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 6th and 8th 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

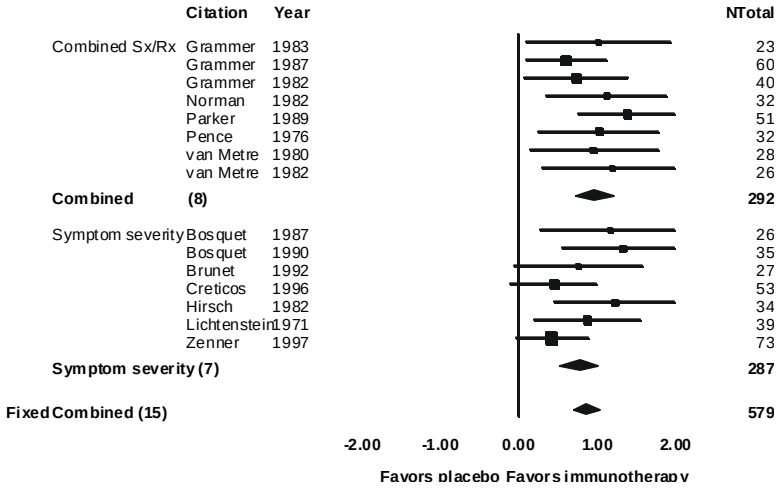

Figure 3. Meta-analysis of trials comparing antihistamine + decongestant combinations versus antihistamine alone: effect size based on differences in total symptom severity

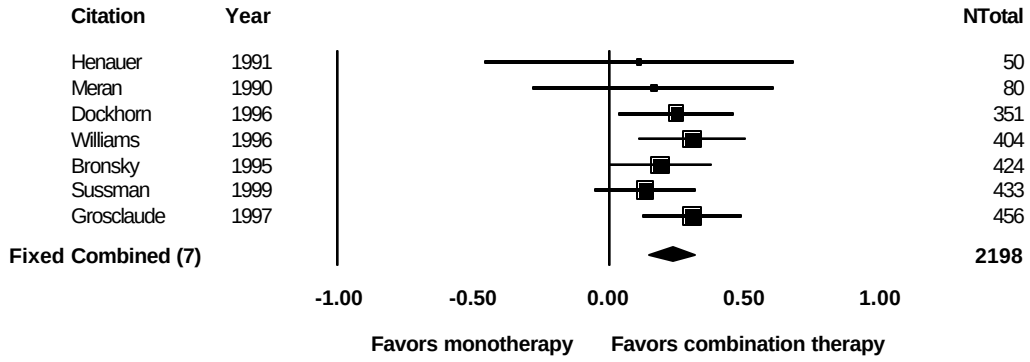

Figure 4. Meta-analysis of trials comparing antihistamine + decongestant combinations versus antihistamine alone: effect size based on differences in nasal symptom severity

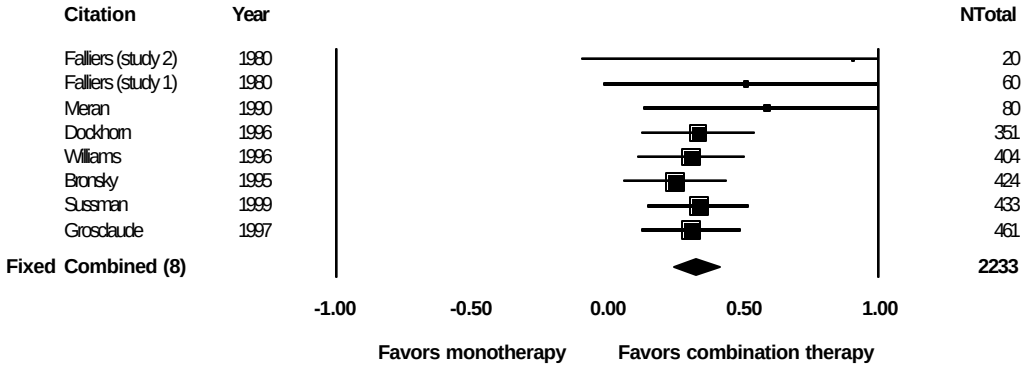

Figure 5. Meta-analysis of trials comparing antihistamine + decongestant combinations versus decongestant alone: effect size based on differences in total symptom severity

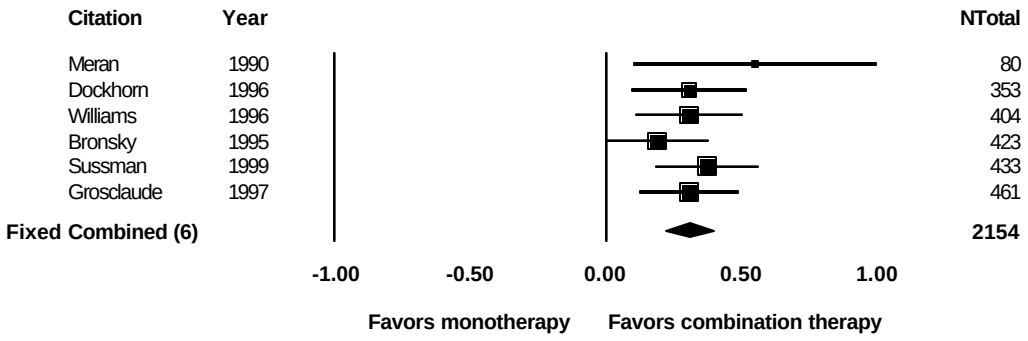

Figure 6. Meta-analysis of trials comparing antihistamine + decongestant combinations versus decongestant alone: effect size based on differences in nasal symptom severity

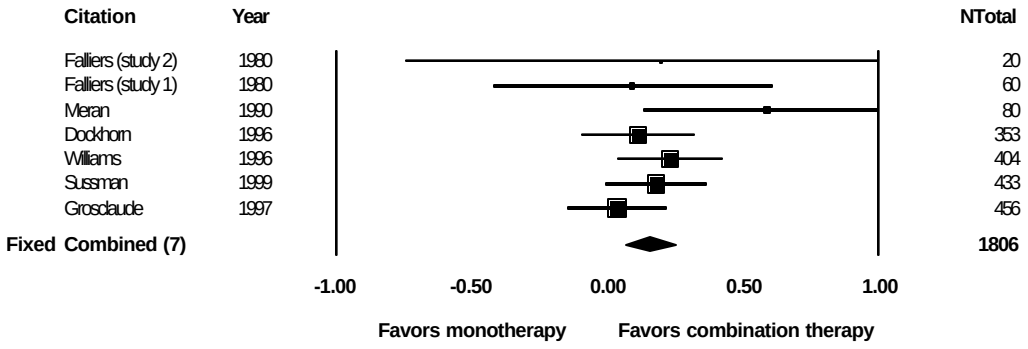

Figure 7. Meta-analysis of trials comparing antihistamine + nasal glucocorticoid combinations versus antihistamine alone: effect size based on differences in nasal symptom severity

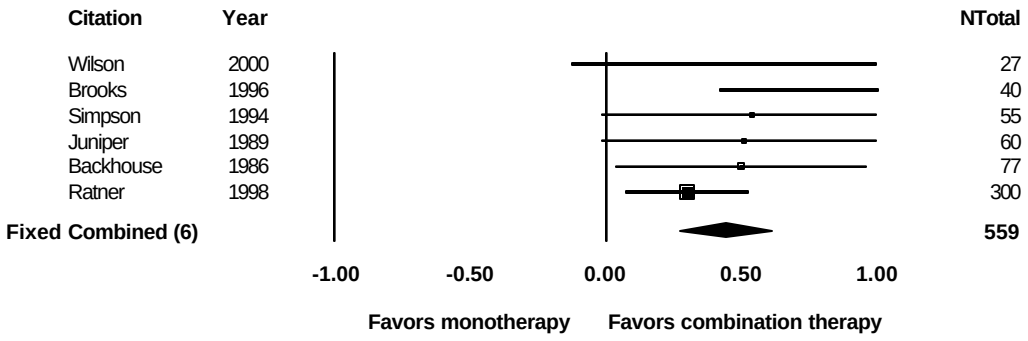

Figure 8. Meta-analysis of trials comparing antihistamine + nasal glucocorticoid combinations versus nasal glucocorticoid alone: effect size based on differences in nasal symptom severity

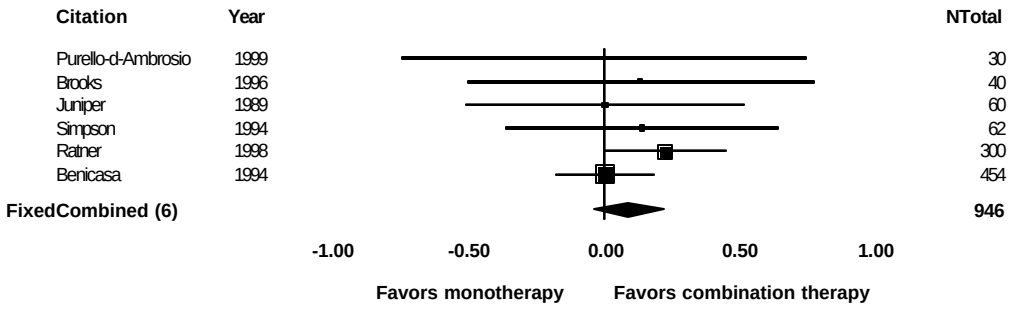

Table 13. Summary of types of data reported in studies abstracted in Evidence Table 1

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

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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

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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

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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

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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

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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

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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

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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

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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

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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

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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)