Cost-Effectiveness of Second-Generation Antihistamines and Montelukast in Relieving Allergic Rhinitis Nasal Symptoms

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Objective: Allergic rhinitis imposes a significant health and economic burden both on individuals and the healthcare system. Second-generation prescription antihistamines, levocetirizine, fexofenadine, and desloratadine, and the leukotriene receptor antagonist, montelukast, differ in their ability to relieve common rhinitis symptoms. The purpose of this study was to compare the cost-effectiveness of prescription agents based on their effectiveness in relieving nasal symptoms.

Methods: Effectiveness was measured as the composite of nasal symptoms, including congestion, rhinorrhea, and sneezing, from clinical studies that compared each of the 4 comparators to placebo. Direct costs included prescription therapy and rhinitis-related physician office visits. Physician office visit costs were collected from an analysis of the PharMetrics insurance claims database. Sensitivity analyses were conducted using a Monte Carlo simulation to assess the robustness of the average and incremental cost-effectiveness ratios.

Results: The cost per clinically significant improvement of nasal symptoms for levocetirizine was less than for the other model comparator agents. The incremental cost-effectiveness ratio for levocetirizine dominated montelukast and desloratadine and was lower than either branded or generic fexofenadine.

Conclusion: Levocetirizine is a cost-effective therapy for the relief of nasal symptoms of allergic rhinitis. [*AHDB*. 2008;1(8):26-34.]

Allergic rhinitis (AR) is one of the most common chronic conditions in the United States, affecting approximately 40 million people.[1] Although AR is rarely considered a severe medical condition, its bothersome symptoms, such as sneezing, rhinorrhea, and congestion, can negatively affect important domains of quality of life, including sleep, social interaction, and work.[2-7] In a recent large national survey of adults with AR, 78% of those surveyed indicated that nasal congestion was a moderately or extremely bothersome symptom of AR.[5] Other nasal symptoms often cited as moderately to extremely bothersome included runny nose (62%), postnasal drip (61%), and repeated sneezing (51%).[5]

As such, the goal of therapy is to relieve the symptoms associated with AR. Antihistamines have long been a mainstay of AR therapy. Second-generation antihistamines (SGAs) are some of the most widely prescribed medications in the United States and cause fewer adverse effects, including sedation and anticholinergic activity, than first-generation antihistamines.[8]

The prevalence of AR results in significant economic burden associated with symptom treatment.[5-7,9] Estimates of the economic burden of AR in the United States range from $1.4 billion to nearly $6 billion in direct costs annually.[7,8,10] Goetzel and colleagues estimated that allergies were the fifth most expensive condition for employers when factors such as presenteeism, absenteeism, and direct medical costs were all taken into account.[11] These estimates probably understate the full economic impact because they do not

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consider spending on over-the-counter (OTC) products. One estimate of spending on prescription and nonprescription AR agents placed the cost at more than $6 billion annually (in 2000 US dollars).[10]

Despite the sizable economic burden of AR, there are no studies that compare the cost-effectiveness of the different SGAs or alternative oral AR therapies, such as the leukotriene-receptor antagonist montelukast (Singulair). Only 1 cost-effectiveness study has considered SGAs, but that study compared the choice of SGAs to older, first-generation antihistamines that produced a significant sedating effect.[12] Current treatment patterns call for more advanced modeling that directly compares the economic outcomes of treatment patterns with newer agents. The current analysis was designed to assess the cost-effectiveness of reducing nasal symptoms with the recently US Food and Drug Administration (FDA)-approved SGA levocetirizine (Xyzal) relative to other prescription SGAs and to montelukast, which is FDA-approved for seasonal AR treatment.

KEY POINTS

- The direct costs of allergic rhinitis to the US economy are estimated at $1.4 billion to $6 billion annually.
- In 2004, allergies were estimated to represent the fifth most expensive condition for employers when considering presenteeism, absenteeism, and direct medical costs.
- The goal of this study was to inform US formulary and benefit design decision makers about the relative cost-effectiveness of available treatments for allergic rhinitis.
- In this first cost-effective comparison of the various second-generation antihistamines and the leukotriene-receptor antagonist montelukast, levocetirizine had the lowest average cost per clinically significant improvement in nasal symptom score, followed by generic fexofenadine.

Methods

The goal of this study was to inform US formulary and clinical decision makers in managed care organizations about the relative cost-effectiveness of treatments for AR. Since it is common for payers to exclude OTC products from prescription benefit coverage, this study was limited to products available by prescription during the first quarter of 2008. The analysis included the SGAs levocetirizine, desloratadine (Clarinex), and fexofenadine (Allegra; branded and generic), and montelukast. The model was constructed using a 1-year time frame. The target population for this analysis was patients diagnosed with AR and treated with a single prescription therapy for symptom relief. The model excluded patients with asthma requiring daily corticosteroid treatment and focused on the use of SGAs and a leukotriene receptor antagonist as monotherapy for the treatment of AR. Although combination therapy with an SGA and montelukast is occasionally used to treat the symptoms of AR, combination therapy was excluded in this analysis because this would introduce additional heterogeneity into the model.

The effectiveness measure chosen as the basis for this model was a composite nasal symptom score (NSS), defined as the average effect size for each comparator versus placebo for 3 nasal symptoms: rhinorrhea, nasal congestion, and sneezing. Improvement in composite NSS was chosen as the outcome measure of interest because of the documented burden of nasal symptoms in patients with AR.[5] Other AR symptoms, such as ocular and nasal itching, were not included because of insufficient information in published clinical trials to calculate an effect size for each comparator or because the measure differed across model comparator agents.

To estimate treatment effectiveness, we calculated the standardized mean difference (SMD) for each study reporting a significant improvement in study drug compared with placebo. Relevant studies were identified by searching MEDLINE from 1950 to May 2007 using the comparator names levocetirizine, fexofenadine, desloratadine, and montelukast, in combination with the terms nasal symptoms, allergic rhinitis, rhinitis, congestion, obstruction, rhinorrhea, discharge, sneezing, itching, pruritus, and NSS. Additional studies were located by reviewing the reference lists of applicable articles.

Trials investigating the efficacy of at least 1 of the model comparator agents in patients with AR were included in the model. In addition, trials had to be randomized, blinded, placebo-controlled, and exclude individuals with asthma requiring daily corticosteroid use. Studies had to have patients rate the severity of at least 1 of the following individual nasal symptoms throughout the duration of the trial on an ordinal scale: congestion, rhinorrhea, or sneezing. Outcomes that were physician-reported or that comprised more than 1 symptom (ie, nasal/eye itching) were excluded. Trials had to be a minimum of 7 days to be included in the analysis. Furthermore, studies had to disclose patient-reported individual symptom score results for study inclusion. When clinical trials reported individual symptom scores at various time points throughout a study, it was decided a priori to extract data from the latest time period for data analysis. Studies involving patients aged younger than 12 years were excluded because not all end points

Table 1 Nasal Symptom Score Standardized Mean Differences, 95% CI

	Levocetirizine	Fexofenadine (generic)	Fexofenadine (brand)	Desloratadine	Montelukast
Nasal congestion	–0.366 (–0.495, –0.236)	–0.250 (–0.344, –0.157)	–0.250 (–0.344, –0.157)	–0.241 (–0.320, –0.162)	–0.173 (–0.225, –0.121)
Sneezing	–0.402 (–0.532, –0.273)	–0.327 (–0.419, –0.236)	–0.327 (–0.419, –0.236)	–0.309 (–0.383, –0.235)	–0.211 (–0.263, –0.159)
Rhinorrhea	–0.408 (–0.538, –0.278)	–0.289 (–0.375, –0.202)	–0.289 (–0.375, –0.202)	–0.228 (–0.300, –0.157)	–0.190 (–0.242, –0.138)
Average	–0.392	–0.289	–0.289	–0.259	–0.191

CI indicates confidence interval.

Table 2 Model Inputs

Treatment arm	Annual drug cost, $*	Annual medical cost, $†	Total cost, $	Effectiveness, marginal probability of significant improvement in NSS, $‡	Effectiveness, probability of significant improvement in NSS, $‡
Levocetirizine	203	284	487	11	27
Desloratadine	249	326	575	7	23
Fexofenadine (generic)	168	326	494	8	24
Fexofenadine (branded)	216	326	542	8	24
Montelukast	275	356	631	5	21

*Annual drug cost assumes 90-day therapy annually and daily wholesale acquisition cost.
†Annual outpatient allergy visit costs based on an analysis of the PharMetrics database.
‡The fourth column shows the marginal effect given treatment with the target drug (the fifth column minus 33%). The fourth column was used in the cost-effectiveness analysis calculations. The fifth column shows the proportion of the population with a mean below the threshold after treatment at baseline.
NSS indicates nasal symptom score.

were available for pediatric patients. Data were extracted from studies only when the total daily dose was the FDA-approved total daily dose for the age-group of patients included in that particular study.

A total of 25 clinical trials met the inclusion criteria (**Appendix, page 33**)[13-37]; an additional 27 studies were excluded. The SMD between the comparator and the placebo group was calculated for each study using the following equation:

$$\text{SMD} = \frac{\text{Difference in mean outcome between comparator and placebo}}{\text{Standard deviation}}$$

The pooled SMD across all studies was calculated as the weighted average of the studies for that model comparator agent, where the weight for each study was the inverse of the variance (1/variance). To convert the individual symptom score SMD into a usable measure for the cost-effectiveness ratio, a composite NSS was created as the average of the SMD for nasal congestion, rhinorrhea, and sneezing.

The composite NSS represents improvement in standard deviation units. For the cost-effectiveness analysis, this measure was converted to the probability of clinically significant improvement, which required 3 steps. First, the baseline mean and standard deviation for each symptom were calculated from published clinical trials and averaged to form a composite mean and standard deviation. Second, the postintervention mean was calculated as the baseline mean plus the SMD multiplied by the baseline standard deviation:

Postintervention mean = baseline mean + (SMD baseline standard deviation).

Third, the postintervention mean was translated into the probability of significant improvement by comparing the proportion of the study population below the clinically significant improvement threshold at baseline to the proportion of the study population below the threshold, given use of each of the comparators.

The threshold for significant improvement in nasal symptoms has not been well-defined. For the purposes of our model, a 25% placebo-adjusted improvement from baseline in the composite NSS was defined as the threshold for clinically significant improvement. The proportion of the population meeting or exceeding a 25% reduction over placebo in the baseline mean was calculated as the area under the normal curve. The marginal probability of significant improvement was defined as the marginal difference in the proportion of the population that was below the threshold for significant improvement. For example, if, at baseline, 30% of the population was below the significant improvement threshold, and after treatment with drug X 50% of the population was below the significant improvement threshold, then the marginal probability of clinically significant improvement was 20%.

Drug costs for the model were calculated as the expected days of therapy per year multiplied by the daily wholesale acquisition cost.[38] The model assumed 90 days of therapy for a calendar year. The costs of AR-related physician office visits were calculated from an analysis of the proprietary PharMetrics dataset for a 1-year period from July 1, 2005, to June 30, 2006. Patients were included in the analysis if they had a diagnosis of AR without a diagnosis of asthma. Treatment groups were created based on the first treatment agent.

An analysis found limited switching. Pharmacy and outpatient visit costs were inflated to 2007 dollars by Bureau of Labor Statistics series CUUR0000SAM.[39] Levocetirizine was approved in May 2007 and was not available in the United States during the period in which the PharMetrics data were captured; therefore its costs were imputed using a linear fit of the effect size for the composite NSS to the physician office visit costs for the other model comparator agents. Laboratory costs are often billed as part of the physician office visit, so they are not a separate component. Inpatient costs were not included because they would rarely be observed as a result of AR. Indirect costs were not included in the model because productivity has not been assessed in clinical trials for all comparators. Models were run separately, including just drug costs and drug costs plus the cost of AR-related office visits.

Results of the comparative cost-effectiveness analysis are presented as average and incremental ratios, including 95% confidence intervals (CIs). The average cost-effectiveness is calculated as the ratio of costs to the probability of clinically significant improvement. The incremental cost-effectiveness ratio (ICER) is calculated as the ratio of the difference in cost to the difference in the probability of clinically significant improvement for any comparator relative to levocetirizine.

$$ICER = \frac{Cost_{levocetirizine} - Cost_{desloratadine}}{Effectiveness_{levocetirizine} - Effectiveness_{desloratadine}}$$

To understand the variability in the cost-effectiveness estimates, a Monte Carlo simulation was performed. The SMD and the total cost were varied by ±10%. Random draws were run 1000 times using Microsoft Excel 2003, Service Pack 2. The 95% CIs for the cost-effectiveness ratios were calculated as the 26th and 974th ordered values in the simulation. Significance for a cost-effectiveness ratio is defined by whether the CI overlaps the point estimate for the cost-effectiveness ratio. Significance for an ICER is defined as a CI around the point estimate that does not overlap 0.0.

Results

The effectiveness of the model comparator agents (as measured in the 25 studies[13-37]) is shown in **Table 1**. The effectiveness of each agent is presented as the SMD relative to placebo (95% CI). All comparators showed statistically significant improvement in the 3 NSSs compared with placebo (all statistically significant).

Table 2 presents the annual drug and medical costs by model comparator agent and the effectiveness of each agent. The imputed medical visit costs of levocetirizine were lower than the other comparators. Montelukast medical visit costs were higher than for the other comparators. Annual AR drug therapy costs, assuming 90 days of therapy, ranged from $168 to $275.

Results of this decision-analytic model for AR using combined prescription drug and AR-related physician office visit costs are shown in **Table 3**. (Results from the prescription drug–only model were similar.) Cost-effectiveness ratio is defined as the cost per clinically significant improvement in composite nasal symptoms. Levocetirizine had the lowest average cost per clinically significant improvement in NSS, followed by generic fexofenadine. The average cost-effectiveness ratio for levocetirizine was significantly lower compared with all other model comparator agents.

Table 3 Cost-Effectiveness Ratios for Treating Nasal Symptoms

Treatment arm	Significant symptom improvement: CER, $	95% CI: CER, $	ICER, $	95% CI: ICER, $
Levocetirizine	4343	(3712, 5075)	n/r	n/r
Desloratadine	8190	(7013, 9611)	–2107	(–4586, –82)
Fexofenadine (generic)	6236	(5305, 7342)	–205	(–3134, 2389)
Fexofenadine (brand)	6841	(5824, 7992)	–1658	(–5393, 797)
Montelukast	12,556	(10,717, 14,694)	–2335	(–4064, –858)

CER indicares cost-effectiveness ratio; CI, confidence interval; ICER, incremental CER; n/r, not calculated/reference group.

The **Figure** shows the ICER for each model comparator agent relative to levocetirizine. Negative ICERs can reflect either lower cost and higher effectiveness or higher cost and lower effectiveness, so they are conventionally reported as dominated to avoid confusion. The comparisons between levocetirizine and montelukast and between levocetirizine and desloratadine are significant. The remaining ICERs overlapped zero. Another way to put these ICERs in context is to examine how many times the simulated ICER was negative, which indicated that levocetirizine dominated the comparator in that simulation. In the comparison between levocetirizine and branded fexofenadine, the simulated ICER was negative 898 times (90%). In the comparison between levocetirizine and generic fexofenadine, the ICER was negative 576 times. ICERs that are positive require a tradeoff between cost and effectiveness.

Discussion

To our knowledge, this is the first time the cost-effectiveness of individual SGAs and montelukast has been compared for the relief of nasal symptoms of AR. This is surprising given the prevalence and economic impact of AR symptoms. As the most prevalent respiratory condition in the United States, AR affects approximately 20% of the US population.[40] The symptoms of AR are often bothersome, resulting in decreased quality of life. A national survey revealed that 66% of AR sufferers polled felt that AR had some effect on their daily lives.[5] The model results in this article, indicating a significant difference in the cost-effectiveness of the different SGAs and montelukast for the treatment of AR, can assist managed care decision makers in determining economically efficient AR treatment options.

This current analysis was designed to assess the cost-effectiveness of levocetirizine compared with other oral prescription medications available for AR symptom management. One of the reasons that such an analysis has not been undertaken before now may be due to the lack of standard outcome measures across AR studies. The symptoms of AR manifest in myriad ways, including itchy and watery red eyes, itchy palate, nasal congestion, rhinorrhea, nasal pruritus, and sneezing. Most clinical trials of AR measure efficacy in terms of improvement from baseline in a composite NSS. The difficulty in comparing composite NSS across clinical trials is that the composite NSS is often a uniquely defined set of symptoms for each clinical trial. To overcome this obstacle, we chose to synthesize a composite NSS based on 3 individual scores often reported in the literature—nasal congestion, rhinorrhea, and sneezing.

The clinical trial designs used to construct the composite nasal symptoms differed in several ways: (1) The populations ranged in age from 12 to 75 years; (2) the observation time varied from 7 days to 6 months; (3) we did not include studies conducted in environmental exposure units that measured outcomes over very short intervals; and (4) the studies were not designed as head-to-head comparisons.

Nasal congestion has been reported as a bothersome symptom by patients with AR.[5] Although some may argue that nasal congestion should not be part of the NSS for an evaluation of SGAs because decongestants or intranasal steroids are superior at relieving nasal congestion, there are instances when decongestants or intranasal steroids may not be the appropriate or preferred therapy. For example, because decongestants can cause difficulty sleeping, an antihistamine or montelukast may be the preferred therapy for night-time relief of AR symptoms. Furthermore, decongestants are not recommended for use in individuals with high blood pressure, thyroid disease, or those taking certain antidepressants. Finally, some patients do not want to take steroids or prefer an oral drug to an intranasal spray; in

such cases, an antihistamine or montelukast may be prescribed even to a patient with nasal congestion.

To make the denominator of the cost-effectiveness ratio more meaningful for decision makers, we converted the SMD in our composite NSS to the probability of a clinically significant improvement (defined a priori as at least a 25% improvement in NSS over placebo). This method accounts for the placebo effect often observed during AR clinical trials. Because we compared the placebo-adjusted change from baseline, our results are generally conservative.

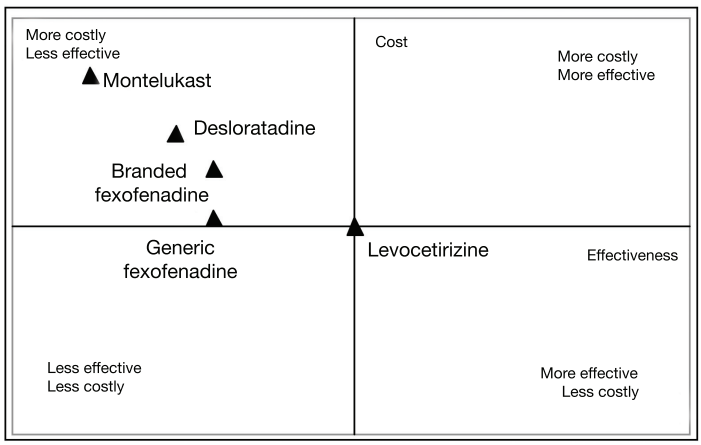
This model indicated that levocetirizine is more effective and less costly than montelukast and desloratadine for the management of nasal symptoms of AR in patients without asthma requiring daily corticosteroid use. Because the 95% CIs of the ICERs comparing levocetirizine to branded and generic fexofenadine cross zero, levocetirizine does not have complete dominance over these comparators. Thus, a tradeoff is warranted in some cases, taking into account the higher effectiveness of levocetirizine compared with the lower cost of generic fexofenadine.

Although a number of prescription and OTC medications are approved for AR symptom relief, the objective of this analysis was to assess the cost-effectiveness of SGAs and montelukast, relative to levocetirizine. Only comparators available by prescription were included because the model perspective was that of a managed care organization; many health plans do not reimburse for OTC medications. Cetirizine (Zyrtec) was excluded because it became available OTC at the end of 2007.

The generalizability of our results to the overall population of patients with AR may be limited by our decision to exclude clinical trials that enrolled patients with AR and concomitant asthma requiring daily corticosteroid use. It is estimated that nearly 40% of those with allergies also have asthma.[9] And between 60% and 78% of patients with asthma have AR.[9] Montelukast is indicated for the management of asthma and AR, whereas the SGAs are not FDA-approved for asthma. Therefore, we chose to eliminate studies involving patients with asthma requiring daily corticosteroids so as to not bias the results with respect to montelukast. Because the majority of AR patients are not asthmatic and/or do not require daily steroid inhalation, our results likely apply to a substantial portion of patients with AR who would be seen in a managed care population.

The model included direct costs only, specifically drug costs and costs of outpatient physician office visits for AR. Studies indicate a sizable amount of the economic burden associated with AR is due to lost productivity from absenteeism and presenteeism.[11,41] In an employee survey, Lamb and colleagues found that employees with AR were absent roughly 3.6 days annually because of AR and lost 2.3 hours per workday in productivity when symptoms were present.[41] Indirect costs were excluded from the analysis because of lack of relevant data substantiating differences between comparators. This may be because most AR clinical trials are of a short duration. Costs associated with lack of effectiveness and adverse events are also not accounted for in this model.

Figure Incremental Cost-Effectiveness Ratios



Note: A treatment is said to be dominated if an alternative exists that is more effective and less costly.

The lack of a standardized outcome measure across AR trials presented some challenges. Because we specifically defined the 3 individual symptoms that served as the basis of our composite NSS, some data concerning the efficacy of each comparator agent may not have been fully captured. Our choice to use common nasal symptoms as the basis of the effectiveness measure does not take into account AR symptoms that affect other body parts (eg, eyes, palate, or throat).

Construction of a synthetic NSS created a point estimate of the effect size versus placebo for each model comparator agent without CIs. Therefore, a sensitivity analysis, which varied the effect size and the cost estimates by a defined percentage, was undertaken to assess the robustness of the model results. This differs somewhat from what could have been done if the model used a single symptom score and an exact CI around the effectiveness estimate. Conversely, the CI around individual symptom scores is dependent on sample

size; so if only a few small studies provide data on a symptom, they would have wide CIs that overstate what would be observed in larger trials. Additional trials of these agents would tighten all CIs and strengthen our conclusions.

Conclusions

Levocetirizine is cost-effective for the relief of nasal symptoms of AR in patients without severe asthma compared with other second-generation prescription antihistamines and the leukotriene receptor antagonist, montelukast. The ICERs of levocetirizine versus the other model comparator agents showed that it dominated montelukast and desloratadine and was favorable compared with the other products. ■

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Appendix Studies Included in This Analysis

Author, date	Compound(s)	Treated patients, N	Congestion	Nasal itch	Rhinorrhea	Sneezing	Ocular itching
Bachert, 2004[13]	Levocetirizine	257	x	x	x	x	x
Berger, 2002[14]	Desloratadine	166	x	x	x	x	
Berger, 2006[15]	Desloratadine Fexofenadine	257 260	x		x	x	
Bernstein, 1997[16]	Fexofenadine	141	x		x	x	
Bronsky, 1998[17]	Fexofenadine	138	NS		x	x	
Casale, 1999[18]	Fexofenadine	287	x		x	x	
Chervinsky, 2004[19]	Montelukast		x	x	x	x	
Ciebiada, 2006[20]	Desloratadine Levocetirizine Montelukast	20 20 20	x	x	x	x	
Ciprandi, 2004[21]	Desloratadine Levocetirizine	10 10	x	x	x	x	
Ciprandi, 2005[22]	Desloratadine Levocetirizine	10 10	x	x	x	x	
Howarth, 1999[23]	Fexofenadine	211	x		x	x	
Kurowski, 2004[24]	Montelukast	11	x	x	x	x	x
Meltzer, 2006[25]	Desloratadine	108	NS	x	x	x	
Nayak, 2001[26]	Desloratadine	172	x				
Nayak, 2002[27]	Montelukast	155	x	x	x	x	x
Patel, 2005[28]	Montelukast	1002	x	x	x	x	
Philip, 2002[29]	Montelukast	348	x	x	x	x	x
Potter, 2003[30]	Levocetirizine	150	x	x	x	x	x
Pradalier, 2007[31]	Desloratadine	234	x	x	x	x	
Raphael, 2006[32]	Desloratadine	190	x	x	x	x	x
Salmun, 2002[33]	Desloratadine	171	x	x	x	x	
Simons, 2003[34]	Desloratadine	337	NS	x	x	x	
van Adelsberg (spring), 2003[35]	Montelukast	522	x	x	x	x	
van Adelsberg (fall), 2003[36]	Montelukast	448	x	x	x	x	
Wilson, 2002[37]	Desloratadine Fexofenadine	49	x		x		

All studies required patients with allergic rhinitis. NS indicates not significant ($P < .05$).

Stakeholder Perspective

Relieving Nasal Symptoms: Uncommon Excellence in a Common Clinical Condition

Scholarly and rigorous, richly annotated with relevant references, with very precise descriptions of methodology and every assumption used within the analysis, this article represents one of the only published analyses of economic burden using prospective, placebo-controlled trial data for this class of frequently used compounds. Although analyses regarding use and cost of new-generation antihistamines have been presented elsewhere using retrospective database review (eg, Lee J, et al. *Am J Manag Care*. 2001;7:S103-S112), cost-effectiveness data presented using clinical trials data are the first for second-generation antihistamines and montelukast and provide an exceptional example of methodological rigor applied to a ubiquitous clinical condition.

The perspective for the analysis was that of a managed care decision maker within the United States with the intent of informing formulary and clinical decision makers. A composite of patient-reported outcomes, as opposed to physician-reported measures, was used as the dependent variable, a threshold for clinically important change was defined, and fully justified assumptions regarding drug cost as well as pharmacy and outpatient visit cost are included. Only adult patients using monotherapy without asthma and daily corticosteroid treatment are considered. The absence of clinical trial data for certain parameters, such as the indirect costs of absenteeism and presenteeism, precluded their incorporation in the model, thus adhering to the standard for methodological rigor adopted by the authors, while retaining the managed care perspective as intended.

Appropriate to the perspective adoptive, only prescription medication was considered. The number of trials/compound, the number of subjects within each study used to estimate effectiveness, the number of key individual nasal symptoms reported/study, and the comparability of the patient population in each of the studies in the database are presented. Sensitivity analyses varying the effect size of each medication and cost estimates qualify the interpretation.

Results provide insight regarding cost-effectiveness for second-generation antihistamines versus the leukotriene receptor antagonist, montelukast, in allergic rhinitis. However, it is the approach to this question, as much as the result of the analysis that warrants attention. The limitations of the database, in fact, provide insights for cooperative research among multiple stakeholders. By appreciating the algorithm used in cost-effectiveness analyses, the design of prospective clinical trials for investigational agents can be significantly informed. Patient characteristics, including the type and severity of comorbid conditions and permitted concomitant medication optimized for detection of an effect in a clinical trial population, may not be as informative for evaluating healthcare utilization in a clinical care environment as they can eschew patients disproportionately contributing to those estimates. Similarly, outcome measures suitable for registration purposes may be incomplete for cost-effectiveness modeling. Knowledge of optimal parameters for model construction can be captured by clinical trialists a priori, in the design stage of a registration program, substantially facilitating the perspective of multiple stakeholders.

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