Beclomethasone 100.2% placebo pills, 94.1% spray Combination 99.2% pills, 91.3% spray	

Evidence Table 4: Combined Treatments (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Lanier, Gross, Marks, et al., 2001	Design: RCT, parallel-group Interventions: 1) Loratadine 10 mg once per day + olopatadine ophthalmic solution 0.1%, one drop in each eye 2 times per day (n = 45) 2) Loratadine 10 mg once per day (n = 49) Duration of study treatment: 1 week No mention of rescue med; immunotherapy and inhalers OK if use greater than 3 months Trial preceded by 1-week washout period Dates: May - Nov 1998 Location: US Setting: 3 outpatient sites Type(s) of providers: Family practice	No. of subjects at start: 94 Dropouts/withdrawals: 10 pts without follow-up or did not meet criteria for efficacy analysis 12 pts (6 per group) withdrew (3 AEs, 2 lost to follow-up, 4 protocol violations, 3 screen failure – numbers overlap with above). No. of subjects at end: 84 Inclusion criteria: Age ≥ 7; moderate-severe seasonal allergic conjunctivitis for at least one season (ocular itching, conjunctival redness); positive skin test Exclusion criteria: Pregnant; lactating; other ocular disorder; ocular surgery within 3 months; concomitant systemic, ocular, or nasal medications with potential to interfere with response to therapy Age: Mean 38, range 9-74 Sex: 33 (35%) M, 61 (65%) F Race: 81 (86%) white, 9 (10%) black, 4 (4%) other Other:	1) Patient-assessed symptom severity (*in-clinic*): During clinic visits on days 0, 3, and 7, patients graded ocular itching on scale of 1 (none/never) to 4 (very frequently/2 or more times each day) 2) Patient-assessed symptom severity (*diary data*): ocular itching and redness graded 4 times each day on scale of 0 (none) to 9 (severe) 3) Investigator-assessed symptom severity (immediate, post-dose ocular itching and redness) 4) Patient global assessment of efficacy for ocular symptoms: graded relative to baseline during clinic visits on days 3 and 7 on scale of 0 (clinical cure) to 5 (significantly clinically worse) 5) Investigator global assessment of efficacy for ocular symptoms 6) Quality of life: Assessed using the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) at baseline and end-of-treatment (day 7) clinic visits	1) Patient-assessed symptom severity (*in-clinic*): Itching (day 7): Combination 2.21, loratadine 2.74, P = 0.0436 2) Patient-assessed symptom severity (*diary data for 7 days*): Values shown in figures. Itching significantly lower on days 3, 4, and 6 in combination group (P < 0.05). Redness significantly lower on day 6 for combination. 3) Investigator-assessed symptom severity: Not abstracted 4) Patient global assessment of efficacy for ocular symptoms: Ocular symptoms (day 7): Combination 1.49, loratadine 2.15, P = 0.0022 5) Investigator global assessment of efficacy for ocular symptoms: Not abstracted 6) Quality of life: Overall mean score day 7: Combination 1.45 Loratadine 2.09 P < 0.05 Significant differences also noted for sleep, eye symptoms, activities, and emotions domains. 7) Adverse events: 13 total AEs from 10 patients 2 AEs due to loratadine use (1 asthenia and dry mouth, 1 dyspepsia); patients continued with study 2 AEs caused withdrawal (1 bronchitis,	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Not applicable Objectively confirmed: Not applicable Outcome measures valid: Yes Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: No Blinding adequate: Not applicable Dropouts described: Yes Intention-to-treat: Yes Note: Patients not blinded to treatment (no placebo eye drops).

(continued on next page)

Evidence Table 4: Combined Treatments (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
			7) Adverse events: Both spontaneous and elicited AEs recorded throughout study (method of eliciting not described); AEs defined as "any changes from baseline other than efficacy parameters in a patient's ophthalmic or medical condition"	1 allergy exacerbation)	
Lau, Wei, Van Hasselt, et al., 1990	Design: RCT, parallel-group Interventions: 1) Budesonide nasal aerosol 200 µg bid + oxymetazoline nasal drop pipette (0.5 mg/ml), 3 drops 15 minutes before administration of budesonide for first 3 days only (n = 47) 2) Budesonide nasal aerosol 200 µg bid (n = 48) 3) Terfenadine 60 mg bid (n = 47) Duration of study treatment: 3 weeks No mention of rescue med No pre-trial washout period; pts who had received other steroid treatment during previous 4 weeks were excluded Dates: June 1986-May 1988 Location: Hong Kong Setting: Outpatient	No. of subjects at start: 142 Dropouts/withdraw als: 12 4 due to AEs (1 nasal pain due to budesonide, 1 HA from budesonide, 2 ulcer pain from taking terfenadine) 8 lost to follow-up No. of subjects at end: 130 Inclusion criteria: Age 15-70; perennial rhinitis for 2 years; blocked nose and 2 other symptoms (runny nose, itchy nose, sneezing) Exclusion criteria: Steroid treatment within 4 weeks; infection; nasal polyps; septal deviation; pregnant; lactating Age: Mean 26.7 (range 15-68) Sex: 65 M, 77 F Race: 140 Chinese, 2 Indian Other:	1) Patient-assessed symptom severity: blocked nose, runny nose, itchy nose, sneezing bouts, sore eyes, and runny eyes graded once per day on scale of 0 (no symptoms) to 3 (severe/ sufficiently troublesome to interfere with daily activity or sleep) 2) Patient global assessment of efficacy: treatment graded as ineffective, slightly effective, moderately effective, and extremely effective during last clinic visit (3 weeks) 3) Adverse events: AEs noted on diary cards; patients asked non-leading question about AEs during clinic visits at 1 and 3 weeks	1) Patient-assessed symptom severity: Values shown in figures. Improvement for all nasal symptoms in the two budesonide groups compared to baseline ($P < 0.05$). Terfenadine improved only in nasal blockage compared to baseline ($P < 0.05$). Between-group comparison showed two budesonide groups better than terfenadine group ($P < 0.05$) Budesonide with oxymetazoline showed faster relief than budesonide alone, 1 day vs. 7 days, $P < 0.05$. 2) Patient global assessment of efficacy: No significant differences among the three groups. 3) Adverse events: N = 6 budesonide + oxymetazoline (2 nasal irritation, 2 throat irritation, 2 headache, 1 GI distress) N = 10 budesonide (3 nasal irritation, 2 headache, 2 GI distress, 1 each dizziness, nausea, and other) N = 17 terfenadine (10 gi distress, 3 nasal irritation, 1 each dizziness, nausea, dry mouth, and other)	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: No Objectively confirmed: No Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: Can't determine Note: Double-dummy blinding technique employed. *(continued on next page)*

Evidence Table 4: Combined Treatments (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	Type(s) of providers: Otolaryngology				
Meran, Morse, and Gibbs, 1990	Design: RCT, crossover Interventions: 1) Acrivastine 8 mg + pseudoephedrine 60 mg, 3 times daily 2) Acrivastine 8 mg, 3 times daily 3) Pseudoephedrine 60 mg, 3 times daily 4) Placebo Duration of study treatment: 6 days each treatment period, with a 1-day washout between periods No rescue med permitted Trial preceded by washout period of 24 hours to 1 month, depending on pre-trial medication Dates: Apr-Jul 1984 Location: Switzerland Setting: Outpatient Type(s) of providers: Otolaryngology	No. of subjects at start: 40 (3 with perennial rhinitis, 37 with seasonal rhinitis) Dropouts/withdrawals: 5 noncompleters – 3 withdrew due to lack of treatment effect (placebo group), 1 left country, 1 due to headache associated with pseudoephedrine. Data up to withdrawal included in analysis. No. of subjects at end: 40 Inclusion criteria: Age 12-70; seasonal allergic rhinitis; positive skin test to mixed grasses Exclusion criteria: Nasal deformity; patients who operated dangerous machinery; other acute or chronic disease; pregnant, lactating, or not on contraception Age: Mean 28, range 17-56 Sex: 15 M, 25 F Race: NR Other:	1) Patient-assessed symptom severity: sneezing, itchy nose/throat, runny nose, blocked nose, watery eyes, itchy eyes, and overall symptoms graded at end of each day on scale of 0 (no symptoms) to 9 (very severe) 2) Patient global assessment of efficacy: graded on day 7 of each treatment period as excellent, good, satisfactory, poor, or abysmal 3) Investigator global assessment of efficacy 4) Acceptability/patient preference: Patients asked on day 7 of each treatment period if they would continue with the current treatment if that treatment were available 5) Adverse events: Incidence of AEs recorded during day 7 clinic visit of each treatment period, as reported spontaneously or in response to indirect questioning	1) Patient-assessed symptom severity: Overall symptom score: Placebo 3.37, pseudoephedrine 2.92, acrivastine 2.04 **, combination 1.66** ** P < 0.01 vs. placebo. No significant difference between acrivastine and combination. Combination significantly better than acrivastine, P < 0.01, for symptoms of sneezing, itchy nose/throat, runny nose, blocked nose, and watery eyes (mean values available from table). 2) Patient global assessment of efficacy: Values shown combine patient and investigator responses; no significant differences between patient and MD responses. Pseudoephedrine better than placebo (P < 0.01); acrivastine alone or in combination better than placebo or pseudoephedrine (P < 0.01). 3) Investigator global assessment of efficacy: Not abstracted 4) Acceptability/patient preference: 45% placebo, 69% pseudoephedrine, 82% acrivastine,** 87% for combination** **P < 0.01 vs. placebo 5) Adverse events: 16 placebo group 18 pseudoephedrine group 7 acrivastine group 19 combination group More insomnia with pseudoephedrine	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 1b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: [??] Intention-to-treat: Yes Note: Double-dummy blinding technique employed.

(continued on next page)

Evidence Table 4: Combined Treatments (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
				than with placebo or acrivastine, P < 0.05. More fatigue with placebo than with pseudoephedrine, P < 0.01.	
Negrini, Troise, Voltolini, et al., 1995	Design: RCT, parallel-group Interventions: 1) Astemizole 10 mg + pseudoephedrine 240 mg once daily (n = 102) 2) Beclomethasone nasal spray (0.05 mg/ml), 2 puffs per nostril twice per day (n = 102) Duration of study treatment: 4 weeks Vasoconstrictor eye drops (phenylephrine, xylo-metazoline, or naphazoline) provided for use as rescue med Trial preceded by washout period ranging from 3 days to 6 weeks, as follows: decongestants (3 days); oral antihistamines (3 days, except for astemizole [6 weeks]); topical corticosteroids and sodium cromoglycate (2 weeks); oral corticosteroids (1 month); immunotherapy (1 month) Dates: 1992 hay fever season Location: Austria, Belgium, Germany, Italy Setting: Outpatient	No. of subjects at start: 204 Dropouts/withdrawals: Total of 31 patients (15 astemizole-D group, 16 beclomethasone); 12 withdrew due to AEs (9 and 3, respectively); 8 withdrew from treatment inefficacy (4 per group); 1 lost to follow-up; 1 lack of symptoms in beclomethasone group No. of subjects at end: 173 Inclusion criteria: Age 12-70 with 1-year history of seasonal allergic rhinitis requiring therapy; positive skin test or RAST for pollen; moderately severe nasal congestion and at least one other nasal symptom of moderate severity Exclusion criteria: Pregnancy; serious concurrent medical illness; concomitant therapy that could interfere with assessment Age: Astemizole-D mean 28.4 (range 12-66) Beclomethasone mean 29.2 (13-66) Sex: Astemizole-D 56 M/46 F Beclomethasone 54 M/48 F Race: NR Other:	1) Use of rescue med (eye drops): recorded by patients in study diaries 2) Investigator-assessed symptom severity 3) Patient-assessed symptom severity: sneezing, rhinorrhea, nasal itching, congestion, and concurrent ocular symptoms graded daily on scale of 0 (absent) to 3 (severe); severity of rhinitis also graded daily using a visual analog scale ranging from "absent" to "very severe" 4) Investigator global evaluation of efficacy 5) Patient global evaluation of efficacy: effect of therapy graded at end of trial as "excellent," "good," "moderate," or "poor" 6) Adverse events: recorded by patients in study diaries	1) Use of rescue med (eye drops): Astemizole-D: 16% of patients, mean frequency of use 5.5% of treatment days (P < 0.05 compared to beclomethasone) Beclomethasone: 29%, mean frequency of use 10% of treatment days 2) Investigator-assessed symptom severity: Not abstracted 3) Patient-assessed symptom severity: Mean (SEM) Area under the Curve results shows in Figure 1 (1st 2 weeks of therapy) and Figure 2 (entire study period) No significant difference in nasal congestion, sneezing, rhinorrhea, nasal itching, VAS rhinitis, total nasal, or total symptom scores. Trend towards fewer ocular symptoms on astemizole-D (P = 0.07) at end of study (at 2 weeks P = 0.03). 4) Investigator global evaluation of efficacy: Not abstracted 5) Patient global evaluation of efficacy: Excellent or good response: Astemizole-D: 63% Beclomethasone: 72% 6) Adverse events: Astemizole-D 38 pts (38%) Beclomethasone 26 pts (27%) No statistically significant difference Most common = headache (7 pts	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 1b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: Yes Note: Double-dummy blinding technique employed. *(continued on next page)*

Evidence Table 4: Combined Treatments (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	Type(s) of providers: Specialists (allergy and ENT)			asthemizole, 3 beclomethasone), dry mouth (9, 1), nausea (4,4), somnolence (5,2) and fatigue (4,1)	
Panda and Mann, 1998	Design: RCT, parallel-group Interventions: 1) Terfenadine 60 mg + pseudoephedrine 120 mg (10 mg immediate-release and 110 mg extended-release), combined in one tablet, 2 times per day (n = 22) 2) Terfenadine 60 mg 2 times per day (n = 19) Duration of study treatment: 2 weeks Rescue med not permitted No pre-trial washout period described; patients who had taken oral or topical steroids or sodium cromoglycate in the previous month, and those who had taken antihistamines or decongestants in the previous 48 hours, were excluded Dates: NR Location: India Setting: Outpatient Type(s) of providers: Otolaryngology	No. of subjects at start: 41 Dropouts/withdrawals: 4 due to AEs (2 per group) 5 lost to follow-up (5 combo, 1 single) No. of subjects at end: 32 completers, but results shown for 31 subjects Inclusion criteria: Moderate-severe allergic rhinitis Exclusion criteria: Hyper-sensitivity to study meds; pregnant, lactating, or not on contraception; renal, cardiac, or respiratory disorder; non-responsive to antihistamines (new and classic); immunotherapy Age: Range 15-56 Sex: 23 M, 18 F Race: NR Other:	1) Patient *and* investigator global assessment of efficacy: graded by patient and physician together (?) at 2 weeks on scale ranging from excellent (virtually all signs and symptoms stopped [reduction of 90% or more]) to poor/no response/deterioration 2) Patient global assessment of efficacy *and* adverse events: graded at 2 weeks on scale ranging from excellent (excellent efficacy with no or mild side effects) to poor 3) Investigator global assessment of efficacy and adverse events 4) Adverse events: Recorded at clinic visits at 1 and 2 weeks	1) Patient *and* investigator global assessment of efficacy: Excellent: 10/22 (45.5%) combination group, 2/19 (10.5%) single treatment group Good: 6/22 (27.3%) combination group, 7/19 (36.8%) single treatment group Fair: 4/19 (21%) single treatment group Poor: 3/19 (5.7%) single treatment group. P = 0.0485 2) Patient global assessment of efficacy: Excellent: 10/22 (45.5%) combination group, 2/19 (10.5%) single treatment group Good: 6/22 (27.2%) combination group, 6/19 (31.5%) single treatment group Fair: 5/19 (26.3%) single treatment group Poor: 3/19 (15.7%) single treatment group. P = 0.0236 3) Investigator global assessment of efficacy and adverse events: Not abstracted 4) Adverse events (treatment discontinued): 2 AEs in combination group (cloudy urine, dizziness/insomnia) 2 AEs in single treatment group (somnolence, insomnia)	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: No Objectively confirmed: No Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: No Notes:

Evidence Table 4: Combined Treatments (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Purello-D'Ambrosio, Isola, Ricciardi, et al., 1999	Design: RCT, parallel-group Interventions: 1) Flunisolide, two 25-µg puffs per nostril twice per day + loratadine 10 mg once per day (n = 15) 2) Flunisolide, two 25-µg puffs per nostril twice per day + placebo once per day (n = 15) Duration of study treatment: 3 weeks Rescue med not permitted Trial preceded by 8-week washout period Dates: NR Location: Italy Setting: Outpatient Type(s) of providers: Allergy specialist	No. of subjects at start: 30 Dropouts/withdrawals: 0 No. of subjects at end: 30 Inclusion criteria: Nonallergic rhinitis with eosinophilia for at least 3 years; symptom score ≥ 5; eosinophil count > 10% Exclusion criteria: Positive skin test or positive IgE tests to common allergens; nasal polyposis or sinusitis; on drugs that would interfere with treatment; severe disease; pregnant or lactating women Age: Mean 38.7 (range 32-48) Sex: 12 M, 18 F Race: NR Other:	1) Patient-assessed symptom severity: sneezes, rhinorrhea, and nasal blockage graded daily on scale of 0 (no symptoms) to 3 (severe symptoms) 2) Investigator-assessed symptom severity 3) Eosinophil counts 4) Adverse events: Patients instructed to record any unexpected symptom on their diary cards, along with its duration, severity, and presumed relationship to treatment	1) Patient-assessed symptom severity: Flunisolide + loratadine group had decrease in sneezing compared to flunisolide alone (change of 73.4% vs. 46.6%, P < 0.000001); rhinorrhea (66.7% vs. 26.7%, P < 0.0006). No differences in nasal blockage (19.9% vs. 20.0%). 2) Investigator-assessed symptom severity: Not abstracted 3) Eosinophil counts: Not abstracted 4) Adverse events: 2 AEs total (1 per group), both subjects with nasal irritation.	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Not applicable Objectively confirmed: Not applicable Outcome measures valid: No Level of evidence: 1b Randomized: Yes Allocation concealed: Yes Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: Yes Notes:

Evidence Table 4: Combined Treatments (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Ratner, van Bavel, Martin, et al., 1998	Design: RCT, parallel-group Intervention(s): 1) Fluticasone propionate aqueous nasal spray (two 50-µg sprays per nostril once per day + loratadine 10 mg once per day (FP+LOR) (n = 150) 2) Fluticasone propionate aqueous nasal spray (two 50-µg sprays per nostril once per day (FP) (n = 150) 3) Loratadine 10 mg once per day (LOR) (n = 150) 4) Placebo (n = 150) Duration of study treatment: 2 weeks No rescue med permitted Trial preceded by 7- to 30-day run-in period. In addition, patients who had taken following drugs, in time frame indicated, were excluded: loratadine (1 week); astemizole (6 weeks); cromolyn sodium (2 weeks); other OTC or prescription drugs that might affect rhinitis symptomatology (e.g., nasal decongestants) (72 hours); inhaled, intranasal, or systemic corticosteroids (1 month). Dates: Actual dates NR, during mountain cedar allergy season	No. of subjects at start: 600 Dropouts/withdrawals: 31 total 8 due to AEs 13 due to lack of efficacy 7 withdrew from other reasons 3 lost to follow-up No. of subjects at end: 569 Inclusion criteria: Seasonal AR (positive skin test to mountain cedar allergen, nasal mucosa allergic changes, seasonal symptoms over 2 or more seasons); moderate-severe symptoms on diary during run-in period Exclusion criteria: Loratadine within 1 week; astemizole within 6 weeks; cromolyn NA within 2 weeks; OTC nasal meds within 72 hours; steroids (MDI, nasal, oral) within 1 month; septal deviation, nasal polyp; history of nasal septal surg/perforation; candida infection; pregnant/lactating; other impairment Age: 12 or older Sex: 272 M (45.3%), 328 (54.7%) Race: 462 white (77%); 106 Hispanic (17.7%); 32 other (5.3%) Other:	1) Investigator-assessed symptom severity 2) Patient-assessed symptom severity: sneezing, nasal blockage, rhinorrhea, and nasal itching graded once per day on visual analog scale ranging from 0 (absent) to 100 (severe) 3) Investigator global evaluation of treatment efficacy 4) Patient global evaluation of treatment efficacy: overall response to treatment graded at end of trial on 7-point scale ranging from "significant improvement" to "significant worsening" 5) Quality of life: assessed using the Rhinoconjunctivities Quality of Life Questionnaire (RQLQ) at baseline and 2 weeks 6) Adverse events: Defined as any untoward medical occurrence, drug-related or not; recorded by clinicians during clinic visits at 1 and 2 weeks	1) Investigator-assessed symptom severity: Not abstracted 2) Patient-assessed symptom severity: Values shown in Figure 1 FP+LOR vs. FP alone, P = 0.006 days 1-7, and P = 0.017 days 8-14 FP+LOR and FP alone vs. LOR, P < 0.05; vs. placebo, P < 0.001 3) Investigator global evaluation of treatment efficacy: Not abstracted 4) Patient global evaluation of treatment efficacy: Values shown in Figure 3 FP alone and FP+LOR more effective than placebo or LOR alone (P < 0.001). No difference between FP alone vs. FP+LOR. No difference between placebo and LOR. 5) Quality of life (global RQLQ score): Mean change score (SEM): Placebo: -1.3 (0.1) LOR alone: -1.3 (0.1) FP alone: 2.2 (0.1), P < 0.05 vs. placebo or LOR FP+LOR: 2.3 (0.1), P < 0.05 vs. placebo or LOR 6) Adverse events: 5-8% each group with AEs due to study drug 1-2% blood in nasal mucus in active treatment groups, 3% blood in nasal mucus in placebo ≤1% epistaxis all groups ≤2% xerostomia all groups	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: Yes Level of evidence: 1b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: Yes Notes: Double-dummy blinding technique employed. Patient population: 90% PC, 10% allergy

(continued on next page)

Evidence Table 4: Combined Treatments (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	Location: South central Texas Setting: Professional research centers Type(s) of providers: Research center MDs				
Simpson, 1994	Design: RCT, parallel-group Interventions: 1) Budesonide nasal spray, 200 µg (2 puffs in each nostril) bid + terfenadine 60 mg bid (n = 32) 2) Terfenadine 60 mg bid (n = 23) 3) Budesonide nasal spray, 200 µg (2 puffs in each nostril) bid (n = 30) 4) Placebo (n = 21) Duration of study treatment: 3 weeks Xylometazoline or metazoline eye drops could be used for "troublesome eye symptoms"; no other rescue med permitted No pre-trial washout period described; patients taking oral corticosteroids at the time of recruitment, or who had had desensitization therapy in previous 12 months, were excluded Dates: May 1-Aug 31	No. of subjects at start: 143 Dropouts/withdrawals: 6 records unusable 20 withdrew due to lack of efficacy (12 from placebo group) 3 withdrew due to AEs 5 noncompliant with follow-up 3 protocol violations No. of subjects at end: 106 Inclusion criteria: Age ≥ 15; hay fever between May 1 and Aug 31 for ≥ 2 years; 2 symptoms (blocked nose, runny nose, itching nose, sneezing) Exclusion criteria: Oral steroids; upper respiratory infection; desensitization treatment within 12 months; hay fever symptoms outside specified period; pregnancy Age: Mean 25.7-29.7 (SD 7.8-12.4) Sex: Placebo 71% M, 29% F Budesonide 43% M, 57% F Terfenadine 53% M, 47% F Combination 41% M, 39% F Higher proportion of men in placebo group	1) Patient-assessed symptom severity: blocked nose, sneezing, nasal itching, runny nose, sore eyes, and runny eyes graded at end of each day on scale of 0 (no symptoms) to 3 (severe symptoms/discomfort experienced during most waking hours) 2) Patient global assessment of efficacy: graded on scale of 0 (ineffective) to 3 (very effective) at end-of-trial clinic visit (3 weeks) 3) Use of rescue med (eye drops): Number of drops used recorded each day by patients on diary cards 4) Adverse events: Not clear who reported/ recorded	1) Patient-assessed symptom severity: Mean symptom scores at 1 week shown in figure. Terfenadine reached maximum efficacy within 1-2 days; budesonide scores were lower than terfenadine after 2-3 days and continued to improve over days 3-7. Combination treatment had similar effect to budesonide alone. Mean symptom scores at week 3 graphically shown. Terfenadine resulted in significant ($P < 0.05$) reductions in symptom scores for runny and itchy nose compared to placebo. Budesonide alone reduced all mean symptom scores compared to placebo ($P < 0.05$); also more than terfenadine but only statistically significant for nasal blockage. Combination therapy symptom scores were similar to budesonide for blocked/itchy/runny nose. Combination reduced mean sneezing score than terfenadine or budesonide alone ($P < 0.05$). 2) Patient global assessment of efficacy: Proportion rating treatment as noticeably effective or very effective: Placebo 40%, terfenadine 46%, 85% budesonide alone or in combination. $P < 0.05$ for budesonide alone or in combination vs. placebo or terfenadine.	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: No Objectively confirmed: No Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: No Note: Double-dummy blinding technique employed.

(continued on next page)

Evidence Table 4: Combined Treatments (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	Location: UK Setting: Outpatient Type(s) of providers: Primary care	Race: NR Other:		3) Use of rescue med (eye drops): Eye drop use in all groups remained constant; use in budesonide group higher than terfenadine group (NS) 4) Adverse events: 19 total AEs (5 placebo, 2 terfenadine, 7 budesonide, 8 combination). Most common sneezing and nasal irritation (1 combination pt with palpitations) 3 withdrawals due to AE (1 placebo pt with nausea, 1 budesonide patient with fatigue, 1 combination patient with sneezing and headache)	
Sussman, Mason, Compton, et al., 1999	Design: RCT, parallel-group Interventions: 1) Fexofenadine 60 mg + pseudoephedrine 120 mg (extended-release), twice per day (n = 215) 2) Fexofenadine 60 mg twice per day (n = 218) 3) Pseudoephedrine 120 mg (extended-release) twice per day (n = 218) Duration of study treatment: 14-20 days Rescue med not permitted Trial preceded by a 3- to 5-day placebo run-in period; no other washout period described Dates: NR Location: Canada	No. of subjects at start: 651 Dropouts/withdrawals: 63 discontinued therapy (3.8% subject/MD decision, 2.8% AEs) No. of subjects at end: 588 Inclusion criteria: Age 12-65; ragweed allergy confirmed by positive skin test; clinical response to antihistamines Exclusion criteria: Hyper-sensitivity to drug, URI or sinusitis within 30 days, alcohol or drug abuse, pregnant or lactating women Age: Mean 31.7-34.9 (SD 11.12-12.35) Sex: 275 M (42%), 376 F (58%) Race: 566 (87%) white, 35 (5%) black, 42 (6%) Asian, 8 (1%) multiracial	1) Patient-assessed symptom severity: sneezing; rhinorrhea; itchy nose, palate, and/or throat; itchy, watery, or red eyes; and nasal congestion graded twice each day (7 PM and bedtime) on scale of 0 (symptom absent) to 4 (symptom so severe as to warrant an immediate visit to the physician) TSS = total symptom score; NCS = nasal congestion score 2) Adverse events: Patients "were required to record any adverse events" 3) Work-related productivity: Assessed using the Work Productivity Activities Index, completed at	1) Patient-assessed symptom severity: Primary outcome: reduction in 7 PM reflective total symptom/nasal congestion score (TSS-NCS): Combination therapy reduction (2.32) significantly greater than pseudo-ephedrine alone (1.42, P < 0.0001), but not significantly different than fexofenadine alone (2.05, P = 0.1579). Change in 7 PM NCS: Combination therapy reduction (0.56) significantly greater than fexofenadine (0.36, P < 0.0005), but not significantly different from pseudoephedrine (0.45, P = 0.059). Change in individual symptom scores showed significantly greater reductions in combination therapy compared to pseudoephedrine for all symptoms (P-values 0.0002 for all symptoms except P < 0.0001 for sneezing). Combination therapy had greater improvement than fexofenadine for nasal congestion only (P = 0.0005).	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 1b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: Yes Notes: Double-dummy blinding technique employed. Pollen levels measured daily throughout study.

(continued on next page)

Evidence Table 4: Combined Treatments (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	Setting: 18 medical centers Type(s) of providers: NR	Other:	baseline and at end of treatment	2) Adverse events: 280/651 (43%) had at least 1 AE. Combination 51.2%, pseudoephedrine 45.4%, 36.2% fexofenadine. P < 0.001 in fexofenadine group. 29% of 651 had treatment-related AEs. Combination 34.9%, pseudoephedrine 36.7%, 16.5% fexofenadine. P < 0.001 compared to fexofenadine group. Most common were headache (combo 9.3%, pseudoephedrine 12.4%, fexofenadine 7.3%) and insomnia (combo 11.2%, pseudoephedrine 12.8%, fexofenadine 1.8%). 3) Work-related productivity: Reduction in work impairment scores: Fexofenadine 9.8%, pseudoephedrine 7.9%, combination 13% (P < 0.0001 for each group compared to baseline). Reductions in combination group significant (P = 0.006) compared to pseudoephedrine group, but not different compared to fexofenadine group. Improvement in work productivity among employed patients: combination 9.3% compared to pseudoephedrine 6.2%, P < 0.05. No difference compared to fexofenadine group 8.1%. Overall work productivity in combination (8.5%) and fexofenadine (8.0%) groups significantly improved from baseline (P < 0.001) compared to pseudoephedrine (4.9%, P < 0.12).	

Evidence Table 4: Combined Treatments (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Vuurman, van Veggel, Sanders, et al., 1996	Design: RCT, parallel-group (see Notes) Interventions: Allergic rhinitis patients randomized to one of following treatments during 3-day training period: 1) Acrivastine 8 mg + pseudo-ephedrine 60 mg qid (A+P) (n = 22) 2) Diphenhydramine 50 mg qid (D) (n = 24) 3) Placebo (n = 22) In all three groups, treatment was started the evening before the first of three evening training sessions and continued for 3 days. At the end of the 3-day training period, all allergic rhinitis patients were treated with acrivastine + pseudo-ephedrine, as above, for 14 days, after which they returned for examination phase. Duration of study treatment: 17 days+, as follows: 2-hour introduction phase, 3-day training phase, 14-day interval, and 1-hour examination phase No mention of rescue med No pre-trial washout period described Dates: April - August 1993, Dutch pollen season	No. of subjects at start: 68? with seasonal allergic rhinitis (see Table 1) Dropouts/withdrawals: 1 No. of subjects at end: 67 with seasonal allergic rhinitis (see Notes); complete symptom score data on 59 patients Inclusion criteria: Documented medical treatment for seasonal allergic rhinitis over the prior 2 years; diary symptom score = 9 prior to treatment Exclusion criteria: Severe mental of physical disorders; alcohol or drug abuse; chronic medication use; drug hypersensitivity Age: Overall mean 20.0 (SD 2.3), range 16-25 Control 20.2 (SD 2.6) Acrivastine + pseudophedrine 20.0 (2.7) Placebo 19.8 (2.0) Diphenhydramine 20.1 (1.7) Sex: Control 10 M/18 F Acrivastine + Pseudophedrine: 13 M/9 F Placebo 7 M/15 F Diphenhydramine 14 M/10 F Race: NR Other:	1) Patient-assessed symptom severity (training and examination phases): rhinorrhea, nasal congestion, sneezing, mouth-breathing, itchy nose/throat, and tearing or red eyes graded daily on 5-point scale ranging from "absent" to "very severe, interfering with daily activities" 2) Performance on memory tests (training phase) 3) Performance on learning tests (training and examination phases)	1) Patient-assessed symptom severity: Mean (SEM) values shows in Figure 1. Symptom scores improved for drug treatments (A+P and D groups) compared to placebo. Significant treatment effect on day 1, P = 0.037, but not days 2 and 3. Placebo vs. A+P, P = 0.029 Placebo vs. D, P = 0.024 2) Performance on memory tests (training phase): Not abstracted 3) Performance on learning tests (training and examination phases): Not abstracted	Quality Scoring: Population similar: No Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: No Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: No Dropouts described: Yes Intention-to-treat: No Notes: Study also completed by 28 normal controls with no history of allergic rhinitis, matched for age and intelligence. Study designed primarily to test performance on a didactic computer simulation. Patients randomized to separate treatments during 3-day training phase at start of trial. After training period, all allergic rhinitis patients treated with acrivastine + pseudo-ephedrine for 14 days preceding the examination phase. Examination lasted approximately 1 hour and was designed to assess retention of knowledge acquired during training phase and measure group differences in performance attributable to the combined effects of allergies and treatment during the

(continued on next page)

Evidence Table 4: Combined Treatments (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	Location: The Netherlands Setting: Academic center Type(s) of providers: NR; authors from psychiatry, neuropsychology, and psychopharmacology departments				training period.
Williams, Hull, McSorley, et al., 1996	Design: RCT, parallel-group, randomization stratified to assure uniform sex distribution Interventions: 1) Acrivastine 8 mg + pseudoephedrine 60 mg, combined in a single capsule, four times per day (n = 202-3) 2) Acrivastine 8 mg four times per day (n = 202-3) 3) Pseudoephedrine 60 mg four times per day (n = 202-3) 4) Placebo four times per day (n = 68) Duration of study treatment: 2 weeks No mention of rescue med No pre-trial washout period described; individuals taking antihistamines, decongestants, MAOIs, cromolyn sodium, or corticosteroids within specified times prior to study (based on half-lives of respective drugs) were excluded	No. of subjects at start: 676 Dropouts/withdrawals: None reported No. of subjects at end: 676 Inclusion criteria: Age ≥ 18; positive skin test reaction to mountain cedar; 2-year history of symptoms Exclusion criteria: Nasal obstruction (turbinates, septal deviation); vasomotor rhinitis; contraindication to study medications; pregnant, lactating, or not on acceptable form of contraception; use of meds known to effect response to study drug within specified times based on drug half-life Age: Mean 36-37, range 18-76 Sex: 367 F, 309 M Race: 81-91% white per group Other:	1) Patient-assessed symptom severity: runny nose; sneezing; itchy nose/throat; tearing, itching, or redness of eyes; and nasal congestion graded twice each day (upon arising and at bedtime) on scale of 0 (absent) to 5 (very severe) 2) Investigator global assessment of efficacy 3) Adverse events: spontaneous reports of AEs evaluated	1) Patient-assessed symptom severity: Mean diary symptom scores days 1-14: Combination 8.5 Acrivastine 9.8 Pseudoephedrine 10.8 Placebo 11.3 P < 0.001 for combination compared to other 3 treatment groups Mean nasal congestion scores days 1-14: Combination 2.3 Acrivastine 2.7 Pseudoephedrine 2.6 Placebo 2.9 P < 0.001 for combination compared to acrivastine Mean allergy symptom scores days 1-14: Combination 6.2 Acrivastine 7.1 Pseudoephedrine 8.2 Placebo 8.4 P < 0.001 for combination compared to pseudoephedrine 2) Investigator global assessment of efficacy: Not abstracted 3) Adverse events: 12 types of AEs , total number not reported. Most common in	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 1b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: yes Intention-to-treat: Yes Note: Precise numbers of patients in active treatment groups not reported (all 202 or 203). *(continued on next page)*

Evidence Table 4: Combined Treatments (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	Dates: NR (discussion states season lasts from Christmas through February) Location: South central Texas Setting: 6 outpatient centers Type(s) of providers: NR			combination group relative to placebo group were dry mouth (8%), insomnia (7%), somnolence (7%), and headache (6%).	
Wilson, Dempsey, Sims, et al., 2000	Design: RCT, parallel-group Interventions: 1) Cetirizine 10 mg + mometasone furoate nasal spray 200 µg (two squirts in each nostril), once daily (n = 14) 2) Cetirizine 10 mg + montelukast 10 mg, once daily (n = 11) 3) Cetirizine 10 mg + placebo, once daily (n = 13) Duration of study treatment: 4 weeks No mention of rescue med Trial preceded by placebo run-in period, lasting a minimum of 1 week, during which usual medications were suspended Dates: June-July 1998 Location: Scotland Setting: Outpatient medical school	No. of subjects at start: 40 Dropouts/withdrawals: 2 withdrew during placebo run-in phase prior to randomization No. of subjects at end: 38 Inclusion criteria: Symptomatic seasonal allergic rhinitis; positive skin to at least 1 pollen extract Exclusion criteria: None specified Age: Mean 30 (SEM 1.4), range 16-65 Sex: 26 F, 12 M Race: NR Other:	1) Patient-assessed symptom severity: runny nose, blocked/stuffy nose, itchy nose, sneezing, itchy eyes, watery eyes, red eyes, and tickly throat graded twice each day on scale of 0 (no symptoms) to 3 (maximal symptoms) 2) Patient-assessed impact of symptoms on daily activities: graded twice per day on scale of 0 (no interference with daily activity) to 10 (maximal interference with daily activity) 3) Nasal peak inspiratory flow	1) Patient-assessed symptom severity: Total symptom score mean (SEM) after 4 weeks: Cetirizine 4.3 (1.4) ** Cetirizine + mometasone 2.1 (1.1) *** Cetirizine + montelukast 5.5 (1.2) ** ** P < 0.01 vs. run-in, ***P < 0.001 vs. run-in Cetirizine significantly improved all symptoms at 4 weeks except eye symptoms. Cetirizine + mometasone significantly improved all symptoms at 4 weeks. Cetirizine + montelukast significant improved total, nasal, and eye symptoms only at 4 weeks. 2) Patient-assessed impact of symptoms on daily activities: Daily activity score after 4 weeks Cetirizine 1.1 (0.4) ** Cetirizine + mometasone 0.5 (0.3) *** Cetirizine + montelukast 1.8 (0.5) ** P < 0.01 vs. run-in, ***P < 0.001 vs. run-in Daily activity not improved significantly in cetirizine + montelukast group. 3) Nasal peak inspiratory flow: Not abstracted	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 1b Randomized: Yes Allocation concealed: Not described Double-blind: No Blinding adequate: Not applicable Dropouts described: Yes Intention-to-treat: Yes Notes: Double-dummy blinding technique employed. Pollen levels measured daily during trial. No data on adverse events.

(continued on next page)

Evidence Table 4: Combined Treatments (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	Type(s) of providers: Allergy specialist				

[†] Quality scoring criteria were as follows:
Population similar: Was the study population described and reasonably similar to an adult working US population? (Yes [described and similar], No [described, but not similar], Not adequately described)
Intervention(s) described: Were the intervention protocols referenced or described in sufficient detail to replicate? (Yes, No)
Comorbidities described: Was the presence of comorbid asthma (or other upper respiratory conditions) described in the study population? (Yes, No)
Diagnosis by MD: Was the diagnosis of allergic rhinitis based on physician diagnosis? (Yes, No, Not applicable [asthma patients only])
Objectively confirmed: If physician-diagnosed, was the diagnosis supported by objective evidence of allergy (e.g., skin prick or serum IgE antibody testing)? (Yes, No, Not applicable)
Outcome measures valid: Were the main outcomes of interest to us measured in a way that has been demonstrated empirically to be valid and reliable (e.g., using a standardized scale such the RQLQ or SF-36)? (Yes, No, Not adequately described)
Level of evidence: Based on Oxford Center for Evidence-Based Medicine Levels of Evidence (1a, 1b, 1c, 2a, 2b, 2c, 3a, 3b, 4, 5)
Randomized: Was the study described as "randomized"? (Yes, No)
Allocation concealed: If the method for concealing allocation from the investigators was described, was it *adequate* (table of random numbers, computer-generated, coin tossing, etc.) or *inadequate* (alternating, date of birth, hospital number, etc.)? (Not described, Yes [described and adequate], No [described, but inadequate])
Double-blind: Was the study described as "double-blind"? (Yes, No)
Blinding adequate: If the method of double-blinding was described, was it *adequate* (e.g., identical placebo, active placebo, injection vs. tablet with double dummy) or *inadequate* (e.g., tablet vs. injection with no double dummy)? (Not described, Yes [described and adequate], No [described, but inadequate])
Dropouts described: Did the study describe dropouts and withdrawals so that all patients entering the trial could be accounted for? (Yes, No)
Intention-to-treat: Was the analysis performed according to the intention-to-treat principle? (Yes, No, Can't determine)

Evidence Table 5: Clinician Specialty Differences

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Brydon, 1993	Design: Prospective before-after comparison Intervention(s): Consultation with allergy nurse practitioner Duration of study treatment: 9 months prior to consultation and 9 months after Dates: 11/90-3/91 Location: UK Setting: Patients referred for consultation by general practitioners (GPs) Type(s) of providers: GPs, nurse practitioners	No. of subjects at start: 53 Dropouts/withdrawals: 14 No. of subjects at end: 39 Inclusion criteria: Referred to nurse practitioner for allergy consultation Exclusion criteria: NR Age: Median 38 yrs Sex: 44% female Race: NR	1) GP visits 2) Number of prescriptions written	1) Of 23 patients with positive skin tests, GP visits dropped 71% ($p < 0.001$) after consultation with the nurse practitioner. 2) Of 23 patients with skin positive skin tests, number of scripts dropped 39% ($p < 0.001$) in the 9 months after consultation with the nurse practitioner.	Quality Scoring: Population similar: Yes Intervention(s) described: No Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 4 Notes: High dropout rate (25%). Article implies that nurse practitioners spend more time with allergy sufferers and better educate them, resulting in better management of allergic rhinitis and decreased GP utilization.
Camilleri, 1991	Design: Case series, survey Intervention(s): None Duration of study treatment: NA Dates: NR Location: Glasgow, UK Setting: Rhinitis clinic Type(s) of providers: Otolaryngologist	No. of subjects at start: NR Dropouts/withdrawals: NR No. of subjects at end: 60 Inclusion criteria: Referred to otolaryngologist rhinitis clinic for the first fine; report previous failed nasal steroid treatment Exclusion criteria: NR Age: Mean 27 years (range 14-68 years) Sex: 52% female Race: NR 80% confirmed to have allergic or	1) Duration of steroid use 2) Mean dose per month 3) Reported symptoms 4) Mean standardized total course steroid dose, calculated based on equivalent budesonide dose	1) Mean duration 4.8 months; only 12% used nasal steroid spray for < 4 weeks 2) Mean 12 mg (range 4.3 – 30.9 mg) 56.5% used recommended dose 15% more than recommended dose 28.5% less than recommended dose 3) Reported symptoms Blocked 51% Catarrh 27% Drip 12% Sneeze 5% Loss of smell 5% 4) Mean 61 mg (range 2 – 228 mg); median 36 mg (equivalent to 4 spray canisters)	Quality Scoring: Population similar: Yes Intervention(s) described: No Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: No Outcome measures valid: No Level of evidence: 4 Notes: Author concluded that no more than 29% of treatment failures could be attributed to lack of patient education.

Evidence Table 5: Clinician Specialty Differences (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Demoly, Allaert Lecasble, et al., 2002	Design: Survey Intervention(s): None Duration of study treatment: NA Dates: May 2000 Location: France Setting: General medical practices throughout France Type(s) of providers: GPs	No. of subjects at start: 3026 patients 1321 physicians Dropouts/withdrawals: NA No. of subjects at end: NA Inclusion criteria: First 4 patients consulting physician for intermittent allergic rhinitis during study period. Exclusion criteria: Patient previously enrolled in a clinical trial or another epidemiological survey. Age: Mean 36.5 ± 13.6 yrs Sex: 47.5% female Race: NR	1) Duration of symptoms at consultation 2) Past allergy consultation 3) Patient-reported impairments 4) Specialist consultation 5) Treatments prescribed 6) Predictors of sick leave based on multivariable analysis of patients ordered sick leave (n=137) versus not. 7) Patient assessment of information/ education needs/ plans	1) Current episode 19.6 ± 40.4 days 2) Past history None 15.3% 55.5% identified allergen 42.2% had previous allergy testing 44% previously treated 3) Patient –reported impairments 79.2% Occupational impairment 91.8% impaired ADL 4) Consultation of specialist for 10.3% 78.8% allergologist 23.2% ENT specialist 11.8% pulmonologist 5) Treatments prescribed Oral antihistamines 92.4% Topical corticosteroids 45.2% Antiallergic eyedrops 32.2% Topical antihistamines 16.8% Local vasoconstrictors 8.7% Systemic corticosteroid 11.7% Two or more meds 74.4% Sick leave ordered in 4.6% for 5.7 ± 4.8d 6) Predictors of ordering sick leave 1st episode p<0.001) impaired work p<0.001 impaired personal life p<0.02 sleeping difficulty p<0.05 7) 79% considered information form physician adequate and easy to understand 58.2% wanted more advice 94.6% from family doctor 13.3% books and magazines 11.6% pharmacist 54.7% completely adherent to treatment	Quality Scoring: Population similar: Yes Intervention(s) described: No Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: No Outcome measures valid: No Level of evidence: 4 Notes:

Evidence Table 5: Clinician Specialty Differences (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Francillon, Burnand, Frei, et al., 1995	Design: Survey Intervention(s): NA Duration of study treatment: NA Dates: 6-8/92 Location: Switzerland Setting: Allergy clinics Type(s) of providers: GP, allergist	No. of subjects at start: NR Dropouts/withdrawals: NR No. of subjects at end: 126 Inclusion criteria: Referral to clinic and willingness to complete survey Exclusion criteria: Chief complaint related primarily to asthma or allergic conditions other than hay fever Age: Adults (age > 16) Sex: 50% female Race: Italian and French	1) Hay fever score 2) Reason for referral	1) Hay fever scores not associated with socioprofessional status, referral pattern, age, sex, duration of symptoms or geographic locations. 2) 30% referred by a physician. Reason for referral because of patients reported symptom severity (63%), or they were looking for a specialist skill (37%). Of those looking for a specialist, 24% wanted optimal treatment, 23% wanted a specific and accurate diagnosis.	Quality Scoring: Population similar: Not adequately described Intervention(s) described: Not applicable Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: No Outcome measures valid: No Level of evidence: 4 Note: No data on whether specialist care offers benefits to patients with allergic rhinitis

Evidence Table 5: Clinician Specialty Differences (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Gani, Pozzi, Crivellaro, et al., 2001	Design: RCT Intervention(s): Patient education adjunct to nasal glucocorticoid spray. 1) written drug information from manufacturer (package insert) 2) training on use of nasal spray and simplified written information 3) detailed lesson on nature of disease All patients received regular therapy with mometasone furoate nasal spray (2 puffs per nostril q.i.d. = 200 mcg/d) Dates: NR Location: Genoa, Italy Setting: Allergy clinic Type(s) of providers: Allergists	No. of subjects at start: 101 Dropouts/withdrawals: 6 No. of subjects at end: 95 Inclusion criteria: 2 year history of SAR solely due to pollens; positive skin test; positive RAST. Referred to nurse practitioner for allergy consultation Exclusion criteria: Sensitization to cat dander, mites or mold; anatomical abnormalities of upper respiratory airways; previous or ongoing SIT; chronic systemic corticosteroid treatment. Age: Mean 30 yrs Sex: 39% female Race: NR 32 patients also had mild asthma and were stratified into 3 treatment groups	1) Compliance rate 2) Nasal symptoms 3) Ocular symptoms 4) Respiratory symptoms (cough, wheezing, tightness) 4) Drug consumption for symptom control	1) Dropout/noncompliance rate A B C Dropouts 4 0 2 Noncompliant 9 3 4 Total 13 3 6 P=0.001 (A vs. B+C) 2) Nasal symptoms Group A 62.6 ± 51 Group B 64.7 ± 50 Group C 54.1 ± 62 P=NS 3) Ocular symptoms Group A 51.3 ± 52.8 Group B 46.0 ± 52 Group C 42.6 ± 55 P=0.02 4) Respiratory symptoms Group A 16.2 ± 24 Group B 11.7 ± 20 Group C 6.0 ± 15 P=0.02 (A vs. C) 1) Drug consumption for sx control Oral antihistamines (tablets taken) Group A 8.3 ± 15 Group B 4 ± 11.3 Group C 1.3 ± 6.1 P=0.08 (A vs. C) 6) Inhaled albuterol (at least one dose) Group A 6 (23.8%) Group B 2 (5.7%) Group C 0 P=0.05 (A vs. B+C); P=0.005 (A vs. C) 7) Any drug (at least one dose) Group A 13 (50%) Group B 12 (34%) Group C 5 (14.7%) P=0.02 (A vs. B+C); P=0.003 (A vs. C)	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed : Not described Double-blind: No Blinding adequate: NA Dropouts described: Yes Intention-to-treat: No Notes:

Evidence Table 5: Clinician Specialty Differences (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Lane, Pine, and Pillsbury, 2001	Design: Case series Intervention(s): Allergy skin testing by intradermal skin end point titration (SET) with a panel of aeroallergens diluted serially in 5-fold decreasing concentrations of the following antigens: Epidermals, mold mix, *Trichophyton*, *Candida*, and *Epidermophyton* species, cotton, house dust mixture (w/o mite antigens, mite (Der f 1), ragweed, weed mix, grass mix, tree mix, and fescue. Duration of study treatment: NA Dates: 1979-1999 Location: Chapel Hill, NC Setting: Allergy clinic at academic medical center Type(s) of providers: Otolaryngologist, allergy nurses	No. of subjects at start: 3,329 Dropouts/withdrawals: NR No. of subjects at end: NA Inclusion criteria: Referral to clinic for allergy skin testing Exclusion criteria: None Age: 45.2 ± 14.5 years Sex: 58% female Race: NR	1) Positive skin test responses, defined as 3 or more 2+ reactions or 1 or more 3+ reactions 2) Proportion of patients with positive skin test response who underwent immunotherapy 3) Self-rated effectiveness of immunotherapy 4) Proportion of current IT patients who underwent nasal or sinus surgery	1) 2,653 (79.7%) had positive skin test responses. 2) 2,008 (75.7%) patients underwent immunotherapy 3) Among patients undergoing immunotherapy, improvement was 3.9 on a 1- to 5-point scale. Patients with no improvement in nasal congestion symptoms had an average rating of 3.57, significantly lower than all patients ($p = 0.015$). 4) A survey of 275 patients currently undergoing immunotherapy showed that 84 (30.5%) had a history of nasal or sinus surgery, either before IT (35.6%), after IT (57.8%) or during IT (6%). Nasal congestion was the symptom most often reported to be improved with surgery (74.3%). Surgical procedures (131 procedures in 72 patients) included septoplasty (59 patients), reduction of inferior turbinates (38 patients) or endoscopic sinus surgery (34 patients), with 54% of patients having more than one procedure. The most frequent combination was septoplasty and reduction of inferior turbinates (n = 18). Mean self-reported effectiveness of IT was not significantly different between patients who had and had not undergone surgery.	Quality Scoring: Population similar: Yes Intervention(s) described: Not applicable Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 4

Evidence Table 5: Clinician Specialty Differences (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Scadding, Richards, and Price, 2000	Design: Population-based survey Intervention(s): NA Duration of study treatment: NA Dates: Grass pollen season Location: Southern England Setting: Community Type(s) of providers: NA	No. of subjects at start: NR Dropouts/withdrawals: NR No. of subjects at end: 2139 Inclusion criteria: Adults listed in the UK electoral register followed by telephone contact; screening criteria not listed Exclusion criteria: NR Age: 16-65+ years Sex: 42% M, 58% F Race: NR	1) Consultation distribution 2) Prevalence of seasonal allergic rhinitis 3) Symptoms 4) Satisfaction with treatment	1) GPs were the main point of contact for education and treatment: 54% of patients consulted GPs 27% consulted pharmacists 7% a health food consultant 2% a specialist 2) Prevalence of seasonal allergic rhinitis: 15% overall 23% 16-34 age group 13% 35-54 age group 8% 55+ age group 3) Symptoms (seasonal allergic rhinitis [SAR] vs. perennial allergic rhinitis [PAR]): Sneezing 78% 65% Runny nose 64% 59% Itchy eyes 52% 31% Watery eyes 42% 33% Itchy nose 41% 38% Headache 25% 41% Wheeze 15% 25% Blocked nose 37% 46% Blocked sinuses 37% 21% Sore nose 18% 10% 4) Satisfaction with treatment: Level of Satisfaction: All 32%, SAR 17%, PAR 34% Reasonably: All 28%, SAR 36%, PAR 27% Some: All 14%, SAR 18%, PAR 12% Not: All 3%, SAR 10%, PAR 2% Not applicable: All 24%, SAR 19%, PAR 25%	Quality Scoring: Population similar: Yes Intervention(s) described: Not applicable Comorbidities described: Yes Diagnosis by MD: No Objectively confirmed: Not applicable Outcome measures valid: No Level of evidence: 1b Note: Does not really provide any information between health care providers other than the aforementioned distribution regarding consultation.

Evidence Table 5: Clinician Specialty Differences (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
White, Smith, Baker, et al., 1998	Design: Postal survey (cohort) Intervention(s): 1) Nonsedating antihistamine 2) Steroid nasal spray Duration of study treatment: NR Dates: 1994-95 Location: UK Setting: Patients selected from GP practices Type(s) of providers: GPs	No. of subjects at start: 846 Dropouts/withdrawals: 219 No. of subjects at end: 627 (74.1%) Inclusion criteria: Identified as having been prescribed a non-sedating antihistamine and a nasal steroid spray by GP Exclusion criteria: NR Age: 32.8 years ± 13.3 Sex: 54.9% female Race: NR	1) Usage pattern of the antihistamine and steroid spray by the patient in relation to overall control of symptoms	1) 54% of patients reported partial or poor control of their symptoms. 69.4% of these were not taking their meds appropriately. 30.6% of patients were taking their meds appropriately, but did not have full control of their symptoms. At least 15% of the 54% of patients would be suitable for immunotherapy by a specialist.	Quality Scoring: Population similar: Yes Intervention(s) described: No Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: No Outcome measures valid: No Level of evidence: 2b Note: The article indicates that 54% of the patients seen at the GP clinics are partially/poorly controlled with the medication and dosing regimen they were using. The authors suggest that better control of the symptoms would be achieved with referral to a specialist for immunotherapy but offer no data to support this conclusion.

[†] Quality scoring criteria were as follows:
Population similar: Was the study population described and reasonably similar to an adult working US population? (Yes [described and similar], No [described, but not similar], Not adequately described)
Intervention(s) described: Were the intervention protocols referenced or described in sufficient detail to replicate? (Yes, No)
Comorbidities described: Was the presence of comorbid asthma (or other upper respiratory conditions) described in the study population? (Yes, No)
Diagnosis by MD: Was the diagnosis of allergic rhinitis based on physician diagnosis? (Yes, No, Not applicable [asthma patients only])
Objectively confirmed: If physician-diagnosed, was the diagnosis supported by objective evidence of allergy (e.g., skin prick or serum IgE antibody testing)? (Yes, No, Not applicable)
Outcome measures valid: Were the main outcomes of interest to us measured in a way that has been demonstrated empirically to be valid and reliable (e.g., using a standardized scale such the RQLQ or SF-36)? (Yes, No, Not adequately described)
Level of evidence: Based on Oxford Center for Evidence-Based Medicine Levels of Evidence (1a, 1b, 1c, 2a, 2b, 2c, 3a, 3b, 4, 5)

Evidence Table 6: Racial and Ethnic Variation

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Fagan, Scheff, Hryhorczuk, et al., 2001	Design: Cross-sectional, population-based survey Assessment method: Self-administered survey Definitions: Rhinitis – sneezing or a runny or blocked nose not associated with a cold or the flu Hay fever – "yes" response to the question, "Have you ever had hay fever?" Response rate: 90% Dates: 1993 Location: Illinois, USA	Inclusion criteria: Schoolchildren in grades 7 through 12 Sample size: 2044 Age: 7th to 12th graders Sex: 1034 males; 1010 females Race: 1551 white; 332 Hispanic; 163 African-American; 154 other or not reported	1) Prevalence – unadjusted 2) Prevalence – adjusted for age, gender, family history of asthma, active smoking and exposure to dampness in past 12 months 3) Functional impairment defined as "interferes with daily activities"	1) Unadjusted prevalence: Rhinitis (lifetime) – 36.3% Rhinitis (12 months) – 31.9% Hay fever – 22.4% 2) Adjusted prevalence African-American vs. other: Current rhinitis – Odds ratio 1.0 (95% CI 0.68 – 1.47) Hay fever – Odds ratio 1.18 (95% CI 0.78 – 1.78) 3) Rhinitis functional impairment: Not at all – 79.9% Little – 15.8% Moderate – 3.6% A lot 0.7% African-Americans were significantly more likely to report functional impairment.	Quality Scoring: Population similar: No Intervention(s) described: Not applicable Comorbidities described: Yes Diagnosis by MD: No Objectively confirmed: Not applicable Outcome measures valid: No Level of evidence: 1b Notes:
Lebowitz, Cassell, and McCarroll, 1972	Design: Prospective incidence study of minor illnesses Assessment method: Weekly interview, using standardized questions to assess 14 symptoms Definitions: Rhinitis – "yes" response to "Did you have a stuffy or runny nose…" that was not associated with a common cold? Dates: 1962 - 1965 Location: New York City, USA	No. of subjects at start: 448 families Dropouts/withdrawals: NR No. of subjects at end: NR Inclusion criteria: Volunteers from a 2-stage cluster sample Average follow-up: 45 weeks; 1168 person-years of observation Age: NR Sex: NR Race: NR Other:	1) Illness episodes (person days) 2) Illness duration (mean) 3) Illness incidence by sex, age, and race	1) Illness episodes: Out of 61,893 person-days of illness, 4255 (6.9%) were due to rhinitis 2) Illness duration: Average duration of rhinitis was 7.4 days 3) Incidence of rhinitis per person year: White – 0.7 per person year Black – 0.4 per person year Puerto Rican – 0.3 per person year	Quality Scoring: Population similar: No Intervention(s) described: Not applicable Comorbidities described: No Diagnosis by MD: No Objectively confirmed: Not applicable Outcome measures valid: No Level of evidence: 1b Notes: No adjustments for age differences in race comparison. Follow-up rate is unclear.

Evidence Table 6: Racial and Ethnic Variation (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Lower, Henry, Mandik, et al., 1993	Design: Retrospective cohort study Intervention: Immunotherapy given weekly for up to 8 months, then maintenance doses every 2 to 4 weeks for 2 to 4 years Dates: NR Location: Pittsburgh, USA Setting: University-affiliated allergy clinic Type(s) of providers: Allergy specialists	No. of subjects: 315 Inclusion criteria: Allergic rhinitis, asthma, or atopic dermatitis; computerized medical records; immunotherapy treatment based on specific allergens identified by skin testing, begun at least 1 year prior to study start Exclusion criteria: None Age: "Pediatric population" (range, 5-18 years) Sex: 190 male; 125 female Race: 254 white; 59 non-white Other: 52 allergic rhinitis with asthma; 34 allergic rhinitis with atopic dermatitis	1) Non-adherence – patients who had discontinued immunotherapy for ≥ 6 months (presumably prior to completing the full 2- to 4-year course of treatment) 2) Reasons for non-adherence – response to open-ended question administered by telephone 3) Factors associated with non-adherence, including gender, race, and type of health insurance	1) Non-adherence: 138 (44%) 2) Reasons for non-adherence: Inconvenient: 17 Symptoms not decreased: 15 Symptoms improved: 14 Changed clinic: 14 Child refused: 9 Local reaction: 6 Financial burden: 6 Other: 7 Could not contact to determine: 50 3) Non-adherence factors: Non-white race and non-private insurance were associated with non-adherence.	Quality Scoring: Population similar: No Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Notes:
Strachan, Sibbald, Weiland, et al., 1997	Design: International survey (prospective cohort) Definitions: Rhinitis – "yes" response to question, "Have you ever had a problem with sneezing or a runny or blocked nose, when you did not have a cold or the flu?" Hay fever – "yes" response to question, "Have you ever had hay fever?" Assessment: Questionnaire (self- or parent-completed) Dates: NR	No. of subjects 721,601 Response rate: 149 of 155 centers achieved response rates of ≥ 80% in the 13- to 14-year-old groups; 89 of 91 centers achieved response rates of ≥ 70% in the 6- to 7-year-old group Inclusion criteria: School enrollment and appropriate age or grade level Age: 6- to 7- (257,800) and 13- to 14-year-olds (463,801) Sex: NR Race: NR	1) Prevalence – reported as a range and by percentiles for the 155 centers	1) Prevalence: Rhinitis (lifetime): ranged from 2.0% to 80.5% Rhinitis (12 months): ranged from 1.5% to 66.6% Hay fever (lifetime): ranged from 0% to 54.4%	Quality Scoring: Population similar: No Intervention(s) described: Not applicable Comorbidities described: No Diagnosis by MD: No Objectively confirmed: Not applicable Outcome measures valid: No Level of evidence: 1b Notes: *(continued on next page)*

Evidence Table 6: Racial and Ethnic Variation (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	Location: 155 centers in 56 countries Setting: Schools selected randomly within each participating center	Other:			
Turkeltaub and Gergen, 1991	Design: Population-based survey Definitions: Chronic rhinitis – no physician's diagnosis of hay fever, but frequent nasal and/or eye symptoms that did not vary by both season and pollen during the past 12 months, not counting colds or the flu Allergic rhinitis – physician diagnosis of hay fever or frequent nasal and/or eye symptoms that varied by both season and pollen during the past 12 months, not counting colds or the flu Assessments: Interviews using structured questionnaires Response rate: 73.1% Dates: 1976-1980 Location: USA Setting: Community-based	No. of subjects: 12,742 Inclusion criteria: None Exclusion criteria: None Age: Range, 12-74 years Sex: 6,174 males; 6,568 females Race: 11,260 white (88%); 1,482 Black	1) Prevalence, weighted for the sampling design, reported separately for whites and blacks 2) Prevalence, weighted for sampling design, and adjusted for age, sex, smoking, poverty level and urban/rural residence	1) Prevalence (whites, blacks) Chronic rhinitis: 20.4% (SE 0.5); 19.2% (SE 1.2), p = ns Allergic rhinitis: 9.8% (SE 0.5); 8.1% (SE 0.9), p = ns Allergic rhinitis without asthma: 7.8% (SE 0.4); 5.1 (SE 0.6), p < 0.01 Allergic rhinitis with asthma: 2.0% (SE 0.2); 3.1% (SE 0.5), p < 0.05 2) Adjusted prevalence☹whites, blacks) Chronic rhinitis: 20.4% (SE 0.5); 18.8% (SE 1.2), p = ns Allergic rhinitis: 10.0% (SE 0.5); 8.4% (SE 1,1), p = ns Allergic rhinitis without asthma: 7.9% (SE 0.4); 5.3 (SE 0.8), p < 0.01 Allergic rhinitis with asthma: 2.0% (SE 0.2); 3.1% (SE 0.6), p = ns	Quality Scoring: Population similar: Yes Intervention(s) described: Not applicable Comorbidities described: ?? Diagnosis by MD: No Objectively confirmed: Not applicable Outcome measures valid: No Level of evidence: 1b Notes:

[†] Quality scoring criteria were as follows:
Population similar: Was the study population described and reasonably similar to an adult working US population? (Yes [described and similar], No [described, but not similar], Not adequately described)

Intervention(s) described: Were the intervention protocols referenced or described in sufficient detail to replicate? (Yes, No)
Comorbidities described: Was the presence of comorbid asthma (or other upper respiratory conditions) described in the study population? (Yes, No)
Diagnosis by MD: Was the diagnosis of allergic rhinitis based on physician diagnosis? (Yes, No, Not applicable [asthma patients only])
Objectively confirmed: If physician-diagnosed, was the diagnosis supported by objective evidence of allergy (e.g., skin prick or serum IgE antibody testing)? (Yes, No, Not applicable)
Outcome measures valid: Were the main outcomes of interest to us measured in a way that has been demonstrated empirically to be valid and reliable (e.g., using a standardized scale such the RQLQ or SF-36)? (Yes, No, Not adequately described)
Level of evidence: Based on Oxford Center for Evidence-Based Medicine Levels of Evidence (1a, 1b, 1c, 2a, 2b, 2c, 3a, 3b, 4, 5)

Bibliography

Aabel S. No beneficial effect of isopathic prophylactic treatment for birch pollen allergy during a low-pollen season: a double-blind, placebo-controlled clinical trial of homeopathic Betula 30c. Br Homeopath J 2000;89(4):169-73.

Aabel S. Prophylactic and acute treatment with the homeopathic medicine, Betula 30c for birch pollen allergy: a double-blind, randomized, placebo-controlled study of consistency of VAS responses. Br Homeopath J 2001;90(2):73-8.

Aabel S, Laerum E, Dolvik S, et al. Is homeopathic 'immunotherapy' effective? A double-blind, placebo-controlled trial with the isopathic remedy Betula 30c for patients with birch pollen allergy. Br Homeopath J 2000;89(4):161-8.

Aalbers R, Kauffman HF, Groen H, et al. The effect of nedocromil sodium on the early and late reaction and allergen-induced bronchial hyperresponsiveness. J Allergy Clin Immunol 1991;87(5):993-1001.

Aaronson DW. Side effects of rhinitis medications. J Allergy Clin Immunol 1998;101(2 II):S379-S382.

Abd-El-Al AM, Bayoumy AM, Abou Salem EA. A study on Demodex folliculorum in rosacea. J Egyptian Soc Parasitol 1997;27(1):183-95.

Abelson MB, Lanier RQ. The added benefit of local Patanol therapy when combined with systemic Claritin for the inhibition of ocular itching in the conjunctival antigen challenge model. Acta Ophthalmol Scand Suppl 1999;(228):53-6.

Aberg N. Asthma and allergic rhinitis in Swedish conscripts. Clin Exp Allergy 1989;19(1):59-63.

Aberg N, Hesselmar B, Aberg B, et al. Increase of asthma, allergic rhinitis and eczema in Swedish schoolchildren between 1979 and 1991. Clin Exp Allergy 1995;25(9):815-9.

Abramson M, Puy R, Weiner J. Immunotherapy in asthma: an updated systematic review. [Review]. Allergy 1999;54(10):1022-41.

Abramson MJ, Puy RM, Weiner JM. Is allergen immunotherapy effective in asthma? A meta-analysis of randomized controlled trials. Am J Respir Crit Care Med 1995;151(4):969-74.

Acero S, Tabar AI, Alvarez MJ, et al. Occupational asthma and food allergy due to carmine. Allergy Eur J Allergy Clin Immunol 1998;53(9):897-901.

Adelroth E, Rak S, Haahtela T, et al. Recombinant humanized mAb-E25, an anti-IgE mAb, in birch pollen-induced seasonal allergic rhinitis. J Allergy Clin Immunol 2000;106(2):253-9.

Adelsberg BR. Sedation and performance issues in the treatment of allergic conditions. [Review]. Arch Intern Med 1997;157(5):494-500.

Adkins JC, Brogden RN. Zafirlukast: A review of its pharmacology and therapeutic potential in the management of asthma. Drugs 1998;55(1):121-44.

Adkinson NF. Immunotherapy for allergic rhinitis. N Engl J Med 1999;341:522-4.

Agostini JV, Leo-Summers LS, Inouye SK. Cognitive and other adverse effects of diphenhydramine use in hospitalized older patients. Arch Intern Med 2001;161(17):2091-7.

Agrawal DK. Pharmacology and clinical efficacy of desloratadine as an anti-allergic and anti-inflammatory drug. Expert Opin Invest Drugs 2001;10(3):547-60.

Ahman M, Holmstrom M, Ingelman-Sundberg H. Inflammatory markers in nasal lavage fluid from industrial arts teachers. Am J Ind Med 1995;28(4):541-50.

Akaho E, Runion HI, Inoue K. American and Japanese drug distribution and information systems in 1994 and a proposed system for improved pharmaceutical care. Drug Inf J 1999;33(2):487-508.

Akcakaya N, Hassanzadeh A, Camcioglu Y, et al. Local and systemic reactions during immunotherapy with adsorbed extracts of house dust mite in children. Ann Allergy Asthma Immunol 2000;85(4):317-21.

Akmanlar N, Altintas DU, Guneser KS, et al. Comparison of conventional and rush immunotherapy with der PI in childhood respiratory allergy. Allergol Immunopathol (Madr) 2000;28(4):213-8.

Al Frayh AR, Shakoor Z, Gad El Rab MO, et al. Increased prevalence of asthma in Saudi Arabia. Ann Allergy Asthma Immunol 2001;86(3):292-6.

Al-Shammari SA, Khoja TA, Al-Ansary LA, et al. Care of asthmatic patients in primary health care centers. Ann Saudi Med 1996;16(1):24-8.

Alam R, Dejarnatt A, Stafford S, et al. Selective inhibition of the cutaneous late but not immediate allergic response to antigens by misoprostol, a PGE analog. Results of a double-blind, placebo-controlled randomized study. Am Rev Respir Dis 1993;148(4 Pt 1):1066-70.

Alldred A. Etanercept in rheumatoid arthritis. Expert Opin Pharmacother 2001;2(7):1137-48.

Allsup SJ, Gosney M, Regan M, et al. Side effects of influenza vaccination in healthy older people: A randomised single-blind placebo-controlled trial. Gerontology 2001;47(6):311-4.

Althaus MA, Pichler WJ. Nasal application of a gel formulation of N-acetyl-aspartyl glutamic acid (NAAGA) compared with placebo and disodium cromoglycate in the symptomatic treatment of pollinosis. Allergy Eur J Allergy Clin Immunol 1994;49(3):184-8.

Altman DG, Bland JM. Absence of evidence is not evidence of absence. BMJ 1995;311(7003):485.

Alvarez-Cuesta E, Cuesta-Herranz J, Puyana-Ruiz J, et al. Monoclonal antibody-standardized cat extract immunotherapy: Risk-benefit effects from a double-blind placebo study. J Allergy Clin Immunol 1994;93(3):556-66.

Alvarez-Cuesta E, Gonzelez-Mancebo E. Immunotherapy in bronchial asthma. Curr Opin Pulm Med 2000;6(1):50-4.

Alves B, Sheikh A, Hurwitz B, et al. Allergen injection immunotherapy for seasonal allergic rhinitis (Protocol for a Cochrane Review). In: The Cochrane Library, Issue 1, 2002. Oxford: Update Software.

American Academy of Allergy, Asthma & Immunology. The allergy report. Milwaukee, WI: American Academy of Allergy, Asthma & Immunology, Inc.; 2000.

Andersen NH, Jeppesen F, Schioler T, et al. Treatment of hay fever with sodium cromoglycate, hyposensitization, or a combination. Allergy 1987;42(5):343-51.

Anderson ER, Murphy MP, Weymuller Jr EA. Clinimetric evaluation of the Sinonasal Outcome Test-16. Otolaryngol Head Neck Surg 1999;121(6):702-7.

Anderson HR, Pottier AC, Strachan DP. Asthma from birth to age 23: incidence and relation to prior and concurrent atopic disease. Thorax 1992;47(7):537-42.

Andersson M, Berglund R, Greiff L, et al. A comparison of budesonide nasal dry powder with fluticasone propionate aqueous nasal spray in patients with perennial allergic rhinitis. Rhinology 1995;33(1):18-21.

Andersson M, Rimmer J, Salome C, et al. Dual symptomatic and exudative nasal responses are not characteristics of perennial allergic rhinitis. Acta Oto-Laryngol 2001;121(3):407-13.

Andre C, Vatrinet C, Galvain S, et al. Safety of sublingual-swallow immunotherapy in children and adults. Int Arch Allergy Immunol 2000;121(3):229-34.

Andri L, Senna G, Andri G, et al. Local nasal immunotherapy for birch allergic rhinitis with extract in powder form. Clin Exp Allergy 1995;25(11):1092-9.

Andri L, Senna G, Betteli C, et al. Local nasal immunotherapy with extract in powder form is effective and safe in grass pollen rhinitis: a double-blind study. J Allergy Clin Immunol 1996;97(1 Pt 1):34-41.

Andri L, Senna G, Betteli C, et al. Local nasal immunotherapy for Dermatophagoides-induced rhinitis: efficacy of a powder extract. J Allergy Clin Immunol 1993;91(5):987-96.

Andri L, Senna GE, Betteli C, et al. Local nasal immunotherapy in allergic rhinitis to Parietaria. A double-blind controlled study. Allergy 1992;47(4 Pt 1):318-23.

Andri L, Senna GE, Betteli C, et al. Combined treatment of allergic rhinitis with terfenadine and nimesulide, a non-steroidal antiinflammatory drug. Allerg Immunol (Paris) 1992;24(8):313-4, 317-9.

Ankier SI, Warrington SJ. A double-blind placebo-controlled study of the efficacy and tolerability of ebastine against hayfever in general practice patients. J Intern Med 1989;226(6):453-8.

Anonymous. A trial of house dust mite extract in bronchial asthma. Mite Allergy Subcommittee of the Research Committee of the British Thoracic Association. Br J Dis Chest 1979;73(3):260-70.

Anonymous. Regulatory control and standardization of allergenic extracts. Clinical studies with "standardized" extracts. Arbeiten Aus Dem Paul-Ehrlich-Institut, Dem Georg-Speyer-Haus Und Dem Ferdinand-Blum-Institut Zu Frankfurt A.M. 1985;(79):279-309.

Anonymous. Astemizole - Another non-sedating antihistamine. Med Lett Drugs Ther 1989;31(791):43-4.

Anonymous. A large-scale, office-based study evaluates the use of a new class of non-sedating antihistamines. A report from CEN. J Am Board Fam Pract 1990;3(4):241-52.

Anonymous. Intranasal triamcinolone for allergic rhinitis. Med Lett Drugs Ther 1991;33(859):116-7.

Anonymous. English physicians favor extended role for pharmacists. Am J Hosp Pharm 1992;49(11):2648, 2651.

Anonymous. Entex pse tabs. Pharmindex 1992;34(9):7.

Anonymous. Safety of terfenadine and astemizole. Med Lett Drugs Ther 1992;34(863):9-10.

Anonymous. Tritan tabs. Pharmindex 1992;34(9):6.

Anonymous. Information your patient can use: A directional study. Part I. Immunol Allergy Pract 1993;15(9-10):303-6.

Anonymous. Itraconazole. Med Lett Drugs Ther 1993;35(888):7-10.

Anonymous. Loratadine - A new antihistamine. Med Lett Drugs Ther 1993;35(902):71-2.

Anonymous. Acrivastine/pseudoephedrine (Semprex-D) for seasonal allergic rhinitis. Med Lett Drugs Ther 1994;36(930):78-80.

Anonymous. Cisapride for nocturnal heartburn. Med Lett Drugs Ther 1994;36(915):11-3.

Anonymous. Intranasal budesonide for allergic rhinitis. Med Lett Drugs Ther 1994;36(926):63-4.

Anonymous. Ophthalmic levocabastine for allergic conjunctivitis. Med Lett Drugs Ther 1994;36(920):35-6.

Anonymous. Oral pilocarpine for xerostomia. Med Lett Drugs Ther 1994;36(929):76.

Anonymous. Claritin. Formulary 1995;30(12):745.

Anonymous. Fluticasone propionate nasal spray for allergic rhinitis. Med Lett Drugs Ther 1995;37(940):5-6.

Anonymous. Antihistamine cleared. P T 1996;21(3):111.

Anonymous. Cetirizine - A new antihistamine. Med Lett Drugs Ther 1996;38(970):21-3.

Anonymous. Fexofenadine. Med Lett Drugs Ther 1996;38(986):95-6.

Anonymous. Ipratropium bromide nasal spray available. Female Patient Ob Gyn Ed 1996;21(5):83.

Anonymous. Once-daily formulation for allergy drug approved. P T 1996;21(11):582.

Anonymous. Azelastine for seasonal allergic rhinitis. Am Fam Phys 1997;55(7):2541.

Anonymous. Azelastine nasal spray for allergic rhinitis. Med Lett Drugs Ther 1997;39(1000):45-7.

Anonymous. Ceclor CD. Formulary 1997;32(2):119.

Anonymous. Claritin reditabs. Formulary 1997;32(4):333.

Anonymous. Flomax: Alpha-adrenergic blocker for BPH. Formulary 1997;32(7):659-60.

Anonymous. Mibefradil release expands calcium-channel-blocker choices. Am J Health-Syst Pharm 1997;54(18):2033.

Anonymous. Pulmozyme. Formulary 1997;32(2):114.

Anonymous. Budesonide turbuhaler for asthma. Med Lett Drugs Ther 1998;40(1018):15-6.

Anonymous. Executive summary. Allergy Eur J Allergy Clin Immunol Suppl 1998;53(41):7-31.

Anonymous. Irbesartan: How does it stack up against others of its class? Drugs Ther Perspect 1998;11(5):1-5.

Anonymous. Mizolastine expands the choice of second-generation antihistamines for allergic rhinitis. Drugs Ther Perspect 1998;12(9):1-6.

Anonymous. Rhinitis. Ann Allergy Asthma Immunol 1998;80(4):287.

Anonymous. Treatment of childhood allergic rhinitis is less than optimal. Drugs Ther Perspect 1998;12(2):5-9.

Anonymous. Allergic factors associated with the development of asthma and the influence of cetirizine in a double-blind, randomised, placebo-controlled trial: first results of ETAC. Early Treatment of the Atopic Child. Pediatr Allergy Immunol 1998;9(3):116-24.

Anonymous. Aventis. Formulary 1999;34(10 Suppl):19-27.

Anonymous. Concluding points. Round Table Ser R Soc Med 1999;67:65.

Anonymous. Infusion reactions associated with the therapeutic use of monoclonal antibodies in the treatment of malignancy. Cancer Metastasis Rev 1999;18(4):465-71.

Anonymous. Johnson and Johnson (A focus on Ortho-McNeil and Janssen). Formulary 1999;34(10 Suppl):51-5.

Anonymous. Natural selection: Exploring alternative remedies. Occup Health 1999;51(12):30-1.

Anonymous. New preparation of terfenadine, without cardiotoxicity. Can Fam Phys 1999;45:2073-81.

Anonymous. Sinus woes cost billions to treat each year: bad situation gets worse. Case Manage Advisor 1999;10(12):190, 196.

Anonymous. Cevimeline (Evoxac) for dry mouth. Med Lett Drugs Ther 2000;42(1084):70.

Anonymous. CME Quiz. Am J Manag Care 2000;6(1 Suppl):S19-S20.

Anonymous. Drugs for prevention and treatment of postmenopausal osteoporosis. Med Lett Drugs Ther 2000;42(1090):97-100.

Anonymous. Fexofenadine a first-line option for seasonal allergic rhinitis and chronic idiopathic urticaria. Drugs Ther Perspect 2000;16(8):1-5.

Anonymous. New drugs for allergic conjunctivitis. Med Lett Drugs Ther 2000;42(1077):39-46.

Anonymous. Approval for Schering-Plough drug. Manuf Chem 2001;72(2):8.

Anonymous. AstraZeneca opens new Pound Sterling45m high tech r&d site. Manuf Chem 2001;72(11):12.

Anonymous. Aventis increases Allegra production. Manuf Chem 2001;72(4):12.

Anonymous. Nebulized budesonide for asthma in children. Med Lett Drugs Ther 2001;43(1096):6-7.

Anonymous. Thunderstorms and asthma excerbations. Med Today 2001;2(7):10.

Anonymous. Budesonide (Entocort EC) for Crohn's disease. Med Lett Drugs Ther 2002;44(1122):6-8.

Antonicelli L, Bilò MB, Pucci S, et al. Efficacy of an air-cleaning device equipped with a high efficiency particulate air filter in house dust mite respiratory allergy. Allergy 1991;46(8):594-600.

Ariano R, Kroon AM, Augeri G, et al. Long-term treatment with allergoid immunotherapy with Parietaria. Clinical and immunologic effects in a randomized, controlled trial. Allergy 1999;54(4):313-9.

Ariano R, Panzani RC, Chiapella M, et al. Local immunotherapy of seasonal allergic rhinitis in children due to Parietaria officinalis pollen: A preliminary report. Pediatr Asthma Allergy Immunol. 1993;7(4):227-37.

Ariano R, Panzani RC, Chiapella M, et al. Local intranasal immunotherapy with allergen in powder in atopic patients sensitive to Parietaria officinalis pollen. J Investig Allergol Clin Immunol 1995;5(3):126-32.

Ariano R, Panzani RC, Saraga J. New clinical data and therapeutic prospects in Cupressaceae pollen allergy. Allerg Immunol (Paris) 2000;32(3):135-8.

Arlian LG, Morgan MS. Serum antibody to Sarcoptes scabiei and house dust mite prior to and during infestation with S. scabiei. Vet Parasitol 2000;90(4):315-26.

Arruda LK, Platts-Mills TA, Longbottom JL, et al. Aspergillus fumigatus: identification of 16, 18, and 45 kd antigens recognized by human IgG and IgE antibodies and murine monoclonal antibodies. J Allergy Clin Immunol 1992;89(6):1166-76.

Arvidsson MB, Löwhagen O, Rak S. Effect of 2-year placebo-controlled immunotherapy on airway symptoms and medication in patients with birch pollen allergy. J Allergy Clin Immunol 2002;109(5):777-83.

Aschan G. Decongestion of nasal mucous membranes by oral medication in acute rhinitis. A rhinomanometric study to demonstrate synergism between antihistamines and adrenergic substance. Acta Otolaryngol (Stockh) 1974;77(6):433-8.

Asher BF, Seidman M, Snyderman C. Complementary and alternative medicine in otolaryngology. Laryngoscope 2001;111(8):1383-9.

Asher MI, Keil U, Anderson HR, et al. International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. Eur Respir J 1995;8(3):483-91.

Assa'ad A, Lierl M. Effect of acellular pertussis vaccine on the development of allergic sensitization to environmental allergens in adults. J Allergy Clin Immunol 2000;105(1 Pt 1):170-5.

Astarita C, Scala G, Sproviero S, et al. Effects of enzyme-potentiated desensitization in the treatment of pollinosis: a double-blind placebo-controlled trial. J Investig Allergol Clin Immunol 1996;6(4):248-55.

Aversa A, Fabbri A. New oral agents for erectile dysfunction: What is changing in our practice? Asian J Androl 2001;3(3):175-9.

Babu KS, Arshad SH, Holgate ST. Anti-IgE treatment: An update. Allergy Eur J Allergy Clin Immunol 2001;56(12):1121-8.

Babu KS, Salvi SS. Aspirin and asthma. Chest 2000;118(5):1470-6.

Bachert CI. Importance of quality of life in patients with seasonal allergic rhinitis. Rev Fr Allergol Immunol Clin 2000;40(1):74-7.

Backhouse CI. Intra-nasal flunisolide in the treatment of allergic rhinitis in general practice. Curr Med Res Opin 1979;6(1):14-9.

Backhouse CI, Finnamore VP, Gosden CW. Treatment of seasonal allergic rhinitis with flunisolide and terfenadine. J Int Med Res 1986;14(1):35-41.

Bagenstose SE, Bernstein JA. Treatment of chronic rhinitis by an allergy specialist improves quality of life outcomes. Ann Allergy Asthma Immunol 1999;83(6 Pt 1):524-8.

Bahceciler NN, Isik U, Barlan IB, et al. Efficacy of sublingual immunotherapy in children with asthma and rhinitis: a double-blind, placebo-controlled study. Pediatr Pulmonol 2001;32(1):49-55.

Bahir A, Goldberg A, Mekori YA, et al. Continuous avoidance measures with or without acaricide in dust mite-allergic asthmatic children. Ann Allergy Asthma Immunol 1997;78(5):506-12.

Baiardini I, Pasquali M, Giardini A, et al. Quality of life in respiratory allergy. [Review]. Allergy Asthma Proc 2001;22(3):177-81.

Bailey DA, Gilleran LG, Merchant PG. Waivers for disqualifying medical conditions in U.S. Naval Aviation personnel. Aviat Space Environ Med 1995;66(5):401-7.

Baker SB. The dilemma of anesthetizing the child with an upper respiratory tract infection. Semin Anesth 1992;11(4):265-73.

Baldwin CM, Bell IR, O'Rourke MK, et al. The association of respiratory problems in a community sample with self-reported chemical intolerance. Eur J Epidemiol 1997;13(5):547-52.

Balkissoon R, Shusterman DJ. Occupational upper airway disorders. Semin Respir Crit Care Med 1999;20(6):569-80.

Banks DE, Shah AA, Lopez M, et al. Chest illnesses and the decline of FEV1 in steelworkers. J Occup Environ Med 1999;41(12):1085-90.

Banz K, Schwicker D, Thomas AM. Economic evaluation of immunoprophylaxis in children with recurrent ear, nose and throat infections. Pharmacoeconomics 1994;6(5):464-77.

Baraldi E, Azzolin NM, Carra S, et al. Effect of topical steroids on nasal nitric oxide production in children with perennial allergic rhinitis: a pilot study. Respir Med 1998;92(3):558-61.

Baraniuk JM, Meltzer EO, Spector SL. Impact of allergic rhinitis and related airway disorders. J Respir Dis 1996;17(Suppl):511-23.

Bardana Jr EJ. Occupational asthma and related respiratory disorders. Dis Mon 1995;41(3):145-90.

Bardare M, Zani G, Novembre E, et al. Local nasal immunotherapy with a powder extract for grass pollen induced rhinitis in pediatric ages: a controlled study. J Investig Allergol Clin Immunol 1996;6(6):359-63.

Barnes C, Tuck J, Simon S, et al. Allergenic materials in the house dust of allergy clinic patients. Ann Allergy Asthma Immunol 2001;86(5):517-23.

Baroody FM. Developments in the drug treatment of allergic rhinitis. Curr Opin Otolaryngol Head Neck Surg 1998;6(1):6-17.

Barrett J, Dunkin JW, Shelton M. Examination of the NHANES data set: pets, wheezing, and allergy symptoms. South Online J Nurs Res 2001;2(1):1-11.

Barth D, Hair JA, Kunkle BN, et al. Efficacy of eprinomectin against mange mites in cattle. Am J Vet Res 1997;58(11):1257-9.

Bascom R. Environmental factors and respiratory hypersensitivity: the Americas. Toxicol Letters 1996;86(2-3):115-30.

Basnyet D, Basnyet J. Allergies understood: conventional and complementary approaches. Positive Health 2000;56:19-22.

Bast G. WAO invites Member Societies to host GLORIA(TM) program. Allergy Clin Immunol Int 2001;13(4):182.

Baur X. New aspects of isocyanate asthma. Lung 1990;168(Suppl):606-13.

Baur X, Chen Z, Marczynski B. Respiratory diseases caused by occupational exposure to 1,5-naphthalene-diisocyanate (NDI): Results of workplace-related challenge tests and antibody analyses. Am J Ind Med 2001;39(4):369-72.

Beck HI, Korsgaard J. Atopic dermatitis and house dust mites. Br J Dermatol 1989;120(2):245-51.

Becker A. Clinical evidence with montelukast in the management of chronic childhood asthma. Drugs 2000;59(Suppl 1):29-34.

Becker A. Leukotriene receptor antagonists: efficacy and safety in children with asthma. Pediatr Pulmonol 2000;30(2):183-6.

Beckman DB, Grammer LC. Pharmacotherapy to prevent the complications of allergic rhinitis. [Review]. Allergy Asthma Proc 1999;20(4):215-23.

Belchi-Hernandez J, Mora-Gonzalez A, Iniesta-Perez J. Baker's asthma caused by Saccharomyces cerevisiae in dry powder form. J Allergy Clin Immunol 1996;97(1 I):131-4.

Bellanti JA, Wallerstedt DB. Allergic rhinitis update: epidemiology and natural history. [Review]. Allergy Asthma Proc 2000;21(6):367-70.

Bellussi L, Passali D. Treatment of upper airways inflammation with nimesulide. Drugs 1993;46(Suppl 1):107-10.

Benincasa C, Lloyd RS. Evaluation of fluticasone propionate aqueous nasal spray taken alone and in combination with cetirizine in the prophylactic treatment of seasonal allergic rhinitis. Drug Invest 1994;8(4):225-33.

Benninger MS, Sedory Holzer SE, Lau J. Diagnosis and treatment of uncomplicated acute bacterial rhinosinusitis: summary of the Agency for Health Care Policy and Research evidence-based report. Otolaryngol Head Neck Surg 2000;122(1):1-7.

Benninger MS, Senior BA. The development of the Rhinosinusitis Disability Index. Arch Otolaryngol Head Neck Surg 1997;123(11):1175-9.

Bentley S. Performance in students with seasonal allergy. J Int Med Res 1980;8(3):221-3.

Berdeaux G, Hervie C, Smajda C, et al. Parental quality of life and recurrent ENT infections in their children: development of a questionnaire. Rhinitis Survey Group. Qual Life Res 1998;7(6):501-12.

Berdeaux G, Lafuma A, Perruchet AM, et al. Cost effectiveness of immunoprophylaxis in the prevention of recurrent infectious rhinitis in adults. Pharmacoeconomics 1998;14(3):313-22.

Berger I, Argaman Z, Schwartz SB, et al. Efficacy of corticosteroids in acute bronchiolitis: short-term and long-term follow-up. Pediatr Pulmonol 1998;26(3):162-6.

Berger WE, Fineman SM, Lieberman P, et al. Double-blind trials of azelastine nasal spray monotherapy versus combination therapy with loratadine tablets and beclomethasone nasal spray in patients with seasonal allergic rhinitis. Rhinitis Study Groups. Ann Allergy Asthma Immunol 1999;82(6):535-41.

Bergmann RL, Edenharter G, Bergmann KE, et al. Socioeconomic status is a risk factor for allergy in parents but not in their children. Clin Exp Allergy 2000;30(12):1740-5.

Bergqvist A, Jacobson J, Harris S. A double blind randomized study of the treatment of endometriosis with nafarelin or nafarelin plus norethisterone. Gynecol Endocrinol 1997;11(3):187-94.

Berman BA, Ross RN. Antihistamines and the management of allergic rhinitis in the workplace. Adv Ther 1996;13(2):95-102.

Bernstein DI. Desloratadine: A viewpoint. Drugs 2001;61(6):797.

Bernstein DI, Schoenwetter WF, Nathan RA, et al. Efficacy and safety of fexofenadine hydrochloride for treatment of seasonal allergic rhinitis. Ann Allergy Asthma Immunol 1997;79(5):443-8.

Bernstein IL, Tennenbaum J, Georgakis N, et al. Fraction A: a new immunotherapeutic approach for ragweed pollinosis. Int Arch Allergy Appl Immunol 1976;50(2):181-91.

Bernstein JA. Cost-benefit analysis for allergen immunotherapy. Immunol Allergy Clin North Am 2000;20(3):593-608.

Bertoni M, Cosmi F, Bianchi I, et al. Clinical efficacy and tolerability of a steady dosage schedule of local nasal immunotherapy. Results of preseasonal treatment in grass pollen rhinitis. Ann Allergy Asthma Immunol 1999;82(1):47-51.

Bertrand B, Jamart J, Marchal JL, et al. Cetirizine and pseudoephedrine retard alone and in combination in the treatment of perennial allergic rhinitis: a double-blind multicentre study. Rhinology 1996;34(2):91-6.

Besag FMC, Dulac O, Alving J, et al. Long-term safety and efficacy of lamotrigine (Lamictal(R)) in paediatric patients with epilepsy. Seizure 1997;6(1):51-6.

Beyzarov EP. Eye relief: New ophthalmic product promises to bring fast relief to allergic conjunctivitis sufferers. Drug Topics 2000;144(13):15.

Biostat. Comprehensive Meta-analysis [computer program]. Version 1.25. Englewood, NJ: Biostat; 1999.

Black HR, Sollins JS, Garofalo JL. The addition of doxazosin to the therapeutic regimen of hypertensive patients inadequately controlled with other antihypertensive medications: A randomized, placebo-controlled study. Am J Hypertens 2000;13(5 I):468-74.

Black PN, Blasi F, Jenkins CR, et al. Trial of roxithromycin in subjects with asthma and serological evidence of infection with Chlamydia pneumoniae. Am J Respir Crit Care Med 2001;164(4):536-41.

Blainey AD, Phillips MJ, Ollier S, et al. Hyposensitization with a tyrosine adsorbed extract of Dermatophagoides pteronyssinus in adults with perennial rhinitis. A controlled clinical trial. Allergy 1984;39(7):521-8.

Blair H. Natural history of childhood asthma. 20-year follow-up. Arch Dis Child 1977;52(8):613-9.

Blair H, Viner AS. A double blind trial of a 2% solution of sodium cromoglycate in perennial rhinitis. Clin Allergy 1975;5(2):139-43.

Blaiss MS. How to determine the cost-effectiveness of available allergic rhinitis treatments. Drug Benefit Trends 1998;10:32-6.

Blaiss MS. Quality of life in allergic rhinitis. [Review]. Ann Allergy Asthma Immunol 1999;83(5):449-54.

Blaiss MS. Cognitive, social, and economic costs of allergic rhinitis. [Review]. Allergy Asthma Proc 2000;21(1):7-13.

Blanc PD, Trupin L, Earnest G, et al. Alternative therapies among adults with a reported diagnosis of asthma or rhinosinusitis: data from a population-based survey. Chest 2001;120(5):1461-7.

Blanc PD, Trupin L, Eisner M, et al. The work impact of asthma and rhinitis: findings from a population-based survey. J Clin Epidemiol 2001;54(6):610-8.

Blomqvist AM, Axelsson IGK, Danielsson D, et al. Atopic allergy to chloramine-T and the demonstration of specific IgE antibodies by the radioallergosorbent test. Int Arch Occup Environ Health 1991;63(5):363-5.

Blose JS, Adams Jr KF, Patterson JH. Torsemide: A pyridine-sulfonylurea loop diuretic. Ann Pharmacother 1995;29(4):396-402.

Blumenthal MN, Schwartz RH, Kaiser H. Nedocromil sodium 2% ophthalmic solution for the treatment of ragweed pollen seasonal allergic conjunctivitis. Ocul Immunol Inflamm 2000;8(3):159-67.

Bødtger U, Poulsen LK, Jacobi HH, et al. The safety and efficacy of subcutaneous birch pollen immunotherapy -- a one-year, randomised, double-blind, placebo-controlled study. Allergy 2002;57:297-305.

Bolhaar STHP, Van Ginkel CJW. Occupational allergy to cyclamen. Allergy Eur J Allergy Clin Immunol 2000;55(4):411-2.

Bonifazi F, Bilo MB. Efficacy of specific immunotherapy in allergic asthma: myth or reality? Allergy 1997;52(7):698-710.

Boonsawat W, Salome CM, Woolcock AJ. Effect of allergen inhalation on the maximal response plateau of the dose-response curve to methacholine. Am Rev Respir Dis 1992;146(3):565-9.

Bousquet J. Allergic rhinitis: Review of guidelines. Rev Fr Allergol Immunol Clin 1998;38(10):938-41.

Bousquet J. Allergy - A global problem. Allergy Clin Immunol Int 2000;12(4):141-2.

Bousquet J. Allergic rhinitis as a global health problem. Allergy Clin Immunol Int 2001;13(4):137.

Bousquet J, Bullinger M, Fayol C, et al. Assessment of quality of life in patients with perennial allergic rhinitis with the French version of the SF-36 Health Status Questionnaire. J Allergy Clin Immunol 1994;94(2 Pt 1):182-8.

Bousquet J, Chanal I, Murrieta M, et al. Lack of subsensitivity to mizolastine over 8-week treatment. Allergy 1996;51(4):251-6.

Bousquet J, Davies RJ. Chairmen's introduction. Clin Exp Allergy Suppl 1998;28(6):1.

Bousquet J, Demoly P, Michel F-B. Specific immunotherapy in rhinitis and asthma. Ann Allergy Asthma Immunol 2001;87(1 Suppl):38-42.

Bousquet J, Duchateau J, Pignat JC, et al. Improvement of quality of life by treatment with cetirizine in patients with perennial allergic rhinitis as determined by a French version of the SF-36 questionnaire. J Allergy Clin Immunol 1996;98(2):309-16.

Bousquet J, Frank E, Soussana M, et al. Double-blind, placebo-controlled immunotherapy with a high-molecular-weight, formalinized allergoid in grass pollen allergy. Int Arch Allergy Appl Immunol 1987;82(3-4):550-2.

Bousquet J, Hejjaoui A, Skassa-Brociek W, et al. Double-blind, placebo-controlled immunotherapy with mixed grass-pollen allergoids. I. Rush immunotherapy with allergoids and standardized orchard grass-pollen extract. J Allergy Clin Immunol 1987;80(4):591-8.

Bousquet J, Hejjaoui A, Soussana M, et al. Double-blind, placebo-controlled immunotherapy with mixed grass-pollen allergoids. IV. Comparison of the safety and efficacy of two dosages of a high-molecular-weight allergoid. J Allergy Clin Immunol 1990;85(2):490-7.

Bousquet J, Lockey R, Malling HJ. Allergen immunotherapy: therapeutic vaccines for allergic diseases. A WHO position paper. [Review]. J Allergy Clin Immunol 1998;102(4 Pt 1):558-62.

Bousquet J, Lockey R, Malling HJ, et al. Allergen immunotherapy: therapeutic vaccines for allergic diseases. World Health Organization. American Academy of Allergy, Asthma and Immunology. [Review]. Ann Allergy Asthma Immunol 1998;81(5 Pt 1):401-5.

Bousquet J, Lockey RF, Malling H-J. Preface: Allergen immunotherapy: Therapeutic vaccines for allergic diseases. Allergy Eur J Allergy Clin Immunol Suppl 1998;53(44):1-42.

Bousquet J, Maasch HJ, Hejjaoui A, et al. Double-blind, placebo-controlled immunotherapy with mixed grass-pollen allergoids. III. Efficacy and safety of unfractionated and high-molecular-weight preparations in rhinoconjunctivitis and asthma. J Allergy Clin Immunol 1989;84(4 Pt 1):546-56.

Bousquet J, Scheinmann P, Guinnepain MT, et al. Sublingual-swallow immunotherapy (SLIT) in patients with asthma due to house-dust mites: a double-blind, placebo-controlled study. Allergy 1999;54(3):249-60.

Bousquet J, van Cauwenberge P, Khaltaev N, et al. Allergic rhinitis and its impact on asthma (ARIA). J Allergy Clin Immunol 2001;108:S147-336.

Bowler SD, Mitchell CA, Miles J. House dust control and asthma: a placebo-control trial of cleaning air filtration. Ann Allergy 1985;55(3):498-500.

Boyce EG, Umland EM. Sildenafil citrate: A therapeutic update. Clin Ther 2001;23(1):2-23.

Bramer SL, Suri A. Inhibition of CYP2D6 by quinidine and its effects on the metabolism of cilostazol. Clin Pharmacokinet 1999;37(Suppl 2):41-51.

Branco-Ferreira M, dos Santos MC, Palma-Carlos ML, et al. Antihistamines and serum adhesion molecule levels. Allergi Immunol (Paris) 2001;33(6):233-6.

Braun JJ, Alabert JP, Michel FB, et al. Adjunct effect of loratadine in the treatment of acute sinusitis in patients with allergic rhinitis. Allergy 1997;52(6):650-5.

Breitenbach JM, Ferreira F, Jilek A, et al. Biological and immunological importance of Bet v 1 isoforms. Adv Exp Med Biol 1996;409:117-26.

Bridi AA, Rehbein S, Carvalho LA, et al. Efficacy of ivermectin in a controlled release formulation against Psoroptes ovis (Hering, 1838) gervais, 1841 (Acari: Psoroptidae) on sheep. Vet Parasitol 1998;78(3):215-21.

Brigden ML. A practical workup for eosinophilia: You can investigate the most likely causes right in your office. Postgrad Med 1999;105(3):193-210.

Briggs AH, O'Brien BJ. The death of cost-minimization analysis? [Review]. Health Econ 2001;10(2):179-84.

Brisman J, Jarvholm B, Lillienberg L. Exposure-response relations for self reported asthma and rhinitis in bakers. Occup Environ Med 2000;57(5):335-40.

Broder I, Higgins MW, Mathews KP, et al. Epidemiology of asthma and allergic rhinitis in a total community, Tecumseh, Michigan. 3. Second survey of the community. J Allergy Clin Immunol 1974;53(3):127-38.

Brogden RN, McTavish D. Budesonide. An updated review of its pharmacological properties, and therapeutic efficacy in asthma and rhinitis. Drugs 1992;44(3):375-407.

Bronsky E, Boggs P, Findlay S, et al. Comparative efficacy and safety of a once-daily loratadine-pseudoephedrine combination versus its components alone and placebo in the management of seasonal allergic rhinitis. J Allergy Clin Immunol 1995;96(2):139-47.

Bronsky EA, Druce H, Findlay SR, et al. A clinical trial of ipratropium bromide nasal spray in patients with perennial nonallergic rhinitis. J Allergy Clin Immunol 1995;95(5 II):1117-22.

Brooks CD, Francom SF, Peel BG, et al. Spectrum of seasonal allergic rhinitis symptom relief with topical corticoid and oral antihistamine given singly or in combination. Am J Rhinol 1996;10(3):193-9.

Brooks CD, Karl KJ. Hay fever treatment with combined antihistamine and cyclooxygenase-inhibiting drugs. J Allergy Clin Immunol 1988;81(6):1110-7.

Brooks CD, Nelson A, Parzyck R, et al. Protective effect of hydroxyzine and phenylpropanolamine in the challenged allergic nose. Ann Allergy 1981;47(5 Pt 1):316-9.

Brown CS, Parker NG, Stegbauer CC. Managing allergic rhinitis. Nurse Pract 1999;24:107-8, 110-1, 115-7, 120.

Brown CW, Hawkins L. Allergy prevalence and causal factors in the domestic environment: results of a random population survey in the United Kingdom. Ann Allergy Asthma Immunol 1999;83(3):240-4.

Brown HM, Merrett TG. Effectiveness of an acaricide in management of house dust mite allergy. Ann Allergy 1991;67(1):25-31.

Bruce CA, Norman PS, Rosenthal RR, et al. The role of ragweed pollen in autumnal asthma. J Allergy Clin Immunol 1977;59(6):449-59.

Bruce H. Rhinitis. Prim Care Clin Off Pract 1990;17(2):309-22.

Brunet C, Bedard PM, Lavoie A, et al. Allergic rhinitis to ragweed pollen. I. Reassessment of the effects of immunotherapy on cellular and humoral responses. J Allergy Clin Immunol 1992;89(1 Pt 1):76-86.

Brunet C, Bedard PM, Lavoie A, et al. Allergic rhinitis to ragweed pollen. II. Modulation of histamine-releasing factor production by specific immunotherapy. J Allergy Clin Immunol 1992;89(1 Pt 1):87-94.

Brunton S. Allergic rhinitis: breaking the cycle of disease and treatment. Fam Pract Recertification 1997;19(9):14-6, 23-6, 29-32.

Bryant DH, Burns MW, Lazarus L. The correlation between skin tests, bronchial provocation tests and the serum level of IgE specific for common allergens in patients with asthma. Clin Allergy 1975;5(2):145-57.

Brydon M. The effectiveness of a peripatetic allergy nurse practitioner service in managing atopic allergy in general practice--a pilot study. Clin Exp Allergy 1993;23(12):1037-44.

Buchanan DJ, Hillis A, Williams PN. A double blind controlled trial of Bencard house dust mite (Migen) hyposensitisation in Zambian asthmatics. Med J Zambia 1980-1981;15(1):14-6.

Buckman R, Lewith G. What does homoeopathy do - and how? BMJ 1994;309(6947):103-6.

Bukstein DA, Biondi RM, Blumenthal MM, et al. Tilarin in combination with astemizole. Allergy 1996;51(28 Suppl):20-7.

Bumsted RM. Cryotherapy for chronic vasomotor rhinitis: Technique and patient selection for improved results. Laryngoscope 1984;94(4):539-44.

Buntinx F, Van Krunkelsven P, Morabia A, et al. Antibiotics for the common cold. Lancet 1996;348(9029):754-5.

Burney P, Malmberg E, Chinn S, et al. The distribution of total and specific serum IgE in the European Community Respiratory Health Survey. J Allergy Clin Immunol 1997;99(3):314-22.

Burr ML, Dean BV, Butland BK, et al. Prevention of mite infestation of bedding by means of an impregnated sheet. A randomized controlled trial. Allergy 1988;43(4):299-302.

Burr ML, Dean BV, Merrett TG, et al. Effects of anti-mite measures on children with mite-sensitive asthma: a controlled trial. Thorax 1980;35(7):506-12.

Burr ML, Miskelly FG, Butland BK, et al. Environmental factors and symptoms in infants at high risk of allergy. J Epidemiol Community Health 1989;43(2):125-32.

Burr ML, Neale E, Dean BV, et al. Effect of a change to mite-free bedding on children with mite-sensitive asthma: a controlled trial. Thorax 1980;35(7):513-4.

Burr ML, St Leger AS, Neale E. Anti-mite measurements in mite-sensitive adult asthma. A controlled trial. Lancet 1976;1(7955):333-5.

Burris JF, Davidov ME, Jenkins P, et al. Comparison of the antihypertensive effects of betaxolol and chlorthalidone as monotherapy and in combination. Arch Intern Med 1989;149(11):2437-41.

Burtin B, Duchateau J, Pignat JC, et al. Further improvement of quality of life by cetirizine in perennial allergic rhinitis as a function of treatment duration. J Investig Allergol Clin Immunol 2000;10(2):66-70.

Burton WN, Conti DJ, Chen CY, et al. The impact of allergies and allergy treatment on worker productivity. J Occup Environ Med 2001;43(1):64-71.

Busse W, Janssens M, Eisen G. A multicenter, double-blind, randomized, placebo-controlled trial comparing the efficacy and tolerability of levocabastine-oxymetazoline nasal spray with levocabastine and oxymetazoline alone in the symptomatic treatment of seasonal allergic rhinitis. Am J Rhinol 1996;10(2):105-11.

Butterfield JH, Gleich GJ, Yunginger JW, et al. Immunotherapy with short ragweed fraction A:D-glutamic acid:D-lysine polymer in ragweed hay fever. J Allergy Clin Immunol 1981;67(4):272-8.

Butz AM, Larson E, Fosarelli P, et al. Occurrence of infectious symptoms in children in day care homes. Am J Infect Control 1990;18(6):347-53.

Caffarelli C, Sensi LG, Marcucci F, et al. Preseasonal local allergoid immunotherapy to grass pollen in children: a double-blind, placebo-controlled, randomized trial. Allergy 2000;55(12):1142-7.

Calhoun KH. Chronic rhinosinusitis: Cost-effective work-up, guidelines for treatment. Consultant 1997;37(12):3112-22.

Call RS, Smith TF, Morris E, et al. Risk factors for asthma in inner city children. J Pediatr 1992;121(6):862-6.

Call RS, Ward G, Jackson S, et al. Investigating severe and fatal asthma. J Allergy Clin Immunol 1994;94(6 Pt 1):1065-72.

Camilleri AE. Information leaflets in the rhinitis clinic? J Laryngol Otol 1991;105(4):282-4.

Campbell F, Jones K. Feather vs. non-feather bedding for asthma (Cochrane Review). In: the Cochrane Library, Issue 4, 2001, Oxford: Update Software, 2001.

Canady RG, Platts-Mills T, Murphy A, et al. Vital capacity reservoir and online measurement of childhood nitrosopnea are linearly related. Clinical implications. Am J Respir Crit Care Med 1999;159(1):311-4.

Cantani A, Arcese G, Lucenti P, et al. A three-year prospective study of specific immunotherapy to inhalant allergens: Evidence of safety and efficacy in 300 children with allergic asthma. J Investig Allergol Clin Immunol 1997;7(2):90-7.

Canter D, Frank GJ, Knapp LE, et al. Quinapril and hydrochlorothiazide combination for control of hypertension: Assessment by factorial design. J Hum Hypertens 1994;8(3):155-62.

Caramia G, Franceschini F, Cimarelli ZA, et al. The efficacy of E.P.D., a new immunotherapy, in the treatment of allergic diseases in children. Allerg Immunol (Paris) 1996;28(9):308-10.

Cariski AT. Cilostazol: A novel treatment option in intermittent claudication. Int J Clin Pract Suppl 2001;-(119):11-8.

Carlsen KH, Kramer J, Fagertun HE, et al. Loratadine and terfenadine in perennial allergic rhinitis. Treatment of nonresponders to the one drug with the other drug. Allergy 1993;48(6):431-6.

Carosso A, Ruffino C, Bugiani M. The effect of birth season on pollenosis. Ann Allergy 1986;56(4):300-3.

Carpenter LL, McDougle CJ, Epperson CN, et al. A risk-benefit assessment of drugs used in the management of obsessive-compulsive disorder. Drug Saf 1996;15(2):116-34.

Carsons S. A review and update of Sjogren's syndrome: Manifestations, diagnosis, and treatment. Am J Manag Care 2001;7(14 Suppl):S433-S443.

Carswell F, Birmingham K, Oliver J, et al. The respiratory effects of reduction of mite allergen in the bedrooms of asthmatic children--a double-blind controlled trial. Clin Exp Allergy 1996;26(4):386-96.

Carswell F, Oliver J, Weeks J. Do mite avoidance measures affect mite and cat airborne allergens? Clin Exp Allergy 1999;29(2):193-200.

Carswell F, Robinson DW, Oliver J, et al. House dust mites in Bristol. Clin Allergy 1982;12(6):533-45.

Carter MC, Perzanowski MS, Raymond A, et al. Home intervention in the treatment of asthma among inner-city children. J Allergy Clin Immunol 2001;108(5):732-7.

Casale TB. Anti-immunoglobulin E (omalizumab) therapy in seasonal allergic rhinitis. Am J Respir Crit Care Med 2001;164(8 II):S18-S21.

Casale TB. Experience with monoclonal antibodies in allergic mediated disease: Seasonal allergic rhinitis. J Allergy Clin Immunol 2001;108(2 Suppl):S84-S88.

Casale TB, Bernstein IL, Busse WW, et al. Use of an anti-IgE humanized monoclonal antibody in ragweed-induced allergic rhinitis. J Allergy Clin Immunol 1997;100(1):110-21.

Casale TB, Condemi J, LaForce C, et al. Effect of Omalizumab on symptoms of seasonal allergic rhinitis: a randomized controlled trial. JAMA 2001;286:2956-67.

Casanovas M, Guerra F, Moreno C, et al. Double-blind, placebo-controlled clinical trial of preseasonal treatment with allergenic extracts of Olea europaea pollen administered sublingually. J Investig Allergol Clin Immunol 1994;4(6):305-14.

Casiano RR. Treatment of acute and chronic rhinosinusitis. Semin Respir Infect 2000;15(3):216-26.

Castelain M, Birnbaum J, Castelain PY, et al. Patch test reactions to mite antigens: a GERDA multicentre study. Groupe d'Etudes et de Recherches en Dermato-Allergie. Contact Dermatitis 1993;29(5):246-50.

Centers for Disease Control and Prevention, National Center for Health Statistics. Current estimates from the National Health Interview Survey, 1996. Vital and Health Statistics, Series 10, No. 200. DHHS Publication No. (PHS) 99-1528. Hyattsville, MD: US Department of Health and Human Services. October 1999.

Cereghino JJ, Biton V, Abou-Khalil B, et al. Levetiracetam for partial seizures: results of a double-blind, randomized clinical trial. Neurology 2000;55(2):236-42.

Chan-Yeung M, Ferguson A, Chan H, et al. Umbilical cord blood mononuclear cell proliferative response to house dust mite does not predict the development of allergic rhinitis and asthma. J Allergy Clin Immunol 1999;104(2 Pt 1):317-21.

Chan-Yeung M, Manfreda J, Dimich-Ward H, et al. A randomized controlled study on the effectiveness of a multifaceted intervention program in the primary prevention of asthma in high-risk infants. Arch Pediatr Adolesc Med 2000;154(7):657-63.

Chan-Yeung M, Manfreda J, Dimich-Ward H, et al. Mite and cat allergen levels in homes and severity of asthma. Am J Respir Crit Care Med 1995;152(6 Pt 1):1805-11.

Chang JH, Becker A, Ferguson A, et al. Effect of application of benzyl benzoate on house dust mite allergen levels. Ann Allergy Asthma Immunol 1996;77(3):187-90.

Chang MY, Hogan AD, Rakes GP, et al. Salivary cotinine levels in children presenting with wheezing to an emergency department. Pediatr Pulmonol 2000;29(4):257-63.

Chapman J, Girardeau C, O'Coneell EJ. We have made progress but there is still work to be done. Ann Allergy Asthma Immunol 2000;85(3):159.

Chapman JA. How relevant are pollen and mold spore counts to clinical practice? Ann Allergy Asthma Immunol 2000;84(5):467-8.

Chapman MD, Heymann PW, Wilkins SR, et al. Monoclonal immunoassays for major dust mite (Dermatophagoides) allergens, Der p I and Der f I, and quantitative analysis of the allergen content of mite and house dust extracts. J Allergy Clin Immunol 1987;80(2):184-94.

Chapman MD, Platts-Mills TA, Gabriel M, et al. Antibody response following prolonged hyposensitization with Dermatophagoides pteronyssinus extract. Int Arch Allergy Appl Immunol 1980;61(4):431-40.

Chapman MD, Pollart SM, Luczynska CM, et al. Hidden allergic factors in the etiology of asthma. [Review]. Chest 1988;94(1):185-90.

Chapman MD, Rowntree S, Mitchell EB, et al. Quantitative assessments of IgG and IgE antibodies to inhalant allergens in patients with atopic dermatitis. J Allergy Clin Immunol 1983;72(1):27-33.

Charman C. Clinical evidence: atopic eczema. [Review]. BMJ 1999;318(7198):1600-4.

Charpin D, Kleisbauer JP, Lanteaume A, et al. Asthma and allergy to house-dust mites in populations living in high altitudes. Chest 1988;93(4):758-61.

Chatterjee S. Immunotherapeutic strategies to combat allergic respiratory diseases. Indian J Pharmacol 2001;33(4):293.

Chen CC, Hsieh KH. Effects of Microstop-treated anti-mite bedding on children with mite-sensitive asthma. Acta Paed Sin 1996;37(6):420-7.

Chen JL. Failure of desensitization in the management of vancomycin hypersensitivity. [Abstract]. ASHP Midyear Clin Mtg 1993;28:P-443(D).

Chesnut ICH, Silverman S, Andriano K, et al. A randomized trial of nasal spray salmon calcitonin in postmenopausal women with established osteoporosis: The prevent recurrence of osteoporotic fractures study. Am J Med 2000;109(4):267-76.

Chew FT, Goh DY, Lee BW. Effects of an acaricide on mite allergen levels in the homes of asthmatic children. Acta Paediatr Japonica 1996;38(5):483-8.

Chinn S. A simple method for converting an odds ratio to effect size for use in meta-analysis. Stat Med 2000;19(22):3127-31.

Chinn S, Jarvis D, Luczynska C, et al. Individual allergens as risk factors for bronchial responsiveness in young adults. Thorax 1998;53(8):662-7.

Chowdhury I, Chatterjee B. The immunological and clinical effects of immunotherapy in patients suffering from house dust allergy. Ann Agric Environ Med 1999;6(2):91-7.

Chowgule RV, Shetye VM, Parmar JR, et al. Prevalence of respiratory symptoms, bronchial hyperreactivity, and asthma in a megacity. Results of the European community respiratory health survey in Mumbai (Bombay). Am J Respir Crit Care Med 1998;158(2):547-54.

Cicutto LC, Chapman KR. Approaches to unresponsive asthma. Drug Benefit Trends 2001;13(6):34-6, 55-60.

Cipolla C, Lugo G, Sassi C, et al. A new risk of occupational disease: Allergic asthma and rhinoconjunctivitis in persons working with beneficial arthropods. Int Arch Occup Environ Health 1996;68(2):133-5.

Ciprandi G. Relationships between allergic diseases: Conjunctivitis, rhinitis and asthma. Drug News Perspect 1997;10(5):317-20.

Ciprandi G, Cosentino C, Milanese M, et al. Fexofenadine reduces nasal congestion in perennial allergic rhinitis. Allergy Eur J Allergy Clin Immunol 2001;56(11):1068-70.

Ciprandi G, Pronzato C, Ricca V, et al. Loratadine treatment of rhinitis due to pollen allergy reduces epithelial ICAM-1 expression. Clin Exp Allergy 1997;27(10):1175-83.

Ciprandi G, Ricca V, Tosca M, et al. Continuous antihistamine treatment controls allergic inflammation and reduces respiratory morbidity in children with mite allergy. Allergy 1999;54(4):358-65.

Ciprandi G, Tosca M, Passalacqua G, et al. Long-term cetirizine treatment reduces allergic symptoms and drug prescriptions in children with mite allergy. Ann Allergy Asthma Immunol 2001;87(3):222-6.

Ciprandi G, Tosca M, Ricca V, et al. Cetirizine treatment of rhinitis in children with pollen allergy: Evidence of its antiallergic activity. Clin Exp Allergy 1997;27(10):1160-6.

Cirla AM, Sforza N, Roffi GP, et al. Preseasonal intranasal immunotherapy in birch-alder allergic rhinitis. A double-blind study. Allergy 1996;51(5):299-305.

Clavel R, Bousquet J, Andre C. Clinical efficacy of sublingual-swallow immunotherapy: a double-blind, placebo-controlled trial of a standardized five-grass-pollen extract in rhinitis. Allergy 1998;53(5):493-8.

Cleophas TJM, Tavenier P. Clinical trials in chronic diseases. J Clin Pharmacol 1995;35(6):594-8.

Clerico DM. Sources and effects of indoor air pollution, including sick building syndrome. Curr Opin Otolaryngol Head Neck Surg 1996;4(1):44-9.

Cloosterman SG, Bijl-Hofland ID, van Herwaarden CL, et al. A placebo-controlled clinical trial of regular monotherapy with short-acting and long-acting beta(2)-agonists in allergic asthmatic patients. Chest 2001;119(5):1306-15.

Cloosterman SG, Hofland ID, Lukassen HG, et al. House dust mite avoidance measures improve peak flow and symptoms in patients with allergy but without asthma: a possible delay in the manifestation of clinical asthma? J Allergy Clin Immunol 1997;100(3):313-9.

Cloosterman SG, Schermer TR, Bijl-Hofland ID, et al. Effects of house dust mite avoidance measures on Der p 1 concentrations and clinical condition of mild adult house dust mite-allergic asthmatic patients, using no inhaled steroids. Clin Exp Allergy 1999;29(10):1336-46.

Cloud ML, Enas GC, Kemp J, et al. A specific LTD4/LTE4-receptor antagonist improves pulmonary function in patients with mild, chronic asthma. Am Rev Respir Dis 1989;140(5):1336-9.

Clover A. Patient benefit survey: Tunbridge Wells Homoeopathic Hospital 1997. Br Homeopath J 2000;89(Suppl 1):S45.

Cockburn IM, Bailit HL, Berndt ER, et al. Loss of work productivity due to illness and medical treatment. J Occup Environ Med 1999a;41(11):948-53.

Cockburn IM, Bailit HL, Berndt ER, et al. Costing out care: when antihistamines go to work. Bus Health 1999b;17(3):49-50.

Cockcroft DW, Cuff MT, Tarlo SM, et al. Allergen injection therapy with glutaraldehyde-modified--ragweed pollen-tyrosine adsorbate. A double-blind trial. J Allergy Clin Immunol 1977;60(1):56-62.

Coffman DA, Jenkins M. Intranasal betamethasone valerate in seasonal rhinitis. Practitioner 1975;215(1289):665-8.

Cohen J. Statistical power analysis for the behavioral sciences. Hillsdale, NJ: L. Erlbaum Associates; 1988.

Cohen L. Indoor air quality a major public-health issue, workshop told. Can Med Assoc J 1995;153(1):92-3.

Cohen SG, King JR. Skin tests: A historic trail. Immunol Allergy Clin North Am 2001;21(2):191-249.

Colberg K, Hettich M, Sigmund R, et al. The efficacy and tolerability of an 8-day administration of intravenous and oral meloxicam: A comparison with intramuscular and oral diclofenac in patients with acute lumbago. Curr Med Res Opin 1995;13(7):363-77.

Colgan R, Powers JH. Appropriate antimicrobial prescribing: Approaches that limit antibiotic resistance. Am Fam Phys 2001;64(6):999-1004.

Collard Ph, Rodenstein DO. Nasal continuous positive airway pressure for sleep apnoea. Eur Respir Monogr 1998;3(10):179-204.

Colloff MJ. House dust mite control with Acarosan--an extreme test? Clin Exp Allergy 1992;22(7):657-8.

Colloff MJ, Lever RS, McSharry C. A controlled trial of house dust mite eradication using natamycin in homes of patients with atopic dermatitis: effect on clinical status and mite populations. Br J Dermatol 1989;121(2):199-208.

Compston JE. Pharmacological interventions for post-menopausal osteoporosis: An evidence-based approach. Rheumatology (UK) 2000;39(12):1309-12.

Comstock GW, Stone RW, Tonascia JA, et al. Respiratory survey findings as predictors of disability from respiratory diseases. Am Rev Respir Dis 1981;124(4):367-71.

Conde HDJ, Palma AJL, Delgado RJ, et al. Comparison of azelastine nasal spray and oral ebastine in treating seasonal allergic rhinitis. Curr Med Res Opin 1995;13(6):299-304.

Condemi J, Schulz R, Lim J. Triamcinolone acetonide aqueous nasal spray versus loratadine in seasonal allergic rhinitis: efficacy and quality of life. Ann Allergy Asthma Immunol 2000;84(5):533-8.

Cook PR, Farias C. The safety of allergen immunotherapy: a literature review. [Review]. Ear Nose Throat J 1998;77(5):378-9, 383-8.

Cools M, Van Bever HP, Weyler JJ, et al. Long-term effects of specific immunotherapy, administered during childhood, in asthmatic patients allergic to either house-dust mite or to both house-dust mite and grass pollen. Allergy 2000;55(1):69-73.

Cooper C, Srakkestad JA, Radowicki S, et al. Matrix delivery transdermal 17beta-estradiol for the prevention of bone loss in postmenopausal women. Osteoporosis Int 1999;9(4):358-66.

Cooper NK. A cheaper preparation of disodium cromoglycate in the treatment of allergic rhinitis. J R Army Med Corps 1989;135(1):34.

Cooper PJ, Darbyshire J, Nunn AJ, et al. A controlled trial of oral hyposensitization in pollen asthma and rhinitis in children. Clin Allergy 1984;14(6):541-50.

Corey JP, Kemker BJ, Branca JT, et al. Health status in allergic rhinitis. Otolaryngol Head Neck Surg 2000;122(5):681-5.

Corne J, Djukanovic R, Thomas L, et al. The effect of intravenous administration of a chimeric anti-IgE antibody on serum IgE levels in atopic subjects: efficacy, safety, and pharmacokinetics. J Clin Invest 1997;99(5):879-87.

Cornere M, Fitzharris P, Douglas R. Immunotherapy: practical guide to administration. New Ethicals 1999;2:67-72.

Corrado OJ, Pastorello E, Ollier S, et al. A double-blind study of hyposensitization with an alginate conjugated extract of D. pteronyssinus (Conjuvac) in patients with perennial rhinitis. 1. Clinical aspects. Allergy 1989;44(2):108-15.

Corren J. Allergic rhinitis and asthma: How important is the link? J Allergy Clin Immunol 1997;99(2):S781-S786.

Corren J. The impact of allergic rhinitis on bronchial asthma. J Allergy Clin Immunol 1998;101(2 II):S352-S356.

Corren J, Harris AG, Aaronson D, et al. Efficacy and safety of loratadine plus pseudoephedrine in patients with seasonal allergic rhinitis and mild asthma. [erratum appears in J Allergy Clin Immunol 1998 Jun;101(6 Pt 1):792]. J Allergy Clin Immunol 1997;100(6 Pt 1):781-8.

Cote J, Cartier A, Robichaud P, et al. Influence of asthma education on asthma severity, quality of life and environmental control. Can Respir J 2000;7(5):395-400.

Craig-McFeely PM, Acharya NV, Shakir SAW. Evaluation of the safety of fexofenadine from experience gained in general practice use in England in 1997. Eur J Clin Pharmacol 2001;57(4):313-20.

Craig T, Sawyer AM, Fornadley JA. Use of immunotherapy in a primary care office. Am Fam Physician 1998;57(8):1888-94.

Crane J, Ellis I, Siebers R, et al. A pilot study of the effect of mechanical ventilation and heat exchange on house-dust mites and Der p 1 in New Zealand homes. Allergy 1998;53(8):755-62.

Crater SE, Peters EJ, Martin ML, et al. Expired nitric oxide and airway obstruction in asthma patients with an acute exacerbation. Am J Respir Crit Care Med 1999;159(3):806-11.

Crater SE, Peters EJ, Phillips CD, et al. Prospective analysis of CT of the sinuses in acute asthma. AJR Am J Roentgenol 1999;173(1):127-31.

Creticos PS. Immunotherapy with allergens. J Am Med Assoc 1992;268(20):2834-9.

Creticos PS, Reed CE, Norman PS, et al. Ragweed immunotherapy in adult asthma. N Engl J Med 1996;334(8):501-6.

Criner GJ, Brennan K, Travaline JM, et al. Efficacy and compliance with noninvasive positive pressure ventilation in patients with chronic respiratory failure. Chest 1999;116(3):667-75.

Crobach M, Hermans J, Kaptein A, et al. Nasal smear eosinophilia for the diagnosis of allergic rhinitis and eosinophilic non-allergic rhinitis. Scand J Prim Health Care 1996;14(2):116-21.

Crobach MJJ, Hermans J, Kaptein AA, et al. The diagnosis of allergic rhinitis: How to combine the medical history with the results of radioallergosorbent tests and skin prick tests. Scand J Prim Health Care 1998;16(1):30-6.

Cross S. Mould spores: the unusual suspects in hay fever. Community Nurse 1997;3(4):25-6.

Cross S, Buck S, Hubbard J. ABC of allergies: Allergy in general practice. BMJ 1998;316(7144):1584-7.

Crown WH. Productivity measurement in pharmaceutical studies. Drug Benefit Trends 2000;12(2):5BH-8BH.

Crystal-Peters J, Crown WH, Goetzel RZ, et al. The cost of productivity losses associated with allergic rhinitis. Am J Manag Care 2000;6(3):373-8.

Crystal-Peters J, Neslusan C, Crown WH, et al. Treating allergic rhinitis in patients with comorbid asthma: The risk of asthma-related hospitalizations and emergency department visits. J Allergy Clin Immunol 2002;109(1 Pt 1):57-62.

Cuffel B, Wamboldt M, Borish L, et al. Economic consequences of comorbid depression, anxiety, and allergic rhinitis. Psychosomatics 1999;40(6):491-6.

Cunningham JM, Chiu EJ, Landgraf JM, et al. The health impact of chronic recurrent rhinosinusitis in children. Arch Otolaryngol Head Neck Surg 2000;126(11):1363-8.

Curtis VA, Kerwin RW. A risk-benefit assessment of risperidone in schizophrenia. Drug Saf 1995;12(2):139-45.

Custovic A, Simpson BM, Simpson A, et al. Manchester Asthma and Allergy Study: low-allergen environment can be achieved and maintained during pregnancy and in early life. J Allergy Clin Immunol 2000;105(2 Pt 1):252-8.

Custovic A, Taggart SC, Francis HC, et al. Exposure to house dust mite allergens and the clinical activity of asthma. J Allergy Clin Immunol 1996;98(1):64-72.

Custovic A, Woodcock A. Clinical effects of allergen avoidance. [Review]. Clin Rev Allergy Immunol 2000;18(3):397-419.

Cuthbert OD, Jeffrey IG, McNeill HB, et al. Barn allergy among Scottish farmers. Clin Allergy 1984;14(2):197-206.

Cvitanovic S, Zekan L, Capkun V, et al. Specific hyposensitization in patients allergic to Parietaria officinalis pollen allergen. J Investig Allergol Clin Immunol 1994;4(6):283-90.

D'Amato G, Liccardi G, Russo M, et al. Measurement of serum levels of eosinophil cationic protein to monitor patients with seasonal respiratory allergy induced by Parietaria pollen (treated and untreated with specific immunotherapy). Allergy 1996;51(4):245-50.

D'Amato G, Lobefalo G, Liccardi G, et al. A double-blind, placebo-controlled trial of local nasal immunotherapy in allergic rhinitis to Parietaria pollen. Clin Exp Allergy 1995;25(2):141-8.

D'Souza MF, Pepys J, Wells ID, et al. Hyposensitization with Dermatophagoides pteronyssinus in house dust allergy: a controlled study of clinical and immunological effects. Clin Allergy 1973;3(2):177-93.

Damm M, Jungehulsing M, Eckel HE, et al. Effects of systemic steroid treatment in chronic polypoid rhinosinusitis evaluated with magnetic resonance imaging. Otolaryngol Head Neck Surg 1999;120(4):517-23.

Davies BH. Epidemiology of building-associated illness. Immunol Allergy Clin North Am 1994;14(3):483-93.

Davies R. The health economics of quality of life. Eur Respir Rev 1997;7(47):303-6.

Davis KL, Powchik P. Tacrine. Lancet 1995;345(8950):625-30.

De Alarcon A, Walsh EE, Carper HT, et al. Detection of IgA and IgG but not IgE antibody to respiratory syncytial virus in nasal washes and sera from infants with wheezing. J Pediatr 2001;138(3):311-7.

de Andrade AD, Charpin D, Birnbaum J, et al. Indoor allergen levels in day nurseries. J Allergy Clin Immunol 1995;95(6):1158-63.

De Blay F, Sanchez J, Platts-Mills T, et al. [Metrology of airborne particles carrying the principal air allergens]. [French]. Rev Mal Respir 1995;12(4):343-52.

de Bock GH, Reijneveld SA, van Houwelingen JC, et al. Multiattribute utility scores for predicting family physicians' decisions regarding sinusitis. Med Decis Making 1999;19(1):58-65.

de Graaf-in't Veld C, Garrelds IM, van Toorenenbergen AW, et al. Nasal responsiveness to allergen and histamine in patients with perennial rhinitis with and without a late phase response. Thorax 1997;52(2):143-8.

de Graaf-in 't Veld T, Garrelds IM, van Toorenenbergen AW, et al. Effect of topical levocabastine on nasal response to allergen challenge and nasal hyperreactivity in perennial rhinitis. Ann Allergy Asthma Immunol 1995;75(3):261-6.

de Graaf-in 't Veld T, Koenders S, Garrelds IM, et al. The relationships between nasal hyperreactivity, quality of life, and nasal symptoms in patients with perennial allergic rhinitis. J Allergy Clin Immunol 1996;98(3):508-13.

De Zotti R, Molinari S, Larese F, et al. Pre-employment screening among trainee bakers. Occup Environ Med 1995;52(4):279-83.

Dekkers CPM, Beker JA, Thjodleifsson B, et al. Comparison of rabeprazole 20 mg vs. omeprazole 20 mg in the treatment of active gastric ulcer - A European multicentre study. Aliment Pharmacol Ther 1998;12(8):789-95.

Demoly P, Allaert F-A, Lecasble M, et al. ERASM, a pharmacoepidemiologic survey on management of intermittent allergic rhinitis in every day general medical practice in France. Allergy 2002;57:546-54.

Denman AM, Cornthwaite D. Control of house dust mite antigen in bedding. Lancet 1990;335(8696):1038.

Derebery MJ, Berliner KI. Allergy and health-related quality of life. Otolaryngol Head Neck Surg 2000;123(4):393-9.

Desrosiers MY, Salas-Prato M. Treatment of chronic rhinosinusitis refractory to other treatments with topical antibiotic therapy delivered by means of a large-particle nebulizer: results of a controlled trial. Otolaryngol Head Neck Surg 2001;125(3):265-9.

Deuell B, Arruda LK, Hayden ML, et al. Trichophyton tonsurans allergen. I. Characterization of a protein that causes immediate but not delayed hypersensitivity. J Immunol 1991;147(1):96-101.

Devlin J, David TJ, Stanton RH. Elemental diet for refractory atopic eczema. Arch Dis Child 1991;66(1):93-9.

Dharmage SC, Abramson M, Raven J, et al. Why do only some of the young adults with bronchial hyperreactivity wheeze? J Asthma 1998;35(5):391-9.

Di Stanislao C, Di Berardino L, Bianchi I, et al. A double-blind, placebo-controlled study of preventive immunotherapy with E.P.D., in the treatment of seasonal allergic disease. Allerg Immunol (Paris) 1997;29(2):39-42.

Diamant Z, Fokkens WJ. Leukotriene receptor antagonists: Clinical potential in allergic rhinitis. Rhinology 2001;39(4):187-90.

Diamant Z, Timmers MC, van der Veen H, et al. Effect of inhaled heparin on allergen-induced early and late asthmatic responses in patients with atopic asthma. Am J Respir Crit Care Med 1996;153(6 Pt 1):1790-5.

Diamond L, Gerson K, Cato A, et al. An evaluation of triprolidine and pseudoephedrine in the treatment of allergic rhinitis. Ann Allergy 1981;47(2):87-91.

Dietemann A, Bessot JC, Hoyet C, et al. A double-blind, placebo controlled trial of solidified benzyl benzoate applied in dwellings of asthmatic patients sensitive to mites: clinical efficacy and effect on mite allergens. J Allergy Clin Immunol 1993;91(3):738-46.

DiGioacchino M, Cavallucci E, Verna N, et al. Allergens in occupational allergy. Prevention and management. Int J Immunopathol Pharmacol 2000;13(3):163-8.

Dockery DW, Speizer FE, Stram DO, et al. Effects of inhalable particles on respiratory health of children. Am Rev Respir Dis 1989;139(3):587-94.

Dockhorn R, Aaronson D, Bronsky E, et al. Ipratropium bromide nasal spray 0.03% and beclomethasone nasal spray alone and in combination for the treatment of rhinorrhea in perennial rhinitis. Ann Allergy Asthma Immunol 1999;82(4):349-59.

Dockhorn RJ, Williams BO, Sanders RL. Efficacy of acrivastine with pseudoephedrine in treatment of allergic rhinitis due to ragweed. Ann Allergy Asthma Immunol 1996;76(2):204-8.

Dolor RJ, Witsell DL, Hellkamp AS, et al. Comparison of cefuroxime with or without intranasal fluticasone for the treatment of rhinosinusitis. The CAFFS Trial: a randomized controlled trial. JAMA 2001;286(24):3097-105.

Dolz I, Martinez-Cocera C, Bartolome JM, et al. A double-blind, placebo-controlled study of immunotherapy with grass-pollen extract Alutard SQ during a 3-year period with initial rush immunotherapy. Allergy 1996;51(7):489-500.

Donahue JG, Greineder DK, Connor-Lacke L, et al. Utilization and cost of immunotherapy for allergic asthma and rhinitis. Ann Allergy Asthma Immunol 1999;82(4):339-47.

Donovan JP, Buckeridge DL, Briscoe MP, et al. Efficacy of immunotherapy to ragweed antigen tested by controlled antigen exposure. Ann Allergy Asthma Immunol 1996;77(1):74-80.

Dooms-Goossens A. Sensitisation to corticosteroids: Consequences for anti-inflammatory therapy. Drug Saf 1995;13(2):123-9.

Dorward AJ, Colloff MJ, MacKay NS, et al. Effect of house dust mite avoidance measures on adult atopic asthma. Thorax 1988;43(2):98-102.

Dorward AJ, Waclawski E, Kerr JW. A comparison of the clinical and immunological effects of an alum-precipitated five-grass extract with a conjugated two-grass extract in the desensitization of hay fever. Clin Allergy 1984;14(6):561-70.

Douglass JA, Thien FCK, O'Hehir RE. Immunoteraphy in asthma. Thorax 1997;52(Suppl 3):S22-S29.

Dreborg S, Sjogren I, Eriksson NE, et al. Selection of patients for biological standardization as exemplified by standardization of mugwort, goosefoot and English plantain pollen allergen extracts/preparations. Allergy Eur J Allergy Clin Immunol 1987;42(7):485-95.

Drettner B. Why does research in rhinology matter? J Laryngol Otol 1984;98(12):1193-205.

Drouin MA, Yang WH, Horak F, et al. Adding loratadine to topical nasal steroid therapy improves moderately severe seasonal allergic rhinoconjunctivitis. Adv Ther 1995;12(6):340-9.

Druce HM, Spector SL, Fireman P, et al. Double-blind study of intranasal ipratropium bromide in nonallergic perennial rhinitis. Ann Allergy 1992;69(1):53-60.

Duarte C, Baehre M, Gharakhanian S, et al. Treatment of severe seasonal rhinoconjunctivitis by a combination of azelastine nasal spray and eye drops: a double-blind, double-placebo study. J Investig Allergol Clin Immunol 2001;11(1):34-40.

DuBuske LM. Introduction: Risk management in asthma and allergic diseases. J Allergy Clin Immunol 1996;98(6 III):S289-S290.

DuBuske LM. Appropriate and inappropriate use of immunotherapy. Ann Allergy Asthma Immunol 2001;87(1 Suppl):56-67.

Duff AL, Pomeranz ES, Gelber LE, et al. Risk factors for acute wheezing in infants and children: viruses, passive smoke, and IgE antibodies to inhalant allergens. Pediatrics 1993;92(4):535-40.

Dunlop G. Management of patients with rhinitis. Med Today 2001;2(10):61-7.

Durham SR, Kay AB, Hamid Q. Changes in allergic inflammation associated with successful immunotherapy. [Review]. Int Arch Allergy Immunol 1995;107(1-3):282-4.

Durham SR, Varney V, Gaga M, et al. Immunotherapy and allergic inflammation. Clin Exp Allergy 1991;21 (Suppl 1):206-10.

Durham SR, Walker S. Immunotherapy for hayfever. Chem Immunol 2000;78:199-208.

Durham SR, Walker SM, Varga EM, et al. Long-term clinical efficacy of grass-pollen immunotherapy. N Engl J Med 1999;341(7):468-75.

Durr DG, Desrosiers MY, Dassa C. Quality of life in patients with rhinosinusitis. J Otolaryngol 1999;28(2):108-11.

Dykewicz MS. Primary care update: brief summaries for clinical practice. Rhinitis update: a guide to treatment. Consultant 1999;39(5):1446, 1448-50.

Dykewicz MS. Rhinitis update: A guide to diagnosis. Consultant 1999;39(4):1253-5.

Dykewicz MS, Fineman S. Diagnosis and management of rhinitis: Parameter documents of the Joint Task Force on Practice Parameters in Allergy, Asthma, and Immunology: Preface. Joint Task Force on Practice Parameters in Allergy, Asthma, and Immunology, representing the American Academy of Allergy, Asthma and Immunology, the American College of Allergy, Asthma and Immunology, and the Joint Council of Allergy, Asthma and Immunology. Ann Allergy Asthma Immunol 1998;81(5 II):vi.

Dykewicz MS, Fineman S. Executive Summary of Joint Task Force practice parameters on diagnosis and management of rhinitis. Ann Allergy Asthma Immunol 1998;81(5 Pt 2):463-8.

Dykewicz MS, Fineman S, Nicklas R, et al. Joint Task Force algorithm and annotations for diagnosis and management of rhinitis. Ann Allergy Asthma Immunol 1998;81(5 Pt 2):469-73.

Dykewicz MS, Fineman S, Skoner DP. Joint Task Force summary statements on diagnosis and management of rhinitis. Ann Allergy Asthma Immunol 1998;81(5 Pt 2):474-7.

Easthope S, Jarvis B. Omalizumab. Drugs 2001;61(2):253-60.

Eccles R. Nasal airflow in health and disease. Acta Oto-Laryngol 2000;120(5):580-95.

Edsbacker S, Sachar, Pena. Budesonide capsules: Scientific basis. Drugs Today 2000;36(Suppl G):9-23.

Eggleston PA. Urban children and asthma: Morbidity and mortality. Immunol Allergy Clin North Am 1998;18(1):75-84.

Ehnert B, Lau-Schadendorf S, Weber A, et al. Reducing domestic exposure to dust mite allergen reduces bronchial hyperreactivity in sensitive children with asthma. J Allergy Clin Immunol 1992;90(1):135-8.

el-Azazy OM. Camel tick (Acari:Ixodidae) control with pour-on application of flumethrin. Vet Parasitol 1996;67(3-4):281-4.

el-Dahr JM, Fink R, Selden R, et al. Development of immune responses to Aspergillus at an early age in children with cystic fibrosis. Am J Respir Crit Care Med 1994;150(6 Pt 1):1513-8.

Eldridge MW, Peden DB. Allergen provocation augments endotoxin-induced nasal inflammation in subjects with atopic asthma. J Allergy Clin Immunol 2000;105(3):475-81.

Ellis AK, Day JH, Lundie MJ. Impact on quality of life during an allergen challenge research trial. Ann Allergy Asthma Immunol 1999;83(1):33-9.

Ellis AK, Rafeiro E, Day JH. Quality of life indices may be predictive of placebo and medication response to treatment for allergic rhinitis. Ann Allergy Asthma Immunol 2001;86(4):393-6.

Elmogy M, Fayed H, Marzok H, et al. Oral ivermectin in the treatment of scabies. Int J Dermatol 1999;38(12):926-8.

Emanuel IA, Shah SB. Chronic rhinosinusitis: allergy and sinus computed tomography relationships. Otolaryngol Head Neck Surg 2000;123(6):687-91.

Endicott NA. Chronic fatigue syndrome in psychiatric patients: lifetime and premorbid personal history of physical health. Psychosom Med 1998;60(6):744-51.

Englender M. Nasal laser mucotomy (L-mucotomy) of the interior turbinates. J Laryngol Otol 1995;109(4):296-9.

Engvall K, Norrby C, Norback D. Asthma symptoms in relation to building dampness and odour in older multifamily houses in Stockholm. Int J Tuberculosis Lung Dis 2001;5(5):468-77.

Enright PL, McClelland RL, Newman AB, et al. Underdiagnosis and undertreatment of asthma in the elderly. Cardiovascular Health Study Research Group. Chest 1999;116(3):603-13.

Eriksson NE, Ahlstedt S, Lövhagen O. Immunotherapy in spring-time hay fever. A clinical and immunological study comparing two different treatment extract compositions. Allergy 1979;34(4):233-47.

Escudero AI, Sanchez-Guerrero IM, Mora AM, et al. Cost-effectiveness of various methods of diagnosing hypersensitivity to Alternaria. Allergol Immunopathol (Madr) 1993;21(4):153-7.

Euba R, Chalder T, Wallace P, et al. Self-reported allergy-related symptoms and psychological morbidity in primary care. Int J Psychiatry Med 1997;27(1):47-56.

European Agency for Evaluation of Medicinal Products. Committee for Proprietary Medicinal Products European Public Assessment Report (EPAR): Neoclarityn. 2001. Available at: http://www.eudra.org/humandocs/humans/epar/neoclarityn/neoclarityn.htm. Accessed August 31, 2002.

Ewan PW, Alexander MM, Snape C, et al. Effective hyposensitization in allergic rhinitis using a potent partially purified extract of house dust mite. Clin Allergy 1988;18(5):501-8.

Eysink PED, Bindels PJE, Huisman JS, et al. Development of specific immunoglobulin E in coughing toddlers: A medical records review of symptoms in general practice. Pediatr Allergy Immunol 2001;12(3):133-41.

Fagan JK, Scheff PA, Hryhorczuk D, et al. Prevalence of asthma and other allergic diseases in an adolescent population: association with gender and race. Ann Allergy Asthma Immunol 2001;86(2):177-84.

Fahlbusch B, Hornung D, Heinrich J, et al. Quantification of group 5 grass pollen allergens in house dust. Clin Exp Allergy 2000;30(11):1645-52.

Fakhri ZI, Erwa HH. Skin test survey in castor bean allergic working population in Eastern Sudan, with frequency response of first dilutions giving skin reactions. J Soc Occup Med 1988;38(4):128-33.

Falk JE, Juto JE, Stridh G, et al. Dose-response study of formaldehyde on nasal mucosa swelling. A study on residents with nasal distress at home. Am J Rhinol 1994;8(3):143-6.

Falliers CJ, Redding MA. Controlled comparison of anew antihistamine-decongestant combination to its individual components. Ann Allergy 1980;45(2):75-80.

Fanales-Belasio E, Ciofalo A, Zambetti G, et al. Intranasal immunotherapy with Dermatophagoides extract: in vivo and in vitro results of a double-blind placebo-controlled trial. Rhinology 1995;33(3):126-31.

Farooqi IS, Hopkin JM. Early childhood infection and atopic disorder. Thorax 1998;53(11):927-32.

Fasce L, Ciprandi G, Pronzato C, et al. Cetirizine reduces ICAM-I on epithelial cells during nasal minimal persistent inflammation in asymptomatic children with mite-allergic asthma. Int Arch Allergy Immunol 1996;109(3):272-6.

Fawcett IV WA. Allergen immunotherapy and avoidance. Prim Care Clinics in Office Practice 1998;25(4):869-83.

Fearby S, Frew AJ. Hunting the magic bullet in immunotherapy: New forms of old treatment or something completely different? Clin Exp Allergy 2001;31(7):969-74.

Fell P, Brostoff J. A single dose desensitization for summer hay fever. Results of a double blind study-1988. Eur J Clin Pharmacol 1990;38(1):77-9.

Fell WR, Mabry RL, Mabry CS. Quality of life analysis of patients undergoing immunotherapy for allergic rhinitis. Ear Nose Throat J 1997;76(8):528-32, 534-6.

Feo F, Martinez J, Martinez A, et al. Occupational allergy in saffron workers. Allergy Eur J Allergy Clin Immunol 1997;52(6):633-41.

Ferguson BJ. Allergic rhinitis: options for pharmacotherapy and immunotherapy. Postgrad Med 1997;101(5):117-20, 123-6, 131.

Ferguson BJ. Options for pharmacotherapy and immunotherapy. Postgrad Med 1997;101(5):117-31.

Ferguson BJ. What role do systemic corticosteroids, immunotherapy, and antifungal drugs play in the therapy of allergic fungal rhinosinusitis? Arch Otolaryngol Head Neck Surg 1998;124(10):1174-8.

Ferguson BJ. Cost-effective pharmacotherapy for allergic rhinitis. [Review]. Otolaryngol Clin North Am 1998;31(1):91-110.

Ferguson BJ, Blom HM, Mulder P. Is cigarette smoke exposure a confounder in the evaluation or efficacy of nasal steroid sprays in nonallergic, noninfectious perennial rhinitis? (multiple letters). J Allergy Clin Immunol 1998;102(1):155-6.

Filipiak B, Heinrich J, Schafer T, et al. Farming, rural lifestyle and atopy in adults from southern germany - Results from the MONICA/KORA study Augsburg. Clin Exp Allergy 2001;31(12):1829-38.

Filon FL, Bosco A, Fiorito A, et al. Latex symptoms and sensitisation in health care workers. Int Arch Occup Environ Health 2001;74(3):219-23.

Finn AF Jr, Aaronson D, Korenblat P, et al. Ipratropium bromide nasal spray 0.03% provides additional relief from rhinorrhea when combined with terfenadine in perennial rhinitis patients; a randomized, double-blind, active-controlled trial. Am J Rhinol 1998;12(6):441-9.

Finn R. John Bostock, hay fever, and the mechanism of allergy. Lancet 1992;340(8833):1453-5.

Fireman P. Treatment of allergic rhinitis: effect on occupation productivity and work force costs. [Review]. Allergy Asthma Proc 1997;18(2):63-7.

Fireman P. Treatment strategies designed to minimize medical complications of allergic rhinitis. [erratum appears in Am J Rhinol 1997 May-Jun;11(3):217]. [Review]. Am J Rhinol 1997;11(2):95-102.

Fireman P. Therapeutic approaches to allergic rhinitis: Treating the child. J Allergy Clin Immunol 2000;105(6 II):S616-S621.

Fokkens WJ. Who should treat patients with seasonal allergic rhinitis? Allergy 2002;57:469-71.

Fontana VJ, Holt LE, Mainland D. Effectiveness of hyposensitization therapy in ragweed hay-fever in children. JAMA 1966;195(12):985-92.

Forbes AB, Pitt SR, Baggott DG, et al. A review of the use of a controlled-release formulation of ivermectin in the treatment and prophylaxis of Psoroptes ovis infestations in sheep. [Review]. Vet Parasitol 1999;83(3-4):319-26.

Ford AW, Platts-Mills TA. Standardized extracts, dust mite, and other arthropods (inhalants). [Review]. Clin Rev Allergy 1987;5(1):49-73.

Ford AW, Rawle FC, Lind P, et al. Standardization of Dermatophagoides pteronyssinus: assessment of potency and allergen content in ten coded extracts. Int Arch Allergy Appl Immunol 1985;76(1):58-67.

Foresi A. A comparison of the clinical efficacy and safety of intranasal fluticasone propionate and antihistamines in the treatment of rhinitis. Allergy Eur J Allergy Clin Immunol Suppl 2000;55(62):12-4.

Fornadley JA, Corey JP, Osguthorpe JD, et al. Allergic rhinitis: clinical practice guideline. Committee on Practice Standards, American Academy of Otolaryngic Allergy. Otolaryngol Head Neck Surg 1996;115(1):115-22.

Forray C, Noble SA. Subtype selective alpha1-adrenoceptor antagonists for the treatment of benign prostatic hyperplasia. Expert Opin Invest Drugs 1999;8(12):2073-94.

Francillon C, Burnand B, Frei P, et al. Referral pattern to the allergist for hay fever in a health-care system with open access to specialists. Allergy 1995;50(12):959-63.

Frankland AW. House dust mites and allergy. [Review]. Arch Dis Child 1972;47(253):327-9.

Frankland AW. Practice of allergy in the United Kingdom. Ann Allergy 1993;71(4):335-7.

Frankum B. Management of hay fever. New Ethicals 1998;1:55, 57-9.

Frederick JM, Warner JO, Jessop WJ, et al. Effect of a bed covering system in children with asthma and house dust mite hypersensitivity. Eur Respir J 1997;10(2):361-6.

Freebairn AJE, Last ATJ, Illidge TM. Trastuzumab: Designer drug or fashionable fad? Clin Oncol 2001;13(6):427-33.

Freedman SO. First-line treatment of hay fever: What is the best option? Can Med Assoc J 1997;156(8):1141-3.

Frenz DA. Foundational readings concerning pollen for allergists and aerobiologists. Ann Allergy Asthma Immunol 2000;84(3):320-2.

Frew AJ, Smith HE. Sublingual immunotherapy. J Allergy Clin Immunol 2001;107(3):441-4.

Friedmann PS. The role of dust mite antigen sensitization and atopic dermatitis: Editorial. Clin Exp Allergy 1999;29(7):869-72.

Friedmann PS, Tan BB. Mite elimination--clinical effect on eczema. Allergy 1998;53(48 Suppl):97-100.

Fritschi L, DeKlerk N, Sim M, et al. Respiratory morbidity and exposure to bauxite, alumina and caustic mist in alumina refineries. J Occup Health 2001;43(5):231-7.

Frostad AB, Grimmer O, Sandvik L, et al. Hyposensitization. Comparing a purified (refined) allergen preparation and a crude aqueous extract from timothy pollen. Allergy 1980;35(2):81-95.

Frostad AB, Grimmer O, Sandvik L, et al. Clinical effects of hyposensitization using a purified allergen preparation from Timothy pollen as compared to crude aqueous extracts from Timothy pollen and a four-grass pollen mixture respectively. Clin Allergy 1983;13(4):337-57.

Furin MJ, Norman PS, Creticos PS, et al. Immunotherapy decreases antigen-induced eosinophil cell migration into the nasal cavity. J Allergy Clin Immunol 1991;88(1):27-32.

Gabriel M Sister, Ng HK, Allan WG, et al. Study of prolonged hyposensitization with D. pteronyssinus extract in allergic rhinitis. Clin Allergy 1977;7(4):325-39.

Gaddie J, Skinner C, Palmer KN. Hyposensitisation with house dust mite vaccine in bronchial asthma. BMJ 1976;2(6035):561-2.

Gaglani B, Borish L, Bartelson BL, et al. Nasal immunotherapy in weed-induced allergic rhinitis. Ann Allergy Asthma Immunol 1997;79(3):259-65.

Gaig P, Enrique E, Garcia-Ortega P, et al. Asthma, mite sensitization, and sleeping in bunks. Ann Allergy Asthma Immunol 1999;82(6):531-3.

Galant S, Berger W, Gillman S, et al. Prevalence of sensitization to aeroallergens in California patients with respiratory allergy. Ann Allergy Asthma Immunol 1998;81(3):203-10.

Galant SP, Wilkinson R. Clinical prescribing of allergic rhinitis medication in the preschool and young school-age child: What are the options? Biodrugs 2001;15(7):453-63.

Gani F, Pozzi E, Crivellaro MA, et al. The role of patient training in the management of seasonal rhinitis and asthma: clinical implications. Allergy 2001;56:65-8.

Garrelds IM, de Graaf-in 't Veld T, Nahori M-A, et al. Interleukin-5 and eosinophil cationic protein in nasal lavages of rhinitis patients. Eur J Pharmacol 1995;275(3):295-300.

Garrelds IM, van Amsterdam JG, de Graaf-in't Veld C, et al. Nitric oxide metabolites in nasal lavage fluid of patients with house dust mite allergy. Thorax 1995;50(3):275-9.

Gautrin D, Ghezzo H, Infante-Rivard C, et al. Natural history of sensitization, symptoms and occupational diseases in apprentices exposed to laboratory animals. Eur Respir J 2001;17(5):904-8.

Gawchik SM, Lim J. Comparison of intranasal triamcinolone acetonide with oral loratadine in the treatment of seasonal ragweed-induced allergic rhinitis. Am J Manag Care 1997;3(7):1052-8.

Gebhart F. Allergy care: Pharmacists assuming a wider role. Drug Topics 1999;143(11 Suppl):23s-6s.

Gelber LE, Seltzer LH, Bouzoukis JK, et al. Sensitization and exposure to indoor allergens as risk factors for asthma among patients presenting to hospital. Am Rev Respir Dis 1993;147(3):573-8.

Geller-Bernstein C, Pibourdin JM, Dornelas A, et al. Efficacy of the acaricide: acardust for the prevention of asthma and rhinitis due to dust mite allergy, in children. Allerg Immunol (Paris) 1995;27(5):147-54.

Gendeh BS, Murad S, Razi AM, et al. Skin prick test reactivity to foods in adult Malaysians with rhinitis. Otolaryngol Head Neck Surg 2000;122(5):758-62.

Gentile DA, Skoner DP. The relationship between airway hyperreactivity (AHR) and sodium, potassium adenosine triphosphatase (Na+,K+ ATPase) enzyme inhibition. J Allergy Clin Immunol 1997;99(3):367-73.

Georgitis JW, Banov C, Boggs PB, et al. Ipratropium bromide nasal spray in non-allergic rhinitis: efficacy, nasal cytological response and patient evaluation on quality of life. Clin Exp Allergy 1994;24(11):1049-55.

Georgitis JW, Meltzer EO, Kaliner M, et al. Onset-of-action for antihistamine and decongestant combinations during an outdoor challenge. Ann Allergy Asthma Immunol 2000;84(4):451-9.

Georgitis JW, Reisman RE, Clayton WF, et al. Local intranasal immunotherapy for grass-allergic rhinitis. J Allergy Clin Immunol 1983;71(1 Pt 1):71-6.

Giannarini L, Maggi E. Decrease of allergen-specific T-cell response induced by local nasal immunotherapy. Clin Exp Allergy 1998;28(4):404-12.

Gibbons MD, Gunn CG, Niwas S, et al. Cost analysis of computer-aided endoscopic sinus surgery. Am J Rhinol 2001;15(2):71-5.

Giembycz MA. Cilomilast: A second generation phosphodiesterase 4 inhibitor for asthma and chronic obstructive pulmonary disease. Expert Opin Invest Drugs 2001;10(7):1361-79.

Gill P, Dowell AC, Neal RD, et al. Evidence based general practice: A retrospective study of interventions in one training practice. BMJ 1996;312(7034):819-21.

Gillies DR, Littlewood JM, Sarsfield JK. Controlled trial of house dust mite avoidance in children with mild to moderate asthma. Clin Allergy 1987;17(2):105-11.

Gilmore TM, Alexander BH, Mueller BA, et al. Occupational injuries and medication use. Am J Industrial Med 1996;30(2):234-9.

Giovane AL, Bardare M, Passalacqua G, et al. A three-year double-blind placebo-controlled study with specific oral immunotherapy to Dermatophagoides: evidence of safety and efficacy in paediatric patients. Clin Exp Allergy 1994;24(1):53-9.

Girard JP, el-Habib G, Granjard P. Treatment of hay fever by Allerglobuline: a randomized double-blind study. Clin Allergy 1988;18(4):393-400.

Gleich GJ, Zimmermann EM, Henderson LL, et al. Effect of immunotherapy on immunoglobulin E and immunoglobulin G antibodies to ragweed antigens: a six-year prospective study. J Allergy Clin Immunol 1982;70(4):261-71.

Gliklich RE, Metson R. Techniques for outcomes research in chronic sinusitis. Laryngoscope 1995;105(4 Pt 1):387-90.

Glover D, Norris T, Bryson S, et al. Loratadine post-marketing surveillance by general practice computer network. Pharm Med 1992;6(2):87-97.

Godard PH, Chanez P, Redier H, et al. New therapeutical approaches in the treatment of asthma. Ann New York Acad Sci 1994;725:367-77.

Godfrey RC. Asthma and IgE levels in rural and urban communities of The Gambia. Clin Allergy 1975;5(2):201-7.

Goetzel RZ, Ozminkowski RJ, Del Rosso G, et al. Are drugs a cost or an investment? Bus Health 2000;18(6):39-42, 45.

Gold DR, Burge HA, Carey V, et al. Predictors of repeated wheeze in the first year of life: the relative roles of cockroach, birth weight, acute lower respiratory illness, and maternal smoking. Am J Respir Crit Care Med 1999;160(1):227-36.

Gold MR, Franks P, McCoy KI, et al. Toward consistency in cost-utility analyses: using national measures to create condition-specific values. Med Care 1998;36(6):778-92.

Golden S, Teets SJ, Lehman EB, et al. Effect of topical nasal azelastine on the symptoms of rhinitis, sleep, and daytime somnolence in perennial allergic rhinitis. Ann Allergy Asthma Immunol 2000;85(1):53-7.

Gordon BR. Immunotherapy basics. Otolaryngol Head Neck Surg 1995;113(5):597-602.

Gosepath J, Schaefer D, Amedee RG, et al. Individual monitoring of aspirin desensitization. Arch Otolaryngol Head Neck Surg 2001;127(3):316-21.

Gossel TA. Back to school health issues. US Pharm 1993;18(9):20, 22, 26, 28, 30.

Gotfried M. Relationship between rhinosinusitis and asthma: Is there a link? Infect Med 1998;15(Suppl C):67-73.

Gotzsche PC, Hammarquist C, Burr M. House dust mite control measures in the management of asthma: meta-analysis. BMJ 1998;317(7166):1105-10.

Gøtzsche PC, Johansen HK, Hammarquist C, et al. House dust mite control measures for asthma (Cochrane Review). In: The Cochrane Library, Issue 2, 2001. Oxford: Update Software.

Goudie AC, Evans NA, Gration KA, et al. Doramectin--a potent novel endectocide. Vet Parasitol 1993;49(1):5-15.

Gozalo RF, Estrada RJL, Martin HS, et al. Patient satisfaction and allergen immunotherapy. J Investig Allergol Clin Immunol 1999;9(2):101-5.

Graf P, Enerdal J, Hallen H. Ten days' use of oxymetazoline nasal spray with or without benzalkonium chloride in patients with vasomotor rhinitis. Arch Otolaryngol Head Neck Surg 1999;125(10):1128-32.

Graf P, Hallen H, Juto J-E. Benzalkonium chloride in a decongestant nasal spray aggravates rhinitis medicamentosa in healthy volunteers. Clin Exp Allergy 1995;25(5):395-400.

Grammer LC, Shaughnessey MA, Shaughnessy JJ, et al. Asthma as a variable in a study of immunotherapy for allergic rhinitis. J Allergy Clin Immunol 1984;73(5 Pt 1):557-60.

Grammer LC, Shaughnessy MA, Bernhard MI, et al. The safety and activity of polymerized ragweed: a double-blind, placebo-controlled trial in 81 patients with ragweed rhinitis. J Allergy Clin Immunol 1987;80(2):177-83.

Grammer LC, Shaughnessy MA, Henderson J, et al. A clinical and immunologic study of workers with trimellitic-anhydride- induced immunologic lung disease after transfer to low exposure jobs. Am Rev Respir Dis 1993;148(1):54-7.

Grammer LC, Shaughnessy MA, Shaughnessy JJ, et al. Allergenicity, immunogenicity, and safety of immunotherapy with various molecular weight ranges of polymerized ragweed. J Allergy Clin Immunol 1985;76(2 Pt 1):195-200.

Grammer LC, Shaughnessy MA, Suszko IM, et al. A double-blind histamine placebo-controlled trial of polymerized whole grass for immunotherapy of grass allergy. J Allergy Clin Immunol 1983;72(5 Pt 1):448-53.

Grammer LC, Zeiss CR, Suszko IM, et al. A double-blind, placebo-controlled trial of polymerized whole ragweed for immunotherapy of ragweed allergy. J Allergy Clin Immunol 1982;69(6):494-9.

Grant AC, Roter EP. Circadian sneezing. Neurology 1994;44(3 I):369-75.

Grant JA, Nicodemus CF, Findlay SR, et al. Cetirizine in patients with seasonal rhinitis and concomitant asthma: Prospective, randomized, placebo-controlled trial. J Allergy Clin Immunol 1995;95(5 I):923-32.

Green RJ, Potter P, Plit M, et al. The South African allergic rhinitis working group and allergic rhinitis. S Afr Med J 1998;88(11):1366-7.

Greenbaum J, Hainer S, Sussman G. Letter to the editor. Can J Allergy Clin Immunol 1999;4(1):6.

Gregory C, Cifaldi M, Tanner LA. Targeted intervention programs: creating a customized practice model to improve the treatment of allergic rhinitis in a managed care population. Am J Manag Care 1999;5(4):485-96.

Grembiale RD, Camporota L, Naty S, et al. Effects of specific immunotherapy in allergic rhinitic individuals with bronchial hyperresponsiveness. Am J Respir Crit Care Med 2000;162(6):2048-52.

Grewar J, MacDonald TM. Hay fever symptoms and over-the-counter remedies: A community pharmacy study. Int J Pharm Pract 1998;6(1):22-9.

Griffith CJ. Allergic rhinitis: practical guide to diagnosis and management... recertification series. Phys Assistant 1994;18(7):19-21, 24-6, 29-30 passim.

Groholt E-K, Stigum H, Nordhagen R, et al. Children with chronic health conditions in the Nordic countries in 1996 - Influence of socio-economic factors. Ambul Child Health 2001;7(3-4):177-89.

Gronneberg R, Strandberg K, Stalenheim G, et al. Equivalent inhibition by terbutaline of anti-human IgE skin responses in atopic and non-atopic subjects. Allergy 1985;40(1):27-35.

Grosclaude M, Mees K, Pinelli ME, et al. Cetirizine and pseudoephedrine retard, given alone or in combination, in patients with seasonal allergic rhinitis. Rhinology 1997;35(2):67-73.

Gross NJ. Allergy to laboratory animals: Epidemiologic, clinical, and physiologic aspects, and a trial of cromolyn in its management. J Allergy Clin Immunol 1980;66(2):158-65.

Grupp-Phelan J, Lozano P, Fishman P. Health care utilization and cost in children with asthma and selected comorbidities. J Asthma 2001;38(4):363-73.

Guarderas JC. Rhinitis and sinusitis: Office management. Mayo Clin Proc 1996;71(9):882-8.

Guez S, Vatrinet C, Fadel R, et al. House-dust-mite sublingual-swallow immunotherapy (SLIT) in perennial rhinitis: a double-blind, placebo-controlled study. Allergy 2000;55(4):369-75.

Gunasekara NS, Noble S. Isosorbide 5-mononitrate. A review of a sustained-release formulation (Imdur(R)) in stable angina pectoris. Drugs 1999;57(2):261-77.

Gunter MJ. The role of the ECHO model in outcomes research and clinical practice improvement. Am J Manag Care 1999;5(4 Suppl):S217-24.

Gupta SK. Treating allergies: A perspective in family practice. J Indian Med Assoc 2000;98(3):132-3.

Gutgesell C, Heise S, Seubert S, et al. Double-blind placebo-controlled house dust mite control measures in adult patients with atopic dermatitis. Br J Dermatol 2001;145(1):70-4.

Haahtela T, Jaakonmaki I. Relationship of allergen-specific IgE antibodies, skin prick tests and allergic disorders in unselected adolescents. Allergy 1981;36(4):251-6.

Haahtela T, Wihl JA, Munch E, et al. Hyposensitization in hay fever with grass pollen extracts: a three-year study comparing a dialysed alum adsorbed extract with allpyral. Ann Allergy 1984;52(5):355-62.

Haas N, Sterry W. The use of ELM to monitor the success of antiscabietic treatment. Epiluminescence light microscopy. Arch Dermatol 2001;137(12):1656-7.

Hadley JA. Evaluation and management of allergic rhinitis. Med Clin North Am 1999;83(1):13-25.

Hadley JA, Schaefer SD. Clinical evaluation of rhinosinusitis: History and physical examination. Otolaryngol Head Neck Surg 1997;117(3 II Suppl):S8-S11.

Hajat S, Haines A, Atkinson RW, et al. Association between air pollution and daily consultations with general practitioners for allergic rhinitis in London, United Kingdom. Am J Epidemiol 2001;153(7):704-14.

Halken S, Niklassen U, Hansen LG, et al. Encasing of mattresses in children with asthma and house dust mite allergy. [Abstract]. J Allergy Clin Immunol 1997;99:S320.

Haller V, Williams G. Diving candidates as they present for fitness to dive assessment: Diving medicine case studies Part 1. S Pac Underw Med Soc J 2001;31(3):157-62.

Hamilton RG, Chapman MD, Platts-Mills TAE, et al. House dust aeroallergen measurements in clinical practice: A guide to allergen-free home and work environments. Immunol Allergy Pract 1992;14(3):96-112.

Hansell A, Hollowell J, Nichols T, et al. Use of the General Practice Research Database (GPRD) for respiratory epidemiology: A comparison with the 4th Morbidity Survey in General Practice (MSGP4). Thorax 1999;54(5):413-9.

Harkness P, Brown P, Fowler S, et al. A national audit of sinus surgery. Results of the Royal College of Surgeons of England comparative audit of ENT surgery. Clin Otolaryngol 1997;22(2):147-51.

Harper JI, Ahmed I, Barclay G, et al. Cyclosporin for severe childhood atopic dermatitis: Short course versus continuous therapy. Br J Dermatol 2000;142(1):52-8.

Harrelson GL. Theme introduction. Athl Ther Today 2001;6(5):5.

Harvey RP, Comer C, Sanders B, et al. Model for outcomes assessment of antihistamine use for seasonal allergic rhinitis. J Allergy Clin Immunol 1996;97(6):1233-41.

Harving H, Korsgaard J, Dahl R. House-dust mite exposure reduction in specially designed, mechanically ventilated "healthy" homes. Allergy 1994;49(9):713-8.

Hauschildt P, Molhave L, Kjaergaard SK. Reactions of healthy persons and persons suffering from allergic rhinitis when exposed to office dust. Scand J Work Environ Health 1999;25(5):442-9.

Hayden FG, Diamond L, Wood PB, et al. Effectiveness and safety of intranasal ipratropium bromide in common colds. A randomized, double-blind, placebo-controlled trial. Ann Intern Med 1996;125(2):89-97.

Hayden ML, Perzanowski M, Matheson L, et al. Dust mite allergen avoidance in the treatment of hospitalized children with asthma. Ann Allergy Asthma Immunol 1997;79(5):437-42.

Heald AE, Pieper CF, Schiffman SS. Taste and smell complaints in HIV-infected patients. AIDS 1998;12(13):1667-74.

Hedlin G, Wille S, Browaldh L, et al. Immunotherapy in children with allergic asthma: effect on bronchial hyperreactivity and pharmacotherapy. J Allergy Clin Immunol 1999;103(4):609-14.

Hedman J, Kaprio J, Poussa T, et al. Prevalence of asthma, aspirin intolerance, nasal polyposis and chronic obstructive pulmonary disease in a population-based study. Int J Epidemiol 1999;28(4):717-22.

Heikkinen T, Ruohola A, Ruuskanen O, et al. Intranasally administered immunoglobulin for the prevention of rhinitis in children. Pediatr Infect Dis J 1998;17(5):367-72.

Hellriegel ET, Arora S, Nelson M, et al. Steady-state pharmacokinetics and tolerability of modafinil given alone or in combination with methylphenidate in healthy volunteers. J Clin Pharmacol 2001;41(8):895-904.

Henauer S, Seppey M, Huguenot C, et al. Effects of terfenadine and pseudoephedrine, alone and in combination in a nasal provocation test and in perennial rhinitis. Eur J Clin Pharmacol 1991;41(4):321-4.

Hendeles L. Cetirizine: A new antihistamine with minimal sedation. Pharmacotherapy 1996;16(5 I):967-8.

Hendrix S, Zeiss CR, Levitz D, et al. Polymerized whole ragweed: A two-year follow-up of patients treated with an improved method of immunotherapy. J Allergy Clin Immunol 1980;65(1):57-60.

Hendrix SG, Patterson R, Zeiss CR, et al. A multi-institutional trial of polymerized whole ragweed for immunotherapy of ragweed allergy. J Allergy Clin Immunol 1980;66(6):486-94.

Hendrix WC, Arruda LK, Platts-Mills TA, et al. Aspergillus epidural abscess and cord compression in a patient with aspergilloma and empyema. Survival and response to high dose systemic amphotericin therapy. [Review]. Am Rev Respir Dis 1992;145(6):1483-6.

Hennessy S, Strom BL. Nonsedating antihistamines should be preferred over sedating antihistamines in patients who drive. Ann Intern Med 2000;132(5):405-7.

Henriksen AH, Holmen TL, Bjermer L. Sensitization and exposure to pet allergens in asthmatics versus non-asthmatics with allergic rhinitis. Respir Med 2001;95(2):122-9.

Herman D, Garay R, Le Gal M. A randomized double-blind placebo controlled study of azelastine nasal spray in children with perennial rhinitis. Int J Pediatr Otorhinolaryngol 1997;39(1):1-8.

Hessel PA, Herbert FA, Melenka LS, et al. Lung health in sawmill workers exposed to pine and spruce. Chest 1995;108(3):642-6.

Heymann PW, Rakes GP, Hogan AD, et al. Assessment of eosinophils, viruses and IgE antibody in wheezing infants and children. Int Arch Allergy Immunol 1995;107(1-3):380-2.

Hide DW, Matthews S, Matthews L, et al. Effect of allergen avoidance in infancy on allergic manifestations at age two years. J Allergy Clin Immunol 1994;93(5):842-6.

Hide DW, Matthews S, Tariq S, et al. Allergen avoidance in infancy and allergy at 4 years of age. Allergy 1996;51(2):89-93.

Higgins KM, Davidian M, Chew G, et al. The effect of serial dilution error on calibration inference in immunoassay. Biometrics 1998;54(1):19-32.

Hikal AH, Hikal EM. Cousenling tips for the top OTCs. Drug Topics 1997;141(12):62-71.

Hill D, Ayra A, Solieri A, et al. Survey of computed tomography scanning and endoscopic sinus surgery in a group of district general hospitals in south Essex. J Laryngol Otol 2001;115(1):26-30.

Hill DJ, Hosking CS. The cow milk allergy complex: Overlapping disease profiles in infancy. Eur J Clin Nutr 1995;49(Suppl 1):S1-S12.

Hill DJ, Smart IJ, Hosking CS. Specific cellular and humoral immunity in children with grass pollen asthma. Clin Allergy 1982;12(1):83-9.

Hilliquin P, Allanore Y, Coste J, et al. Reduced incidence and prevalence of atopy in rheumatoid arthritis. Results of a case-control study. Rheumatology (UK) 2000;39(9):1020-6.

Hindmarch I, Riedel WJ. Editorial. Hum Psychopharmacol 1998;13(Suppl 2):S47-S48.

Hirsch SR, Kalbfleisch JH, Cohen SH. Comparison of Rinkel injection therapy with standard immunotherapy. J Allergy Clin Immunol 1982;70(3):183-90.

Hirsch SR, Kalbfleisch JH, Golbert TM, et al. Rinkel injection therapy: a multicenter controlled study. J Allergy Clin Immunol 1981;68(2):133-55.

Hirsck T, Sahn M, Leupold W. Double-blind placebo-controlled study of sublingual immunotherapy with house dust mite extract (D.Pt.) in children. Pediatr Allergy Immunol 1997;8(1):21-7.

Hirvonen M-R, Ruotsalainen M, Roponen M, et al. Nitric oxide and proinflammatory cytokines in nasal lavage fluid associated with symptoms and exposure to moldy building microbes. Am J Respir Crit Care Med 1999;160(6):1943-6.

Ho TM, Yit YH, Husain M. Development of an enzyme-linked immunosorbent assay for detection of IgE antibodies specific to Dermatophagoides pteronyssinus. Asian Pac J Allergy Immunol 1988;6(2):103-6.

Hollingsworth HM. Allergic rhinoconjunctivitis: current therapy. Hospital Pract 1996;31(6):61-2, 65-7, 71-2 passim.

Hollingworth P, de Vere Tyndall A, Ansell BM, et al. Intensive immunosuppression versus prednisolone in the treatment of connective tissue diseases. Ann Rheum Dis 1982;41(6):557-62.

Holm L, Ohman S, Bengtsson A, et al. Effectiveness of occlusive bedding in the treatment of atopic dermatitis--a placebo-controlled trial of 12 months' duration. Allergy 2001;56(2):152-8.

Holt GR. The interface of otolaryngology with occupational medicine. Curr Opin Otolaryngol Head Neck Surg 1996;4(1):59-61.

Honda K, Ooki K, Makishima K. Topical applications of trichloroacetic acid as therapy for nasal allergy. Eur Arch Oto-Rhino-Laryngol 1994;251(Suppl 1):S65-S67.

Honig PK, Cantilena LR. Polypharmacy. Pharmacokinetic perspectives. Clin Pharmacokinet 1994;26(2):85-90.

Hoover GE, Newman LJ, Platts-Mills TA, et al. Chronic sinusitis: risk factors for extensive disease. J Allergy Clin Immunol 1997;100(2):185-91.

Hopper JL, Jenkins MA, Carlin JB, et al. Increase in the self-reported prevalence of asthma and hay fever in adults over the last generation: a matched parent-offspring study. Austr J Publ Health 1995;19(2):120-4.

Horak F, Jager S, Berger U, et al. Controlled exposure to mite allergen for a dose-finding of dimethindene maleate (DMM). Agents & Actions 1994;41:Spec No: C124-6.

Horak F, Jager S, Toth J, et al. Efficacy and tolerability of astemizole-D and loratadine-D during prolonged, controlled allergen challenge in the Vienna Challenge Chamber. Arzneim-Forsch Drug Res 1996;46(11):1077-81.

Horak F, Stubner P, Berger UE, et al. Immunotherapy with sublingual birch pollen extract. A short-term double-blind placebo study. J Investig Allergol Clin Immunol 1998;8(3):165-71.

Horak F, Stubner UP. New trends in allergic rhinitis. Allergy Clin Immunol Int 1998;10(3):81-7.

Horak F, Toth J, Marks B, et al. Efficacy and safety relative to placebo of an oral formulation of cetirizine and sustained-release pseudoephedrine in the management of nasal congestion. Allergy 1998;53(9):849-56.

Hordijk GJ, Antvelink JB, Luwema RA. Sublingual immunotherapy with a standardised grass pollen extract; a double-blind placebo-controlled study. Allergol Immunopathol (Madr) 1998;26(5):234-40.

Horst M, Hejjaoui A, Horst V, et al. Double-blind, placebo-controlled rush immunotherapy with a standardized Alternaria extract. J Allergy Clin Immunol 1990;85(2):460-72.

Howard KB, Bowers BW, Cook CK, et al. Intranasal fluticasone, loratadine tablets, and their use in combination: An evaluation of economic and humanistic outcomes. Drug Benefit Trends 2001;13(10):45-6, 48, 51-2.

Howarth P. The development of guidelines for allergic rhinitis. Rev Fr Allergol Immunol Clin 2001;41(1):116-20.

Howland WC, Hampel FC, Martin BG, et al. The efficacy of fluticasone propionate aqueous nasal spray for allergic rhinitis and its relationship to topical effects. Clin Ther 1996;18(6):1106-17.

Htut T, Higenbottam TW, Gill GW, et al. Eradication of house dust mite from homes of atopic asthmatic subjects: a double-blind trial. J Allergy Clin Immunol 2001;107(1):55-60.

Huang S-L, Lin K-C, Pan W-H. Dietary factors associated with physician-diagnosed asthma and allergic rhinitis in teenagers: Analyses of the first Nutrition and Health Survey in Taiwan. Clin Exp Allergy 2001;31(2):259-64.

Huang S-W. The effects of an air cleaner in the homes of children with perennial allergic rhinitis. Pediatr Asthma Allergy Immunol 1993;7(2):111-7.

Hudmon KS, Corelli RL, Kroon LA, et al. Reducing pulmonary disease: The pharmacist's role in smoking cessation. J Pharm Pract 2001;14(2):143-59.

Huerter Jr JV. Functional endoscopic sinus surgery and allergy. Otolaryngol Clin North Am 1992;25(1):231-8.

Hueston WJ, Eberlein C, Johnson D, et al. Criteria used by clinicians to differentiate sinusitis from viral upper respiratory tract infection. J Fam Pract 1998;46(6):487-92.

Hungin APS, Gunn SD, Bate CM, et al. A comparison of the efficacy of omeprazole 20 mg once daily with ranitidine 150 mg bd in the relief of symptomatic gastro-oesophageal reflux disease in general practice. Br J Clin Res 1993;4:73-88.

Hunskaar S, Fosse RT. Allergy to laboratory mice and rats: A review of its prevention management, and treatment. Lab Anim 1993;27(3):206-21.

Hunt JF, Erwin E, Palmer L, et al. Expression and activity of pH-regulatory glutaminase in the human airway epithelium. Am J Respir Crit Care Med 2002;165(1):101-7.

Hunt JF, Fang K, Malik R, et al. Endogenous airway acidification. Implications for asthma pathophysiology. Am J Respir Crit Care Med 2000;161(3 Pt 1):694-9.

Huss K, Salerno M, Huss RW. Computer-assisted reinforcement of instruction: effects on adherence in adult atopic asthmatics. Res Nurs Health 1991;14(4):259-67.

Huss RW, Huss K, Squire EN, et al. Mite allergen control with acaricide fails. J Allergy Clin Immunol 1994;94(1):27-32.

Huttin C, Andral J. How the reimbursement system may influence physicians' decisions results from focus groups interviews in France. Health Policy 2000;54(2):67-86.

Hyndman SJ, Vickers LM, Htut T, et al. A randomized trial of dehumidification in the control of house dust mite. Clin Exp Allergy 2000;30(8):1172-80.

Ige OM, Onadeko OB. Respiratory symptoms and ventilatory function of the sawmillers in Ibadan, Nigeria. Afr J Med Medical Sci 2000;29(2):101-4.

Iliopoulos O, Proud D, Adkinson NF, et al. Effects of immunotherapy on the early, late, and rechallenge nasal reaction to provocation with allergen: changes in inflammatory mediators and cells. J Allergy Clin Immunol 1991;87(4):855-66.

Illum P, Meistrup-Larsen U, Moesner J, et al. Disodium cromoglycate (Lomudal) in the treatment of hay fever. Acta Allergol 1973;28(5):416-24.

Iloeje UH, Redlich CA. Indoor air pollution: An update for the clinician. Clin Pulm Med 2000;7(3):128-33.

Ingram JM, Rakes GP, Hoover GE, et al. Eosinophil cationic protein in serum and nasal washes from wheezing infants and children. J Pediatr 1995;127(4):558-64.

Institute for Clinical Systems Improvement. Rhinitis. Bloomington: MN: Institute for Clinical Systems Improvement, 2000.

Iribarren C, Friedman GD, Klatsky AL, et al. Exposure to environmental tobacco smoke: association with personal characteristics and self reported health conditions. J Epidemiol Community Health 2001;55(10):721-8.

Irons JS, Pruzansky JJ, Patterson R. Allergy grand rounds: immunotherapy: mechanisms of action suggested by measurements of immunologic and cellular parameters. J Allergy Clin Immunol 1975;56:64-77.

Ishizuka T, Furuya Y. Influence of meals and night shifts on health. J Med Syst 1993;17(3-4):201-6.

Iskandar NM, Naguib MB. Chlamydia trachomatis: An underestimated cause for rhinitis in neonates. Int J Pediatr Otorhinolaryngol 1998;42(3):233-7.

Israel E. Leukotrienes and rhinitis. Clin Exp Allergy Suppl Rev 2001;1(2):160-2.

Ito H, Nakamura Y, Takagi S, et al. Effects of azelastine on the level of serum interleukin-4 and soluble CD23 antigen in the treatment of nasal allergy. Arzneimittelforschung 1998;48(12):1143-7.

Iversen M, Korsgaard J, Hallas T, et al. Mite allergy and exposure to storage mites and house dust mites in farmers. Clin Exp Allergy 1990;20(2):211-9.

Jaakkola JJK, Heinonen OP. Shared office space and the risk of the common cold. Eur J Epidemiol 1995;11(2):213-6.

Jaakkola JJK, Miettinen P. Type of ventilation system in office buildings and sick building syndrome. Am J Epidemiol 1995;141(8):755-65.

Jackson-Menaldi CA, Dzul AI, Holland RW. Allergies and vocal fold edema: A preliminary report. J Voice 1999;13(1):113-22.

Jahnsen FL, Lund-Johansen F, Dunne JF, et al. Experimentally induced recruitment of plasmacytoid (CD123SUPhigh) dendritic cells in human nasal allergy. J Immunol 2000;165(7):4062-8.

Janda P, Sroka R, Tauber S, et al. Diode laser treatment of hyperplastic inferior nasal turbinates. Lasers Surg Med 2000;27(2):129-39.

Janson C, Chinn S, Jarvis D, et al. Effect of passive smoking on respiratory symptoms, bronchial responsiveness, lung function, and total serum IgE in the European Community Respiratory Health Survey: A cross-sectional study. Lancet 2001;358(9299):2103-9.

Järvinen KAJ, Pirilä V, Björksten F, et al. Unsuitability of bakery work for a person with atopy: A study of 234 bakery workers. Ann Allergy 1979;42(3):192-5.

Jarvis D, Chinn S, Luczynska C, et al. The association of family size with atopy and atopic disease. Clin Exp Allergy 1997;27(3):240-5.

Jeebhay MF, Lopata AL, Robins TG. Seafood processing in South Africa: A study of working practices, occupational health services and allergic health problems in the industry. Occup Med 2000;50(6):406-13.

Jen A, Baroody F, de Tineo M, et al. As-needed use of fluticasone propionate nasal spray reduces symptoms of seasonal allergic rhinitis. J Allergy Clin Immunol 2000;105(4):732-8.

Jirapongsananuruk O, Malainual N, Sangsupawanich P, et al. Partial mattress encasing significantly reduces house dust mite antigen on bed sheet surface: a controlled trial. Ann Allergy Asthma Immunol 2000;84(3):305-10.

Jirapongsananuruk O, Vichyanond P. Nasal cytology in the diagnosis of allergic rhinitis in children. Ann Allergy Asthma Immunol 1998;80(2):165-70.

Johansson SGO. Visions for the IAACI. Allergy Clin Immunol Int 2000;12(5):249.

Joint Task Force on Practice Parameters. Practice parameters for allergen immunotherapy. Joint Task Force on Practice Parameters, representing the American Academy of Allergy, Asthma and Immunology, the American College of Allergy, Asthma and Immunology, and the Joint Council of Allergy, Asthma and Immunology. J Allergy Clin Immunol 1996;98(6 Pt 1):1001-11.

Joint Task Force on Practice Parameters in Allergy, Asthma and Immunology. Diagnosis and management of rhinitis: complete guidelines of the Joint Task Force on Practice Parameters in Allergy, Asthma and Immunology. Joint Task Force on Practice Parameters in Allergy, Asthma and Immunology, representing the American Academy of Allergy, Asthma and Immunology; the American College of Allergy, Asthma and Immunology; and the Joint Council of Allergy, Asthma and Immunology. Ann Allergy Asthma Immunol 1998;81(5 Pt 2):478-518.

Jones HS. Allergic rhinitis: A study on the prescribing preferences in general practice. Br J Clin Pract 1989;43(1):30-2.

Jones NS. Nasal manifestations of rheumatic diseases. Ann Rheum Dis 1999;58(10):589-90.
Jones NS, Carney AS, Davis A. The prevalence of allergic rhinosinusitis: A review. J Laryngol Otol 1998;112(11):1019-30.

Jones RCM, Hughes CR, Wright D, et al. Early house moves, indoor air, heating methods and asthma. Respir Med 1999;93(12):919-22.

Jooma OF, Weinberg EG, Berman D, et al. Accumulation of house-dust mite (Der-p-1) levels on mattress covers. S Afr Med J 1995;85(10):1002-5.

Jordan JA, Mabry RL. Geriatric rhinitis: What it is, and how to treat it. Geriatrics 1998;53(6):76-84.

Juliusson S, Bende M. Effect of systemically administered Hinf 1- and Hinf 2-receptor antagonists on nasal blood flow as measured with laser Doppler flowmetry in a provoked allergic reaction. Rhinology 1996;34(1):24-7.

Jüni P, Witschi A, Bloch R, et al. The hazards of scoring the quality of clinical trials for meta-analysis. JAMA 1999;282(11):1054-60.

Juniper E. Rhinitis and quality of life. Rev Fr Allergol Immunol Clin 2001;41(1):111-5.

Juniper EF. Rhinitis and quality of life. Eur Respir Rev 1997;7(47):300-2.

Juniper EF. Measuring health-related quality of life in rhinitis. [Review]. J Allergy Clin Immunol 1997;99(2):S742-9.

Juniper EF. Quality of life in adults and children with asthma and rhinitis. [Review]. Allergy 1997;52(10):971-7.

Juniper EF. Impact of upper respiratory allergic diseases on quality of life. J Allergy Clin Immunol 1998;101(2 II):S386-S391.

Juniper EF. Rhinitis management: the patient's perspective. Clin Exp Allergy 1998;28 (Suppl 6):34-8.

Juniper EF, Guyatt GH. Development and testing of a new measure of health status for clinical trials in rhinoconjunctivitis. Clin Exp Allergy 1991;21(1):77-83.

Juniper EF, Guyatt GH, Andersson B, et al. Comparison of powder and aerosolized budesonide in perennial rhinitis: validation of rhinitis quality of life questionnaire. Ann Allergy 1993;70(3):225-30.

Juniper EF, Guyatt GH, Archer B, et al. Aqueous beclomethasone dipropionate in the treatment of ragweed pollen-induced rhinitis: further exploration of "as needed" use. J Allergy Clin Immunol 1993;92(1 Pt 1):66-72.

Juniper EF, Guyatt GH, Dolovich J. Assessment of quality of life in adolescents with allergic rhinoconjunctivitis: development and testing of a questionnaire for clinical trials. J Allergy Clin Immunol 1994;93(2):413-23.

Juniper EF, Guyatt GH, Ferrie PJ, et al. First-line treatment of seasonal (ragweed) rhinoconjunctivitis. A randomized management trial comparing a nasal steroid spray and a nonsedating antihistamine. Can Med Assoc J 1997;156(8):1123-31.

Juniper EF, Guyatt GH, Ferrie PJ, et al. Sodium cromoglycate eye drops: Regular versus 'as needed' use in the treatment of seasonal allergic conjunctivitis. J Allergy Clin Immunol 1994;94(1):36-43.

Juniper EF, Guyatt GH, Griffith LE, et al. Interpretation of rhinoconjunctivitis quality of life questionnaire data. J Allergy Clin Immunol 1996;98(4):843-5.

Juniper EF, Howland WC, Roberts NB, et al. Measuring quality of life in children with rhinoconjunctivitis. J Allergy Clin Immunol 1998;101(2 Pt 1):163-70.

Juniper EF, Kline PA, Hargreave FE, et al. Comparison of beclomethasone dipropionate aqueous nasal spray, astemizole, and the combination in the prophylactic treatment of ragweed pollen-induced rhinoconjunctivitis. J Allergy Clin Immunol 1989;83(3):627-33.

Juniper EF, Kline PA, Ramsdale EH, et al. Comparison of the efficacy and side effects of aqueous steroid nasal spray (budesonide) and allergen-injection therapy (Pollinex-R) in the treatment of seasonal allergic rhinoconjunctivitis. J Allergy Clin Immunol 1990;85(3):606-11.

Juniper EF, Ponte CD, Shapiro GG. Drug spotlight: the newer antihistamines. Patient Care 1996;30(7):34-8, 39-42, 47-8.

Juniper EF, Thompson AK, Ferrie PJ, et al. Validation of the standardized version of the Rhinoconjunctivitis Quality of Life Questionnaire. J Allergy Clin Immunol 1999;104(2 Pt 1):364-9.

Juniper EF, Thompson AK, Ferrie PJ, et al. Development and validation of the mini Rhinoconjunctivitis Quality of Life Questionnaire. Clin Exp Allergy 2000;30(1):132-40.

Juniper EF, Willms DG, Guyatt GH, et al. Aqueous beclomethasone dipropionate nasal spray in the treatment of seasonal (ragweed) rhinitis. Can Med Assoc J 1992;147(6):887-92.

Kagi MK, Wuthrich B. Different methods of local allergen-specific immunotherapy. Allergy 57:379-88.

Kaiser HB, Findlay SR, Georgitis JW, et al. Long-term treatment of perennial allergic rhinitis with ipratropium bromide nasal spray 0.06%. J Allergy Clin Immunol 1995;95(5 II):1128-32.

Kaiser HB, Kaliner MA, Nelson HS. Who needs allergy testing? Patient Care 1997;31(14):169-72, 175, 179-83.

Kalayci O, Saraclar Y, Adalioglu G, et al. The effect of cetirizine on sulfidoleukotriene production by blood leukocytes in children with allergic rhinitis. Allergy 1995;50(12):964-9.

Kaliner M. Allergy care in the next millennium: Guidelines for the specialty. J Allergy Clin Immunol 1997;99(6 I Suppl):729-34.

Kaliner MA, Osguthorpe JD, Fireman P, et al. Sinusitis: bench to bedside. Current findings, future directions. [erratum appears in J Allergy Clin Immunol 1997 Oct;100(4):510]. [Review]. J Allergy Clin Immunol 1997;99(6 Pt 3):S829-48.

Kalra S, Crank P, Hepworth J, et al. Absence of seasonal variation in concentrations of the house dust mite allergen Der p1 in south Manchester homes. Thorax 1992;47(11):928-31.

Kammermeyer JK, Rajtora DW, Anuras J, et al. Clinical evaluation of intranasal topical flunisolide therapy in allergic rhinitis. J Allergy Clin Immunol 1977;59(4):287-93.

Kanerva L, Vanhanen M. Occupational allergic contact urticaria and rhinoconjunctivitis from a detergent protease. Contact Dermatitis 2001;45(1):49-51.

Kanga JF. Dornase alfa therapy in cystic fibrosis: Who should get it? Chest 1996;110(4):871-2.

Kanthawatana S, Maturim W, Fooanan S, et al. Skin prick reaction and nasal provocation response in diagnosis of nasal allergy to the house dust mite. Ann Allergy Asthma Immunol 1997;79(5):427-30.

Kao NL. Costs of rhinitis and asthma. Ann Allergy Asthma Immunol 1995;74(5):448.

Kaplan AP. Visions for the World Allergy Organization. Allergy Clin Immunol Int 2001;13(2):71.

Karlberg BE, Lins L-E, Hermansson K. Efficacy and safety of telmisartan, a selective ATinf 1 receptor antagonist, compared with enalapril in elderly patients with primary hypertension. J Hypertens 1999;17(2):293-302.

Kaszuba SM, Baroody FM, deTineo M, et al. Superiority of an intranasal corticosteroid compared with an oral antihistamine in the as-needed treatment of seasonal allergic rhinitis. Arch Intern Med 2001;161(21):2581-7.

Katelaris CH. Successful immunotherapy. A partnership between consultant and general practitioner. [Review]. Aust Fam Physician 1998;27(8):687-92.

Katelaris CH. Showcasing Australia. Allergy Clin Immunol Int 2000;12(5):189-90.

Katelaris CH, Carrozzi FM, Burke TV, et al. A springtime olympics demands special consideration for allergic athletes. J Allergy Clin Immunol 2000;106(2):260-6.

Katz RM. Treating the student with seasonal allergic rhinitis. Pediatr Asthma Allergy Immunol 1996;10(3):93-100.

Katzenstein L. Allergies: nothing to sneeze at. Am Health Fitness Body Mind 1993;12(4):44-9.

Kaufman HS, Roth HL. Hyposensitization with alum precipitated extracts in atopic dermatitis: a placebo-controlled study. Ann Allergy 1974;32(6):321-30.

Kay AB. Allergy and allergic diseases. Part 2. New Engl J Med 2001;344:109-13.

Kay AB. Allergy and allergic diseases. First of two parts. [Review]. N Engl J Med 2001;344(1):30-7.

Kay AB, Holgate ST. Good allergy practice. Clin Exp Allergy 1995;25(7):579.

Kay GG. The effects of antihistamines on cognition and performance. J Allergy Clin Immunol 2000;105(6 II):S622-S627.

Keith PK, Haddon J, Birch S. A cost-benefit analysis using a willingness-to-pay questionnaire of intranasal budesonide for seasonal allergic rhinitis. Rhinocort Study Group. Ann Allergy Asthma Immunol 2000;84(1):55-62.

Kelso JM, Jones RT, Tellez R, et al. Oral allergy syndrome successfully treated with pollen immunotherapy. Ann Allergy Asthma Immunol 1995;74(5):391-6.

Kelso JM, Sodhi N, Gosselin VA, et al. Diagnostic performance characteristics of the standard Phadebas RAST, modified RAST, and pharmacia CAP system versus skin testing. Ann Allergy 1991;67(5):511-4.

Kemker BJ, Corey JP, Branca J, et al. Development of the Allergy Outcome Survey for allergic rhinitis. Otolaryngol Head Neck Surg 1999;121(5):603-5.

Kenner D. European botanic therapies, part III: The use of essential oils in clinical practice. Am J Acupunct 1998;26(2-3):105-15.

Kerkhof M, Droste JH, de Monchy JG, et al. Distribution of total serum IgE and specific IgE to common aeroallergens by sex and age, and their relationship to each other in a random sample of the Dutch general population aged 20-70 years. Dutch ECRHS Group, European Community Respiratory Health Study. Allergy 1996;51(11):770-6.

Keslin MH, Jarrell CM, Gregory C. Diagnosis and treatment of allergic rhinitis: primary care in an integrated health system setting. Am J Manag Care 1999;5(4 Suppl):S248-56; quiz S257-8.

Kessler RC, Almeida DM, Berglund P, et al. Pollen and mold exposure impairs the work performance of employees with allergic rhinitis. Ann Allergy Asthma Immunol 2001;87(10):289-95.

Kettis LA, Isacson D, Eriksson C. Assessment of the appropriateness of extemporaneous preparations prescribed in Swedish primary care. Int J Pharm Pract 1996;4(2):117-22.

Kifuji K, McCullough J, Ownby DR. Relationship between dust mite allergen and human IgA in house dust samples. Ann Allergy 1993;70(3):219-24.

Kilpelainen M, Koskenvuo M, Helenius H, et al. Wood stove heating, asthma and allergies. Respir Med 2001;95(11):911-6.

Kim Y, Suzuki K, Kitao S, et al. Clinical review of nasal allergy due to fungus. Acta Oto-Laryngol Supplement 1996;525:105-7.

Kim YK, Park HW, Park HS, et al. Sensitivity to citrus red mite and the development of asthma. Ann Allergy Asthma Immunol 2000;85(6 Pt 1):483-8.

Kimura Y, Kanazawa Y, Kida K, et al. A study of atopic dermatitis in elementary school children in Hirosaki City, Aomori Prefecture, Japan. Environ Health Prev Med 1998; 3(3):141-5.

King HC. Allergy testing by primary care physicians. Postgrad Med 1990;87(4):137-40, 143.

Kiviloog J. Variability of bronchial reactivity to exercise and metacholine in bronchial asthma. Scand J Respir Dis 1973;54(6):359-68.

Kivity S, Sade K, Abu-Arisha F, et al. Epidemiology of bronchial asthma and chronic rhinitis in schoolchildren of different ethnic origins from two neighboring towns in Israel. Pediatr Pulmonol 2001;32(3):217-21.

Kjellman M. Treatment of children with perennial rhinitis with brompheniraminemaleate and phenylpropanolaminehydrochloride (lunerin mite). Acta Allergol 1975;30(1):48-57.

Kjellman NI, Lanner A. Hyposensitization in childhood hay fever. A comparison of refined and whole timothy extracts. Allergy 1980;35(4):323-34.

Klein GL, Timerman V. Pharmacologic and nonpharmacologic treatment of allergic rhinitis. Phys Assistant 1993;17(5):52-6, 59-60, 62 passim.

Klein GL, Ziering RW. Allergy tips of the month: For physicians. Immunol Allergy Pract 1993;15(7):210-1.

Klimek L, Wolf H, Mewes T, et al. The effect of short-term immunotherapy with molecular standardized grass and rye allergens on eosinophil cationic protein and tryptase in nasal secretions. J Allergy Clin Immunol 1999;103(1 Pt 1):47-53.

Klossek JM, Laliberte F, Laliberte MF, et al. Local safety of intranasal triamcinolone acetonide: Clinical and histological aspects of nasal mucosa in the long term treatment of perennial allergic rhinitis. Rhinology 2001;39(1):17-22.

Kniest FM, Wolfs BJ, Vos H, et al. Mechanisms and patient compliance of dust-mite avoidance regimens in dwellings of mite-allergic rhinitic patients. Clin Exp Allergy 1992;22(7):681-9.

Kniest FM, Young E, Van Praag MC, et al. Clinical evaluation of a double-blind dust-mite avoidance trial with mite-allergic rhinitic patients. Clin Exp Allergy 1991;21(1):39-47.

Knight A. The role of levocabastine in the treatment of allergic rhinoconjunctivitis. Br J Clin Pract 1994;48(3):139-43.

Knight A, Underdown BJ, Demanuele F, et al. Disodium cromoglycate in ragweed-allergic rhinitis. J Allergy Clin Immunol 1976;58(2):278-83.

Kobayashi RH, Kiechel IF, Kobayashi ALD, et al. Topical nasal sprays: Treatment of allergic rhinitis. Am Fam Phys 1994;50(1):151-7.

Koch B, Oparil S, Stimpel M. Co-administration of an ACE-inhibitor (moexipril) and hormonal replacement therapy in postmenopausal women. J Hum Hypertens 1999;13(5):337-42.

Kogan H. Hayfever: A modern condition. Occup Health 1993;45(5):166-8.

Kolbeck KG, Ehnhage A, Juto JE, et al. Airway reactivity and exhaled NO following swine dust exposure in healthy volunteers. Respir Med 2000;94(11):1065-72.

Konno A, Yamakoshi T, Terada N, et al. Mode of action of a topical steroid on immediate phase reaction after antigen challenge and nonspecific nasal hyperreactivity in nasal allergy. Int Arch Allergy Immunol 1994;103(1):79-87.

Kooistra JB, Pasch R, Reed CE. The effects of air cleaners on hay fever symptoms in air-conditioned homes. J Allergy Clin Immunol 1978;61(5):315-9.

Kopferschmitt-Kubler MC, Couchot A, Pauli G. Evaluation of the effect of oral cetirizine on antigen-induced immediate asthmatic response. Ann Allergy 1990;65(6):501-3.

Korsgaard J. Preventive measures in hose-dust allergy. Am Rev Respir Dis 1982;125(1):80-4.

Korsgaard J. Preventive measures in mite asthma. A controlled trial. Allergy 1983;38(2):93-102.

Korsgaard J. Mite asthma and residency. A case-control study on the impact of exposure to house-dust mites in dwellings. Am Rev Respir Dis 1983;128(2):231-5.

Kort HS, Schober G, Koren LG, et al. Mould-devouring mites differ in guanine excretion from dust-eating Acari, a possible error source in mite allergen exposure studies. Clin Exp Allergy 1997;27(8):921-5.

Koskinen OM, Husman TM, Meklin TM, et al. The relationship between moisture or mould observations in houses and the state of health of their occupants. Eur Respir J 1999;14(6):1363-7.

Kotwani A, Puri R, Gupta U. Efficacy of nimesulide alone and in combination with cetirizine in acute allergic rhinitis. J Assoc Physicians India 2001;49:518-22.

Kozma CM, Sadik MK, Watrous ML. Economic outcomes for the treatment of allergic rhinitis. [Review]. Pharmacoeconomics 1996;10(1):4-13.

Kozma CM, Schulz RM, Sclar DA, et al. A comparison of costs and efficacy of intranasal fluticasone propionate and terfenadine tablets for seasonal allergic rhinitis. Clin Ther 1996;18(2):334-46.

Krause HF, Squillace SP, Mabry RL, et al. Antihistamines and decongestants. Otolaryngol Head Neck Surg 1992;107(6 I):835-40.

Kray KT, Squire EN, Tipton WR, et al. Cromolyn sodium in seasonal allergic conjunctivitis. J Allergy Clin Immunol 1985;76(4):623-7.

Kremer B, Klimek L, Bullinger M, et al. Generic or disease-specific quality of life scales to characterize health status in allergic rhinitis? Allergy 2001;56:957-63.

Kreuser ED, Kuchler T, Zwingers T, et al. A multicenter prospective randomized trial with assessment of quality of life in patients with metastatic colorectal carcinoma comparing interferon alpha-2b and folinic acid as modulators of 5-fluorouracil. Onkologie 1994;17(1):78-84.

Kristensen O. A prospective study of the development of hand eczema in an automobile manufacturing industry. Contact Dermatitis 1992;26(5):341-5.

Kroidl RF, Göbel D, Balzer D, et al. Clinical effects of benzyl benzoate in the prevention of house-dust-mite allergy. Results of a prospective, double-blind, multicenter study. Allergy 1998;53(4):435-40.

Krouse JH. Computed tomography stage, allergy testing, and quality of life in patients with sinusitis. Otolaryngol Head Neck Surg 2000;123(4):389-92.

Krouse JH, Krouse HJ. Patient use of traditional and complementary therapies in treating rhinosinusitis before consulting an otolaryngologist. Laryngoscope 1999;109(8):1223-7.

Krouse JH, Krouse HJ. Efficacy of immunotherapy based on skin end-point titration. Otolaryngol Head Neck Surg 2000;123(3):183-7.

Kujala VM, Reijula KE. Glove-related rhinopathy among hospital personnel. Am J Ind Med 1996;30(2):164-70.

Kuna P, Alam R, Kuzminska B, et al. The effect of preseasonal immunotherapy on the production of histamine-releasing factor (HRF) by mononuclear cells from patients with seasonal asthma: results of a double-blind, placebo-controlled, randomized study. J Allergy Clin Immunol 1989;83(4):816-24.

Kuo H-W, Jian G-J, Chen C-L, et al. White blood cell count as an indicator of formaldehyde exposure. Bull Environ Contam Toxicol 1997;59(2):261-7.

Kupa A. Allergic rhinitis and immunotherapy. Med J Aust 1992;157(1):9-11.

Kusunoki T, Hosoi S, Asai K, et al. Relationships between atopy and lung function: Results from a sample of one hundred medical students in Japan. Ann Allergy Asthma Immunol 1999;83(4):343-7.

La Rosa M, Ranno C, Andre C, et al. Double-blind placebo-controlled evaluation of sublingual-swallow immunotherapy with standardized Parietaria judaica extract in children with allergic rhinoconjunctivitis. J Allergy Clin Immunol 1999;104(2 Pt 1):425-32.

Lack G. Pediatric allergic rhinitis and comorbid disorders. [Review]. J Allergy Clin Immunol 2001;108(1 Suppl):S9-15.

Lale AM, Mason JDT, Jones NS. Mucociliary transport and its assessment: A review. Clin Otolaryngol Allied Sci 1998;23(5):388-96.

Lamb HM, Culy CR, Faulds D. Inhaled fluticasone propionate: A pharmacoeconomic review of its use in the management of asthma. Pharmacoeconomics 2000;18(5):487-510.

Lander F, Meyer HW, Norn S. Serum IgE specific to indoor moulds, measured by basophil histamine release, is associated with building-related symptoms in damp buildings. Inflamm Res 2001;50(4):227-31.

Lane AP, Pine HS, Pillsbury HC III. Allergy testing and immunotherapy in an academic otolaryngology practice: a 20-year review. Otolaryngol Head Neck Surg 2001;124(1):9-15.

Lang DM, Visintainer PF, Howland WC 3rd, et al. Survey of the extent and nature of care for adults and older adults by allergy/immunology practitioners. Ann Allergy Asthma Immunol 2000;85(2):106-10.

Lanier BQ, Gross RD, Marks BB, et al. Olopatadine ophthalmic solution adjunctive to loratadine compared with loratadine alone in patients with active seasonal allergic conjunctivitis symptoms. Ann Allergy Asthma Immunol 2001;86(6):641-8.

Lanphear BP, Kahn RS, Berger O, et al. Contribution of residential exposures to asthma in US children and adolescents. Pediatrics 2001;107(6):E98.

Lasley MV. Allergic disease prevention and risk factor identification. Immunol Allergy Clin North Am 1999;19(1):149-59.

Lau SK, Wei WI, Van Hasselt CA, et al. A clinical comparison of budesonide nasal aerosol, terfenadine and a combined therapy of budesonide and oxymetazoline in adult patients with perennial rhinitis. Asian Pac J Allergy Immunol 1990;8(2):109-15.

Leaderer BP, Samet JM. Passive smoking and adults: New evidence for adverse effects. Am J Respir Crit Care Med 1994;150(5 I):1216-8.

Leaver-Dunn D, Robinson JB, Laubenthal J. Assessment of respiratory conditions in athletes. Athl Ther Today 2000;5(6):14-9.

Lebacq Jr E, Gline JP, Joue P, et al. Exploratory study of the decongestive effect of Rhinopront syrup in adults and in children with acute rhinitis. Clin Trials Meta-Analyis 1994;29(2-3):113-24.

Lebowitz MD, Cassell EJ, McCarroll J. Health and the urban environment. XI. The incidence and burden of minor illness in a healthy population: methods, symptoms, and incidence. Am Rev Respir Dis 1972;106(6):824-34.

Ledford DK, Lockey RF. Allergic rhinitis: offering relief this season... second in a series of two articles. J Respir Dis 1998;19(8):647-50, 659-60, 662 passim.

Lee J, Cummins G, Okamoto L. A descriptive analysis of the use and cost of new-generation antihistamines in the treatment of allergic rhinitis: a retrospective database analysis. Am J Manag Care 2001;7(4 Suppl):S103-12.

Lee JT, Shy CM. Respiratory function as measured by peak expiratory flow rate and PM10: six communities study. J Expo Anal Environ Epidemiol 1999;9(4):293-9.

Lee M. Tamsulosin for the treatment of benign prostatic hypertrophy. Ann Pharmacother 2000;34(2):188-99.

Lee M, Cho S, Park H, et al. Citrus red mite (Panonychus citri) is a common sensitizing allergen among children living around citrus orchards. Ann Allergy Asthma Immunol 2000;85(3):200-4.

Lees LJ. A trial of house dust mite adsorbed on tyrosine in general practice. Br J Clin Pract 1974;28(10):343-46.

Leickly FE, Sears-Ewald D, Ownby DR. A comparative cost-effectiveness study of two treatment modalities for ragweed hay fever. Am J Rhinol 1989;3(2):99-104.

Leino M, Montan P, Nja F. A double-blind group comparative study of ophthalmic sodium cromoglycate, 2% four times daily and 4% twice daily, in the treatment of seasonal allergic conjunctivitis. Allergy Eur J Allergy Clin Immunol 1994;49(3):147-51.

Leong KP, Chan SP, Tang CY, et al. Quality of life of patients with perennial allergic rhinitis: preliminary validation of the Rhinoconjunctivitis Quality of Life Questionnaire in Singapore. Asian Pac J Allergy Immunol 1999;17(3):163-7.

Leopold D. A perplexing olfactory loss. Arch Otolaryngol Head Neck Surg 2000;126(6):803.

Leopold D, Ferguson BJ, Piccirillo JF. Outcomes assessment. Otolaryngol Head Neck Surg 1997;117(3 II Suppl):S58-S68.

Leroyer C, Malo J-L, Girard D, et al. Chronic rhinitis in workers at risk of reactive airways dysfunction syndrome due to exposure to chlorine. Occup Environ Med 1999;56(5):334-8.

Leung R, Lam CW, Chan A, et al. Indoor environment of residential homes in Hong Kong--relevance to asthma and allergic disease. Clin Exp Allergy 1998;28(5):585-90.

Levien T, Baker DE. Reviews of fexofenadine and nicotine nasal spray. Hosp Pharm 1997;32(5):694-721.

Levien T, Baker DE. Tamulosin hydrochloride and samarium-153 lexidronam injection. Hosp Pharm 1998;33(1):75-96.

Levine B. Effect of eprosartan and enalapril in the treatment of black hypertensive patients: Subgroup analysis of a 26-week, double-blind, multicentre study. Curr Med Res Opin 1999;15(1):25-32.

Lewis SA, Weiss ST, Platts-Mills TA, et al. Association of specific allergen sensitization with socioeconomic factors and allergic disease in a population of Boston women. J Allergy Clin Immunol 2001;107(4):615-22.

Leynadier F, Banoun L, Dollois B, et al. Immunotherapy with a calcium phosphate-adsorbed five-grass-pollen extract in seasonal rhinoconjunctivitis: a double-blind, placebo-controlled study. Clin Exp Allergy 2001;31(7):988-96.

Leynadier F, Herman D, Vervloet D, et al. Specific immunotherapy with a standardized latex extract versus placebo in allergic healthcare workers. J Allergy Clin Immunol 2000;106(3):585-90.

Leynaert B, Neukirch C, Liard R, et al. Quality of life in allergic rhinitis and asthma. A population-based study of young adults. Am J Respir Crit Care Med 2000;162(4 Pt 1):1391-6.

Li JT. Grass-pollen immunotherapy for 3 to 4 years was still effective 3 years after being discontinued... commentary on Durham SR, Walker SM, Varga E, et al. Long-term clinical efficacy of grass-pollen immunotherapy. N Engl J Med1999 Aug 12;341:468-75. ACP Journal Club 2000;132(2):65.

Li JT. Asthma and allergy: A four-article symposium. Postgrad Med 2001;109(5):43.

Li JTC, Andrist D, Bamlet WR, et al. Accuracy of patient prediction of allergy skin test results. Ann Allergy Asthma Immunol 2000;85(5):382-4.

Liao E, Leahy M, Cummins G. The costs of nonsedating antihistamine therapy for allergic rhinitis in managed care: an updated analysis. Am J Manag Care 2001;7(15 Suppl):S459-68.

Lichtenstein LM, Ishizaka K, Norman PS, et al. IgE antibody measurements in ragweed hay fever. Relationship to clinical severity and the results of immunotherapy. J Clin Invest 1973;52(2):472-82.

Lichtenstein LM, Norman PS, Winken-Werder WL, et al. In vitro studies of human ragweed allergy. Changes in cellular and humoral activity associated with specific desensitization. J Clin Invest 1966;45:1126-36.

Lichtenstein LM, Norman PS, Winkenwerder WL. Clinical and in vitro studies on the role of immunotherapy in ragweed hay fever. Am J Med 1968;44(4):514-24.

Lichtenstein LM, Norman PS, Winkenwerder WL. A single year of immunotherapy for ragweed hay fever. Immunologic and clinical studies. Ann Intern Med 1971;75(5):663-71.

Lieberman P. American Academy of Asthma, Allergy and Immunology - 55th Annual Meeting: 26 February - 3 March 1999, Orlando, FL, USA. Idrugs 1999;2(5):405-9.

Lieberman P. American Academy of Asthma, Allergy and Immunology - 56th annual meeting: 3-8 March 2000, San Diego, CA, USA. Curr Opin Anti-Inflammatory Immunomodulatory Invest Drugs 2000;2(2):153-9.

Lin RY, Nahal A, Lee M, et al. Changes in nasal leukocytes and epithelial cells associated with topical beclomethasone treatment. Ann Allergy Asthma Immunol 2000;84(6):618-22.

Linneberg A, Nielsen NH, Madsen F, et al. Secular trends of allergic asthma in Danish adults. The Copenhagen Allergy Study. Respir Med 2001;95(4):258-64.

Lipiec A, Jurkiewicz D, Rapiejko P. Mould hypersensitivity in allergic rhinitis patients. Int Rev Allergol Clin Immunol 2000;6(2):57-62.
Lipold AG. Six ideas to boost employee productivity. Bus Health 2001;19(9):26-30.

Lipworth BJ. Emerging role of antileukotriene therapy in allergic rhinitis. Clin Exp Allergy 2001;31(12):1813-21.

Littorin M, Truedsson L, Welinder H, et al. Acute respiratory disorder, rhinoconjunctivitis and fever associated with the pyrolysis of polyurethane derived from diphenylmethane diisocyanate. Scand J Work Environ Health 1994;20(3):216-22.

Liu C-M, Hsu M-C. Clinical evaluation of azelastine nasal spray versus terfenadine in the treatment of allergic rhinitis. J Taiwan Otolaryngol Head Neck Surg 1999;34(6):471-8.

Liu JT, Hammitt JK, Wang JD, et al. Mother's willingness to pay for her own and her child's health: a contingent valuation study in Taiwan. Health Econ 2000;9(4):319-26.

LoBuono C. Eliminating allergy triggers. Patient Care 2000;34(7):107-9, 120-1.

Lockey RF. Building- and home-related complaints and illnesses: Summary statement. J Allergy Clin Immunol 1994;94(2 II Suppl):423-4.

Lockey RF. "ARIA": Global guidelines and new forms of allergen immunotherapy. J Allergy Clin Immunol 2001;108(4):497-9.

Lockey RF, Widlitz MD, Mitchell DQ, et al. Comparative study of cetirizine and terfenadine versus placebo in the symptomatic management of seasonal allergic rhinitis. Ann Allergy Asthma Immunol 1996;76(5):448-54.

Lombardero M, Heymann PW, Platts-Mills TA, et al. Conformational stability of B cell epitopes on group I and group II Dermatophagoides spp. allergens. Effect of thermal and chemical denaturation on the binding of murine IgG and human IgE antibodies. J Immunol 1990;144(4):1353-60.

Lombardi C, Gargioni S, Melchiorre A, et al. Safety of sublingual immunotherapy with monomeric allergoid in adults: Multicenter post-marketing surveillance study. Allergy Eur J Allergy Clin Immunol 2001;56(10):989-92.

Lombardi E, Stein RT, Wright AL, et al. The relation between physician-diagnosed sinusitis, asthma, and skin test reactivity to allergens in 8-year-old children. Pediatr Pulmonol 1996;22(3):141-6.

Long A, McFadden C, DeVine D, et al. Management of allergic and nonallergic rhinitis. Evidence Report/Technology Assessment No. 54 (Prepared by New England Medical Center Evidence-based Practice Center under Contract No. 290-97-0019). AHRQ Publication No. 02-E024. Rockville, MD: Agency for Healthcare Research and Quality. May 2002.

Long L, Soeken K, Ernst E. Herbal medicines for the treatment of osteoarthritis: A systematic review. Rheumatology (UK) 2001;40(7):779-93.

Lonneux JF, Losson B. Field efficacy of injectable and pour-on moxidectin in cattle naturally infested with Psoroptes ovis (Acarina: Psoroptidae). Vet Parasitol 1992;45(1-2):147-52.

Lonneux JF, Nguyen TQ, Delhez M, et al. Antibody response after treatment in cattle infected with Psoroptes ovis. Res Vet Sci 1997;63(1):57-60.

Lorette G, Giannetti A, Pereira RS, et al. One-year treatment of chronic urticaria with mizolastine: Efficacy and safety. J Eur Acad Dermatol Venereol 2000;14(2):83-90.

Losson B, Lonneux JF. Field efficacy of injectable moxidectin in cattle naturally infested with Chorioptes bovis and Sarcoptes scabiei. Vet Parasitol 1993;51(1-2):113-21.

Lovering AM. Counting the cost of rhinosinusitis. Round Table Ser R Soc Med 1999;67:51-8.

Lowe F. Alpha-1-adrenoceptor blockade in the treatment of benign prostatic hyperplasia. Prostate Cancer Prostatic Dis 1999;2(3):110-9.

Lowell FC, Franklin W. A double-blind study of the effectiveness and specificity of injecton therapy in ragweed hay fever. N Engl J Med 1965;273(13):675-9.

Lowenthal DT, Flannery M, Mader SL, et al. Benign prostatic hyperplasia: Maximizing treatment with alpha blockers. Geriatrics 1998;53(10 Suppl 2):S4-S26.

Lower T, Henry J, Mandik L, et al. Compliance with allergen immunotherapy. Ann Allergy 1993;70(6):480-2.

Luczynska C, Sterne J, Bond J, et al. Indoor factors associated with concentrations of house dust mite allergen, Der p 1, in a random sample of houses in Norwich, UK. Clin Exp Allergy 1998;28(10):1201-9.

Lum LC, Lum LM, Lum LC. Medications in the allergy/asthma office. Immunol Allergy Clin North Am 1999;19(1):101-27.

Lund V. Summary of discussion. Round Table Ser R Soc Med 1999;67:59-63.

Lund VJ. Health related quality of life in sinonasal disease. Rhinology 2001;39(4):182-6.

Lundback B. Epidemiology of rhinitis and asthma. [Review]. Clin Exp Allergy 1998;(Suppl 2):3-10.

Lundberg L, Isacson D. The impact of over-the-counter availability of nasal sprays on sales, prescribing, and physician visits. Scand J Prim Health Care 1999;17(1):41-5.

Lundblad FP. House dust mite allergy in an office building. Appl Occup Environ Hyg 1991;6(2):94-6.

Lundblad L, Sipila P, Farstad T, et al. Mometasone furoate nasal spray in the treatment of perennial non-allergic rhinitis: a Nordic, multicenter, randomized, double-blind, placebo-controlled study. Acta Oto-Laryngol 2001;121(4):505-9.

Lurie A, Nadel JA, Roisman G, et al. Role of neutral endopeptidase and kininase II on substance P-induced increase in nasal obstruction in patients with allergic rhinitis. Am J Respir Crit Care Med 1994;149(1):113-7.

Lusk RP, Stankiewicz JA. Pediatric rhinosinusitis. Otolaryngol Head Neck Surg 1997;117(3 II Suppl):S53-S57.

Lutsky II, Neuman I. Laboratory animal dander allergy: I. An occupational disease. Ann Allergy 1975;35(4):201-5.

Lynoe N, Svensson T. Doctors' attitudes towards empirical data -- a comparative study. Scand J Soc Med 1997;25(3):210-6.

M'Raihi L, Charpin D, Thibaudon M, et al. Bronchial challenge to house dust can induce immediate bronchoconstriction in allergic asthmatic patients. Ann Allergy 1990;65(6):485-8.

Mabry RL, Mabry CS. Allergic fungal rhinosinusitis: experience with immunotherapy. Arch Otolaryngol Head Neck Surg 1998;124(10):1178.

Macchia L, Caiaffa MF, Di Felice G, et al. Changes in skin reactivity, specific IgE and IgG levels after one year of immunotherapy in olive pollinosis. Allergy 1991;46(6):410-8.

Machiels JJ, Buche M, Somville MA, et al. Complexes of grass pollen allergens and specific antibodies reduce allergic symptoms and inhibit the seasonal increase of IgE antibody. Clin Exp Allergy 1990;20(6):653-60.

Machiels JJ, Somville MA, Jacquemin MG, et al. Allergen-antibody complexes can efficiently prevent seasonal rhinitis and asthma in grass pollen hypersensitive patients. Allergen-antibody complex immunotherapy. Allergy 1991;46(5):335-48.

Mackay IS, Durham SR. ABC of allergies. Perennial rhinitis. BMJ 1998;316(7135):917-20.

Mackay IS, Durham SR. Perennial rhinitis. BMJ 1998;316:917-20.

Mackowiak JI. The health and economic impact of rhinitis. Am J Manag Care 1997;3:S8-S18.

Mackowiak JI, Stempel DA. Nasal steroids lead to superior outcomes in rhinitis: an outcomes monitoring pilot study in an HMO. [Abstract]. Ann Allergy Asthma Immunol 1997;78:155.

Maderazo EG, Albano SD. Granulocyte migration abnormality in patients suffering from seasonal allergic rhinitis: failure of treatment with cimetidine. Int Arch Allergy Appl Immunol 1984;74(3):211-5.

Mahe C, Chevret S. Analysis of recurrent failure times data: Should the baseline hazard be stratified? Stat Med 2001;20(24):3807-15.

Mahmoudi M, Gershwin ME. Sick building syndrome. III. Stachybotrys chartarum. J Asthma 2000;37(2):191-8.

Maini R, St CEW, Breedveld F, et al. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: A randomised phase III trial. Lancet 1999;354(9194):1932-9.

Maini RN, Breedveld FC, Kalden JR, et al. Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. Arthritis Rheum 1998;41(9):1552-63.

Majani G, Baiardini I, Giardini A, et al. Health-related quality of life assessment in young adults with seasonal allergic rhinitis. Allergy 2001;56(4):313-7.

Malling HJ. Practical immunotherapy. Rev Esp Alergol Inmunol Clin 1996;11(Spec Iss 1):55-62.
Malling H-J. Indications and contraindications for allergen-specific immunotherapy. Allergy Clin Immunol Int 1998;10(3):76-80.

Malmberg H, Holopainen E, Grahne B, et al. Astemizole in the treatment of hay fever. Allergy Eur J Allergy Clin Immunol 1983;38(4):227-31.

Malo J-L, Chan-Yeung M. Current reviews of allergy and clinical immunology: Occupational asthma. J Allergy Clin Immunol 2001;108(3):317-28.

Malone DC, Lawson KA, Smith DH, et al. A cost of illness study of allergic rhinitis in the United States. J Allergy Clin Immunol 1997;99(1 Pt 1):22-7.

Mamikoglu B, Corey J. Safety of antihistamine therapy. Curr Opin Otolaryngol Head Neck Surg 1998;6(1):75-9.

Manjra A, Berman D, Toerien A, et al. The effects of a single treatment of an acaricide, Acarosan, and a detergent, Metsan, on Der p 1 allergen levels in the carpets and mattresses of asthmatic children. S Afr Med J 1994;84(5):278-80.

Mann KV, Crowe SJP, Tietze KJ. Nonsedating histamine Hinf 1-receptor antagonists. Clin Pharm 1989;8(5):331-44.

Manor O, Matthews S, Power C. Self-rated health and limiting longstanding illness: inter-relationships with morbidity in early adulthood. Int J Epidemiol 2001;30(3):600-7.

Mansour M, Lanphear BP, Hornung R, et al. A side-by-side comparison of sampling methods for settled, indoor allergens. Environ Res 2001;87(1):37-46.

Mao SJ, Kluge K, Squillace SJ. Apolipoprotein A-II can incorporate into plasma very low density lipoproteins. FEBS Lett 1981;132(2):289-92.

Marchesani F, Cecarini L, Pela R, et al. Causes of chronic persistent cough in adult patients: The results of a systematic management protocol. Monaldi Arch Chest Dis 1998;53(5):510-4.

Marinella MA. Rhinosinusitis possibly caused by Pasteurella multocida. Infect Dis Clin Pract 1996;5(3):208-9.

Marini A, Agosti M, Motta G, et al. Effects of a dietary and environmental prevention programme on the incidence of allergic symptoms in high atopic risk infants: three years' follow-up. Acta Paediatr Suppl 1996;414:1-21.

Marks GB. House dust mite exposure as a risk factor for asthma: benefits of avoidance. [Review]. Allergy 1998;53(48 Suppl):108-14.

Marks GB, Tovey ER, Green W, et al. House dust mite allergen avoidance: a randomized controlled trial of surface chemical treatment and encasement of bedding. Clin Exp Allergy 1994;24(11):1078-83.

Marks GB, Tovey ER, Green W, et al. The effect of changes in house dust mite allergen exposure on the severity of asthma. Clin Exp Allergy 1995;25(2):114-8.

Marks GB, Tovey ER, Peat JK, et al. Variability and repeatability of house dust mite allergen measurement: implications for study design and interpretation. Clin Exp Allergy 1995;25(12):1190-7.

Marogna M, Tiri A, Riva G. Clinical practice improvement program for immunotherapy of respiratory allergic diseases. Int J Immunopathol Pharmacol 2001;14(2):93-101.

Marques Rezende R, Dos Santos AC, Anselmo-Lima WT, et al. Computed tomography for the evaluation of children with chronic rhinosinusitis: Proposal of a reduced examination and comparison with the standard examination. Int J Pediatr Otorhinolaryngol 2000;55(1):11-5.

Marsa L. Making a case for easier access to allergy drugs. Los Angeles Times, (Health):S1, S6, 2001 Apr 9.

Marsland TW, Newton WP. Do antihistamines impair school performance in children? J Fam Pract 2001;50(9):738.

Martin IR, Henwood JL, Wilson F, et al. House dust mite and cat allergen levels in domestic dwellings in Christchurch. New Zealand Med J 1997;110(1046):229-31.

Martinati LC, Boner AL. Optimum treatment of allergic rhinitis in children. Biodrugs 1997;8(5):348-59.

Mason J, Reynolds R, Rao N. The systemic safety of fexofenadine HCl. Clin Exp Allergy Suppl 1999;29(3):163-70.

Massey DG, Fournier-Massey G, James RH. Minimizing acarians and house dust in the tropics. Ann Allergy 1993;71(5):439-44.

Massey DG, Furumizo RT, Fournier-Massey G, et al. House dust mites in university dormitories. Ann Allergy 1988;61(3):229-32.

Maunsell K, Wraith DG, Hughes AM. Hyposensitisation in mite asthma. Lancet 1971;1(7706):967-8.

Mazzaglia G, Greco S, Lando C, et al. Adult acute respiratory tract infections in Sicily: Pattern of antibiotic drug prescription in primary care. J Antimicrob Chemother 1998;41(2):259-66.

McAllen MK. Hyposensitisation in grass pollen hay fever. A double blind trial of alumn precipitated pollen extract and depot emulsion pollen extract compared with placebo injections. Acta Allergol 1969;24(6):421-31.

McAllen MK, Assem ES, Maunsell K. House-dust mite asthma. Results of challenge tests on five criteria with Dermatophagoides pteronyssinus. BMJ 1970;2(708):501-4.

McAuley DF, McGovern V, Dick PT, et al. Churg-Strauss syndrome associated with leukotriene receptor antagonists. Ulster Med J 2001;70(2):152-4.

McClellan K, Jarvis B. Desloratadine. Drugs 2001;61(6):789-96.

McClennen W, Wilson T. Felodipine extended release versus conventional diuretic therapy for the treatment of systolic hypertension in elderly patients. Clin Invest Med 1998;21(3):142-50.

McEwen LM, Birtwistle S, Kay AB, et al. Immunotherapy. BMJ 1991;302(6775):530-1.

McFadden EA, Gungor A, Ng B, et al. Loratadine/pseudoephedrine for nasal symptoms in seasonal allergic rhinitis: a double-blind, placebo-controlled study. Ear Nose Throat J 2000;79(4):254, 257-8, 260 passim.

McHugh SM, Ewan PW. Reduction of increased serum neutrophil chemotactic activity following effective hyposensitization in house dust mite allergy. Clin Exp Allergy 1989;19(3):327-34.

McHugh SM, Ewan PW. A clinical index: a new method to assess efficacy of allergen immunotherapy. Allergy 1992;47(2 Pt 1):115-20.

McHugh SM, Lavelle B, Kemeny DM, et al. A placebo-controlled trial of immunotherapy with two extracts of Dermatophagoides pteronyssinus in allergic rhinitis, comparing clinical outcome with changes in antigen-specific IgE, IgG, and IgG subclasses. J Allergy Clin Immunol 1990;86(4 Pt 1):521-31.

McKeever TM, Lewis SA, Smith C, et al. Siblings, multiple births, and the incidence of allergic disease: A birth cohort study using the West Midlands general practice research database. Thorax 2001;56(10):758-62.

McLarty MR, Whittman L, Lawrence DB. Comparison of first generation antihistamines and cetirizine using an allergic rhinitis quality of life questionnaire. [Abstract]. ASHP Midyear Clin Mtg 1997;32:P-198E.

McMenamin P. Costs of hay fever in the United States in 1990. Ann Allergy 1994;73(1):35-9.

McSherry J. Rhinosinusitis in primary care: What can guidelines achieve? Round Table Ser R Soc Med 1999;67:45-9.

McWhorter WP. Allergy and risk of cancer. A prospective study using NHANESI followup data. Cancer 1988;62(2):451-5.

Mead M. Allergic rhinitis. Practice Nurse 1997;13(9):556-7.

Medleau L, Willemse T. Efficacy of daily amitraz on generalised demodicosis in dogs. J Small Animal Pract 1995;36(1):3-6.

Medrala W, Wolanczyk-Medrala A, Wrzyszcz M, et al. The influence of the first course of immunotherapy in patients with pollinosis on sulfidoleukotriene release from peripheral blood leukocytes. Int Rev Allergol Clin Immunol 1999;5(1):13-6.

Meggs WJ. Rads and ruds - The toxic induction of asthma and rhinitis. J Toxicol Clin Toxicol 1994;32(5):487-501.

Mehta SB, Smith JM. Nasal hyposensitization and hay fever. Clin Allergy 1975;5(3):279-84.

Mellerup MT, Hahn GW, Poulsen LK, et al. Safety of allergen-specific immunotherapy. Relation between dosage regimen, allergen extract, disease and systemic side-effects during induction treatment. Clin Exp Allergy 2000;30(10):1423-9.

Meltzer EO. An overview of current pharmacotherapy in perennial rhinitis. J Allergy Clin Immunol 1995;95(5 II):1097-110.

Meltzer EO. Allergy and clinical immunology. J Allergy Clin Immunol 1997;99(6 II Suppl):S807.

Meltzer EO. The prevalence and medical and economic impact of allergic rhinitis in the United States. Introduction. J Allergy Clin Immunol 1997;99(6 Pt 2):S807.

Meltzer EO. Clinical and antiinflammatory effects of intranasal budesonide aqueous pump spray in the treatment of perennial allergic rhinitis. Ann Allergy Asthma Immunol 1998;81(2):128-34.

Meltzer EO. Role for cysteinyl leukotriene receptor antagonist therapy in asthma and their potential role in allergic rhinitis based on the concept of 'one linked airway disease'. Ann Allergy Asthma Immunol 2000;84(2):176-87.

Meltzer EO. Quality of life in adults and children with allergic rhinitis. [Review]. J Allergy Clin Immunol 2001;108(1 Suppl):S45-53.

Meltzer EO, Casale TB, Nathan RA, et al. Once-daily fexofenadine HCl improves quality of life and reduces work and activity impairment in patients with seasonal allergic rhinitis. Ann Allergy Asthma Immunol 1999;83(4):311-7.

Meltzer EO, Ehrlich PM. Step approach to the clinical management of allergic rhinitis: prescription and over the counter therapeutic reference summary. Manag Care Interface 1999;12:70-7.

Meltzer EO, Grant JA. Impact of cetirizine on the burden of allergic rhinitis. [Review]. Ann Allergy Asthma Immunol 1999;83(5):455-63.

Meltzer EO, Malmstrom K, Lu S, et al. Concomitant montelukast and loratadine as treatment for seasonal allergic rhinitis: a randomized, placebo-controlled clinical trial. J Allergy Clin Immunol 2000;105(5):917-22.

Meltzer EO, Orgel HA, Biondi R, et al. Ipratropium nasal spray in children with perennial rhinitis. Ann Allergy Asthma Immunol 1997;78(5):485-91.

Meltzer EO, Orgel HA, Bronsky EA, et al. Ipratropium bromide aqueous nasal spray for patients with perennial allergic rhinitis: a study of its effect on their symptoms, quality of life, and nasal cytology. J Allergy Clin Immunol 1992;90(2):242-9.

Meltzer EO, Tyrell RJ, Rich D, et al. A pharmacologic continuum in the treatment of rhinorrhea: the clinician as economist. [Review]. J Allergy Clin Immunol 1995;95(5 Pt 2):1147-52.

Meran A, Morse J, Gibbs TG. A cross-over comparison of acrivastine, pseudoephedrine and their combination in seasonal allergic rhinitis. Rhinology 1990;28(1):33-40.

Merget R, Heger M, Globisch A, et al. Quantitative bronchial challenge tests with wheat flour dust administered by spinhaler: comparison with aqueous wheat flour extract inhalation. J Allergy Clin Immunol 1997;100(2):199-207.

Metintas S, Metintas M, Kalyoncu C, et al. Prevalence of asthma and other allergic diseases in primary schoolchildren of Eskisehir (Turkey). Allergy Clin Immunol Int 2001;13(6):250-5.

Metlzer IO, Nathan RA, Selner JC, et al. Quality of life and rhinitic symptoms: Results of a nationwide survey with the SF-36 and RQLQ questionnaires. J Allergy Clin Immunol 1997;99:S815-9.

Metso T, Bjorksten F, Kilpio K, et al. Serum myeloperoxidase and sick building syndrome. Lancet 1993;342(8863):113-4.

Metson R, Cosenza M, Gliklich RE, et al. The role of image-guidance systems for head and neck surgery. Arch Otolaryngol Head Neck Surg 1999;125(10):1100-4.

Metson RB, Gliklich RE. Clinical outcomes in patients with chronic sinusitis. Laryngoscope 2000;110(3 Pt 3):24-8.

Metzger WJ, Patterson R, Seiss CR, et al. Comparison of polymerized and unpolymerized antigen E for immunotherapy of ragweed allergy. New Engl J Med 1976;295:1160-64.

Meyer HW, Larsen FO, Jacobi HH, et al. Sick building syndrome: Association of symptoms with serum IgE specific to fungi. Inflamm Res 1998;47(Suppl 1):S9-S10.

Miadonna A, Cottini M, Milazzo N, et al. In vivo and ex vivo inhibitory effects of loratadine on histamine release in patients with allergic rhinitis. Allergy 1998;53(12):1183-8.

Miesen WMAJ, DeMonchy JGR, Dubois AEJ. Anaphylaxis on skin exposure to grass. Allergy Eur J Allergy Clin Immunol 2001;56(8):799.

Mihrshahi S, Peat JK, Webb K, et al. The childhood asthma prevention study (CAPS): design and research protocol of a randomized trial for the primary prevention of asthma. Controlled Clinical Trials 2001;22(3):333-54.

Miles VH, Fischer PR, Freij BJ, et al. Variations in the treatment of common infections (multiple letters). Pediatr Infect Dis J 1997;16(8):826-7.

Milgrom H, Biondi R, Georgitis JW, et al. Comparison of ipratropium bromide 0.03% with beclomethasone dipropionate in the treatment of perennial rhinitis in children. Ann Allergy Asthma Immunol 1999;83(2):105-11.

Miller AC, Tees EC. A metabolizable adjuvant: clinical trial of grass pollen-tyrosine adsorbate. Clin Allergy 1974;4(1):49-55.

Milosevic DN, Janosevic LJB, Janosevic SB. Intradermal tests with vasomotor agents perennial non-allergic rhinitis. Acta Oto-Rhino-Laryngol Belg 2000;54(4):465-71.

Minatre D, Baker DE, Blanch MC, et al. Reviews of interferon-beta (preliminary evaluation) and loratadine. Hosp Pharm 1993;28(11):1118-24.

Mischler TW, O'Brien WM, Rugloski RJ, et al. Multiclinic trial with glutaraldehyde modified tyrosine adsorbed ragweed pollen immunotherapy (Pollinex). Curr Therap Res 1981;29:745-56.

Mitchell EA, Elliott RB. Controlled trial of an electrostatic precipitator in childhood asthma. Lancet 1980;2(8194):559-61.

Mitchell TN, Sander JW. Levetiracetam: A new antiepileptic drug for the adjunctive therapy of chronic epilepsy. Drugs Today 2001;37(10):665-73.

Moffett LM. Allergic rhinitis: new guidelines for the millennium. Nebraska Mortar Pestle 2000;64:16-9.

Moher D, Cook DJ, Jadad AR, et al. Assessing the quality of randomised trials: current issues and future directions. Int J Tech Assess Health Care 1996;12(2):195-208.

Moher D, Schulz KF, Altman D, et al. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. [Review]. JAMA 2001;285(15):1987-91.

Moller C. Pediatric peculiarities of immunotherapy. Rev Esp Alergol Inmunol Clin 1996;11(Spec Iss 1):35-8.

Möller C, Dreborg S, Ferdousi HA, et al. Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT-study). J Allergy Clin Immunol 2002;109(2):251-6.

Moller C, Dreborg S, Lanner A, et al. Oral immunotherapy of children with rhinoconjunctivitis due to birch pollen allergy. A double blind study. Allergy 1986;41(4):271-9.

Moller C, Mygind N. Nasal blockage in children with non-infectious rhinitis: Consequences and treatment. Allergy Eur J Allergy Clin Immunol Suppl 1997;52(40):45-51.

Mollet JA, Vailes LD, Avner DB, et al. Evaluation of German cockroach (Orthoptera:Blattellidae) allergen and seasonal variation in low-income housing. J Med Entomol 1997;34(3):307-11.

Monfrecola G, Masturzo E, Riccardo AM, et al. Solar urticaria: a report on 57 cases. Am J Contact Dermat 2000;11(2):89-94.

Moon CAL, Davey A. The efficacy and residual effects of trazodone (150 mg nocte) and mianserin in the treatment of depressed general practice patients. Psychopharmacology 1988;95(Suppl):S7-S13.

Moon JS, Choi SO. Environmental controls in reducing house dust mites and nasal symptoms in patients with allergic rhinitis. Yonsei Med J 1999;40(3):238-43.

Moreland LW. Soluble tumor necrosis factor receptor (p75) fusion protein (Enbrel) as a therapy for rheumatoid arthritis. Rheum Dis Clin North Am 1998;24(3):579-91.

Mori S, Fujieda S, Sunaga H, et al. Expression of platelet-derived endothelial cell growth factor and vascularity in the nasal mucosa from allergic rhinitis. Clin Exp Allergy 2000;30(11):1637-44.

Moriguchi H, Matsumoto M, Nishimoto Y, et al. The development of a pollen information system for the improvement of QOL. J Med Investig 2001;48(3-4):198-209.

Mortimer MJ, Kay J, Gawkrodger DJ, et al. The prevalence of headache and migraine in atopic children: An epidemiological study in general practice. Headache 1993;33(8):427-31.

Mortz CG, Lauritsen JM, Bindslev-Jensen C, et al. Prevalence of atopic dermatitis, asthma, allergic rhinitis, and hand and contact dermatitis in adolescents. The Odense adolescence cohort study on atopic diseases and dermatitis. Br J Dermatol 2001;144(3):523-32.

Mosbech H. Who will benefit from hyposensitization? Predictive parameters in house dust mite allergic asthmatics. Allergy 1990;45(3):209-12.

Mosbech H, Dirksen A, Dreborg S, et al. Hyposensitization in asthmatics with mPEG-modified and unmodified house dust mite extract. IV. Occurrence and prediction of side effects. Allergy 1990;45(2):142-50.

Mosbech H, Dreborg S, Madsen F, et al. High dose grass pollen tablets used for hyposensitization in hay fever patients. A one-year double blind placebo-controlled study. Allergy 1987;42(6):451-5.

Mosbech H, Osterballe O. Does the effect of immunotherapy last after termination of treatment? Follow-up study in patients with grass pollen rhinitis. Allergy 1988;43(7):523-9.

Moscato G, Galdi E, Scibilia J, et al. Occupational asthma, rhinitis and urticaria due to piperacillin sodium in a pharmaceutical worker. Eur Respir J 1995;8(3):467-9.

Moss MH, Bush RK. Patient selection and administration of aeroallergen vaccines. Immunol Allergy Clin North Am 2000;20(3):533-52.

Motta G, Passali D, De Vincentiis I, et al. A multicenter trial of specific local nasal immunotherapy. Laryngoscope 2000;110(1):132-9.

Moverare R, Rak S, Elfman L. Allergen-specific increase in interleukin (IL)-4 and IL-5 secretion from peripheral blood mononuclear cells during birch-pollen immunotherapy. Allergy 1998;53(3):275-81.

Moverare R, Vesterinen E, Metso T, et al. Pollen-specific rush immunotherapy: clinical efficacy and effects on antibody concentrations. Ann Allergy Asthma Immunol 2001;86(3):337-42.

Muirhead GJ, Wulff MB, Fielding A, et al. Pharmacokinetic interactions between sildenafil and saquinavir/ritonavir. Br J Clin Pharmacol 2000;50(2):99-107.

Muncer SJ. Control of house dust mite in managing asthma. Power dressing is important in meta-analysis. BMJ 1999;318(7187):871.

Mungan D, Misirligil Z, Gurbuz L. Comparison of the efficacy of subcutaneous and sublingual immunotherapy in mite-sensitive patients with rhinitis and asthma--a placebo controlled study. Ann Allergy Asthma Immunol 1999;82(5):485-90.

Munir AK, Einarsson R, Dreborg SK. Vacuum cleaning decreases the levels of mite allergens in house dust. Pediatr Allergy Immunol 1993;4(3):136-43.

Munoz Lejarazu D, Bernaola G, Fernandez E, et al. Seasonal versus perennial immunotherapy: evaluation after three years of treatment. J Investig Allergol Clin Immunol 1993;3(4):210-6.

Munro CS, Levell NJ, Shuster S, et al. Maintenance treatment with cyclosporin in atopic eczema. Br J Dermatol 1994;130(3):376-80.

Muro MD, Tabar AI, Lizaso MT, et al. Cluster versus conventional immunotherapy in patients allergic to Dermatophagoides pteronyssinus: a controlled study of in vivo and in vitro parameters. J Investig Allergol Clin Immunol 1999;9(3):146-54.

Murphy AW, Platts-Mills TA, Lobo M, et al. Respiratory nitric oxide levels in experimental human influenza. Chest 1998;114(2):452-6.

Murphy III EE, Slavin RG. Occupational rhinitis: when to suspect, what to do: does the problem originate or simply worsen at work? J Respir Dis 2001;22(6):347-50, 352.

Murray AB, Ferguson AC. Dust-free bedrooms in the treatment of asthmatic children with house dust or house dust mite allergy: a controlled trial. Pediatrics 1983;71(3):418-22.

Musk AW, deKlerk NH, Beach JR, et al. Respiratory symptoms and lung function in alumina refinery employees. Occup Environ Med 2000;57(4):279-83.

Mygind N. Clinical investigation of allergic rhinitis and allied conditions. [Review]. Allergy 1979;34(4):195-208.

Mygind N. Introduction. Rhinology 2000;38(Suppl 16):2.

Mygind N. Nasal inflammation and anti-inflammatory treatment. Semantics or clinical reality? Rhinology 2001;39(2):61-5.

Naclerio R, Solomon W. Rhinitis and inhalant allergens. [Review]. JAMA 1997;278(22):1842-8.

Naclerio RM. Allergic rhinitis. [Review]. New Engl J Med 1991;325(12):860-9.

Naclerio RM. Dose-dependent effects of intranasal steroids: How relevant? Ann Allergy Asthma Immunol 2000;85(4):248-9.

Naclerio RM, Baroody FM. Response of nasal mucosa to histamine or methacholine challenge: use of a quantitative method to examine the modulatory effects of atropine and ipratropium bromide. J Allergy Clin Immunol 1992;90(6 Pt 2):1051-4.

Naclerio RM, deTineo ML, Baroody FM. Ragweed allergic rhinitis and the paranasal sinuses. A computed tomographic study. Arch Otolaryngol Head Neck Surg 1997;123(2):193-6.

Naclerio RM, Proud D, Moylan B, et al. A double-blind study of the discontinuation of ragweed immunotherapy. J Allergy Clin Immunol 1997;100(3):293-300.

Nagata M, Yamamoto H, Tabe K, et al. Effect of rush immunotherapy in house-dust-mite (HDM)-sensitive adult bronchial asthma: changes in in vivo and in vitro responses to HDM. Intern Med 1993;32(9):702-9.

Nagy G. The use of Paxirasol in clinical practice. [Review]. Ther Hung 1993;41(3):100-6.

Nalebuff DJ. Use of RAST screening in clinical allergy: a cost-effective approach to patient care. Ear Nose Throat J 1985;64(3):107-21.

Nascimento Silva MG, Naspitz CK, Sole D. Evaluation of quality of life in children and teenagers with allergic rhinitis: adaptation and validation of the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ). Allergol Immunopathol 2001;29(4):111-9.

Nash DB, Sullivan SD, Mackowiak J. Optimizing quality of care and cost effectiveness in treating allergic rhinitis in a managed care setting. Am J Manag Care 2000;6(1 Suppl):S3-15; quiz S19-20.

Naspitz CK, Rizzo MC, Fernandez-Caldas E, et al. Environmental control in childhood asthma. Pediatr Pulmonol Suppl 1995;11:47-8.

Nathan RA, Meltzer EO, Seiner JC, et al. Prevalence of allergic rhinitis in the United States. J Allergy Clin Immunol 1997;99:S808-14.

National Heart Lung and Blood Institute. Practical guide for the diagnosis and management of asthma. NIH Publication No. 97-4053. Rockville, MD: National Institutes of Health, 1997.

National Institute of Allergy and Infectious Diseases, National Institutes of Health. Allergy statistics. NIAID Fact Sheet. Bethesda, MD: National Institute of Allergy and Infectious Diseases. January 2002.

National Institutes of Health. Fighting seasonal allergies. NIH Word on Health. Bethesda, MD: National Institutes of Health. June 2002.

Nayak AS, Philip G, Lu S, et al. Efficacy and tolerability of montelukast alone or in combination with loratadine in seasonal allergic rhinitis: a multicenter, randomized, double-blind, placebo-controlled trial performed in the fall. Ann Allergy Asthma Immunol 2002;88(6):592-600.

Negrini AC, Troise C, Voltolini S, et al. Oral antihistamine/decongestant treatment compared with intranasal corticosteroids in seasonal allergic rhinitis. Clin Exp Allergy 1995;25(1):60-5.

Nelson HS, Areson J, Reisman R. A prospective assessment of the remote practice of allergy: comparison of the diagnosis of allergic disease and the recommendations for allergen immunotherapy by board-certified allergists and a laboratory performing in vitro assays. J Allergy Clin Immunol 1993;92(3):380-6.

Nelson HS, Hirsch SR, Ohman Jr JL, et al. Recommendations for the use of residential air-cleaning devices in the treatment of allergic respiratory diseases. J Allergy Clin Immunol 1988;82(4):661-9.

Nelson HS, Oppenheimer J, Vatsia GA, et al. A double-blind, placebo-controlled evaluation of sublingual immunotherapy with standardized cat extract. J Allergy Clin Immunol 1993;92(2):229-36.

Neri M, Spanevello A. Chronic bronchial asthma from challenge to treatment: Epidemiology and social impact. Thorax 2000;55(Suppl 2):S57-S58.

Neutel JM, Smith DHG, Reilly PA. The efficacy and safety of telmisartan compared to enalapril in patients with severe hypertension. Int J Clin Pract 1999;53(3):175-8.

Newill CA, Evans III R, Khoury MJ. Preemployment screening for allergy to laboratory animals: Epidemiologic evaluation of its potential usefulness. J Occup Med 1986;28(11):1158-64.

Newton DA. Sinusitis in children and adolescents. Prim Care Clin Off Pract 1996;23(4):701-17.

Newton DA, Maberley DJ, Wilson R. House dust mite hyposensitization. Br J Dis Chest 1978;72(1):21-8.

Ng TP, Tan WC. Epidemiology of chronic (perennial) rhinitis in Singapore: prevalence estimates, demographic variation and clinical allergic presentation. Ann Acad Med Singapore 1994;23(1):83-8.

Nickel JC. Long-term implications of medical therapy on benign prostatic hyperplasia end points. Urology 1998;51(4 Suppl A):50-7.

Nickelsen JA, Goldstein S, Mueller U, et al. Local intranasal immunotherapy for ragweed allergic rhinitis. II. Immunologic response. J Allergy Clin Immunol 1981;68(1):41-5.

Nickelsen JA, Goldstein S, Mueller U, et al. Local intranasal immunotherapy for ragweed allergic rhinitis. I. Clinical response. J Allergy Clin Immunol 1981;68(1):33-40.

Niehaus MD, Gwaltney Jr MJ, Hendley JO, et al. Lactoferrin and eosinophilic cationic protein in nasal secretions of patients with experimental rhinovirus colds, natural colds, and presumed acute community-acquired bacterial sinusitis. J Clin Microbiol 2000;38(8):3100-2.

Nielsen L, Johnsen CR, Mosbech H, et al. Antihistamine premedication in specific cluster immunotherapy: a double-blind, placebo-controlled study. J Allergy Clin Immunol 1996;97(6):1207-13.

Nielsen LP, Mygind N, Dahl R. Intranasal corticosteroids for allergic rhinitis: Superior relief. Drugs 2001;61(11):1563-79.

Nieters A, Brems S, Becker N. Cross-sectional study on cytokine polymorphisms, cytokine production after T-cell stimulation and clinical parameters in a random sample of a German population. Hum Genet 2001;108(3):241-8.

Nightingale CH. Treating allergic rhinitis with second-generation antihistamines. Pharmacotherapy 1996;16(5 I):905-14.

Nikkels AF, Henry F, Pierard GE. Allergic reactions to decorative skin paintings. J Eur Acad Dermatol Venereol 2001;15(2):140-2.

Nimmagadda SR, Evans R 3rd. Allergy: etiology and epidemiology. [Review]. Pediatr Rev 1999;20(4):111-5; quiz 116.

Nishioka GJ, Barbero GJ, Konig P, et al. Symptom outcome after functional endoscopic sinus surgery in patients with cystic fibrosis: a prospective study. Otolaryngol Head Neck Surg 1995;113(4):440-5.

Nishioka K, Yasueda H, Saito H. Preventive effect of bedding encasement with microfine fibers on mite sensitization. J Allergy Clin Immunol 1998;101(1 Pt 1):28-32.

Niven RM, Pickering CAC. Is atopy and smoking important in the workplace? Occup Med 1999;49(3):197-200.

Nolen TM. Sedative effects of antihistamines: safety, performance, learning, and quality of life. [Review]. Clin Ther 1997;19(1):39-55.

Norback D, Bjornsson E, Janson C, et al. Asthmatic symptoms and volatile organic compounds, formaldehyde, and carbon dioxide in dwellings. Occup Environ Med 1995;52(6):388-95.

Nordstrom K, Norback D, Akselsson R. Influence of indoor air quality and personal factors on the sick building syndrome (SBS) in Swedish geriatric hospitals. Occup Environ Med 1995;52(3):170-6.

Norman P. Desloratadine Sepracor. Curr Opin Anti-Inflammatory Immunomodulatory Invest Drugs 2000;2(2):117-26.

Norman PS. A review of immunotherapy. [Review]. Allergy 1978;33(2):62-70.

Norman PS. Allergic rhinitis: combined therapy improves control. Consultant 1991;31(8):25-9.

Norman PS, Lichtenstein LM, Kagey-Sobotka A, et al. Controlled evaluation of allergoid in the immunotherapy of ragweed hay fever. J Allergy Clin Immunol 1982;70(4):248-60.

Norris PG, Schofield O, Camp RD. A study of the role of house dust mite in atopic dermatitis. Br J Dermatol 1988;118(3):435-40.

Numata T, Hanazawa T, Konno A, et al. Comparative role of peptide leukotrienes and histamine in the development of nasal mucosal swelling in nasal allergy. Ann Otol Rhinol Laryngol 1999;108(5):467-73.

Nunes C, Ladeira S. Double-blind study of cetirizine and loratadine versus placebo in patients with allergic rhinitis. J Investig Allergol Clin Immunol 2000;10(1):20-3.

Nutting CM, Page SR. Iatrogenic Cushing's syndrome due to nasal betamethasone: A problem not to be sniffed at! Postgrad Med J 1995;71(834):231-2.

Nuutinen J, Holopainen E, Malmberg H, et al. Terfenadine with or without phenylpropanolamine in the treatment of seasonal allergic rhinitis. Clin Exp Allergy 1989;19(6):603-8.

O'Hollaren MT. Update in allergy and immunology. JK Pract 1999;6(4):333-7.

Ogino S, Irifune M, Harada T, et al. Nasal allergy in medical students. Rhinology 1990;28(3):163-8.

Ogino S, Kawashima K, Nibu M, et al. Comparison of multiple-antigen simultaneous test and CAP systems for diagnosis of nasal allergy. ORL: J Oto-Rhino-Laryngol Related Spec 1995;57(4):210-3.

Ohashi Y, Nakai Y, Ohno Y, et al. Natural course of serum-specific immunoglobulin E and immunoglobulin G4 for a span of eight years in untreated patients with perennial allergic rhinitis. Laryngoscope 1997;107(3):382-5.

Ohashi Y, Nakai Y, Tanaka A, et al. Immunotherapy decreases seasonal rise in serum-soluble CD23 in seasonal allergic rhinitis. Laryngoscope 1998;108(5):706-11.

Ohashi Y, Nakai Y, Tanaka A, et al. Serologic study of the working mechanisms of immunotherapy for children with perennial allergic rhinitis. Arch Otolaryngol Head Neck Surg 1998;124(12):1337-46.

Ohashi Y, Tanaka A, Kakinoki Y, et al. Effect of immunotherapy on seasonal changes in serum-specific IgE and IgG4 in patients with pollen allergic rhinitis. Laryngoscope 1997;107(9):1270-5.

Ohashi Y, Tanaka A, Nakai Y. Decrease of serum levels of soluble CD23 during immunotherapy in patients with perennial allergic rhinitis. Ann Otol Rhinol Laryngol 1999;108(2 part 1):193-200.

Ohman Jr JL. Allergen immunotherapy: Review of efficacy and current practice. Med Clin North Am 1992;76(4):977-91.

Oldham G, Platts-Mills TA, Chalmers DM, et al. A quantitative method for measuring in vitro synthesis of IgA and IgG by human rectal mucosa: studies on normal controls and patients with hypogammaglobulinaemia. Immunology 1979;37(3):661-8.

Oliveira CAA, Sole D, Naspitz CK, et al. Improvement of bronchial hyperresponsiveness in asthmatic children treated for concomitant sinusitis. Ann Allergy Asthma Immunol 1997;79(1):70-4.

Olivieri M, Mohaddes Zadeh MR, Talamini G, et al. Local nasal immunotherapy and bronchial hyperreactivity in seasonal allergic rhinitis: an observational pilot study. J Investig Allergol Clin Immunol 2000;10(5):300-4.

Olsen OT, Frolund L, Heinig J, et al. A double-blind, randomized study investigating the efficacy and specificity of immunotherapy with Artemisia vulgaris or Phleum pratense/betula verrucosa. Allergol Immunopathol (Madr) 1995;23(2):73-8.

Omenaas E, Bakke P, Eide GE, et al. Serum house-dust-mite antibodies and reduced FEV1 in adults of a Norwegian community. Am J Respir Crit Care Med 1995;152(4 Pt 1):1158-63.

Omenaas E, Bakke P, Eide GE, et al. Serum house dust mite antibodies: predictor of increased bronchial responsiveness in adults of a community. Eur Respir J 1996;9(5):919-25.

Ortolani C, Pastorello EA, Incorvaia C, et al. A double-blind, placebo-controlled study of immunotherapy with an alginate-conjugated extract of Parietaria judaica in patients with Parietaria hay fever. Allergy 1994;49(1):13-21.

Orzano AJ, Eaton L, Cody RP. The otitis media repeater - A 9-year family practice experience with children and adults. Dis Manage Clin Outcomes 1998;1(6):218-23.

Osguthorpe JD. Turf battles diminish the credibility of all allergists. Ear Nose Throat J 1988;67(8):554, 556.

Osterballe O. Immunotherapy in hay fever with two major allergens 19, 25 and partially purified extract of timothy grass pollen. A controlled double blind study. In vivo variables, season I. Allergy 1980;35(6):473-89.

Osterballe O. Nasal and skin sensitivity during immunotherapy with two major allergens 19, 25 and partially purified extract of timothy grass pollen. Allergy 1982;37(3):169-77.

Osterballe O. Immunotherapy with grass pollen major allergens. Allergy 1982;37(6):379-88.

Osterballe O. Side effects during immunotherapy with purified grass pollen extracts. Allergy 1982;37(8):553-62.

Osterballe O, Egeskjold EM, Johansen AS, et al. Anti-IgG antibodies during immunotherapy with purified grass pollen extracts. Allergy 1982;37(3):209-16.

Osterballe O, Lowenstein H, Norn S, et al. Immunotherapy with grass pollen major allergens. Immunological results from a prospective 3-year double blind study. Allergy 1982;37(7):491-501.

Owen GO, Canter RJ, Robinson A. Snoring, apnoea and ENT symptoms in the paediatric community. Clin Otolaryngol Allied Sci 1996;21(2):130-4.
Owen S, Morganstern M, Hepworth J, et al. Control of house dust mite antigen in bedding. Lancet 1990;335(8686):396-7.

Owerbach J, Winters B, Villella W. Pharmacist selection of allergy medication based on patient response to trial regimens. Am J Hosp Pharm 1981;38(6):856-8.

Oxford Centre for Evidence-based Medicine. Levels of evidence. May 2001. Produced by Phillips B, Ball C, Sackett D, et al., since November 1998. Available at: http://163.1.96.10/docs/levels.html#levels. Accessed May 30, 2002.

Paddon D. Intranasal corticosteroids in allergic rhinitis. Paper did not include all data on adverse effects. BMJ 1999;318(7194):1350.

Paggiaro PL, Dente FL, Morelli MC, et al. Postallergen inhaled budesonide reduces late asthmatic response and inhibits the associated increase of airway responsiveness to methacholine in asthmatics. Am J Respir Crit Care Med 1994;149(6):1447-51.

Pajno GB, Morabito L, Barberio G, et al. Clinical and immunologic effects of long-term sublingual immunotherapy in asthmatic children sensitized to mites: a double-blind, placebo-controlled study. Allergy 2000;55(9):842-9.

Palczynski C, Walusiak J, Hanke W, et al. Natural rubber-latex immediate hypersensitivity in surgeons. A cross-sectional study. Int Rev Allergol Clin Immunol 2000;6(1):15-9.

Panda NK, Mann SB. Comparative efficacy and safety of terfenadine with pseudoephedrine and terfenadine alone in allergic rhinitis. Otolaryngol Head Neck Surg 1998;118(2):253-5.

Pariente PD, LePen C, Los F, et al. Quality-of-life outcomes and the use of antihistamines in a French national population-based sample of patients with perennial rhinitis. Pharmacoeconomics 1997;12(5):585-95.

Parikh A, Scadding GK. Seasonal allergic rhinitis. BMJ 1997;314:1392-5.

Parker WA, Whisman BA, Apaliski SJ, et al. The relationships between late cutaneous responses and specific antibody responses with outcome of immunotherapy for seasonal allergic rhinitis. J Allergy Clin Immunol 1989;84(5 Pt 1):667-77.

Passalacqua G, Albano M, Fregonese L, et al. Randomised controlled trial of local allergoid immunotherapy on allergic inflammation in mite-induced rhinoconjunctivitis. Lancet 1998;351(9103):629-32.

Passalacqua G, Albano M, Pronzato C, et al. Long-term follow-up of nasal immunotherapy to Parietaria: clinical and local immunological effects. Clin Exp Allergy 1997;27(8):904-8.

Passalacqua G, Albano M, Ruffoni S, et al. Nasal immunotherapy to Parietaria: evidence of reduction of local allergic inflammation. Am J Respir Crit Care Med 1995;152(2):461-6.

Passalacqua G, Canonica GW. Allergen-specific sublingual immunotherapy for respiratory allergy. Biodrugs 2001;15(8):509-19.

Passalacqua G, Venturi S, Zoccali P, et al. Oral and sublingual immunotherapy: General aspects and critical considerations. Wien Med Wochenschr 1999;149(14-15):433-7.

Pastorello EA, Ortolani C, Incorvaia C, et al. A double-blind study of hyposensitization with an alginate-conjugated extract of Dermatophagoides pteronyssinus (Conjuvac) in patients with perennial rhinitis. II. Immunological aspects. Allergy 1990;45(7):505-14.

Pastorello EA, Pravettoni V, Incorvaia C, et al. Clinical and immunological effects of immunotherapy with alum-absorbed grass allergoid in grass-pollen-induced hay fever. Allergy 1992;47(4 Pt 1):281-90.

Patchett K, Lewis S, Crane J, et al. Cat allergen (Fel d 1) levels on school children's clothing and in primary school classrooms in Wellington, New Zealand. J Allergy Clin Immunol 1997;100(6 Pt 1):755-9.

Patterson R. The role of immunotherapy in respiratory allergic diseases. J Allergy Clin Immunol 1998;101(2 II):S403-S404.

Patterson R, Harris KE, Grammer LC, et al. Potential effect of the administration of substance P and allergen therapy on immunoglobulin E-mediated allergic reactions in human subjects. J Lab Clin Med 1999;133(2):189-99.

Pauley TR, Magee MJ, Cury JD. Pharmacist-managed, physician-directed asthma management program reduces emergency department visits. Ann Pharmacother 1995;29(1):5-9.

Pawankar R. Anti-lgE treatment in allergic disease. Allergy Clin Immunol Int 2001;13(1):4-10.

Payton KB, Hebert J, Clarke KD. Assessing and treating rhinitis. A pratical guide for Canadian physicians. Can Med Assoc J 1994;151(4 Suppl):1-27.

Pearce N, Douwes J, Beasley R. Is allergen exposure the major primary cause of asthma? [Review]. Thorax 2000;55(5):424-31.

Peat JK, Tovey E, Gray EJ, et al. Asthma severity and morbidity in a population sample of Sydney schoolchildren: Part II--Importance of house dust mite allergens. Austral NZ J Med 1994;24(3):270-6.

Peat JK, Tovey E, Mellis CM, et al. Importance of house dust mite and Alternaria allergens in childhood asthma: an epidemiological study in two climatic regions of Australia. Clin Exp Allergy 1993;23(10):812-20.

Peat JK, Tovey E, Toelle BG, et al. House dust mite allergens. A major risk factor for childhood asthma in Australia. Am J Respir Crit Care Med 1996;153(1):141-6.

Peckham C, Butler N. A national study of asthma in childhood. J Epidemiol Community Health 1978;32(2):79-85.

Pecoud A, Nicod L, Badan M, et al. Effects of one-year hyposensitization in allergic rhinitis. Comparison of two house dust mite extracts. Allergy 1990;45(5):386-92.

Peden DB. The use of nasal lavage for objective measurement of irritant-induced nasal inflammation. Regul Toxicol Pharmacol 1996;24(1 II):S76-S78.

Peden DB, Setzer RW, Devlin RB. Ozone exposure has both a priming effect on allergen-induced responses and an intrinsic inflammatory action in the nasal airways of perennially allergic asthmatics. Am J Respir Crit Care Med 1995;151(5):1336-45.

Pedersen PA, Weeke ER. Allergic rhinitis in Danish general practice. Prevalence and consultation rates. Allergy 1981;36(6):375-9.

Pedersen PA, Weeke ER. Asthma and allergic rhinitis in the same patients. Allergy 1983;38(1):25-9.

Pedersen S. Introduction. J Allergy Clin Immunol 2001;108(1 Suppl):S1.

Pedinoff AJ. Approaches to the treatment of seasonal allergic rhinitis. South Med J 1996;89(12):1130-9.

Pegelow KO, Belin L, Broman P, et al. Immunotherapy with alginate-conjugated and alum-precipitated grass pollen extracts in patients with allergic rhinoconjunctivitis. Allergy 1984;39(4):275-90.

Peggs JF, Shimp LA, Opdycke RAC. Antihistamines: The old and the new. Am Fam Phys 1995;52(2):593-600.

Pelikan Z, de Vries K. Effects of some drugs applied topically to the nasal mucosa before nasal provocation tests with allergen. Acta Allergol 1974;29(5):337-53.

Pence HL, Mitchell DQ, Greely RL, et al. Immunotherapy for mountain cedar pollinosis. A double-blind controlled study. J Allergy Clin Immunol 1976;58(1 Pt 1):39-50.

Peng ZK, Naclerio RM, Norman PS, et al. Quantitative IgE- and IgG-subclass responses during and after long-term ragweed immunotherapy. J Allergy Clin Immunol 1992;89(2):519-29.

Peroni DG, Piacentini GL, Martinati LC, et al. Double-blind trial of house-dust mite immunotherapy in asthmatic children resident at high altitude. Allergy 1995;50(11):925-30.

Persi L, Demoly P, Harris AG, et al. Comparison between nasal provocation tests and skin tests in patients treated with loratadine and cetirizine. J Allergy Clin Immunol 1999;103(4):591-4.

Persky V, Coover L, Hernandez E, et al. Chicago community-based asthma intervention trial: feasibility of delivering peer education in an inner-city population. Chest 1999;116(4 Suppl 1):216S-23S.

Perzanowski MS, Ronmark E, Nold B, et al. Relevance of allergens from cats and dogs to asthma in the northernmost province of Sweden: schools as a major site of exposure. J Allergy Clin Immunol 1999;103(6):1018-24.

Perzanowski MS, Sporik R, Squillace SP, et al. Association of sensitization to Alternaria allergens with asthma among school-age children. J Allergy Clin Immunol 1998;101(5):626-32.

Pescollderungg L, Peroni D, Locatelli F, et al. Determination of serum eosinophil cationic protein, eosinophil count, and total IgE in children with different severities of atopic diseases. Pediatr Asthma Allergy Immunol 2000;14(2):109-18.

Petersson G. Allergy practice and the otolaryngologist. Curr Opin Otolaryngol Head Neck Surg 1995;3(3):218-23.

Philip G, Togias A. Allergic rhinitis: up-to-date strategies for management. J Respir Dis 1999;20(9):580-2, 585-8.

Philip G, Togias AG. Allergic rhinitis: today's approach to treatment. J Respir Dis 1995;16(4):367-72.

Piacentini GL, Peroni DG, Sette L, et al. Inhibition of different dosages of oxatomide or placebo on skin prick test and nasal allergen provocation. J Allergy Clin Immunol 1991;88(2):218-25.

Pichler CE, Helbling A, Pichler WJ. Three years of specific immunotherapy with house-dust-mite extracts in patients with rhinitis and asthma: significant improvement of allergen-specific parameters and of nonspecific bronchial hyperreactivity. Allergy 2001;56(4):301-6.

Pichler CE, Marquardsen A, Sparholt S, et al. Specific immunotherapy with Dermatophagoides pteronyssinus and D. farinae results in decreased bronchial hyperreactivity. Allergy 1997;52(3):274-83.

Pickard BH. Nasal disease in relation to fitness of a pilot. Aviat Space Environ Med 1984;55(5):429-30.

Pieckova E, Jesenska Z. Microscopic fungi in dwellings and their health implications in humans. Ann Agric Environ Med 1999;6(1):1-11.

Pien LC. The role of allergy evaluation and immunotherapy in asthma. Clin Pulm Med 1995;2(3):165-71.

Pigatto PD, Bigardi AS, Valsecchi RH, et al. Mite patch testing in atopic eczema: a search for correct concentration. Australasian J Dermatol 1997;38(4):231-2.

Pirhonen I, Nevalainen A, Husman T, et al. Home dampness, moulds and their influence on respiratory infections and symptoms in adults in Finland. Eur Respir J 1996;9(12):2618-22.

Pitten FA, Scholler M, Kruger U, et al. Filamentous fungi and yeasts on mattresses covered with different encasings. Eur J Dermatol 2001;11(6):534-7.

Pizzi LT, Biskupiak JE. Patient compliance and its impact on treatment outcomes. Dis Manage Health Outcomes 1999;6(5):269-78.

Platts-Mills TA. Allergens and asthma. [Review]. Allergy Proc 1990;11(6):269-71.

Platts-Mills TA, Chapman MD. Dust mites: immunology, allergic disease, and environmental control. [erratum appears in J Allergy Clin Immunol 1988 Nov;82(5 Pt 1):841.]. [Review]. J Allergy Clin Immunol 1987;80(6):755-75.

Platts-Mills TA, Chapman MD, Marsh DG. Human immunoglobulin E and immunoglobulin G antibody responses to the "minor" ragweed allergen Ra3: correlation with skin tests and comparison with other allergens. J Allergy Clin Immunol 1981;67(2):129-34.

Platts-Mills TA, Chapman MD, Wheatly LM. Control of house dust mite in managing asthma. Conclusions of meta-analysis are wrong. BMJ 1999;318(7187):870-1.

Platts-Mills TA, Fiocco GP, Hayden ML, et al. Serum IgE antibodies to Trichophyton in patients with urticaria, angioedema, asthma, and rhinitis: development of a radioallergosorbent test. J Allergy Clin Immunol 1987;79(1):40-5.

Platts-Mills TA, Mueller GA, Wheatley LM. Future directions for allergen immunotherapy. [Review]. J Allergy Clin Immunol 1998;102(3):335-43.

Platts-Mills TA, Rawle F, Chapman MD. Problems in allergen standardization. [Review]. Clin Rev Allergy 1985;3(3):271-90.

Platts-Mills TA, Sporik R, Ingram JM, et al. Dog and cat allergens and asthma among school children in Los Alamos, New Mexico, USA: altitude 7,200 feet. Int Arch Allergy Immunol 1995;107(1-3):301-3.

Platts-Mills TA, Sporik RB, Chapman MD, et al. The role of domestic allergens. [Review]. Ciba Found Symp 1997;206:173-89.

Platts-Mills TA, Sullivan TJ, Kaliner MA. Allergy versus asthma as the focus of the subspecialty. J Allergy Clin Immunol 1996;97(3):865-8.

Platts-Mills TA, Vaughan JW, Carter MC, et al. The role of intervention in established allergy: avoidance of indoor allergens in the treatment of chronic allergic disease. J Allergy Clin Immunol 2000;106(5):787-804.

Platts-Mills TA, Woodfolk JA, Chapman MD, et al. Changing concepts of allergic disease: the attempt to keep up with real changes in lifestyles. [Review]. J Allergy Clin Immunol 1996;98(6 Pt 3):S297-306.

Plavec D, Somogyi-Zalud E, Godnic-Cvar J. Nonspecific nasal responsiveness in workers occupationally exposed to respiratory irritants. Am J Ind Med 1993;24(5):525-32.

Plosker GL, Faulds D. Troglitazone: A review of its use in the management of type 2 diabetes mellitus. Drugs 1999;57(3):409-38.

Pollart S, Chapman MD, Platts-Mills TA. House dust mite and dust control. [Review]. Clin Rev Allergy 1988;6(1):23-33.

Pollart SM, Chapman MD, Fiocco GP, et al. Epidemiology of acute asthma: IgE antibodies to common inhalant allergens as a risk factor for emergency room visits. J Allergy Clin Immunol 1989;83(5):875-82.

Pollart SM, Chapman MD, Platts-Mills TA. House dust sensitivity and environmental control. [Review]. Prim Care 1987;14(3):591-603.

Pollart SM, Mullins DE, Vailes LD, et al. Identification, quantitation, and purification of cockroach allergens using monoclonal antibodies. J Allergy Clin Immunol 1991;87(2):511-21.

Pollart SM, Reid MJ, Fling JA, et al. Epidemiology of emergency room asthma in northern California: association with IgE antibody to ryegrass pollen. J Allergy Clin Immunol 1988;82(2):224-30.

Pollart SM, Smith TF, Morris EC, et al. Environmental exposure to cockroach allergens: analysis with monoclonal antibody-based enzyme immunoassays. J Allergy Clin Immunol 1991;87(2):505-10.

Ponsonby AL, Glasgow N, Gatenby P, et al. The relationship between low level nitrogen dioxide exposure and child lung function after cold air challenge. Clin Exp Allergy 2001;31(8):1205-12.

Por CP, Evans MF. Effective treatment for ragweed allergy: Nasal puffers or antihistamines? Can Fam Phys 1998;44:1625-6.

Pordy RC. Cilazapril plus hydrochlorothiazide: Improved efficacy without reduced safety in mild to moderate hypertension: A double-blind placebo-controlled multicenter study of factorial design. Cardiology 1994;85(5):311-22.

Porst H, Rosen R, Padma-Nathan H, et al. The efficacy and tolerability of vardenafil, a new, oral, selective phosphodiesterase type 5 inhibitor, in patients with erectile dysfunction: The first at-home clinical trial. Int J Impotence Res 2001;13(4):192-9.

Portnoy JM. Immunotherapy for inhalant allergies: Guidelines for why, when, and how to use this treatment. Postgrad Med 2001;109(5):89-106.

Posey WC, Nelson HS. Controlled trials with four per cent cromolyn spray in seasonal allergic rhinitis. Clin Allergy 1977;7(5):485-96.

Pradalier A, Basset D, Claudel A, et al. Sublingual-swallow immunotherapy (SLIT) with a standardized five-grass-pollen extract (drops and sublingual tablets) versus placebo in seasonal rhinitis. Allergy 1999;54(8):819-28.

Prasanna A, Murthy PSN. Vasomotor rhinitis and sphenopalatine ganglion block. J Pain Symptom Management 1997;13(6):332-8.

Pratt CM, Mason J, Russell T, et al. Cardiovascular safety of fexofenadine HCl. Am J Cardiol 1999;83(10):1451-4.

Prescott LM. Highlights of the 96th Annual Meeting of the American Society of Clinical Pharmacology and Therapeutics. P T 1995;20(7):492-4.

Prevost M, Turenne Y, Moote DW, et al. Comparative study of SCH 434 and CTM-D in the treatment of seasonal allergic rhinitis. Clin Ther 1994;16(1):50-6.

Puchner Jr TC, Fink JN. Occupational rhinitis. Immunol Allergy Clin North Am 2000;20(2):303-22.

Pullerits T, Praks L, Ristioja V, et al. Comparison of a nasal glucocorticoid, antileukotriene, and a combination of antileukotriene and antihistamine in the treatment of seasonal allergic rhinitis. J Allergy Clin Immunol 2002;109(6):949-55.

Pullerits T, Praks L, Sjostrand M, et al. An intranasal glucocorticoid inhibits the increase of specific IgE initiated during birch pollen season. J Allergy Clin Immunol 1997;100(5):601-5.

Pullerits T, Praks L, Skoogh BE, et al. Randomized placebo-controlled study comparing a leukotriene receptor antagonist and a nasal glucocorticoid in seasonal allergic rhinitis. Am J Respir Crit Care Med 1999;159(6):1814-8.

Purello-D'Ambrosio F, Gangemi S, Isola S, et al. Sublingual immunotherapy: a double-blind, placebo-controlled trial with Parietaria judaica extract standardized in mass units in patients with rhinoconjunctivitis, asthma, or both. Allergy 1999;54(9):968-73.

Purello-D'Ambrosio F, Gangemi S, Merendino RA, et al. Comparative study between fluticasone propionate and cetirizine in the treatment of allergic rhinitis. Allergol Immunopathol 1998;26(6):277-82.

Purello-D'Ambrosio F, Isola S, Ricciardi L, et al. A controlled study on the effectiveness of loratadine in combination with flunisolide in the treatment of nonallergic rhinitis with eosinophilia (NARES). Clin Exp Allergy 1999;29(8):1143-7.

Purello-D'Ambrosio F, Ricciardi L, Isola S, et al. Rush sublingual immunotherapy in Parietaria allergic patients. [erratum appears in Allergol Immunopathol (Madr) 1996 Nov-Dec;24(6):262]. Allergol Immunopathol (Madr) 1996;24(4):146-51.

Purello DF, Tigano F, Gallesio MT, et al. Astemizole-D compared with triprolidine-D (Actifed(R)) for acute treatment of perennial allergic rhinitis. J Pharm Med 1994;4(1):15-22.

Purohit A, Duvernelle C, Melac M, et al. Twenty-four hours of activity of cetirizine and fexofenadine in the skin. Ann Allergy Asthma Immunol 2001;86(4):387-92.

Quirce S, Gomez M, Bombin C, et al. Glutaraldehyde-induced asthma. Allergy Eur J Allergy Clin Immunol 1999;54(10):1121-2.

Rachelefsky GS. National guidelines needed to manage rhinitis and prevent complications. Ann Allergy Asthma Immunol 1999;82(3):296-305.

Radcliffe MJ, Lampe FC, Brostoff J. Allergen-specific low-dose immunotherapy in perennial allergic rhinitis: a double-blind placebo-controlled crossover study. J Investig Allergol Clin Immunol 1996;6(4):242-7.

Radenne F, Lamblin C, Vandezande LM, et al. Quality of life in nasal polyposis. J Allergy Clin Immunol 1999;104(1):79-84.

Radon K, Schottky A, Garz S, et al. Distribution of dust-mite allergens (Lep d 2, Der p 1, Der f 1, Der 2) in pig-farming environments and sensitization of the respective farmers. Allergy Eur J Allergy Clin Immunol 2000;55(3):219-25.

Ragusa FV, Passalacqua G, Gambardella R, et al. Nonfatal systemic reactions to subcutaneous immunotherapy: a 10-year experience. J Investig Allergol Clin Immunol 1997;7(3):151-4.

Rajakulasingam K, Polosa R, Lau LC, et al. The influence of terfenadine and ipratropium bromide alone and in combination on bradykinin-induced nasal symptoms and plasma protein leakage. Clin Exp Allergy 1992;22(7):717-23.

Rak S, Hakanson L, Venge P. Immunotherapy abrogates the generation of eosinophil and neutrophil chemotactic activity during pollen season. J Allergy Clin Immunol 1990;86(5):706-13.

Rak S, Heinrich C, Jacobsen L, et al. A double-blinded, comparative study of the effects of short preseason specific immunotherapy and topical steroids in patients with allergic rhinoconjunctivitis and asthma. J Allergy Clin Immunol 2001;108(6):921-8.

Rakes GP, Arruda E, Ingram JM, et al. Rhinovirus and respiratory syncytial virus in wheezing children requiring emergency care. IgE and eosinophil analyses. Am J Respir Crit Care Med 1999;159(3):785-90.

Ratner PH, Findlay SR, Hampel Jr F, et al. A double-blind, controlled trial to assess the safety and efficacy of azelastine nasal spray in seasonal allergic rhinitis. J Allergy Clin Immunol 1994;94(5):818-25.

Ratner PH, van Bavel JH, Martin BG, et al. A comparison of the efficacy of fluticasone propionate aqueous nasal spray and loratadine, alone and in combination, for the treatment of seasonal allergic rhinitis. J Fam Pract 1998;47(2):118-25.

Raulf-Heimsoth M, Wirtz C, Papenfuss F, et al. Nasal lavage mediator profile and cellular composition of nasal brushing material during latex challenge tests. Clin Exp Allergy 2000;30(1):110-21.

Rawle FC, Mitchell EB, Platts-Mills TA. T cell responses to the major allergen from the house dust mite Dermatophagoides pteronyssinus, Antigen P1: comparison of patients with asthma, atopic dermatitis, and perennial rhinitis. J Immunol 1984;133(1):195-201.

Ray NF, Baraniuk JN, Thamer M, et al. Direct expenditures for the treatment of allergic rhinoconjunctivitis in 1996, including the contributions of related airway illnesses. J Allergy Clin Immunol 1999;103(3 Pt 1):401-7.

Ray NF, Baraniuk JN, Thamer M, et al. Healthcare expenditures for sinusitis in 1996: contributions of asthma, rhinitis, and other airway disorders. J Allergy Clin Immunol 1999;103(3 Pt 1):408-14.

Rebmann H, Weber AK, Focke I, et al. Does benzyl benzoate prevent colonization of new mattresses by mites? A prospective study. Allergy 1996;51(12):876-82.

Reed CE. Measurement of airborne antigens. J Allergy Clin Immunol 1982;70(1):38-40.

Reed CE. Introduction: New insights into allergic rhinitis: Quality of life, associated airway diseases, and antihistamine potency. J Allergy Clin Immunol 1997;99(2):S740-S741.

Reichenberg K, Broberg AG. Quality of life in childhood asthma: Use of the paediatric asthma quality of life questionnaire in a swedish sample of children 7 to 9 years old. Acta Paediatr 2000;89(8):989-95.

Reichmuth D. Allergic rhinitis. Drugs Today 2001;37(5):283-309.

Reid MJ. Complicating features of asthma. Pediatr Clin North Am 1992;39(6):1327-42.

Reid MJ, Moss RB, Hsu YP, et al. Seasonal asthma in northern California: allergic causes and efficacy of immunotherapy. J Allergy Clin Immunol 1986;78(4 Pt 1):590-600.

Reilly D, Taylor MA, Beattie NG, et al. Is evidence for homoeopathy reproducible? Lancet 1994;344(8937):1601-6.

Reilly MC, Tanner A, Meltzer EO. Work, classroom and activity impairment instruments: validation studies in allergic rhinitis. Clin Drug Invest 1996;11:278-88.

Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. Pharmacoeconomics 1993;4(5):353-65.

Reinstein JA. Self-medication: Editorial. Int Pharm. J 1999;13(1):2-3.

Reisacher WR, Finn DG, Stern J, et al. Manifestations of AIDS in the head and neck. South Med J 1999;92(7):684-97.

Reiser J, Ingram D, Mitchell EB, et al. House dust mite allergen levels and an anti-mite mattress spray (natamycin) in the treatment of childhood asthma. Clin Exp Allergy 1990;20(5):561-7.

Reisman RE. Allergic rhinitis: update on your therapeutic choices. Consultant 1996;36(9):1899-901, 1905-6.

Reisman RE, Mauriello PM, Davis GB, et al. A double-blind study of the effectiveness of a high-efficiency particulate air (HEPA) filter in the treatment of patients with perennial allergic rhinitis and asthma. J Allergy Clin Immunol 1990;85(6):1050-7.

Retailliau HF, Storch GA, Curtis AC, et al. The epidemiology of influenza B in a rural setting in 1977. Am J Epidemiol 1979;109(6):639-49.

Retzow A, Althaus M, DeMey C, et al. Study on the interaction of the dopamine agonist alpha-dihydroergocryptine with the pharmacokinetics of digoxin. Arzneim.-Forsch Drug Res 2000;50(7):591-6.

Revicki DA, Leidy NK, Brennan-Diemer F, et al. Development and preliminary validation of the multiattribute Rhinitis Symptom Utility Index. Qual Life Res 1998;7(8):693-702.

Rheinstein PH. Significant FDA approvals in 1994. Am Fam Phys 1995;51(4):888-90.

Ricard N, Kind P, Christian S, et al. Link between patient preferences and treatment outcomes in seasonal allergic rhinitis: an empiric investigation. Clin Ther 1999;21(1):268-77.

Ricard N, Sauriol L, Christian S. The effect of seasonal allergic rhinitis in children on caregivers' lives: A pilot study. Pediatr Asthma Allergy Immunol 2000;14(2):119-24.

Ricci G, Patrizi A, Specchia F, et al. Effect of house dust mite avoidance measures in children with atopic dermatitis. Br J Dermatol 2000;143(2):379-84.

Rice DH. Endoscopic sinus surgery. Otolaryngol Head Neck Surg 1994;111(1):100-10.

Richards S, Thornhill D, Roberts H, et al. How many people think they have hay fever, and what they do about it. Br J Gen Pract 1992;42(360):284-6.

Risby E, Donnigan D, Nemeroff CB. Formulary considerations for treating psychiatric disorders: Schizophrenia. Formulary 1997;32(2):142-55.

Rischitelli DG. A workers' compensation primer. Ann Allergy Asthma Immunol 1999;83(6 II):614-7.

Rizzo MC, Arruda LK, Chapman MD, et al. IgG and IgE antibody responses to dust mite allergens among children with asthma in Brazil. Ann Allergy 1993;71(2):152-8.

Roberts J. Examination and health history findings among children and youths, 6-17 years, United States. Vital Health Stat 1973;Ser.11(129):71 p.

Robertson AS, Burge PS, Hedge A, et al. Comparison of health problems related to work and environmental measurements in two office buildings with different ventilation systems. Br Med J Clin Res Ed 1985;291(6492):373-6.

Robertson AS, Sherwood BP. Building sickness. Practitioner 1985;229(1404):531-4.

Robinson DS. Allergen immunotherapy: Does it work and, if so, how and for how long? Thorax 2000;55(Suppl 1):S11-S14.

Rodriguez A, Trujillo MJ, Herrero T, et al. Allergy to calcitonin. Allergy Eur J Allergy Clin Immunol 2001;56(8):801.

Ronborg SM, Mosbech H, Johnsen CR, et al. Exposure chamber for allergen challenge. The development and validation of a new concept. Allergy 1996;51(2):82-8.

Ronborg SM, Mosbech H, Poulsen LK. Exposure chamber for allergen challenge. A placebo-controlled, double-blind trial in house-dust-mite asthma. Allergy 1997;52(8):821-8.

Ronborg SM, Poulsen LK, Skov PS, et al. Effect of two different types of vacuum cleaners on airborne Fel d 1 levels. Ann Allergy Asthma Immunol 1999;82(3):307-10.

Rooklin AR, Gawchik SM. Allergic rhinitis -- it's that time again! Contemp Pediatr 1994;11(4):19-20, 23-6, 28 passim.

Root TS, Quan DJ. Histamineinf 2-receptor antagonists do not prevent allergic reactions. J Pharm Technol 1994;10(2):58-60.

Roquet A, Raud J, Hallden G, et al. Effects of loratadine on anti-IgE-induced inflammation, histamine release, and leukocyte recruitment in skin of atopics. Allergy 1995;50(5):414-20.

Rose C. Bioaerosols. West J Med 1994;160(6):566.

Rose G, Arlian L, Bernstein D, et al. Evaluation of household dust mite exposure and levels of specific IgE and IgG antibodies in asthmatic patients enrolled in a trial of immunotherapy. J Allergy Clin Immunol 1996;97(5):1071-8.

Rosenfeld RM. Pilot study of outcomes in pediatric rhinosinusitis. Arch Otolaryngol Head Neck Surg 1995;121(7):729-36.

Ross AM, Corden JM, Fleming DM. The role of oak pollen in hay fever consultations in general practice and the factors influencing patients' decisions to consult. Br J Gen Pract 1996;46(409):451-5.

Ross AM, Fleming DM. Incidence of allergic rhinitis in general practice, 1981-92. BMJ 1994;308(6933):897-900.

Ross RN. The costs of allergic rhinitis. Am J Manag Care 1996;2:285-90.

Ross RN, Nelson HS, Finegold I. Effectiveness of specific immunotherapy in the treatment of allergic rhinitis: an analysis of randomized, prospective, single- or double-blind, placebo-controlled studies. Clin Ther 2000;22(3):342-50.

Rossetti L, Barbieri P, Velati P, et al. The efficacy of the combination of I-moprolol and dipivefrin in reducing the intraocular pressure in primary open-angle glaucoma or in ocular hypertension. Graefe's Arch Clin Exp Ophthalmol 1994;232(11):670-4.

Rossoff LJ, Stempel DA. Cost-effective treatment of rhinitis: a managed care perspective. Am J Manag Care 1997;3(Suppl 1):S1-28.

Rowley JA, Safwan BM. Obstructive sleep apnea: The latest treatment strategies. J Respir Dis 2000;21(9):577-80.

Rowntree S, Cogswell JJ, Platts-Mills TA, et al. Development of IgE and IgG antibodies to food and inhalant allergens in children at risk of allergic disease. Arch Dis Child 1985;60(8):727-35.

Rowntree S, Mitchell EB, Platts-Mills TA. Assessment of skin reactivity and specific antibody to egg and milk proteins in patients with atopic dermatitis: comparison with responses to the house dust mite antigen. Int Arch Allergy Appl Immunol 1986;79(2):132-9.

Rowntree S, Platts-Mills TA, Cogswell JJ, et al. A subclass IgG4-specific antigen-binding radioimmunoassay (RIA): comparison between IgG and IgG4 antibodies to food and inhaled antigens in adult atopic dermatitis after desensitization treatment and during development of antibody responses in children. J Allergy Clin Immunol 1987;80(4):622-30.

Royal College of Physicians, Royal College of Pathologists. Good allergy practice--standards of care for providers and purchasers of allergy services within the National Health Service. Clin Exp Allergy 1995;25(7):586-95.

Rutishauser M, Pitzke P, Grevers G, et al. Use of a polyvalent bacterial lysate in patients with recurrent respiratory tract infections: Results of a prospective, placebo-controlled, randomized, double-blind study. Adv Ther 1998;15(6):330-41.

Ryan D, Cross S. Rhinitis and allergy. Asthma Gen Pract 2000;9(2 Suppl):S24-S26.

Sabbah A, Hassoun S, Le Sellin J, et al. A double-blind, placebo-controlled trial by the sublingual route of immunotherapy with a standardized grass pollen extract. Allergy 1994;49(5):309-13.

Salmun LM, Gates D, Scharf M, et al. Loratadine versus cetirizine: assessment of somnolence and motivation during the workday. Clin Ther 2000;22(5):573-82.

Santilli J, Nathan R, Glassheim J, et al. Patients receiving immunotherapy report it is effective as assessed by the rhinitis outcomes questionnaire (ROQ) in a private practice setting. Ann Allergy Asthma Immunol 2001;86(2):219-21.

Santilli J, Nathan R, Glassheim J, et al. Validation of the rhinitis outcomes questionnaire (ROQ). Ann Allergy Asthma Immunol 2001;86(2):222-5.

Santoni P, Perdona B, Read BH. Seasonal allergic rhinitis. Practitioner 1984;228(1391):460, 462.

Santos R, Cifaldi M, Gregory C, et al. Economic outcomes of a targeted intervention program: the costs of treating allergic rhinitis patients. Am J Manag Care 1999;5(4 Suppl):S225-34.

Sapci T, Karavus A, Onmus H, et al. Impression cytology (IC) in clinical practice. Marmara Med J 2000;13(2):75-81.

Saraclar Y, Sekerel BE, Kalayci O, et al. The effect of house dust mite specific immunotherapy on cysteinyl leukotriene production by blood leukocytes in subjects with perennial allergic rhinitis and asthma. J Investig Allergol Clin Immunol 1998;8(2):98-104.

Scadding G. Diagnosis and management of rhinitis. CPD Bull Immunol Allergy 2000;1(2):42-6.

Scadding GK. Could treating asthma help rhinitis? [Review]. Clin Exp Allergy 1997;27(12):1387-93.

Scadding GK. Treating asthma: Don't forget the nose. Can J Allergy Clin Immunol 1999;4(5):238-43.

Scadding GK, Richards DH, Price MJ. Patient and physician perspectives on the impact and management of perennial and seasonal allergic rhinitis. Clin Otolaryngol Allied Sci 2000;25(6):551-7.

Scalabrin DM, Bavbek S, Perzanowski MS, et al. Use of specific IgE in assessing the relevance of fungal and dust mite allergens to atopic dermatitis: a comparison with asthmatic and nonasthmatic control subjects. J Allergy Clin Immunol 1999;104(6):1273-9.

Schädlich PK, Brecht JG. Economic evaluation of specific immunotherapy versus symptomatic treatment of allergic rhinitis in Germany. Pharmacoeconomics 2000;17:37-52.

Schafheutle EI, Cantrill JA, Nicolson M, et al. Insights into the choice between self-medication and a doctor's prescription: A study of hay fever sufferers. Int J Pharm Pract 1996;4(3):156-61.

Schapowal A, on behalf of the Petasites Study Group. Randomized controlled trial of butterbur and cetirizine for treating seasonal allergic rhinitis. BMJ 2002;324:1-4.

Scherger JE. The spectrum of upper respiratory infections in family practice. Semin Fam Med 1982;3(4):168-73.

Schmidt A, Adam SA, Kolloch R, et al. Antihypertensive effects of valsartan/hydrochlorothiazide combination in essential hypertension. Blood Press 2001;10(4):230-7.

Schmidt BMW, Kusma M, Feuring M, et al. The phosphodiesterase 4 inhibitor roflumilast is effective in the treatment of allergic rhinitis. J Allergy Clin Immunol 2001;108(4):530-6.

Schmidt J, Zalewski P, Olszewski J, et al. Histopathological verification of clinical indications to partial inferior turbinectomy. Rhinology 2001;39(3):147-50.

Schneider LC, Lester MR. Atopic disease, rhinitis and conjunctivitis, and upper respiratory infections. [Review]. Curr Opin Pediatr 1998;10(5):539-47.

Schnitzer T, Morton C, Coker S. Topical capsaicin therapy for osteoarthritis pain: Achieving a maintenance regimen. Semin Arthritis Rheum 1994;23(Suppl 3):34-40.

Schofield M, Fleming S. Go with the flow - A review of the respiratory therapeutic area. Emerg Drugs 2000;5(2):123-33.

Schwab IR. Nonsteroidal eye drops for ocular allergy. West J Med 1994;161(6):594-5.

Schwartz R, Freij BJ, Ziai M, et al. Antimicrobial prescribing for acute purulent rhinitis in children: A survey of pediatricians and family practitioners. Pediatr Infect Dis J 1997;16(2):185-90.

Sears MR, Jones DT, Silva PA, et al. Asthma in seven year old children: a report from the Dunedin Multidisciplinary Child Development Study. N Z Med J 1982;95(713):533-6.

Segura T, Casale TB. Allergic rhinitis: Basic pathophysiology and therapeutic strategies. Can J Allergy Clin Immunol 1999;4(7):318-30.

Self T, Chafin CC. Drug therapy of allergic rhinitis. Am J Manag Care 1999;5(9):1191-200.

Seltzer JM. Building-related illnesses. J Allergy Clin Immunol 1994;94(2 II Suppl):351-62.

Senior BA, Glaze C, Benninger MS. Use of the Rhinosinusitis Disability Index (RSDI) in rhinologic disease. Am J Rhinol 2001;15(1):15-20.

Sensi LG, Seri A, Siracusa A, et al. Allergic rhinitis in children: effects of flunisolide and disodium cromoglycate on nasal eosinophil cationic protein. Clin Exp Allergy 1997;27(3):270-6.

Seppey M, Hausler R, Bruchez M, et al. Facial thermograpy - An assessment of cetirizine effects upon nasal provocation in rhinitis. Allergy Clin Immunol Int 2000;12(5):232-9.

Serra HA, Alves O, Rizzo LF, et al. Loratadine-pseudoephedrine in children with allergic rhinitis, a controlled double-blind trial. Br J Clin Pharmacol 1998;45(2):147-50.

Sette L, Comis A, Marcucci F, et al. Benzyl-benzoate foam: effects on mite allergens in mattress, serum and nasal secretory IgE to Dermatophagoides pteronyssinus, and bronchial hyperreactivity in children with allergic asthma. Pediatr Pulmonol 1994;18(4):218-27.

Settipane GA. Allergic rhinitis--update. Otolaryngol Head Neck Surg 1986;94(4):470-5.

Settipane RA. Complications of allergic rhinitis. [Review]. Allergy Asthma Proc 1999;20(4):209-13.

Settipane RJ, Hagy GW, Settipane GA. Long-term risk factors for developing asthma and allergic rhinitis: a 23-year follow-up study of college students. [Review]. Allergy Proc 1994;15(1):21-5.

Shahar E, Lorber M. Prevalence of self-reported allergic conditions in an adult population in Israel. Isr Med Assoc J 2001;3(3):190-3.

Shaikh WA. Ephedrine-saline nasal wash in allergic rhinitis. J Allergy Clin Immunol 1995;96(5 Pt 1):597-600.

Shapiro GG, Wighton TG, Chinn T, et al. House dust mite avoidance for children with asthma in homes of low-income families. J Allergy Clin Immunol 1999;103(6):1069-74.

Sharkey P, Portnoy J. Rush immunotherapy: experience with a one-day schedule. Ann Allergy Asthma Immunol 1996;76(2):175-80.

Sheikh A, Hurwitz B. House dust mite avoidance measures for perennial allergic rhinitis (Cochrane Review). In: The Cochrane Library, Issue 1, 2002. Oxford: Update Software.

Shibasaki M, Noguchi E, Takeda K, et al. Distribution of IgE and IgG antibody levels against house dust mites in schoolchildren, and their relation with asthma. J Asthma 1997;34(3):235-42.

Shirtcliffe PM, Easthope SE, Cheng S, et al. The effect of delipidated deglycolipidated (DDMV) and heat-killed Mycobacterium vaccae in asthma. Am J Respir Crit Care Med 2001;163(6):1410-4.

Shusterman D, Murphy MA, Balmes J. The influence of sex, allergic rhinitis, and test system on nasal sensitivity to airborne irritants: a pilot study. Environ Health Perspectives 2001;109(1):15-9.

Sibbald B, Kerry S, Strachan DP, et al. Patient characteristics associated with the labelling of asthma. Fam Pract 1994;11(2):127-32.

Sibbald B, Rink E. Labelling of rhinitis and hayfever by doctors. Thorax 1991;46(5):378-81.

Sienra-Monge JJ, Gazca-Aguilar A, Del Rio-Navarro B. Double-blind comparison of cetirizine and loratadine in children ages 2 to 6 years with perennial allergic rhinitis. Am J Ther 1999;6(3):149-55.

Sih T. News from the Interamerican Association of Pediatric Otorhinolaryngology II IAPO's Congress, Sao Paulo, Brazil, September 1997 presidential address: On pollution. Int J Pediatr Otorhinolaryngol 1998;44(2):193-4.

Silva AL, Silva AB, Stankiewicz JA. Nasal obstruction in pregnancy. Prim Care Update Ob Gyns 1995;2(1):37-44.

Silverman M, Turner-Warwick M. Exercise induced asthma: response to disodium cromoglycate in skin-test positive and skin-test negative subjects. Clin Allergy 1972;2(2):137-42.

Silverman SL. Calcitonin. Am J Med Sci 1997;313(1):13-6.

Silvers WS. The skier's nose: a model of cold-induced rhinorrhea. Ann Allergy 1991;67(1):32-6.

Sim TC, Reece LM, Hilsmeier KA, et al. Secretion of chemokines and other cytokines in allergen-induced nasal responses: Inhibition by topical steroid treatment. Am J Respir Crit Care Med 1995;152(3):927-33.

Simola M, Boss I, Holopainen E, et al. Astemizole in combination with pseudoephedrine in the treatment of seasonal allergic rhinitis. Rhinology 1996;34(1):21-3.

Simons FE. Learning impairment and allergic rhinitis. [Review]. Allergy Asthma Proc 1996;17(4):185-9.

Simons FE. The eternal triangle: benefit, risk, and cost of therapeutic agents. [Review]. Ann Allergy Asthma Immunol 1996;77(5):337-40.

Simons FE, Imada M, Li Y, et al. Fel d 1 peptides: effect on skin tests and cytokine synthesis in cat-allergic human subjects. Int Immunol 1996;8(12):1937-45.

Simons FER. The eternal triangle: Benefit, risk, and cost of therapeutic agents. Ann Allergy Asthma Immunol 1996;77(5):337-40.

Simpson K, Jarvis B. Fexofenadine: review of its use in the management of seasonal allergic rhinitis and chronic idiopathic urticaria. Drugs 2000;59:301-21.

Simpson RJ. Budesonide and terfenadine, separately and in combination, in the treatment of hay fever. Ann Allergy 1994;73(6):497-502.

Sin A, Kose S, Terzioglu E, et al. Prevalence of atopy in young healthy population, in Izmir, Turkey. Allergol Immunopathol 1997;25(2):80-4.

Singh S. Preparing your practice for the influenza season. Patient Care 2001;35(17):18-21, 25-6, 28 passim.

Sjostedt L, Willers S, Orbaek P, et al. A seven-year follow-up study of lung function and methacholine responsiveness in sensitized and non-sensitized workers handling laboratory animals. J Occup Environ Med 1998;40(2):118-24.

Skoner DP. Control of allergic rhinitis with antihistamines may prevent the onset or recurrence of otitis media. Pediatr Asthma Allergy Immunol 1997;11(4):193-205.

Skoner DP. Allergic rhinitis: definition, epidemiology, pathophysiology, detection, and diagnosis. [Review]. J Allergy Clin Immunol 2001;108(1 Suppl):S2-8.

Skoner DP, Doyle WJ, Boehm S, et al. Effect of terfenadine on nasal, eustachian tube, and pulmonary function after provocative intranasal histamine challenge. Ann Allergy 1991;67(6):619-24.

Skoner DP, Hodgson MJ, Doyle WJ. Laser-printer rhinitis. New Engl J Med 1990;322(18):1323.

Slavin RG. Occupational and allergic rhinitis: impact on worker productivity and safety. [Review]. Allergy Asthma Proc 1998;19(5):277-84.

Slavin RG. Occupational rhinitis. Ann Allergy Asthma Immunol 1999;83(6 part 2):597-601.

Slawson DC, Squillace SP, Franko JP. Throat culture to rule out GABHS. J Fam Pract 1994;39(5):428.

Slunt JB, Taketomi EA, Platts-Mills TA. Human T-cell responses to Trichophyton tonsurans: inhibition using the serum free medium Aim V. Clin Exp Allergy 1997;27(10):1184-92.

Sly RM. New guidelines for diagnosis and management of asthma. Ann Allergy Asthma Immunol 1997;78(5):427-37.

Sly RM. Changing prevalence of allergic rhinitis and asthma. Ann Allergy Asthma Immunol 1999;82(3):233-48; quiz 248-52.

Smith AM, Yamaguchi H, Platts-Mills TA, et al. Prevalence of IgG anti-Der p 2 antibodies in children from high and low antigen exposure groups: relationship of IgG and subclass antibody responses to exposure and allergic symptoms. Clin Immunol Immunopathol 1998;86(1):102-9.

Smith AP. Hyposensitization with Dermatophagoides pteronyssinus antigen: trial in asthma induced by house dust. BMJ 1971;4(781):204-6.

Smith D. Self-reported glutaraldehyde symptoms: Are they an accurate predictor of workplace risk? J Occup Health Saf Aust New Zealand 2001;17(3):287-93.

Smith JM, Clegg RT, Cook N, et al. Intranasal beclomethasone diproprionate in allergic rhinitis. Br Med J 1975;2(5965):255.

Smith JM, Pizarro YA. Hyposensitization with extracts of Dermatophagoides pteronyssinus and house dust. Clin Allergy 1972;2(3):281-3.

Smith L. Special considerations for the child with airway disease. [Review]. J Allergy Clin Immunol 1998;101(2 Pt 2):S370-2.

Smith LJ. Diagnosis and treatment of allergic rhinitis [corrected] [published erratum appears in Nurse Pract 1996 Jan-Feb;21(1):9]. Nurse Pract 1995;20(10):58, 60, 62 passim.

Smith MA. Norah Schuster student presentations. J R Soc Med 1993;86(11):674-5.

Smolensky M. Knowledge and attitudes of American physicians and public about medical chronobiology and chronotherapeutics. Findings of two 1996 gallup surveys. Chronobiol Int 1998;15(4):377-94.

Smolensky MH, Reinberg A, Labrecque G. Twenty-four hour pattern in symptom intensity of viral and allergic rhinitis: Treatment implications. J Allergy Clin Immunol 1995;95(5 II):1084-96.

Snyman JR, Sommers DK, Van Wyk M, et al. The influence of betahistine on the dynamics of the cutaneous hypersensitivity reaction in patients with grass pollen allergy. Immunopharmacology 1995;30(1):71-8.

Sonenthal KR, Grammer LC. Pulmonary reactions to chemicals in the workplace. Can J Allergy Clin Immunol 2000;5(5):196-202.

Soto-Quiros M, Gutierrez I, Calvo N, et al. Allergen sensitization of asthmatic and nonasthmatic schoolchildren in Costa Rica. Allergy 1998;53(12):1141-7.

Spaeth J, Klimek L, Mosges R. Sedation in allergic rhinitis is caused by the condition and not by antihistamine treatment. Allergy Eur J Allergy Clin Immunol 1996;51(12):893-906.

Spafford CS, Grosser GS, Donatelle JR, et al. Contrast sensitivity differences between proficient and disabled readers using colored lenses. J Learn Disabil 1995;28(4):240-52.

Spector SL. Overview of comorbid associations of allergic rhinitis. [Review]. J Allergy Clin Immunol 1997;99(2):S773-80.

Spector SL, Bernstein IL, Li JT, et al. Parameters for the diagnosis and management of sinusitis. J Allergy Clin Immunol 1998;102(6 Pt 2):S107-44.

Spector SL, Nicodemus CF, Corren J, et al. Comparison of the bronchodilatory effects of cetirizine, albuterol, and both together versus placebo in patients with mild-to-moderate asthma. J Allergy Clin Immunol 1995;96(2):174-81.

Spencer C, Neales K. Minerva. BMJ 2000;320(7234):590.

Spiewak R, Gora A, Horoch A, et al. Atopy, allergic diseases and work-related symptoms among students of agricultural schools: First results of the Lublin study. Ann Agric Environ Med 2001;8(2):261-7.

Sporik R, Hill DJ, Thompson PJ, et al. The Melbourne House Dust Mite Study: long-term efficacy of house dust mite reduction strategies. J Allergy Clin Immunol 1998;101(4 Pt 1):451-6.

Sporik R, Holgate ST, Platts-Mills TA, et al. Exposure to house-dust mite allergen (Der p I) and the development of asthma in childhood. A prospective study. N Engl J Med 1990;323(8):502-7.

Sporik R, Ingram JM, Price W, et al. Association of asthma with serum IgE and skin test reactivity to allergens among children living at high altitude. Tickling the dragon's breath. Am J Respir Crit Care Med 1995;151(5):1388-92.

Sporik R, Platts-Mills TA. Allergen exposure and the development of asthma. [Review]. Thorax 2001;56(Suppl 2):ii58-63.

Sporik R, Platts-Mills TA, Cogswell JJ. Exposure to house dust mite allergen of children admitted to hospital with asthma. Clin Exp Allergy 1993;23(9):740-6.

Sporik R, Squillace SP, Ingram JM, et al. Mite, cat, and cockroach exposure, allergen sensitisation, and asthma in children: a case-control study of three schools. Thorax 1999;54(8):675-80.

Sporik RB, Arruda LK, Woodfolk J, et al. Environmental exposure to Aspergillus fumigatus allergen (Asp f I). Clin Exp Allergy 1993;23(4):326-31.

Squillace S, Berggreen P, Jaffe P, et al. A normal initial colonoscopy after age 50 does not predict a polyp-free status for life. Am J Gastroenterol 1994;89(8):1156-9.

Squillace SP. Environmental control. Otolaryngol Head Neck Surg 1992;107(6 Pt 2):831-4.

Squillace SP. Immunotherapy in adult asthma. J Fam Pract 1996;42(5):455.

Squillace SP. Indoor allergen avoidance: what really works? J Respir Dis 1999;20(1):13-6.

Squillace SP, Slawson DC. Guidelines for managing ankle injuries: the Ottawa ankle rules. J Fam Pract 1994;39(6):593-4.

Squillace SP, Sporik RB, Rakes G, et al. Sensitization to dust mites as a dominant risk factor for asthma among adolescents living in central Virginia. Multiple regression analysis of a population-based study. Am J Respir Crit Care Med 1997;156(6):1760-4.

Stahl E, van Rompay W, Wang EC, et al. Cost-effectiveness analysis of budesonide aqueous nasal spray and fluticasone propionate nasal spray in the treatment of perennial allergic rhinitis. Ann Allergy Asthma Immunol 2000;84(4):397-402.

Starr MS, Weinstock M. Studies in pollen allergy. 3. The relationship between blocking antibody levels and symptomatic relief following hyposensitisation with allpyral in hay fever subjects. Int Arch Allergy Appl Immunol 1970;38(5):514-21.

Stelmach I, Jerzynska J, Brzozowska A, et al. Double-blind, randomized, placebo-controlled trial of effect of nedocromil sodium on clinical and inflammatory parameters of asthma in children allergic to dust mite. Allergy 2001;56(6):518-24.

Stempel DA. Intranasal corticosteroids for first-line treatment of allergic rhinitis: What's the evidence? Formulary 2001;36(4):276-93.

Stempel DA, Brunton S, Clanton M, et al. Issues in diagnosis and therapy. Am J Manag Care 1997;3(Suppl):S29-42, S47-8.

Stempel DA, Richardson M, Mackowiak J, et al. The health and economic impact of rhinitis. Am J Manag Care 1997;3(Suppl):S8-18, S47-8.

Stempel DA, Thomas M. Treatment of allergic rhinitis: an evidence-based evaluation of nasal corticosteroids versus nonsedating antihistamines. Am J Manag Care 1998;4(1):89-96.

Stenberg B, Eriksson N, Hoog J, et al. The sick building syndrome (SBS) in office workers. A case-referent study of personal, psychosocial and building-related risk indicators. Int J Epidemiol 1994;23(6):1190-7.

Stenberg B, Eriksson N, Mild KH, et al. Facial skin symptoms in visual display terminal (VDT) workers. A case-referent study of personal, psychosocial, building- and VDT-related risk indicators. Int J Epidemiol 1995;24(4):796-803.

Sterk PJ, Buist SA, Woolcock AJ, et al. The message from the World Asthma Meeting. The Working Groups of the World Asthma Meeting, held in Barcelona, Spain, December 9-13, 1998. [Review]. Eur Respir J 1999;14(6):1435-53.

Sterk PJ, Leff AR, Pauwels R, et al. Panel discussion. Eur Respir Rev 1999;9(65):21-2.

Stevens DA, Schwartz HJ, Lee JY, et al. A randomized trial of itraconazole in allergic bronchopulmonary aspergillosis. N Engl J Med 2000;342(11):756-62.

Stevens LM, Lynm C, Glass RM. Seasonal allergic rhinitis. J Am Med Assoc 2001;286(23):3038.

Stevenson LA, Gergen PJ, Hoover DR, et al. Sociodemographic correlates of indoor allergan sensitivity among United States children. J Allergy Clin Immunol 2001;108(5):747-53.

Stimpel M, Koch B, Weber MA. Comparison between moexipril and atenolol in obese postmenopausal women with hypertension. Maturitas 1998;30(1):69-77.

Stone M, Ellis H. Dissecting room problem: Prevalence of latex allergy among medical students. Clin Anat 1998;11(3):191-3.

Storms W, Meltzer EO, Nathan RA, et al. Allergic rhinitis: the patient's perspective. J Allergy Clin Immunol 1997;99:S825-8.

Storms W, Meltzer EO, Nathan RA, et al. The economic impact of allergic rhinitis. J Allergy Clin Immunol 1997;99:S820-4.

Storms WW. Risk-benefit assessment of fluticasone propionate in the treatment of asthma and allergic rhinitis. J Asthma 1998;35(4):313-36.

Strachan D, Sibbald B, Weiland S, et al. Worldwide variations in prevalence of symptoms of allergic rhinoconjunctivitis in children: the International Study of Asthma and Allergies in Childhood (ISAAC). Ped Allergy Immunol 1997;8(4):161-76.

Strachan DP. House dust mite allergen avoidance in asthma. Benefits unproved but not yet excluded. BMJ 1998;317(7166):1096-7.

Strangert K. Respiratory illness in preschool children with different forms of day care. Pediatrics 1976;57(2):191-6.

Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. [Review]. JAMA 2000;283(15):2008-12.

Stubner UP, Toth J, Marks B, et al. Efficacy and safety of an oral formulation of cetirizine and prolonged-release pseudoephedrine versus xylometazoline nasal spray in nasal congestion. Arzneimittelforschung 2001;51(11):904-10.

Subiza JL, Subiza J, Barjau MC, et al. Inhibition of the seasonal IgE increase to Dactylis glomerata by daily sodium chloride nasal-sinus irrigation during the grass pollen season. J Allergy Clin Immunol 1999;104(3 I):711-2.

Sullivan SD, Weiss KB. Health economics of asthma and rhinitis. II. Assessing the value of interventions. J Allergy Clin Immunol 2001;107(2):203-10.
Sussman GL. Canadian Journal of Allergy and Clinical Immunology: Editorial. Can J Allergy Clin Immunol 2000;5(3):96.

Sussman GL, Mason J, Compton D, et al. The efficacy and safety of fexofenadine HCl and pseudoephedrine, alone and in combination, in seasonal allergic rhinitis. J Allergy Clin Immunol 1999;104(1):100-6.

Sussman GL, Moote DM, Danoff D, et al. Guidelines for the use of allergen immunotherapy. Can Med Assoc J 1995;152(9):1413-9.

Sutherland M, Czarny D, Douglass J. Allergy in the airway. Aust Fam Physician 1998;27(8):681-5.

Suzuki M, Kawauchi H, Mogi G. Clinical efficacy of an antiallergic drug on otitis media with effusion in association with allergic rhinitis. Auris Nasus Larynx 1999;26(2):123-9.

Svensson C, Klementsson H, Andersson M, et al. Glucocorticoid-induced attenuation of mucosal exudation of fibrinogen and bradykinins in seasonal allergic rhinitis. Allergy Eur J Allergy Clin Immunol 1994;49(3):177-83.

Swims MP. Potential terfenadine-fluoxetine interaction (2). Ann Pharmacother 1993;27(11):1404-5.

Symington IS, O'Neill D, Kerr JW. Comparision of a glutaraldehyde-modified pollen--tyrosine adsorbate with an alum-precipitated pollen vaccine in the treatment of hay fever. Clin Allergy 1977;7(2):189-94.

Szekely G, Gorgenyi F. Postmarketing surveillance-one of the key issues in drug development. Ther Hung 1992;40(4):147-53.

Tabar AI, Muro MD, Garcia BE, et al. Dermatophagoides pteronyssinus cluster immunotherapy. A controlled trial of safety and clinical efficacy. J Investig Allergol Clin Immunol 1999;9(3):155-64.

Taccariello M, Parikh A, Darby Y, et al. Nasal douching as a valuable adjunct in the management of chronic rhinosinusitis. Rhinology 1999;37(1):29-32.

Taivainen AI, Tukiainen HO, Terho EO, et al. Powered dust respirator helmets in the prevention of occupational asthma among farmers. Scand J Work Environ Health 1998;24(6):503-7.

Tan BB, Weald D, Strickland I, et al. Double-blind controlled trial of effect of housedust-mite allergen avoidance on atopic dermatitis. Lancet 1996;347(8993):15-8.

Tanner LA, Reilly M, Meltzer EO, et al. Effect of fexofenadine HCl on quality of life and work, classroom, and daily activity impairment in patients with seasonal allergic rhinitis. Am J Manag Care 1999;5(4 Suppl):S235-47.

Tarchalska-Krynska B, Zawisza E. Effects of fusafungine on the cytologic picture of nose mucosal membranes in patients with acute upper respiratory tract infections: Multicenter study. Med Sci Monit 1998;4(6):1036-9.

Tari MG, Mancino M, Ghezzi E, et al. Immunotherapy with an alum-adsorbed Parietaria-pollen allergoid: a 2-year, double-blind, placebo-controlled study. Allergy 1997;52(1):65-74.

Tari MG, Mancino M, Madonna F, et al. Immunologic evaluation of 24 month course of sublingual immunotherapy. Allergol Immunopathol (Madr) 1994;22(5):209-16.

Tari MG, Mancino M, Monti G. Efficacy of sublingual immunotherapy in patients with rhinitis and asthma due to house dust mite. A double-blind study. Allergol Immunopathol (Madr) 1990;18(5):277-84.

Tari MG, Mancino M, Monti G. Immunotherapy by inhalation of allergen in powder in house dust allergic asthma--a double-blind study. J Investig Allergol Clin Immunol 1992;2(2):59-67.

Tarlo SM, Cockcroft DW, Dolovich J, et al. Beclomethasone dipropionate aerosol in perennial rhinitis. J Allergy Clin Immunol 1977;59(3):232-6.

Tarlo SM, Sussman GL, Holness DL. Latex sensitivity in dental students and staff: A cross-sectional study. J Allergy Clin Immunol 1997;99(3):396-401.

Taudorf E, Laursen LC, Djurup R, et al. Oral administration of grass pollen to hay fever patients. An efficacy study in oral hyposensitization. Allergy 1985;40(5):321-35.

Taudorf E, Laursen LC, Lanner A, et al. Oral immunotherapy in birch pollen hay fever. J Allergy Clin Immunol 1987;80(2):153-61.

Taudorf E, Weeke B. Orally administered grass pollen. Allergy 1983;38(8):561-4.

Tay Y-K, Khoo B-P, Goh C-L. The epidemiology of atopic dermatitis at a tertiary referral skin center in Singapore. Asian Pac J Allergy Immunol 1999;17(3):137-41.

Taylor B, Broom BC. Atopy in medical students. Ann Allergy 1981;47(3):197-9.

Taylor B, Sanders SS, Norman AP. A double blind controlled trial of house mite fortified house dust vaccine in childhood asthma. Clin Allergy 1974;4(1):35-40.

Taylor G, Shivalkar PR. Local nasal desensitization in allergic rhinitis. Clin Allergy 1972;2(2):125-36.

Taylor J, Suveges L. Got a minute? Timing the selection process during the puchase of cough, cold and allergic rhinitis products. Can Pharm J 1991;124(11):507-11, 526.

Taylor MA, Reilly D, Llewellyn-Jones RH, et al. Randomised controlled trial of homoeopathy versus placebo in perennial allergic rhinitis with overview of four trial series. BMJ 2000;321(7259):471-6.

Tee RD, Gordon DJ, Lacey J, et al. Occupational allergy to the common house fly (Musca domestica): Use of immunologic response to identify atmospheric allergen. J Allergy Clin Immunol 1985;76(6):826-31.

TePas EC, Umetsu DT. Immunotherapy of asthma and allergic diseases. Curr Opin Pediatr 2000;12(6):574-8.

Terpstra S. Expectations of a citizen of the European Community concerning Brussels and the pollenosis of his grand children, children and himself: to 1993 and beyond. (Some considerations from a socio-economic point of view). Arb Paul Ehrlich Inst Bundesamt Sera Impfstoffe Frankf A M 1992;(85):25-38; discussion 38-40.

Testa B, Mesolella C, Mosti MR, et al. Changes in serum interferon-gamma, interleukin-4, and interleukin-12 cytokine levels in anti-histamine type 2-treated allergic rhinitis patients. Laryngoscope 2001;111(2):236-9.

Testa B, Mesolella M, Testa D, et al. Glutathione in the upper respiratory tract. Ann Otol Rhinol Laryngol 1995;104(2):117-9.

The SAS Institute. The SAS System for Windows [computer program]. Release 8.02. Cary, NC: The SAS Institute, Inc.; 2001.

Thiam DG, Tim CF, Hoon LS, et al. An evaluation of mattress encasings and high efficiency particulate filters on asthma control in the tropics. Asian Pac J Allergy Immunol 1999;17(3):169-74.

Thomas DHV, Noyce PR. The interface between self medication and the NHS. BMJ 1996;312(7032):688-91.

Thompson AK, Juniper E, Meltzer EO. Quality of life in patients with allergic rhinitis. [Review]. Ann Allergy Asthma Immunol 2000;85(5):338-48.

Thornton Z. Are you on allergy alert? Chemist Druggist 1999;251(Mar Suppl):10, 12.

Tikkanen S, Kokkonen J, Juntti H, et al. Status of children with cow's milk allergy in infancy by 10 years of age. Acta Paediatr 2000;89(10):1174-80.

Tinkelman DG, Bleecker ER, Ramsdell J, et al. Proventil HFA and ventolin have similar safety profiles during regular use. Chest 1998;113(2):290-6.

Tobin MJ. Asthma, airway biology, and allergic rhinitis in AJRCCM 2000. Am J Respir Crit Care Med 2001;164(9):1559-80.

Tom CM, Kane MP. Management of toenail onychomycosis. Am J Health-Syst Pharm 1999;56(9):865-71.

Tommel A-B, Andre C, Frew A-J, et al. Recent clinical and scientific evidences supporting sublingual immunotherapy. Allerg Immunol 2001;33(5):199-201.

Trevino RJ. Comparison of results of immunotherapy based on skin end-point titration, prick testing, and scratch testing. [erratum appears in Otolaryngol Head Neck Surg 1995 Mar;112(3):506]. Otolaryngol Head Neck Surg 1994;111(5):550-2.

Trigg CJ, Bennett JB, Tooley M, et al. A general practice based survey of bronchial hyperresponsiveness and its relation to symptoms, sex, age, atopy, and smoking. Thorax 1990;45(11):866-72.

Triglia JM, Nicollas R. Nasal and sinus polyposis in children. Laryngoscope 1997;107(7):963-6.

Tripathi A, Patterson R. Impact of allergic rhinitis treatment on quality of life. [Review]. Pharmacoeconomics 2001;19(9):891-9.

Troise C, Bignardi D, Modena P, et al. Preventive symptomatic immunotherapy versus placebo in seasonal rhinitis due to grasses in children and to Parietaria in adult patients. Allerg Immunol (Paris) 2000;32(6):246-9.

Troise C, Voltolini S, Canessa A, et al. Sublingual immunotherapy in Parietaria pollen-induced rhinitis: a double-blind study. J Investig Allergol Clin Immunol 1995;5(1):25-30.

Trotter JP. The treatment of seasonal allergic rhinitis: cost implications of pharmacotherapy for managed care. Manag Care Interface 2000;13(1):60-2.

Trotto NE. Asthma, rhinitis, sinusitis, urticaria. Patient Care 1999;33(1):115-39.

Tsai LC, Tang RB, Hung MW, et al. Changes in the levels of house dust mite specific IgG4 during immunotherapy in asthmatic children. Clin Exp Allergy 1991;21(3):367-72.

Tunnicliffe WS, Burge PS, Ayres JG. Effect of domestic concentrations of nitrogen dioxide on airway responses to inhaled allergen in asthmatic patients. Lancet 1994;344(8939-8940):1733-6.

Tunnicliffe WS, Fletcher TJ, Hammond K, et al. Sensitivity and exposure to indoor allergens in adults with differing asthma severity. Eur Respir J 1999;13(3):654-9.

Tupker RA, de Monchy JG, Coenraads PJ. House-dust mite hypersensitivity, eczema, and other nonpulmonary manifestations of allergy. [Review]. Allergy 1998;53(48 Suppl):92-6.

Turkeltaub PC, Gergen PJ. Prevalence of upper and lower respiratory conditions in the US population by social and environmental factors: data from the second National Health and Nutrition Examination Survey, 1976 to 1980 (NHANES II). Ann Allergy 1991;67(2 Pt 1):147-54.

Turkeltaub PC, Norman PS, Crepea S. Treatment of ragweed hay fever with an intranasal spray containing fluinsolide, a new synthetic corticosteroid. J Allergy Clin Immunol 1976;58(5):597-606.

Turkeltaub PC, Norman PS, Johnson JD, et al. Treatment of seasonal and perennial rhinitis with intranasal flunisolide. Allergy 1982;37(5):303-11.

Turner KJ, Stewart GA, Woolcock AJ, et al. Relationship between mite densities and the prevalence of asthma: comparative studies in two populations in the Eastern Highlands of Papua New Guinea. Clin Allergy 1988;18(4):331-40.

Turner MW, Yalcin I, Soothill JF, et al. In vitro investigations in asthmatic children undergoing hyposensitization with tyrosine-adsorbed Dermatophagoides pteronyssinus antigen. Clin Allergy 1984;14(3):221-31.

Turner P, Dear J, Scadding G, et al. Role of kinins in seasonal allergic rhinitis: icatibant, a bradykinin B2 receptor antagonist, abolishes the hyperresponsiveness and nasal eosinophilia induced by antigen. J Allergy Clin Immunol 2001;107(1):105-13.

Ubel PA, Goold S. Recognizing bedside rationing: Clear cases and tough calls. Ann Intern Med 1997;126(1):74-80.

Ulrik CS. Factors associated with increased bronchial responsiveness in adolescents and young adults: the importance of adjustment for prechallenge FEV1. J Allergy Clin Immunol 1996;97(3):761-7.

Vailes LD, Perzanowski MS, Wheatley LM, et al. IgE and IgG antibody responses to recombinant Alt a 1 as a marker of sensitization to Alternaria in asthma and atopic dermatitis. Clin Exp Allergy 2001;31(12):1891-5.

Valovirta E. Capacity of specific immunotherapy in prevention of allergic asthma in children: The preventive allergy treatment study (PAT). J Investig Allergol Clin Immunol 1997;7(5):369-70.

Valovirta E. PAT--the Preventive Allergy Treatment Study design and preliminary results. Wien Med Wochenschr 1999;149(14-15):442-3.

van Agthoven M, Fokkens WJ, van de Merwe JP, et al. Quality of life of patients with refractory chronic rhinosinusitis: effects of filgrastim treatment. Am J Rhinol 2001;15(4):231-7.

Van Berge Henegouwen MTH, Van Driel HF, Kasteleijn-Nolst Trenite DGA. A patient diary as a tool to improve medicine compliance. Pharm World Sci 1999;21(1):21-4.

Van Bever HP, Stevens WJ. Effect of hyposensitization upon the immediate and late asthmatic reaction and upon histamine reactivity in patients allergic to house dust mite (Dermatophagoides pteronyssinus). Eur Respir J 1992;5(3):318-22.

van Cauwenberge P. Management of rhinitis--the specialist's opinion. Clin Exp Allergy 1998;28(Suppl 6):29-33.

Van Cauwenberge P. Intranasal steroids: Friends or foes? Brussels, Belgium July 4, 1999: Summary. Allergy Eur J Allergy Clin Immunol Suppl 2000;55(62):24.

Van Cauwenberge P, Berdeaux G, Morineau A, et al. Use of diagnostic clusters to assess the economic consequences of rhinopharyngitis in children in Italy and France during the winter. Rhinitis Survey Group. Clin Ther 1999;21(2):404-21.

Van Cauwenberge P, Juniper EF. Comparison of the efficacy, safety and quality of life provided by fexofenadine hydrochloride 120 mg, loratadine 10 mg and placebo administered once daily for the treatment of seasonal allergic rhinitis. Clin Exp Allergy 2000;30(6):891-9.

van Cauwenberge PB. Epidemiology of common cold. Rhinology 1985;23(4):273-82.

Van de Maele B. New strategy in the control of house dust mite allergy. Pharmatherapeutica 1983;3(7):441-4.

van der Heide S, Kauffman HF, Dubois AE, et al. Allergen reduction measures in houses of allergic asthmatic patients: effects of air-cleaners and allergen-impermeable mattress covers. Eur Respir J 1997;10(6):1217-23.

van der Heide S, Kauffman HF, Dubois AE, et al. Allergen-avoidance measures in homes of house-dust-mite-allergic asthmatic patients: effects of acaricides and mattress encasings. Allergy 1997;52(9):921-7.

Van Der Veen MJ, Jansen HM, Aalberse RC, et al. Der p 1 and Der p 2 induce less severe late asthmatic responses than native Dermatophagoides pteronyssinus extract after a similar early asthmatic response. Clin Exp Allergy 2001;31(5):705-14.

Van Deusen MA, Angelini BL, Cordoro KM, et al. Efficacy and safety of oral immunotherapy with short ragweed extract. Ann Allergy Asthma Immunol 1997;78(6):573-80.

Van Metre TE, Adkinson NF, Amodio FJ, et al. A comparison of immunotherapy schedules for injection treatment of ragweed pollen hay fever. J Allergy Clin Immunol 1982;69(2):181-93.

Van Metre TE, Adkinson NF Jr, Amodio FJ, et al. A comparative study of the effectiveness of the Rinkel method and the current standard method of immunotherapy for ragweed pollen hay fever. J Allergy Clin Immunol 1980;66(6):500-13.

Van Niekerk CH, De Wet JI. Efficacy of grass-maize pollen oral immunotherapy in patients with seasonal hay-fever: a double-blind study. Clin Allergy 1987;17(6):507-13.

Van Wijk GR, Terreehorst IT, Mulder PG, et al. Intranasal capsaicin is lacking therapeutic effect in perennial allergic rhinitis to house dust mite. A placebo-controlled study. Clin Exp Allergy 2000;30(12):1792-8.

Van Wijk RG. Perennial allergic rhinitis and nasal hyperreactivity. Am J Rhinol 1998;12(1):33-5.

Vanhanen M, Tuomi T, Tiikkainen U, et al. Risk of enzyme allergy in the detergent industry. Occup Environ Med 2000;57(2):121-5.

Varghese BT, Murthy PSN, Rajan R. Clinico-pathological correlation between allergic rhinitis and bronchial asthma. J Laryngol Otol 2000;114(5):354-8.

Varney VA, Gaga M, Frew AJ, et al. Usefulness of immunotherapy in patients with severe summer hay fever uncontrolled by antiallergic drugs. BMJ 1991;302(6771):265-9.

Varney VA, Jacobson MR, Sudderick RM, et al. Immunohistology of the nasal mucosa following allergen-induced rhinitis. Identification of activated T lymphocytes, eosinophils, and neutrophils. Am Rev Respir Dis 1992;146(1):170-6.

Vaughan JW, Platts-Mills TA. New approaches to environmental control. [Review]. Clin Rev Allergy Immunol 2000;18(3):325-39.

Verberne AAPH, Frost C, Duiverman EJ, et al. Addition of salmeterol versus doubling the dose of beclomethasone in children with asthma. Am J Respir Crit Care Med 1998;158(1):213-9.

Verdiani P, Di Carlo S, Baronti A, et al. Effect of inhaled frusemide on the early response to antigen and subsequent change in airway reactivity in atopic patients. Thorax 1990;45(5):377-81.

Verrall B, Muir DC, Wilson WM, et al. Laminar flow air cleaner bed attachment: a controlled trial. Ann Allergy 1988;61(2):117-22.

Verstraeten JM, Verstraeten AF. Clinical evaluation of hyposensitization in allergic rhinitis: comparison of the results obtained with three different extracts. Material from a 3-year study. Ann Allergy 1987;58(6):416-20.

Vervloet D, Charpin D, Birnbaum J. Extrinsic asthma and environmental allergens. [Review]. Allerg Immunol 1991;23(7):281-3.

Vila L, Sanchez G, Ano M, et al. Risk factors for latex sensitization among health care workers. J Investig Allergol Clin Immunol 1999;9(6):356-60.

Virant FS. Allergic rhinitis. Immunol Allergy Clin North Am 2000;20(2):265-82.

Vogel G. New clues to asthma therapies. Science 1997;276(5319):1643-6.

Voltolini S, Modena P, Minale P, et al. Sublingual immunotherapy in tree pollen allergy. Double-blind, placebo-controlled study with a biologically standardised extract of three pollens (alder, birch and hazel) administered by a rush schedule. Allergol Immunopathol 2001;29(4):103-10.

Vourdas D, Syrigou E, Potamianou P, et al. Double-blind, placebo-controlled evaluation of sublingual immunotherapy with standardized olive pollen extract in pediatric patients with allergic rhinoconjunctivitis and mild asthma due to olive pollen sensitization. Allergy 1998;53(7):662-72.

Vuurman EFPM, van Veggel LMA, Sanders RL, et al. Effects of Semprex-D and diphenhydramine on learning in young adults with seasonal allergic rhinitis. Ann Allergy Asthma Immunol 1996;76(3):247-52.

Wagner R, Wendlberger U. Field efficacy of moxidectin in dogs and rabbits naturally infested with Sarcoptes spp., Demodex spp. and Psoroptes spp. mites. Vet Parasitol 2000;93(2):149-58.

Walinder R, Norback D, Wieslander G, et al. Nasal patency and lavage biomarkers in relation to settled dust and cleaning routines in schools. Scand J Work Environ Health 1999;25(2):137-43.

Walinder R, Norback D, Wieslander G, et al. Acoustic rhinometry and lavage biomarkers in relation to some building characteristics in Swedish schools. Indoor Air-Internat J Indoor Air Qual Climate 2001;11(1):2-9.

Walinder R, Wieslander G, Norback D, et al. Influence of personal factors on nasal patency and lavage biomarkers in white-collar workers. Rhinology 2000;38(3):130-5.

Walker C, Williams H, Phelan J. Allergic rhinitis history as a predictor of other future disqualifying otorhinolaryngological defects. Aviat Space Environ Med 1998;69(10):952-6.

Walker S. The impact of allergic rhinitis on daily life. Practice Nurse 1999;18(2):100, 102, 104-5.

Walker S. Management of hayfever: A practical guide. Asthma J 2001;6(2):106-8.

Walker SM, Pajno GB, Lima MT, et al. Grass pollen immunotherapy for seasonal rhinitis and asthma: a randomized, controlled trial. J Allergy Clin Immunol 2001;107(1):87-93.

Walker SM, Varney VA, Gaga M, et al. Grass pollen immunotherapy: efficacy and safety during a 4-year follow-up study. Allergy 1995;50(5):405-13.

Walpole O. Dusty answer. Occup Health 2001;53(5):24-6.

Walshaw MJ, Evans CC. Allergen avoidance in house dust mite sensitive adult asthma. Quarterly J Med 1986;58(226):199-215.

Wang D, Smitz J, DeWaele M, et al. Effect of topical applications of budesonide and azelastine on nasal symptoms, eosinophil count and mediator release in atopic patients after nasal allergen challenge during the pollen season. Int Arch Allergy Immunol 1997;114(2):185-92.

Warburton CJ, Niven RM, Pickering CA, et al. Domiciliary air filtration units, symptoms and lung function in atopic asthmatics. Respir Med 1994;88(10):771-6.

Ward AJ, McKenniff M, Evans JM, et al. Theophylline--an immunomodulatory role in asthma? Am Rev Respir Dis 1993;147(3):518-23.

Ward Jr GW, Karlsson G, Rose G, et al. Trichophyton asthma: sensitisation of bronchi and upper airways to dermatophyte antigen. Lancet 1989;1(8643):859-62.

Ward Jr GW, Woodfolk JA, Hayden ML, et al. Treatment of late-onset asthma with fluconazole. J Allergy Clin Immunol 1999;104(3 Pt 1):541-6.

Warner JA, Frederick JM, Bryant TN, et al. Mechanical ventilation and high-efficiency vacuum cleaning: A combined strategy of mite and mite allergen reduction in the control of mite-sensitive asthma. J Allergy Clin Immunol 2000;105(1 Pt 1):75-82.

Warner JA, Marchant JL, Warner JO. Double blind trial of ionisers in children with asthma sensitive to the house dust mite. Thorax 1993;48(4):330-3.

Warner JO. Seasonal rhinoconjunctivitis and examinations: is this unfair discrimination? Pediatr Allergy Immunol 2000;11(3):129-30.

Wasserfallen JB, Gold K, Schulman KA, et al. Development and validation of a rhinoconjunctivitis and asthma symptom score for use as an outcome measure in clinical trials. J Allergy Clin Immunol 1997;100(1):16-22.

Wasserfallen JB, Gold K, Schulman KA, et al. Item responsiveness of a rhinitis and asthma symptom score during a pollen season. J Asthma 1999;36(5):459-65.

Wasserfallen JB, Leuenberger P, Pecoud A. Effect of cetirizine, a new H1 antihistamine, on the early and late allergic reactions in a bronchial provocation test with allergen. J Allergy Clin Immunol 1993;91(6):1189-97.

Wasserman B. Allergic rhinitis and wellness opportunities. Manag Care Interface 2001;14(8):38-45, 50.

Watrous ML, Kozma CM, Reeder CE. Quality of life assessment in sufferers of rhinitis. [Abstract]. APhA Annual Meeting 1994;141:43.

Watts RW, Perera YS, Allsop J, et al. Immunological and purine enzyme studies on hyperuricaemic and normouricaemic patients with Down's syndrome. Clin Exp Immunol 1979;36(3):355-63.

Weeke ER. Epidemiology of allergic diseases in children. Rhinology 1992;13(Suppl):5-12.

Weeks J, Oliver J, Birmingham K, et al. A combined approach to reduce mite allergen in the bedroom. Clin Exp Allergy 1995;25(12):1179-83.

Weido AJ, Reece LM, Alam R, et al. Intranasal fluticasone propionate inhibits recovery of chemokines and other cytokines in nasal secretions in allergen-induced rhinitis. Ann Allergy Asthma Immunol 1996;77(5):407-15.

Weiland SK, Pless IB, Roghmann KJ. Chronic illness and mental health problems in pediatric practice: Results from a survey of primary care providers. Pediatrics 1992;89(3 Suppl):445-9.

Weiler JM, Bloomfield JR, Woodworth GG, et al. Effects of fexofenadine, diphenhydramine, and alcohol on driving performance. A randomized, placebo-controlled trial in the Iowa driving simulator. Ann Intern Med 2000;132(5):354-63.

Weinblatt ME, Kremer JM, Bankhurst AD, et al. A trial of etanercept, a recombinant tumor necrosis factor receptor:Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. New Engl J Med 1999;340(4):253-9.

Weiner JM, Abramson MJ, Puy RM. Intranasal corticosteroids versus oral H1 receptor antagonists in allergic rhinitis: systematic review of randomised controlled trials. BMJ 1998;317(7173):1624-9.

Weiser M, Gegenheimer LH, Klein P. A randomized equivalence trial comparing the efficacy and safety of Luffa comp.-Heel Nasal Spray with cromolyn sodium spray in the treatment of seasonal allergic rhinitis. Forsch Komplementarmed 1999;6(3):142-8.

Weiss KB. Cost implications of upper respiratory allergic diseases. J Allergy Clin Immunol 1998;101(2 II):S383-S385.

Weiss KB, Haus M, Iikura Y. Chapter 5: The costs of allergy and asthma and the potential benefit of prevention strategies. Allergy Clin Immunol Int 2000;12(6):299-300.

Weiss KB, Sullivan SD. The health economics of asthma and rhinitis. I. Assessing the economic impact. [Review]. J Allergy Clin Immunol 2001;107(1):3-8.

Weiss RJ. Fluvastatin titrate-to-goal clinical practice study. Am J Ther 1998;5(5):281-5.

Weiss ST, O'Connor GT, DeMolles D, et al. Indoor allergens and longitudinal FEV1 decline in older adults: the Normative Aging Study. J Allergy Clin Immunol 1998;101(6 Pt 1):720-5.

Welch MJ, Meltzer EO. Allergic rhinitis: a disease for all seasons. J Am Acad Phys Assistants 1993;6(8):553-60.

Weldon D. Diagnosis and management of rhinitis. [Review]. Prim Care 1998;25(4):831-48.

Welsh PW, Zimmermann EM, Yunginger JW, et al. Preseasonal intranasal immunotherapy with nebulized short ragweed extract. J Allergy Clin Immunol 1981;67(3):237-42.

Wen T, Wang E, Shen S, et al. Allergenic potency of SMU-Df extract in comparison with VUS-Df extract; and diagnosis and immunotherapy for atopic dermatitis and rhinitis with SMU-Df extract in China. Arb Paul Ehrlich Inst Bundesamt Sera Impfstoffe Frankf A M 1992;(85):217-27.

Wessels F, Green R, Luyt D. Cost of therapy for allergic rhinitis. S Afr Med J 1997;87(2):141-5.

Weyer A, Doinel C, Debbia M, et al. Grass pollen hyposensitization versus placebo therapy. II. Immunotherapy-induced changes in serum IgE and IgG levels. Allergy 1981;36(5):319-28.

Weyer A, Donat N, L'Heritier C, et al. Grass pollen hyposensitization versus placebo therapy. I. Clinical effectiveness and methodological aspects of a pre-seasonal course of desensitization with a four-grass pollen extract. Allergy 1981;36(5):309-17.

White P, Smith H, Baker N, et al. Symptom control in patients with hay fever in UK general practice: how well are we doing and is there a need for allergen immunotherapy? Clin Exp Allergy 1998;28(3):266-70.

Whyte KF, Flenley DC. House dust sensitivity and asthma. [Review]. Quarterly J Med 1986;58(226):89-93.

Wickens K, Pearce N, Siebers R, et al. Indoor environment, atopy and the risk of the asthma in children in New Zealand. Pediatr Allergy Immunol 1999;10(3):199-208.

Wiesenauer M, Heidl R. New approaches to treating pollenosis - A pilot study. Complement Ther Med 1999;7(4):222-4.

Wihl JA, Ipsen H, Petersen BN, et al. Immunotherapy with partially purified and standardized tree pollen extracts. II. Results of skin prick tests and nasal provocation tests from a three-year double-blind study of patients treated with pollen extracts either of birch or combinations of alder, birch and hazel. Allergy 1988;43(5):363-9.

Wilde MI, McTavish D. Tamsulosin. A review of its pharmacological properties and therapeutic potential in the management of symptomatic benign prostatic hyperplasia. Drugs 1996;52(6):883-98.

Willes SR, Fitzgerald TK, Permutt T, et al. Acute respiratory response to prolonged, moderate levels of sidestream tobacco smoke. J Toxicol Environ Health. Part A 1998;53(3):193-209.

Williams BO, Hull H, McSorley P, et al. Efficacy of acrivastine plus pseudoephedrine for symptomatic relief of seasonal allergic rhinitis due to mountain cedar. Ann Allergy Asthma Immunol 1996;76(5):432-8.

Williams HC. Commentary. Evid.-Based Med 2001;6(6):178.

Williamson L, Yudkin P, Livingstone R, et al. Hay fever treatment in general practice: A randomised controlled trial comparing standardised Western acupuncture with sham acupuncture. Acupunct Med 1996;14(1):6-10.

Wilson A, Dempsey OJ, Sims EJ, et al. Evaluation of treatment response in patients with seasonal allergic rhinitis using domiciliary nasal peak inspiratory flow. Clin Exp Allergy 2000;30(6):833-8.

Wilson AM, Orr LC, Sims EJ, et al. Antiasthmatic effects of mediator blockade versus topical corticosteroids in allergic rhinitis and asthma. Am J Respir Crit Care Med 2000;162(4 Pt 1):1297-301.

Wilson AM, Orr LC, Sims EJ, et al. Effects of monotherapy with intra-nasal corticosteroid or combined oral histamine and leukotriene receptor antagonists in seasonal allergic rhinitis. Clin Exp Allergy 2001;31(1):61-8.

Wilson AM, Sims EJ, Orr LC, et al. Effects of topical corticosteroid and combined mediator blockade on domiciliary and laboratory measurements of nasal function in seasonal allergic rhinitis. Ann Allergy Asthma Immunol 2001;87(4):344-9.

Wilson DR, Nouri-Aria KT, Walker SM, et al. Grass pollen immunotherapy: symptomatic improvement correlates with reductions in eosinophils and IL-5 mRNA expression in the nasal mucosa during the pollen season. J Allergy Clin Immunol 2001;107(6):971-6.

Wilson DR, Torres Lima M, Durham SR. Sublingual immunotherapy for allergic rhinitis (Cochrane Protocol). In: The Cochrane Library, Issue 1, 2002, Oxford: Update Sofware, 2002.

Wilson RW. Cigarette smoking, disability days and respiratory conditions. J Occup Med 1973;15(3):236-40.

Windom HH, Togias A. Rhinitis and asthma - Manifestations of one disease. Allergy Clin Immunol Int 2001;13(4):154-61.

Winstead W, Barnett SN. Impact of endoscopic sinus surgery on global health perception: an outcomes study. Otolaryngol Head Neck Surg 1998;119(5):486-91.

Winther L, Malling HJ, Moseholm L, et al. Allergen-specific immunotherapy in birch- and grass-pollen-allergic rhinitis. I. Efficacy estimated by a model reducing the bias of annual differences in pollen counts. Allergy 2000;55(9):818-26.

Wiseman LR, Benfield P. Intranasal fluticasone propionate. A reappraisal of its pharmacology and clinical efficacy in the treatment of rhinitis. [Review]. Drugs 1997;53(5):885-907.

Witteman AM, Stapel SO, Perdok GJ, et al. The relationship between RAST and skin test results in patients with asthma or rhinitis: A quantitative study with purified major allergens. J Allergy Clin Immunol 1996;97(1 I):16-25.

Wittig HJ, McLaughlin ET, Leifer KL, et al. Risk factors for the development of allergic disease: analysis of 2,190 patient records. Ann Allergy 1978;41(2):84-8.

Wober W, Diez Crespo C, Bahre M. Efficacy and tolerability of azelastine nasal spray in the treatment of allergic rhinitis: large scale experience in community practice. Curr Med Res Opin 1997;13(10):617-26.

Wojnarowski C, Halmerbauer G, Mayatepek E, et al. Urinary leukotriene E(4), eosinophil protein X, and nasal eosinophil cationic protein are not associated with respiratory symptoms in 1-year-old children. Allergy 2001;56(9):883-8.

Wolfe SP. 'Prevention programmes' - A dietetic minefield. Eur J Clin Nutr 1995;49(Suppl 1):S92-S99.

Wong L, Hendeles L, Weinberger M. Pharmacologic prophylaxis of allergic rhinitis: relative efficacy of hydroxyzine and chlorpheniramine. J Allergy Clin Immunol 1981;67(3):223-8.

Wong WM. Trastuzumab: Anti-HER2 antibody for treatment of metastatic breast cancer. Cancer Pract 1999;7(1):48-50.

Wood RA, Johnson EF, Van Natta ML, et al. A placebo-controlled trial of a HEPA air cleaner in the treatment of cat allergy. Am J Respir Crit Care Med 1998;158(1):115-20.

Wood S. Allergic rhinitis and hayfever. [Review]. Practitioner 1992;236(1513):440-7.

Woodcock A, Custovic A. Allergen avoidance: does it work? [Review]. Brit Med Bull 2000;56(4):1071-86.

Woodward CA, Boyle MH, Offord DR, et al. Correlates of children's use of physician and dentist services: Ontario child health study follow-up. Can J Public Health 1993;84(2):103-6.

Worth J. Neo-natal sensitization to latex: A medical hypothesis. J Nutr Environ Med 1999;9(4):305-12.

Wraith DG, Cunnington AM, Seymour WM. The role and allergenic importance of storage mites in house dust and other environments. Clin Allergy 1979;9(6):545-61.

Wray BB. In my opinion - Interview with the expert. Pediatr Asthma Allergy Immunol 2001;15(1):55-7.

Wright AL, Holberg CJ, Martinez FD, et al. Epidemiology of physician-diagnosed allergic rhinitis in childhood. Pediatrics 1994;94(6 Pt 1):895-901.

Wüthrich B, Brignoli R, Canevascini M, et al. Epidemiological survey in hay fever patients: Symptom prevalence and severity and influence on patient management. Schweiz Med Wochenschr 1998;128(5):139-43.

Yanase DJ, David-Bajar K. The leukotriene antagonist montelukast as a therapeutic agent for atopic dermatitis. J Am Acad Dermatol 2001;44(1):89-93.

Yang SH, Hong CY, Yu CL. Decreased serum IgE level, decreased IFN-gamma and IL-5 but increased IL-10 production, and suppressed cyclooxygenase 2 mRNA expression in patients with perennial allergic rhinitis after treatment with a new mixed formula of Chinese herbs. Int Immunopharmacol 2001;1(6):1173-82.

Yang WH, Dolovich J, Drouin MA, et al. Comparison of budesonide Turbuhaler with budesonide aqua in the treatment of seasonal allergic rhinitis. Rhinocort Study Group. Can Respir J 1998;5(6):455-60.

Yang Y-H, Lin Y-T, Lu M-Y, et al. A double-blind, placebo-controlled, and randomized study of loratadine (clarityne) syrup for the treatment of allergic rhinitis in children aged 3 to 12 years. Asian Pac J Allergy Immunol 2001;19(3):171-5.

Yaniv E, Oppenheim D, Fuchs C. Chronic rhinitis in children. Int J Pediatr Otorhinolaryngol 1992;23(1):51-7.

Yaniv E, Oppenheim D, Gatot A. Nasal histamine challenge: A method to predict the efficiency of antihistamine treatment. Am J Otolaryngol Head in seasonal pediatric allergy. J Investig Allergol Clin Immunol 1999;9(5):305-13.

Zacharisen MC. Rhinitis in children, adolescents, the elderly, and pregnant women. Special considerations. Immunol Allergy Clin North Am 2000;20(2):425-44.

Zeiger RS, Schatz M. Effect of allergist intervention on patient-centered and societal outcomes: allergists as leaders, innovators, and educators. [Review]. J Allergy Clin Immunol 2000;106(6):995-1018.

Zenner HP, Baumgarten C, Rasp G, et al. Short-term immunotherapy: a prospective, randomized, double-blind, placebo-controlled multicenter study of molecular standardized grass and rye allergens in patients with grass pollen-induced allergic rhinitis. J Allergy Clin Immunol 1997;100(1):23-9.

Zernike W, Corish T, Henderson S. An exploratory study from the patients' perspective of living with allergies. J Clin Nurs 1997;6(5):371-7.

Neck Med Surg 1992;12(6):316-9.
Yawn BP, Yunginger JW, Wollan PC, et al. Allergic rhinitis in Rochester, Minnesota residents with asthma: frequency and impact on health care charges. J Allergy Clin Immunol 1999;103(1 Pt 1):54-9.

Yelin E, Trupin L, Cisernas M, et al. A national study of medical care expenditures for respiratory conditions. Eur Respir J 2002;19(3):414-21.

Yemaneberhan H, Bekele Z, Venn A, et al. Prevalence of wheeze and asthma and relation to atopy in urban and rural Ethiopia. Lancet 1997;350(9071):85-90.

Yilmaz M, Bingol G, Altintas D, et al. Effect of SIT on quality of life. Allergy 2000;55(3):302.

Yokota K, Johyama Y, Yamaguchi K. The relationship of airborne methyltetrahydrophthalic Anhydride concentrations to methyltetrahydrophthalic anhydride-induced symptoms. J Occup Health 2001;43(4):201-4.

Young P. Asthma and allergies: an optimistic future. National Institutes of Health (NIH) Publication No. 80-388. Bethesda (MD): US Department of Health and Human Services, NIH, 1980.

Yuksel H, Tanac R, Gousseinov A, et al. Sublingual immunotherapy and influence on urinary leukotrienes

Zetterstrom O, Buhl R, Mellem H, et al. Improved asthma control with budesonide/formeterol in a single inhaler, compared with budesonide alone. Eur Respir J 2001;18(2):262-8.

Zhalnenkov NN. Portable devices adopted by the Russian Ministry of Health for home medical care. Biomed Eng 1997;31(2):120-4.

Zhao X, Niu J, Wang Y, et al. Genotoxicity and chronic health effects of automobile exhaust: a study on the traffic policemen in the city of Lanzhou. Mutat Res 1998;415(3):185-90.

Zheltikova TM, Ovsyannikova IG, Gervazieva VB, et al. Comparative detection of mite allergens in house dust of homes in Moscow by enzyme-linked immunosorbent assay and acarologic analysis. Allergy 1994;49(10):816-9.

Zimmerman RK, Giebink GS. Childhood immunizations: A practical approach for clinicians. Am Fam Phys 1992;45(4):1759-72.

Zuskin E, Mustajbegovic J, Schachter EN, et al. Respiratory function in shoe manufacturing workers. Am J Ind Med 1997;31(1):50-5.

Zwemer RJ, Karibo J. Use of laminar control device as adjunct to standard environmental control measures in symptomatic asthmatic children. Ann Allergy 1973;31(6):284-90.

Appendix: Acronyms and Abbreviations

AHRQ	Agency for Healthcare Research and Quality
AAHP	American Association of Health Plans
CDC	Centers for Disease Control and Prevention
CDSR	Cochrane Database of Systematic Reviews
CI	Confidence interval
CONSORT	Consolidated Standards of Reporting Trials
DARE	Database of Abstracts of Reviews of Effectiveness
DHHS	Department of Health and Human Services
HEPA	High efficiency particulate air
HRQOL	Health-related quality of life
IgE	Immunoglobulin E
IT	Immunotherapy
MSA	Metropolitan Statistical Area
NA	Not available
NHANESII	The National Health and Nutrition Examination Survey, 1976-80
NMES	National Medical Expenditure Survey
OR	Odds ratio
OTC	Over-the-counter
PHS	Public Health Service
QOL	Quality of life
RAST	Radioallergosorbent testing
RCT	Randomized controlled trial

RQLQ	Rhinoconjunctivitis Quality of Life Questionnaire
SE	Standard error
SF-36	Medical Outcome Study Short-Form Health Survey
WPAI-AS	Allergy-specific Work Productivity and Activity Impairment questionnaire