

Economic Evaluation of Quality-of-Life Improvement with Second-Generation Antihistamines and Montelukast in Patients with Allergic Rhinitis

Kim R. Saverno, RPh; Brian Seal, PhD; Michael J. Goodman, PhD; Kellie Meyer, PharmD



Kellie Meyer

Background: Allergic rhinitis causes significant economic losses and substantial reductions in quality of life. Improving a patient's symptoms can therefore enhance the patient's quality of life.

Objective: To measure the relative cost-effectiveness of prescription second-generation antihistamines (levocetirizine, desloratadine, and fexofenadine) and montelukast based on their impact on quality of life in patients with uncomplicated allergic rhinitis.

Methods: A retrospective, cost-effectiveness model was constructed using 1-year costs to managed care payers and using the Rhinoconjunctivitis Quality of Life Questionnaire to measure the quality of life in patients taking prescription second-generation antihistamines or montelukast for the treatment of allergic rhinitis. Clinical trial results for levocetirizine, desloratadine, fexofenadine (brand and generic), or montelukast were combined as standardized mean differences to create a pooled effectiveness measure.

The costs of prescription drugs and physician office visits for allergic rhinitis were used as direct costs measures. Sensitivity was assessed by a Monte Carlo simulation run 1000 times.

Results: All the drugs in the study showed significant improvement in quality of life, with levocetirizine showing the greatest improvement. The incremental cost-effectiveness of levocetirizine dominated montelukast (incremental cost-effective ratio, -1317; 95% confidence interval, -7471, -212). The incremental cost-effectiveness favored levocetirizine compared with desloratadine and branded fexofenadine.

Conclusion: There are significant differences in the cost-effectiveness of various oral prescription agents with regard to improving quality of life of patients with allergic rhinitis. [*AHDB*. 2009;2(7):309-316].

Allergic rhinitis (AR) has a significant detrimental effect on a patient's quality of life (QoL), affecting sleep, normal daily activities, and work.^{1,4} Stempel and Woolf estimated that the 50 million Americans with AR spend more than \$6 billion annually on prescription and nonprescription medications to relieve AR symptoms.^{5,6} Despite a growing body of literature on the effect of AR on QoL, there is a paucity of studies that use QoL findings to assess the cost-effectiveness of various agents used to treat AR. The recent US Food and Drug Administration (FDA) approval of the second-generation antihista-

mine (SGA) levocetirizine, and the lack of studies that compare the cost-effectiveness of oral AR treatments in terms of QoL led to the present analysis.

Although estimates of economic impact vary widely, AR clearly has important economic implications for managed care, employers, and patients. Specifically, estimates of the direct costs to US payers range from \$1.4 billion to \$6 billion annually.^{5,7,8} These estimates may be low, however, because they exclude substantial spending on over-the-counter (OTC) allergy medications, a cost that is largely borne by the patient.⁵ In addition, indirect costs realized by employers through presenteeism and absenteeism represent a significant burden. When these indirect costs are considered in conjunction with direct healthcare costs, allergies are ranked as the fifth most expensive chronic condition for employers.⁹

Lack of rigorous economic evidence has not slowed the adoption of newer SGAs, which are among the

Ms Saverno is a graduate student in Pharmaceutical Economics, Policy, and Outcomes, University of Arizona College of Pharmacy, Tucson; Dr Seal is Senior Director, sanofi-aventis, Bridgewater, NJ; Dr Goodman is Assistant Professor, University of Utah College of Pharmacy, Salt Lake City; Dr Meyer is Associate Director, Xcenda, Palm Harbor, FL.

KEY POINTS

- ▶ Despite a growing understanding of the effect of allergic rhinitis on quality of life, few studies have assessed the cost-effectiveness of various agents for this condition based on quality-of-life improvements.
- ▶ This study compared the cost-effectiveness of levocetirizine and other prescription second-generation antihistamines and the widely used leukotriene receptor antagonist montelukast in terms of quality-of-life improvements.
- ▶ It shows that levocetirizine is a cost-effective option and offers clinically meaningful improvement in quality of life.
- ▶ Levocetirizine is cost-effective compared with montelukast and its cost-effective ratios are favorable compared with the other comparators in this analysis.

most widely prescribed medications in the United States. SGAs have the advantage of fewer side effects, including less sedation, than older antihistamines,¹⁰ making them more acceptable to many patients. The purpose of this study was to estimate the comparative cost-effectiveness of QoL improvements associated with major prescription agents used for AR management.

To date, no cost-effectiveness studies have compared individual SGAs to one another or to alternative oral AR treatments based on QoL improvements. One cost-effectiveness study compared SGAs with older, first-generation antihistamines that produced a significant sedating effect.¹⁰ However, current treatment patterns call for more advanced modeling that directly compares economic outcomes of treatment patterns with newer agents.

The present study was conducted from the perspective of prescription benefit managers from US health plans; therefore, OTC products were not included.

A recent study by some of the present authors compared the cost-effectiveness of SGAs to one another and to alternative AR treatments based on clinical symptom improvement.¹¹ Our current analysis builds on that study by assessing the cost-effectiveness of levocetirizine relative to other prescription SGAs and the widely used leukotriene receptor antagonist montelukast in terms of QoL improvements reported by clinical trials. The present study was conducted from the perspective of pre-

scription benefit managers from US health plans; therefore, OTC products were not included.

Methods

We used a decision-analytic cost-effectiveness model developed from the perspective of managed care decision makers and using costs over a 1-year time period. US payers typically do not include OTC products in their benefit design; therefore, our treatment comparators were limited to prescription products, including the SGAs levocetirizine, desloratadine, and fexofenadine, and the leukotriene receptor antagonist montelukast, which is also FDA approved for AR treatment.

The study population included patients with AR who had been treated with an SGA monotherapy or with montelukast. Although combination therapy with an SGA and montelukast is sometimes used for AR symptoms, combination therapy was excluded in this analysis, because clinical trial evidence supporting such combination therapy is limited, which would limit the generalizability of our findings. Patients with asthma requiring daily corticosteroid treatment were excluded, to preserve homogeneity of the population.

The Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) was selected for our model, because it is specific to AR, widely used, validated, and has a specific clinical interpretation.^{1,2,12-14} The RQLQ includes 28 items on 7 disease-specific domains: activity limitations, practical problems, nonrespiratory symptoms, nasal symptoms, eye symptoms, emotional function, and sleep. The outcome measure in our model was the composite of all 28 items.

We conducted a MEDLINE search to identify eligible articles between January 1950 and May 2007, using the comparator names *levocetirizine*, *fexofenadine*, *desloratadine*, and *montelukast* in combination with the terms *RQLQ*, *QoL*, and *Rhinoconjunctivitis Quality of Life Questionnaire*. Additional studies were identified by searching the references listed in these studies. Eligible studies had to (1) include monotherapy with an FDA-approved dose of one of the model comparator agents; (2) be randomized, blinded, and placebo-controlled; (3) exclude patients with asthma requiring daily corticosteroids; and (4) include RQLQ as an outcome. Study length had to be 14 to 90 days. Patients' age had to be 11 years or older. A total of 12 studies were included in the analysis.¹⁵⁻²⁶

For each study, the standardized mean difference (SMD) between the comparator and placebo was calculated as a ratio of the RQLQ outcome to the standard deviation (see Goodman and colleagues¹¹). To convert

the pooled SMD into a usable measure for the cost-effective ratio, the baseline mean and standard deviation of the RQLQ for placebo and the comparator were combined. Using the baseline mean and the standard deviation as the untreated standard, the mean marginal RQLQ score, assuming treatment with each comparator after removing the effect of placebo observed in the trials, was calculated as the baseline mean plus the SMD multiplied by the standard deviation.

A clinically relevant improvement was defined as a 0.5-point reduction from baseline in marginal RQLQ score—after removing the effect of placebo—which was used as the threshold for clinically relevant improvement. In contrast, Juniper and colleagues' definition does not remove the effect of placebo.¹ Our definition, although conservative, is consistent with the standards for cost-effectiveness analysis. The proportion of the population 0.5 points below the baseline mean was calculated using standard formulas for computing the area under the normal curve. The probability of clinically relevant improvement was defined as the marginal difference in the proportion of the population below the threshold for clinically relevant improvement.¹¹

Drug costs were calculated as the expected days of therapy in a year multiplied by the daily wholesale acquisition cost.²⁷ The model assumed 90 days of therapy for a calendar year. Medical costs for allergy-related physician office visits were calculated from an analysis of the proprietary PharMetrics dataset for a 1-year period for each model comparator agent. Medical costs were inflated to 2007 dollars, using the Bureau of Labor Statistics.²⁸

Because levocetirizine was not available in the United States when the PharMetrics data were captured, its costs were imputed using a linear fit of the RQLQ effect size to the physician's office visit costs for the other model comparator agents, based on a simple linear regression. Indirect costs, such as productivity, were not included, because they were not assessed in the original trials used for our analysis, and because the model's perspective was that of a third-party payer.

The comparative cost-effectiveness of the agents was calculated as the ratio of costs to the probability of clinically relevant improvement. Incremental cost-effective ratio (ICER) between agents was evaluated as the ratio of difference in cost to difference in probability of clinically relevant improvement for any alternative therapy relative to levocetirizine.

A Monte Carlo simulation, which varied the total cost by $\pm 10\%$, was used to obtain 95% confidence

Table 1 Mean QoL Effect Sizes Based on RQLQ

Comparator	Mean effect size vs placebo
Desloratadine	-0.360 (95% CI, -0.539, -0.180)
Fexofenadine ^a	-0.201 (95% CI, -0.301, -0.101)
Levocetirizine	-0.418 (95% CI, -0.573, -0.262)
Montelukast	-0.213 (95% CI, -0.267, -0.159)

^aStudies for brand and generic fexofenadine were used to calculate the mean effect.
CI indicates confidence interval; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire.

interval (CI) values. The effectiveness measure (SMD) for each product varied within the 95% CI range for the pooled SMD across each comparator. Random draws were run 1000 times (using Microsoft Excel 2003, Service Pack 2). Exact 95% CI values for the cost-effective ratios were calculated as the 26th and 974th ordered values in the simulation.

Significance for a cost-effective ratio was defined by a CI that did not overlap the point estimate; significance for an ICER was defined as a CI that did not overlap 0.0.

Results

Effects on Quality of Life

Table 1 compares the mean QoL effect size for each comparator agent versus placebo. All comparators were significantly better than placebo in improving QoL.¹⁵⁻²⁶ Levocetirizine demonstrated greater QoL improvement (-0.418; 95% CI, -0.573, -0.262), as measured by the pooled RQLQ SMD, than desloratadine (-0.360; 95% CI, -0.539, -0.180), montelukast (-0.213; 95% CI, -0.267, -0.159), or fexofenadine (-0.201; 95% CI, -0.301, -0.101).

Table 2 summarizes the annual drug and medical expenditures for each comparator, as well as each agent's efficacy, expressed as the probability of a clinically relevant improvement in RQLQ. The medical costs for AR physician office visits were highest for montelukast. Annual AR drug costs, assuming 90 days of therapy, ranged from \$168 to \$275. Column 5 of Table 2 translates the SMDs into a probability of clinically relevant improvement. Applying these probability estimates to a population of 10,000 AR patients, levocetirizine would lead to clinically relevant improvement in an additional 810 patients compared with montelukast, or 231 additional patients compared with desloratadine.

Cost-Effectiveness

Table 3 outlines the results of this study. Levocet-

Table 2 Model Inputs: Probability of QoL Improvement (Efficacy) Based on RQLQ Values

Treatment arm	Annual drug cost, \$	Annual medical cost, \$	Total cost, \$	Marginal probability of a clinically significant RQLQ improvement, % ^a	Probability of a clinically significant RQLQ improvement, % ^a
Levocetirizine	203	322	525	16.1	49.1
Desloratadine	249	326	575	13.8	46.8
Fexofenadine (generic)	168	326	494	7.6	40.6
Fexofenadine (brand)	216	326	542	7.6	40.6
Montelukast	275	356	631	8.0	41.0

^aAt baseline, assuming a normal distribution, 33% of the sample had RQLQ values below the threshold for clinically significant improvement (0.5 points difference). Column 6 shows the proportion of the population with a mean below the threshold after treatment. Column 5 shows the marginal effect given treatment with the target drug (the last column minus 33%). Column 5 was used in the cost-effectiveness analysis calculations. RQLQ indicates Rhinoconjunctivitis Quality of Life Questionnaire.

Table 3 Cost-Effectiveness Ratios

Treatment arm	CE ratio, cost per patient with clinically significant improvement, \$	ICER, \$ ^a
Levocetirizine	3255 (95% CI, 2293, 5238)	—
Desloratadine	4165 (95% CI, 2704, 8167)	-2189 (95% CI, -10,138, 17,275)
Fexofenadine (generic)	6535 (95% CI, 4183, 12,866)	361 (95% CI, -1166, 3574)
Fexofenadine (brand)	7168 (95% CI, 4625, 13,770)	-198 (95% CI, -3241, 1186)
Montelukast	7871 (95% CI, 5990, 10,721)	-1317 (95% CI, -7471, -212)

^aNegative ICERs are dominated. CE indicates cost-effective; CI, confidence interval; ICERs, incremental cost-effective ratios.

irizine had the lowest average cost (\$3255) for a clinically relevant RQLQ improvement, followed by desloratadine (\$4165). Montelukast had the highest cost (\$7871) per clinically relevant RQLQ improvement and lower efficacy compared with the other comparators.

When the ICERs are positive, a tradeoff is required between cost and effectiveness.

Negative ICERs (Table 3) can reflect either lower cost and higher effectiveness or higher cost and lower effectiveness, which are generally reported as “dominated.” All the comparators in this study are less effective in terms of RQLQ improvement than levocetirizine. Generic fexofenadine is less costly than levocetirizine but results in lower RQLQ improvement. The other comparators have lower RQLQ improvement and are more costly than levocetirizine.

The statistical significance of the ICERs is shown with CI values. The wide CI values reflect the relatively small sample sizes and the resulting large variation in the RQLQ measures in the Monte Carlo simulation. Only the comparison between levocetirizine and montelukast is significant (95% CI, -7471, -212). Because the CIs overlapped zero for the other comparators, another way to understand ICERs is to examine how many times the simulated ICER is negative, which indicates that levocetirizine dominated the comparator in that simulation. The number of negative ICERs of 1000 simulations is 601 for desloratadine, 273 for generic fexofenadine, 644 for branded fexofenadine, and 993 for montelukast. In the case of desloratadine, negative ICERs indicate that 60% of the time levocetirizine has greater RQLQ improvement and is less costly.

When the ICERs are positive, a tradeoff is required between cost and effectiveness. The tradeoff for a positive ICER is between lower cost and lower effectiveness

for one product compared with higher cost, as well as greater clinical benefit for the other. For example, the positive ICER for generic fexofenadine (Table 3) reflects its lower cost and lower impact on RQLQ compared with the greater clinical benefit of levocetirizine. Decision makers will need to weigh the additional clinical benefit against the additional cost.

Discussion

The 4 model comparators vary substantially in their ability to improve QoL for patients with uncomplicated AR. This variation, combined with significant variation in the costs of the comparators, make this cost-effectiveness analysis important for formulary decision makers, clinicians treating AR, and patients undergoing treatment. The results favor levocetirizine, which has the lowest average cost-effective ratio.

To our knowledge, this is the first published analysis of the cost per patient with clinically relevant improvement in RQLQ of the individual SGAs and the only leukotriene receptor antagonist indicated for the treatment of AR. This is surprising given the prevalence and the large economic impact of AR in direct and indirect costs. Sullivan and colleagues noted that the lack of a standard outcome measure across AR studies could contribute to the scant number of studies about cost-effectiveness of AR therapies.²⁹

The effectiveness measure in the present study is important clinically and is consistent with the need for economic decisions that focus on QoL.³⁰ The choice to use the RQLQ as the basis of our cost-effectiveness model was based on several factors. The RQLQ is reproducible, can assess the impact of treatment over multiple dimensions, and has a strict clinical interpretation that has been validated in many studies.^{1,12-14} Our results, however, are conservative. To make the denominator of the cost-effectiveness ratio consistent with standards in economic modeling, we removed the effect observed for placebo from the calculation of clinically relevant improvement. This reduces the number of persons in a population whom we classify as having clinically relevant improvement. A change that is smaller than the clinically relevant threshold may nevertheless represent meaningful improvement in symptom relief for many patients. An alternative measure, the number needed to treat to achieve 1 person with improvement, has been suggested for interpreting the RQLQ.³¹

Our analysis was designed specifically to assess the cost-effectiveness of levocetirizine relative to other oral prescription medications for the management of AR symptoms, where effectiveness is defined as clinically

relevant improvement in RQLQ. Our model indicates that levocetirizine has greater RQLQ improvement and is less costly than montelukast for the management of AR in patients without asthma who require daily corticosteroids. However, because the 95% CI of the ICERs comparing levocetirizine with the other comparators cross zero, levocetirizine does not have complete dominance over the SGA comparators.

Several prescription and OTC medications are approved for the relief of AR symptoms, including nasal corticosteroids, antihistamines, decongestants, and leukotriene receptor antagonists.

The 95% CI of the ICER comparing levocetirizine with desloratadine was wide ($-\$10,138$ and $\$17,275$, respectively; Table 3) for 2 reasons. First, only 2 trials had usable data for changes in RQLQ for levocetirizine, and only 1 study for desloratadine. With such few studies, the resulting variability from the SMD in RQLQ score was large. Second, the difference in probability of a clinically relevant improvement between the 2 drugs was small (16.1% and 13.8%, respectively). When the denominator in an ICER is a probability, a small difference between the 2 comparators leads to very large CI estimates. As additional comparator-specific information on QoL becomes available, the precision of these estimates will be increased and judgments about their relative effectiveness and cost-effectiveness will become more accurate.

Overall, the ICER CI values were very wide, which again reflects the lack of multiple studies for the comparators. For example, the variation for montelukast is smaller than for desloratadine, because there are more montelukast trials with RQLQ data. Although the results are valid for the specific sample sizes, the relatively small number of studies results in CI values that might have obscured effects of clinical significance for improved QoL.³²

Several prescription and OTC medications are approved for the relief of AR symptoms, including nasal corticosteroids, antihistamines, decongestants, and leukotriene receptor antagonists. Although the use of these agents and combination therapy is common for AR management, it was unreasonable to include all these options in our analysis, because of the lack of RQLQ outcomes data and because of the sheer number

of potential comparators. We therefore opted to include comparators available only by prescription, because our goal was to address issues relevant to prescription drug benefit managers. Many health plans do not reimburse for OTC medications.³³

Our model included direct costs only, specifically drug costs and outpatient physician office visit costs for AR. The literature indicates that a sizable amount of the economic burden associated with AR is because of lost productivity from absenteeism and presenteeism.³⁴ An employee survey showed that employees with AR were absent roughly 3.6 days annually due to this condition and lost 2.3 hours per workday in productivity when symptoms were present. In our analysis, indirect costs were excluded due to lack of data substantiating differences in indirect costs between individual model comparators, which may be related to the short duration of most AR clinical trials. Other costs not accounted for in our model include costs associated with lack of effectiveness and adverse events.

Our analysis shows that levocetirizine is a cost-effective option for the treatment of AR that produces clinically meaningful improvement in QoL based on the RQLQ.

Limitations

Several potential limitations of this study warrant discussion. Our rigorous inclusion criteria might have led to unintended bias. For example, Meltzer and colleagues only reported on the significance of a single RQLQ domain, so this study was not included in our analysis.³⁵

In addition, the AR patient population is broad, ranging from young children to the elderly and from relatively healthy patients to patients with severe respiratory conditions. Our decision to exclude clinical trials that enrolled children younger than 11 years old or AR patients with concomitant asthma treated with daily corticosteroids does not accurately reflect the overall population with AR. It is estimated that nearly 40% of individuals with allergies have asthma.³⁶ Furthermore, 60% to 78% of individuals with asthma have AR.³⁶ Montelukast is FDA-approved for the management of asthma and AR, whereas the SGAs are not approved for the treatment of asthma.³⁷⁻⁴⁰ Therefore, we chose to eliminate studies involving patients with asthma requiring daily corticosteroids so as to not bias the results with respect to montelukast. About 40% of individuals younger than age 12 suffer from AR.⁶

Therefore, although our results are robust to the general population, specific subpopulations are not represented, and the cost-effectiveness in the young and in those with significant comorbidities remains to be examined in future research.

We also did not include OTC SGAs, such as loratadine and cetirizine, in our analysis. We believe that this is justified, because the audience for this study is health plan decision makers. Historically, when drugs have been moved to an OTC status, this typically has removed them from coverage by managed care.⁴¹ Therefore, our intended audience is served by this exclusion. In addition, cost and QoL data are not available for all OTC agents.

We only included physician office visits and AR drug costs, and excluded costs for emergency department visits or hospitalizations. Patients with AR without asthma are unlikely to be hospitalized, visit the emergency department, or use additional drugs.

There may be some limitations to using the PharMetrics database to obtain the cost inputs for the analysis. For example, diagnosis codes from claims are based on payment rather than on clinical practice. Therefore, diagnoses from claims data may be less specific than diagnoses or narrative in a medical record. This limitation, however, is offset by the coding bias being consistent across all comparators. In addition, the PharMetrics data contain few elderly patients; however, as with the coding bias noted, this should result in a consistent effect across all comparators.

We also did not separate seasonal and perennial AR. All the agents included in our analysis have an indication for both seasonal and perennial AR, except for fexofenadine, which is only indicated for seasonal AR. In addition, the availability of the clinical trial data would have been limited if we separated our analysis by seasonal and perennial AR, potentially reducing the robustness of the QoL estimates.

Finally, we did not formally analyze statistical heterogeneity in our calculation of comparative effectiveness. Because our goal was to model the economics rather than conduct a full-fledged meta-analysis of comparative effectiveness of AR medications, it was beyond this study's scope to rigorously exclude studies that might introduce heterogeneity. Estimates derived from a full meta-analysis would provide tighter CI values for effectiveness measures, but they would also limit the generalizability of the results.

Conclusion

Our analysis shows that levocetirizine is a cost-

effective option for the treatment of AR that produces clinically meaningful improvement in QoL based on the RQLQ. Levocetirizine is cost-effective compared with montelukast, and its cost-effective ratios are favorable compared with the other comparators in this analysis. Further research is warranted to assess patients with AR and comorbid asthma who require daily corticosteroids and in younger populations, as well as to address the effect of different therapies on indirect costs of AR.

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Disclosure Statement

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STAKEHOLDER PERSPECTIVE

Allergic Rhinitis: A Serious Condition with Many Safe and Effective Pharmaceutical Options

Allergic rhinitis can be a very devastating chronic condition, affecting patients' ability to work productively, hamper their desire for recreation activities, and even prevent a restful sleep. The present article by Meyer and colleagues focuses on quality-of-life (QoL) issues that patients with allergic rhinitis may struggle with on a daily basis. The article also makes a comparison between the second-generation non-sedating antihistamines and montelukast as alternatives for the treatment of this disease.

The good thing is that many safe and effective pharmaceutical products are available that work well for the treatment of the symptoms associated with allergic rhinitis, allowing patients to have normal, productive, and active lives. The many pharmaceutical products available work in a number of ways, including oral systemic products and nasally inhaled products.

PAYERS: Payers will typically have copay incentives for patients to use medications that may be available as generics, or even older products, such as some of the first-generation non-sedating antihistamines that are available over the counter (OTC) and provide relief from the symptoms of allergic rhinitis. These same copay incentives may also apply for nasally inhaled products that may be more attractive than the copay a patient may have for second-generation non-sedating antihistamines or for montelukast.

PATIENTS: Patients can take advantage of inexpensive products for this condition or reduced copays and often have good results in getting symptomatic relief and increased QoL, while avoiding having to deal with a cost difficulty for their medication.

Patients working closely with their physician can reach the best decision of what type of medication will enable them to have their best response to the treatment and enhance their ongoing QoL.

PROVIDERS: Physicians have a large arsenal of medications available to combat allergic rhinitis and often may not be driven to use the more expensive second-generation non-sedating antihistamines or montelukast, unless a patient is unable to get symptomatic relief from first-line products, or the patient has had an adverse reaction to a systemic or a nasally inhaled medication.

CARE STRATEGY: The care strategy that all stakeholders have to consider involves far more than just limiting the decision to a choice among the second-generation non-sedating antihistamines. Stakeholders—including providers, patients, and payers—can have a profound effect on the patient's well-being by working together to use proven clinical guidelines and medication choices according to the best interest of each patient. This allows the optimization of patients' QoL, while also focusing on the best overall treatment cost, whether using an OTC agent for those who are able to take advantage of these options, prescription medications, or a second-generation non-sedating antihistamine or montelukast, if that is determined to be the best treatment for the individual patient.

Paul Anthony Polansky, BSPHarm, MBA
Executive VP & Chief Pharmacy Officer
Sanovia Corporation, Philadelphia, PA