

ORIGINAL RESEARCH

Keys to successful management of patients with allergic rhinitis: Focus on patient confidence, compliance, and satisfaction

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OBJECTIVE: The American Academy of Otolaryngic Allergy (AAOA) convened an expert, multidisciplinary Working Group on Allergic Rhinitis to discuss patients' self-treatment behaviors and how health care providers approach and treat the condition.

PROCEDURES AND DATA SOURCES: Co-moderators, who were chosen by the AAOA Board of Directors, were responsible for initial agenda development and selection of presenters and participants, based on their expertise in diagnosis and treatment of allergic rhinitis. Each presenter performed a literature search from which a presentation was developed, portions of which were utilized in developing this review article.

SUMMARY OF FINDINGS: Allergic rhinitis is a common chronic condition that has a significant negative impact on general health, co-morbid illnesses, productivity, and quality of life. Treatment of allergic rhinitis includes avoidance of allergens, immunotherapy, and/or pharmacotherapy (ie, antihistamines, decongestants, corticosteroids, mast cell stabilizers, anti-leukotriene agents, anticholinergics). Despite abundant treatment options, 60% of all allergic rhinitis patients in an Asthma and Allergy Foundation of America survey responded that they are "very interested" in finding a new medication and 25% are "constantly" trying different

medications to find one that "works." Those who were dissatisfied also said their health care provider does not understand their allergy treatment needs and does not take their allergy symptoms seriously. Dissatisfaction leads to decreased compliance and an increased reliance on multiple agents and over-the-counter products. Furthermore, a lack of effective communication between health care provider and patient leads to poor disease control, noncompliance, and unhappiness in a significant portion of patients.

CONCLUSIONS: Health care providers must gain a greater understanding of patient expectations to increase medication compliance and patient satisfaction and confidence.

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The importance of allergic rhinitis in the clinical practice of general practitioners and specialists prompted the American Academy of Otolaryngic Allergy (AAOA) to convene a Working Group on Allergic Rhinitis in Chicago on January 6, 2006. The expert, multidisciplinary Working Group includes allergists, pediatricians, otolaryngologists,

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family physicians, and a pharmacist. Their presentations and discussion focused on how health care providers approach and treat the condition and patient-treating behaviors, as well as societal impact and managed care issues. Findings from a consumer survey sponsored by the Asthma and Allergy Foundation of America (AAFA) were also presented and discussed.¹ Barriers to patient satisfaction were explored and strategies were identified to help health care providers better meet allergy patients' needs.

The Working Group concluded that health care providers must gain a greater understanding of patient expectations to increase medication compliance and patient satisfaction and confidence.

METHODS

The Working Group co-moderators were chosen by the AAOA Board of Directors. The co-moderators were responsible for initial agenda development and identification of appropriate individual and organizational participants. Participants were chosen based on personal expertise in areas included in the agenda and their representation of a variety of health care concerns involved in diagnosis and treatment of allergic rhinitis.

Once confirmed, all participants met by phone to discuss and approve a final program agenda. The co-moderators and participants agreed to the structure of the Working Group meeting, presentation topics, and parameters for each presenter's topic. Each presenter performed his own literature search and created his own presentation. All presentations were reviewed by the co-moderators in advance of the meeting to ensure continuity and to minimize overlap among presentations.

Role of the Sponsor

Alcon Laboratories provided an unrestricted educational grant to AAOA in support of the Working Group meeting and a resulting publication. The content of the meeting and the publication, as well as the publication format (ie, the decision to publish findings as a supplement) were at the sole discretion of the Working Group.

AAOA contracted with the Cooney/Waters Group, a medical communications company located in New York City, to assist in logistical planning, publication research, and editorial support for all Working Group activities.

EPIDEMIOLOGY AND SOCIETAL IMPACT OF ALLERGIC RHINITIS

Allergic rhinitis, commonly referred to as hay fever, is an inflammatory condition of the nasal mucosa caused by an exaggerated immunologic (immunoglobulin E [IgE]) response to an allergen. Patients may experience symptoms (eg, nasal congestion and discharge, sneezing, pruritus) only

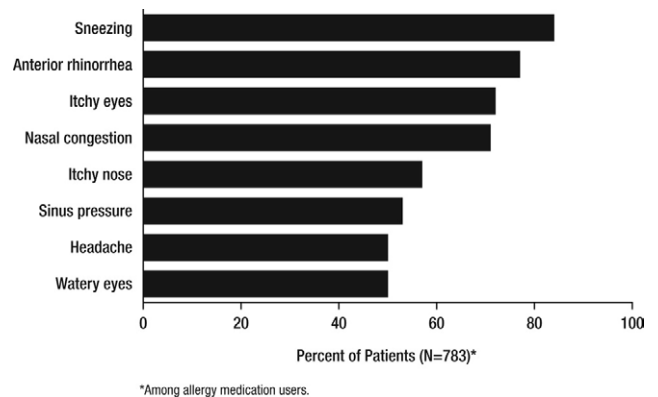


Figure 1 Major symptoms of allergic rhinitis.⁷

during a discrete time(s) of the year (seasonal rhinitis) due to exposure to an outdoor allergen(s) (eg, pollens, environmental molds, foods), whose presence varies seasonally. Others experience symptoms year-round (perennial rhinitis), generally caused by exposure to indoor allergens (eg, animal dander, dust mites). Since 40% of patients suffer from both seasonal and perennial rhinitis,² allergic rhinitis is increasingly classified by frequency and severity of symptoms.³⁻⁵

Epidemiology: There are 30 to 50 Million Allergic Rhinitis Sufferers in the U.S.

Allergic rhinitis is the second leading cause of chronic disease in the U.S.,⁶ with half of affected persons having suffered from the illness for over 10 years.⁷ A total of 35 to 50 million Americans, and at least one person in 25% of U.S. households, is affected by allergic rhinitis each year.^{5,8} The U.S. prevalence of allergic rhinitis has been estimated at 10% to 30% in adults and up to 40% in children,⁶ with the rate having increased substantially over the last 15 years.⁹ A number of theories have been raised to explain the increasing prevalence of allergic rhinitis in developed countries, among them: increased exposure to indoor allergens due to poor ventilation in modern buildings and the increasing tendency for people and their pets to stay indoors; increased exposure to environmental pollutants (eg, tobacco smoke, vehicle exhaust); and dietary and lifestyle factors.

Clinical Findings: Allergic Rhinitis Symptoms can be Debilitating

Allergic rhinitis is characterized by sneezing, rhinorrhea, nasal discharge, nasal congestion, itchy/watery eyes, and/or headaches (Fig 1).⁷ Histamine and leukotrienes are the primary mediators of these symptoms. The symptoms of allergic rhinitis are not only bothersome, but also are perceived by many affected patients as serious and debilitating. When asked about their symptoms, 59% of patients with allergic rhinitis consider their condition moderately severe or severe,⁷ yet one in five feel their health care provider does not take his or her allergy symptoms seriously enough (see section on "Patients also dissatisfied with their health

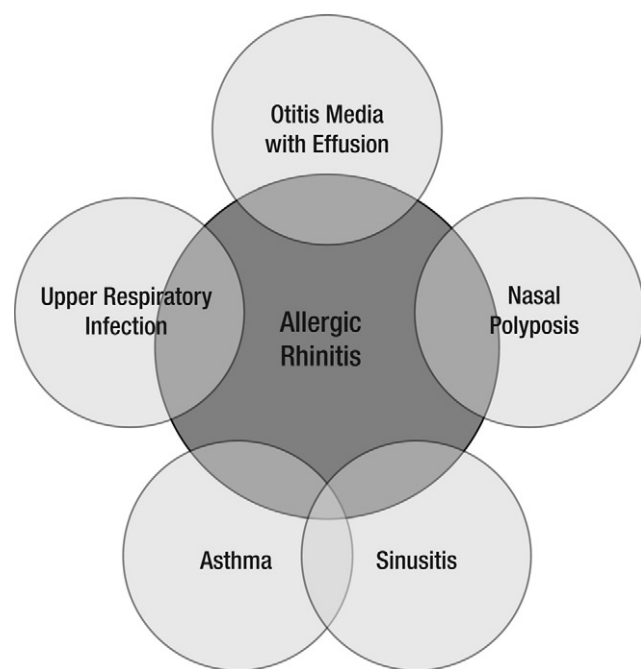


Figure 2 Allergic rhinitis and co-morbid airway disease. (Reprinted with permission.¹⁰)

care providers”). Of note, most patients (~80%) do not seek medical care for treatment of their symptoms; they self-manage their illness with one or more over-the-counter medications, which they select based on the most troubling symptom(s).

Co-morbid Respiratory Diseases are Common in Patients with Allergic Rhinitis

The impact of allergic rhinitis is greater than most health care providers and consumers recognize. While considered by many health care providers to be a bothersome but otherwise inconsequential illness, the burden of illness with allergic rhinitis can be substantial. The majority of patients with allergic rhinitis also suffer from a variety of common, as well as serious, chronic respiratory illnesses (Fig 2).¹⁰

There is an increased association of allergic rhinitis in patients with sinusitis, with 25% of those with acute sinusitis,¹¹ 40% of those with chronic sinusitis, and 80% of those with bilateral disease¹² also having allergic rhinitis. Half of children with otitis media also suffer from symptoms of allergic rhinitis.^{6,10,13}

About 40% of allergic rhinitis patients have asthma and 80% of asthma patients also suffer from allergic rhinitis.^{6,13} In a nested case-control study, which included 173 incident patients with asthma and 2177 subjects with wheezing but without asthma or shortness of breath, rhinitis was determined to be a significant risk factor for asthma, with an odds ratio of 3.2 after adjusting for years of follow-up, age, gender, atopic status, smoking status, and presence of chronic obstructive pulmonary disease.¹⁴ The relationship between allergic rhinitis and asthma is further supported by physiological and immunopathological data as well as the response of co-existing asthma symptoms and improvement in pulmonary function following treatment of allergic rhinitis.¹⁵⁻¹⁷

Sleep disturbance, with its many known adverse sequelae, is also common in patients with persistent allergic rhinitis (defined as more than 4 days per week over a period of more than 4 weeks) that is moderate or severe.¹⁸

Impact on Quality of Life and Functioning

The documented effects of allergic rhinitis on quality of life,^{19,20} learning²¹ (see section on “Compliance and adherence from the allergic rhinitis patient’s perspective”), cognitive processing/memory,²² decision making,²² and psychosocial well-being²³ are substantial. Problems with self-image (attractiveness) as a consequence of allergic rhinitis have also been described.²⁴

The impact that allergic rhinitis has on quality of life is illustrated by the results of a population-based study by Meltzer et al.¹⁹ Declining health status was observed among allergic rhinitis patients, as compared to controls, based on statistically significant effects on general health, physical and social functioning, pain, and vitality as assessed by the Medical Outcomes Study Short Form Health Survey (SF-36) (Fig 3A)

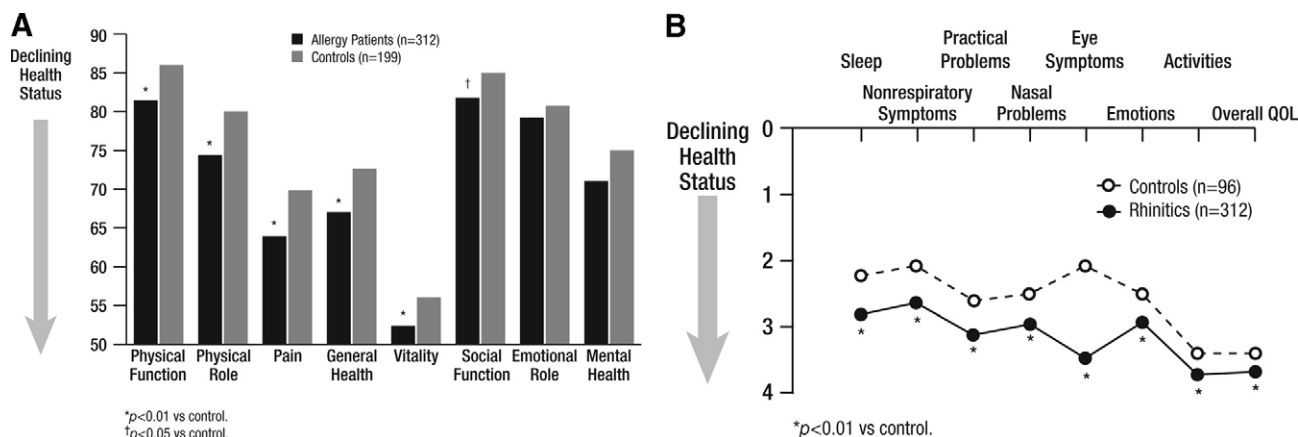
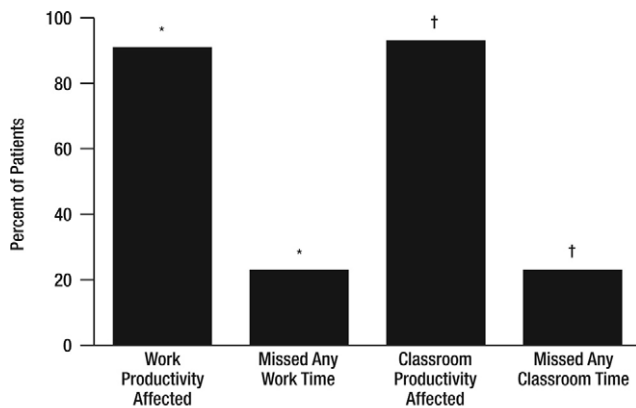


Figure 3 Allergic rhinitis decreases quality of life. (Adapted and reprinted with permission.¹⁹) (A) SF-36 survey. (B) RQLQ.



*n=1,425 employed patients, †n=556 student patients.
Note: Some patients were both employed and students.

Figure 4 Allergic rhinitis decreases employment/school attendance and productivity. (Adapted and reprinted with permission.²⁵)

and sleep, emotions, activities, and other measures as assessed by the Rhinoconjunctivitis Quality-of-Life Questionnaire (RQLQ) (Fig 3B). Similar impairment in quality-of-life dimensions was observed by Bousquet et al.²⁰

The U.S. Health Care System Spends Billions Annually on Allergic Rhinitis

The financial impact of allergic rhinitis is staggering. Allergic rhinitis accounts for three million lost work days and two million lost school days each year. In a survey (RQLQ) of allergic rhinitis patients published in 1999, almost one in four revealed that they missed some time from work or school (Fig 4).²⁵ Among those who continue with their commitments, the majority report their productivity at work and in the classroom is decreased when they are suffering from seasonal allergic rhinitis (Fig 4).²⁵ Using the Work Productivity and Activity Impairment (WPAI) instrument, Meltzer et al documented 23% to 42% work impairment in a study of 845 patients with moderate to severe seasonal allergic rhinitis symptoms.²⁶ In a health/wellness screening conducted in 2001-2002 at 47 U.S. employer locations, 55% of employees reported experiencing allergic rhinitis symptoms for an average of 52.5 days over the previous 12 months, having missed 3.6 days of work per year and being unproductive for 2.3 hours per day while they were symptomatic.²⁷ The employees who cared for a child with allergic rhinitis were absent from work for 3.7 days per year and reported 3.6 nonproductive hours per workday while the child was symptomatic.

The U.S. health care system spends billions of dollars yearly on direct and indirect costs of allergic rhinitis.²⁸ Direct costs alone for allergic rhinitis as a primary diagnosis were estimated (in 2002 dollars) at \$2.4 billion; as a secondary diagnosis (eg, secondary to asthma, otitis media, sinusitis) the estimate rose to nearly \$5 billion. And, while many patients with allergic rhinitis do not seek medical care, approximately 15.2 million office visits to health care

providers were attributed to allergic rhinitis in 2003.²⁹ The impact that allergic rhinitis has on other illnesses (as previously described) has obvious, although difficult-to-quantify, financial implications. And, work absenteeism and productivity losses from allergic rhinitis also have financial implications.

In 1997, the Center for Outcomes Research created a model to estimate the costs of rhinitis.³⁰ The employer cost/benefit model included direct costs (ie, procedures, allergy testing, physician visits, medications) and indirect costs (ie, days lost from work and lost work/school productivity). While secondary costs for sinusitis were accounted for, those of other co-morbidities were not. From that model, the annual estimated cost of rhinitis in the U.S., almost a decade ago, was \$7.9 billion. The cost of missed days/productivity losses in the Center for Outcomes Research calculation of \$3.4 billion was in line with the attributable costs of work productivity losses in 2000 of \$2.4 to \$4.6 billion, as estimated by Crystal-Peters et al.³¹

ARE WE MEETING PATIENT NEEDS? HIGHLIGHTS OF THE ASTHMA AND ALLERGY FOUNDATION OF AMERICA (AAFA) CONSUMER SURVEY

There are many ways consumers access information about allergic rhinitis (eg, Internet, television, another affected person). There is also rapid growth in the number of medications available—both prescription and over-the-counter—for allergic rhinitis treatment. With this in mind, the AAFA commissioned Harris Interactive to conduct a survey to gauge the knowledge of U.S. adult allergic rhinitis patients about their condition and their attitudes toward their medication regimen and the health care providers who treat them for their symptoms.

Survey Methodology

Harris Interactive conducted an online survey on behalf of AAFA from October 10 to 17, 2005, using its Chronic Illness Panel database. Harris Interactive is a worldwide market research company that is known for its use of the Internet to conduct scientifically accurate research. Inclusion criteria for the AAFA survey population included: 1) adult (defined as aged 18 and older), 2) diagnosis of seasonal allergies made by a health care professional, and 3) current use of prescription allergy medication to treat allergies. Of the millions of U.S. members in the database (persons who agreed to participate in survey research), 1214 individuals (68% female, mean [SD] age of 48.6 [15.4] years) agreed to participate in this particular survey, met the survey eligibility criteria, and were included in the national survey sample.

The survey consisted of questions designed to: create an allergy sufferer profile (ie, type and severity of symptoms); determine allergic patients' knowledge about their condition

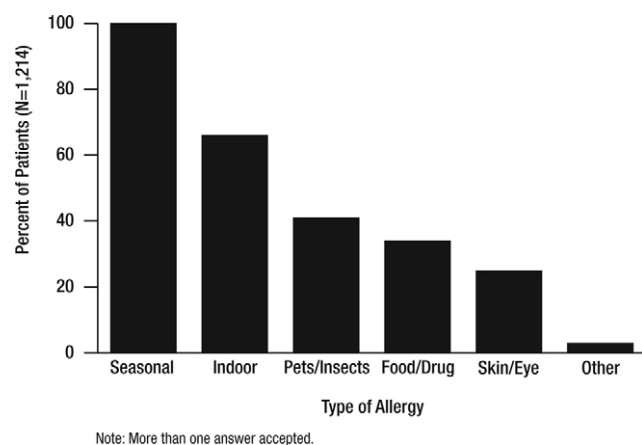


Figure 5 Types of allergies among patients with seasonal allergic rhinitis.

and its treatment; qualify the interaction between allergic patients and their health care professional; and explore the respondents' perception and satisfaction with their allergy medications. It took about 12 minutes for the participants to complete the survey.

Data from the survey were weighted by six variables—age within gender, education, race/ethnicity, region, income, and propensity to be online—to ensure reliable and accurate representation of the total adult allergic rhinitis population. The raw data were weighted by a custom-designed program that automatically develops a weighting factor for each respondent.

Based on the sample size of the survey population, the survey margin of error was $\pm 4.3\%$. Sampling error for the sub-samples of patients who see a health care professional for seasonal allergies ($n = 1194$), patients who are not satisfied with their current prescription allergy medication ($n = 348$), and patients who are not satisfied with the allergy care provided by their doctor or health care provider ($n = 242$) is higher and varies. The online sample was not a probability sample.

Consumer Survey Results: Patients Used Multiple Medications but Remained Dissatisfied

The entire survey population suffered from seasonal allergies, as was required by the inclusion criteria, which most considered severe (28%) or somewhat severe (59%). Allergic rhinitis patients commonly have multiple allergies; this was reflected in the survey population, with 66% also reporting perennial symptoms and sensitivities to indoor allergens (Fig 5). Consistent with results of the 2005 Gallup Poll⁷ (Fig 1), allergic rhinitis in the survey population was characterized most frequently by nasal congestion, sinus pain/pressure, rhinorrhea, and itchy/watery eyes. Asthma was a co-morbid condition of 38% of the respondents, and 26% suffered from migraine headaches. One in seven reported insomnia.

As for their allergy treatment regimen, all used at least one prescription allergy medication (also required by the inclusion criteria) and 47% used 2 or more agents, which was oftentimes supplemented by an over-the-counter allergy product(s) (36% of survey respondents), avoidance of allergens (31%), or immunotherapy (9%), as well as other interventions (eg, acupuncture). For two-thirds (67%), the prescription was for an oral allergy agent, although the majority (81%) were open to treatment with a nasal spray should it provide good symptom relief (70% of all respondents) including quick and long-lasting effects, be inhaled on an “as-needed” basis, and be steroid free (Fig 6).

Patients Also Dissatisfied with Their Health Care Providers

Of the respondents who sought care from a health care provider for their allergic rhinitis, more than two-thirds (70%) said they saw a primary care provider, 13% an allergist, 9% an allied health care professional (eg, nurse practitioner, physician assistant), and 6% an otolaryngologist. Asked about their satisfaction with the care they were receiving from their health care provider, one in five (21%) was only somewhat satisfied or dissatisfied, based on, among other things, the practitioner not spending enough time communicating with them about their condition (48%), their concern that the provider only prescribed certain types of medication (40%), or their belief that the provider did not understand their allergy treatment needs (27%). Among those who were not satisfied with the relief they obtained from their allergy prescription, half (51%) expressed dissatisfaction with the allergy care they received.

Patients' Perceived Allergic Rhinitis Knowledge Exceeds Their Actual Knowledge

While the majority (94%) of patients considered themselves (“somewhat” or “very”) knowledgeable about seasonal allergies, their responses about the etiology of their illness and its treatment suggest otherwise. Seven in 10 (69%) did not identify allergies as a disease of the immune system, and

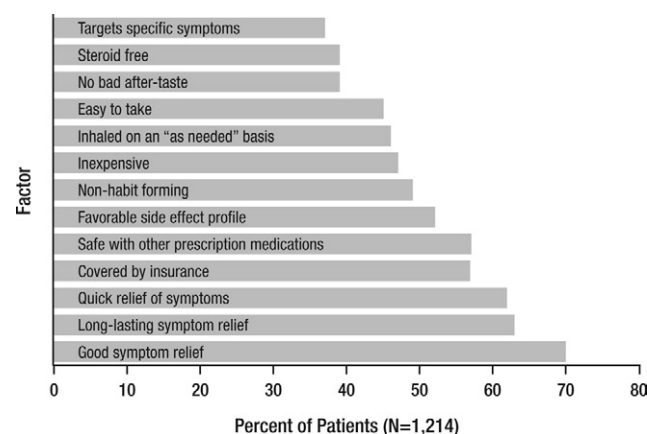


Figure 6 Factors patients want in a new nasal spray for their allergy symptoms.

Table 1
Important features of prescription allergy medication according to allergic rhinitis patients

Feature	Percent of patients
Symptom relief	96
Provides long-lasting relief of symptoms	88
Rapid relief of symptoms	85
Side effects (net)	93
Has minimal side effects (other than causing little to no drowsiness)	84
Does not cause drowsiness	81
Cost (net)	89
Is covered by my health insurance	82
Is inexpensive	65
Can be taken safely with other prescription medications	88
Easy to take	75
Non-habit-forming	75
Dosing flexibility (can be taken on a “prn” basis)	54
Targets specific symptoms	53
Steroid-free	51
No after-taste	47
Other	1

Note: Results from AAFA Allergic Rhinitis Survey, 2005.
 Total survey population = 1214.

almost a third (29%) responded that they did not know what class of allergy medication they were taking (eg, antihistamine, anti-leukotriene agent). Based on the latter finding, it should come as no surprise that half (51%) did not know if their prescription contained a steroid while the same percentage said an important aspect of their medication was that it be steroid-free. These results have important implications for physicians treating allergic patients, because patients' perceived (vs actual) knowledge about allergic rhinitis and its treatment affects their satisfaction. Effective communication between physicians and their allergic rhinitis patients (as discussed in the section “Effective communication needed between providers and patients”) is crucial to patients' understanding of the cause of and treatment for their illness, which influences both medication adherence and outcomes of treatment.

According to the survey results, adults with seasonal allergies who are being treated with prescription allergy medication believe it is important for these medications to provide quick, targeted, and long-lasting symptom relief (Table 1). Although allergic patients know what attributes are important to them in their medication, nearly one-third (31%) responded that they are not fully satisfied with their current prescription allergy medication, which can lead to decreased compliance and increased reliance on over-the-counter products. Almost two-thirds (60%) indicated that they are very interested in finding a new prescription allergy medication, and 26% of patients are “constantly trying dif-

ferent medications to find one that works.” Of those not fully satisfied with their allergic rhinitis prescription medication, 55% wanted a longer period of relief and 44% sought quicker relief. In this regard, most allergy patients (83%) defined “quick” allergy symptom relief as within 30 minutes. More than two in five (42%) allergy patients indicated that they are “confused by all the different prescription allergy medications available today.”

ALLERGIC RHINITIS: A REVIEW OF THE TREATMENT OPTIONS

Allergic rhinitis patients perceive their symptoms to be bothersome and, for many, serious and debilitating, so they want rapid-onset and long-lasting symptom relief without side effects from treatment.^{1,7} There are more than 35 over-the-counter medications (and multiple combination formulations of many of them) as well as 28 prescription medications currently available for relief of allergic rhinitis symptoms (the Appendix).⁵ Despite the large armamentarium, many patients are noncompliant and dissatisfied with their medications. Approximately two-thirds (64%) of allergic rhinitis patients forget to take their medication consistently, and a third consider their drugs ineffective.⁷ Targeted therapy, based on patient characteristics, symptoms (Table 2), and expectations, may increase adherence/compliance and patients' perception of symptom relief.

Appropriate allergy treatment is based on the results of allergy tests, medical history (eg, triggers and seasonality of symptoms, family history of allergies, past and current treatment), and symptom severity and should also take into consideration patient expectations and tolerances. Treatment can include avoidance of allergen, pharmacotherapy, and/or allergen immunotherapy. The treatment plan must also consider co-morbid conditions.

Avoidance of Allergens

Guidelines for the treatment of allergic rhinitis recommend allergen avoidance.³² Although reducing one's exposure to dust, pets, high pollen count, and other triggers will certainly reduce allergen exposure, doing so is impractical for many patients.

Pharmacotherapy for Allergic Rhinitis

The selection of a pharmacologic agent should be based on the underlying etiology and predictability of exposure, pathophysiology of allergy, dominant symptoms and their frequency, drug safety profile, patient's age and health status, co-morbid airway disorders, and patient's drug adherence and preference history.

The available classes of medications for allergic rhinitis treatment—antihistamines, decongestants, corticosteroids, mast cell stabilizers, and anti-leukotriene agents—are summarized below. These medications are most commonly administered either orally or intranasally. Direct delivery of an

Table 2
Symptom relief by drug class^{6,35,36}

	Congestion	Rhinorrhea	Sneezing	Nasal itch	Eye symptoms	Inflammation
Oral antihistamines						
Sedating*	?	+	+	+	+	?
Nonsedating/low-sedating†	?	+	+	+	+	±
Intranasal antihistamines	±	+	+	+	?	±
Decongestants	+	?	?	?	?	?
Intranasal corticosteroids	+	+	+	+	?	+
Oral corticosteroids	+	+	+	±	+	+
Intranasal cromolyn§	±	±	±	±	?	±
Intranasal anticholinergics	?	+	?	?	?	?
Anti-leukotriene agents	+	+	±	±	±	+

+, significant benefit; ?, questionable benefit; ±, mild benefit or current ongoing studies.

*Sometimes referred to as first-generation antihistamines.

†Sometimes referred to as second-generation antihistamines.

§Effect on symptoms when initiated prior to allergen exposure.

effective drug into the nose of a patient with allergic rhinitis has several advantages (Table 3), but also potential problems.³² For instance, many allergic rhinitis patients also present with conjunctivitis and/or asthma, and would therefore require drug delivery by another route in addition to intranasal to achieve therapeutic drug distribution to all target organs.

Intranasal distribution of drug administered via nasal spray is sub-optimal (eg, 50% of a watery spray/powder inhaler), thereby limiting drug delivery to the ostiomeatal complex or to inflamed paranasal sinuses. Furthermore, intranasal drug delivery should be avoided in persons with complete blockage of the nose or nostrils. Medication-specific effects have also been observed (eg, nose bleed with glucocorticoids, nasal dryness, and bloody mucus with ipratropium bromide).

Antihistamines. Exposure to an allergen triggers the release of multiple inflammatory mediators, with histamine having

a major role (Fig 7). Most effects of histamine in allergic disease occur through activation of H₁ receptors. Histamine plays a role in not only the early allergenic response to allergens, but also late response by stimulating the production of cytokines and the expression of cell-adhesion molecules and class II antigens. After being released from mast cells and basophils, histamine dilates blood vessels, increases vascular permeability, and affects the parasympathetic system causing glandular secretion.³⁷

Antihistamines, or H₁ receptor blockers, are the cornerstone of treatment for allergic rhinitis. Clinical studies have demonstrated multi-symptom relief for patients with seasonal and perennial allergic rhinitis,^{38–40} and improvement in quality of life, work productivity, and daily activities.^{26,41} While all H₁ antihistamines block histamine-₁ receptors, leading to symptomatic relief of nasal itching, sneezing, rhinorrhea, and nasal congestion, nonresponders to one may respond favorably to another.⁴² The combination of an H₁ antihistamine and the decongestant pseudoephedrine in a fixed-dose formulation enhances relief of nasal congestion.¹⁶ The efficacy of H₁ antihistamines is comparable or superior to that of the topical mast cell stabilizer cromolyn and similar to that of the leukotriene antagonist montelukast.^{32,43}

H₁ antihistamines are classified into two groups, which helps to characterize their potential for adverse effects: the older, first-generation antihistamines are highly lipophilic and readily cross the blood-brain barrier, and as a result they are sedating, adding to the fatigue and performance impairment associated with allergies.⁴⁴ The alkylamines (eg, chlorpheniramine) are the least sedating, and ethanolamines (eg, diphenhydramine) are the most sedating. The sedative effects of the first-generation antihistamines impair cognitive abilities, psychomotor skills, and driving performance.^{45–47} Work performance studies have also found that employees using first-generation antihistamines sustain the

Table 3
Advantages of intranasal drug administration in patients with allergic rhinitis³²

High drug concentration delivered to the target organ, avoiding or minimizing unwanted systemic effects
Increase bioavailability of some drugs (eg, cromones) that have poor oral bioavailability
Reductions in unwanted systemic effects associated with oral administration of some drugs (eg, glucocorticoids, atropine derivatives)
Faster onset of effect oftentimes associated with intranasal as compared to oral administration (eg, vasoconstrictors, histamine- ₁ [H ₁] antihistamines)

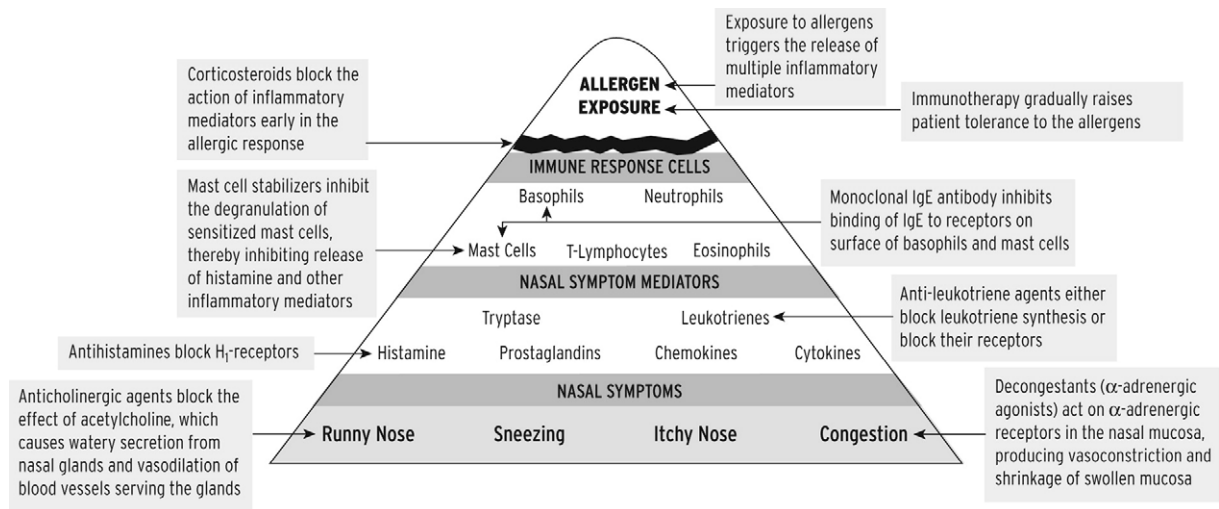


Figure 7 Mechanism of action of anti-allergy medications.

greatest number of work-related injuries, a risk greater than that due to narcotics and sedative hypnotics.^{48,49} Tolerance to the sedation does not develop with chronic treatment.

The use of first-generation antihistamines is also limited by their anticholinergic properties (eg, blurred vision, dry mouth, urinary retention, and constipation).⁴⁴ The anticholinergic effects of the antihistamines contraindicate their use in patients with respiratory disorders such as emphysema and chronic bronchitis and in males with benign prostatic hypertrophy and associated problems with voiding.⁵⁰

In contrast, the newer, second-generation agents do not readily cross the blood-brain barrier due to their lipophobicity, binding preferentially to peripheral H₁-receptors. They cause minimal (cetirizine) to no sedation (desloratadine, fexofenadine, loratadine, olopatadine) at recommended doses, with mental alertness and coordination usually remaining intact during treatment. They also generally lack prominent anticholinergic effects. Reports of corrected QT interval (QTc) interval prolongation and torsades de pointes led to the withdrawal of terfenadine and astemizole from the U.S. market, but lack of similar cardiovascular problems in patients treated with the most recently introduced second-generation agents dismisses concerns about a class effect.⁵¹ The second-generation agents are more costly than the first-generation, over-the-counter antihistamines.

Oral antihistamines generally have an onset of effect within 1 to 3 hours and the duration of effect for many is at least 24 hours, permitting once-daily dosing. Topical (intranasal) H₁ antihistamines have a more rapid onset (<15 minutes), but multiple doses must be given each day. The selection of an H₁ antihistamine should be based primarily on safety profile and the patient's preference for formulation and/or dose regimen.³²

There is currently one prescription antihistamine nasal spray approved in the U.S. In a multi-center, double-blind, randomized, 2-week study, azelastine nasal spray was compared to oral cetirizine in the treatment of 307 patients with

moderate to severe seasonal allergic rhinitis.⁵² At the study endpoint, significant ($P < 0.001$) reductions in total nasal symptom score (TNSS) (combines rhinorrhea, sneezing, itchy nose, and nasal congestion) from baseline were seen in both study groups, with a treatment difference favoring azelastine (29.3% vs 23.0%, $P = 0.015$). A favorable effect on quality of life (RQLQ) was also observed, more so with the antihistamine. In six 2-day to 8-week clinical trials ($n = 391$), the most common adverse event, and that which occurred at a rate significantly higher than with vehicle placebo, was bitter taste (20% of treated patients).⁵³

Decongestants. Oral (ie, phenylephrine, pseudoephedrine) and topical (eg, phenylephrine, xylometazoline, oxymetazoline) α-adrenergic agonists act on α-adrenergic receptors in the nasal mucosa, producing vasoconstriction of the smaller arterioles of the nasal passages that leads to shrinkage of the swollen mucosa and improved ventilation.⁵⁴ Monotherapy with either an oral or intranasal formulation reduces nasal congestion but provides limited relief from other symptoms of allergic rhinitis. The combination of an oral decongestant and second-generation antihistamine provides decongestant efficacy superior to that of either drug alone in patients with seasonal allergic rhinitis.⁵⁵⁻⁵⁷

The recent withdrawal of phenylpropanolamine from U.S. over-the-counter products reflects a new understanding of the hazards of sympathomimetics.^{58,59} Adverse events often reported with the use of systemic decongestants, including cardiovascular stimulation (elevated blood pressure, tachycardia, palpitation, arrhythmias) and central nervous system stimulation (nervousness, excitability, restlessness, dizziness, insomnia), limit the usefulness of oral decongestants for many patients.⁶⁰ Current labeling advises patients with hypertension to avoid pseudoephedrine-containing products unless directed by a physician.⁵⁰

Topical decongestants rarely result in serious systemic side effects, since they are minimally absorbed into the

circulation. More commonly, patients experience propellant- or vehicle-associated local irritation (eg, burning, stinging, sneezing, local dryness) and trauma from the dosage delivery device. More serious effects may result from overuse or prolonged use of an intranasal decongestant. Use of intranasal (α -agonist) decongestants for a period beyond current labeling (3-5 days) commonly causes rebound congestion. Rhinitis medicamentosa—persistent nasal congestion despite frequent administration of the topical decongestant—occurs with chronic use of a topical decongestant.⁶¹

Corticosteroids. Intranasal (topical) corticosteroids are recommended as first-line therapy, especially for patients with moderate-to-severe or persistent symptoms, or when nasal obstruction is problematic.^{62,63} They affect inflammatory response by reducing the number of cells involved in airway inflammation, including eosinophils, mast cells, macrophages, T lymphocytes, and airway epithelial cells.⁶⁴

Currently available corticosteroids are highly potent when administered locally, with clinical efficacy established for late-phase symptoms of allergic rhinitis, including nasal congestion, rhinorrhea, nasal itching, and sneezing.⁶⁵⁻⁶⁸ In comparative studies, intranasal corticosteroids were more effective than an oral H_1 antihistamine alone or combined with a leukotriene antagonist.^{69,70}

In contrast to some of the other classes of anti-allergy agents, the onset of effect with nasal corticosteroids is delayed, taking up to 12 hours to observe significant symptom relief after acute dosing and days to weeks for maximum effect.^{32,71} Many patients will require the addition of an antihistamine for maximum effect.^{72,73} The use of topical steroids on a consistent basis, even in the absence of symptoms, maximizes efficacy and proper administration technique is critical to clinical success.⁷⁴ Demonstrating proper administration techniques to patients and counseling them on reasonable expectations of time to clinical effect is essential.

Intranasal corticosteroids are generally safe, and can be used on a regular basis without mucosal atrophy. Transient, local effects are the most commonly reported adverse events, including nasal bleeding, burning, stinging, and irritation as well as altered taste and smell.^{32,75} Although many fear “corticosteroid-like” adverse effects, patients using intranasal corticosteroids are at very low risk of systemic effects (eg, hypothalamic-pituitary-adrenal axis suppression, growth suppression in children). Increased intraocular pressure and nasal septum perforation are rare.

Mast cell stabilizers. Mast cell stabilizers⁶ (cromolyn sodium) act by inhibiting the degranulation of sensitized mast cells, thereby inhibiting the release of histamine and other inflammatory mediators (eg, prostaglandins, leukotrienes). Their effect on cytokine release also reduces eosinophils and neutrophils, and the activity of sensory nerve endings may also be suppressed. Thus, mast cell stabilizers relieve both early- and late-phase symptoms. They should be initiated be-

fore an anticipated allergen exposure and used daily during the period of exposure associated with allergic rhinitis symptoms. Treatment benefit may require 4 to 7 days of therapy, 2 weeks or more for maximum effect. Cromolyn has been shown to be less effective than intranasal corticosteroids.

The utility of topical cromolyn is mitigated by the necessity for frequent dosing prior to and during exposure (protective effect persists for 4 to 8 hours after inhalation), which adversely affects adherence. As symptoms subside, the number of daily doses should be reduced to address patients' concerns for convenience. The mast cell stabilizers are well tolerated.

Anti-leukotriene agents. Leukotrienes are released in the nasal mucosa following allergen exposure,⁷⁶ leading to increased vascular permeability/edema and mucus production, vasoconstriction, and cellular infiltration. Anti-leukotriene agents control allergic rhinitis symptoms by either inhibiting leukotriene synthesis or blocking their receptors, thereby inhibiting the early phase of antigen response. Montelukast, an oral leukotriene receptor antagonist, is the only agent approved in the U.S. for allergic rhinitis.

In a double-blind, multi-center study, 1302 patients with seasonal allergic rhinitis were randomized to montelukast 10 mg, loratadine 10 mg, or placebo, each administered once daily for 2 weeks.⁷⁷ Both the leukotriene receptor antagonist and the second-generation antihistamine were superior to placebo in relief of nasal symptoms (each $P < 0.001$) and in improvement in quality of life. Other studies have also shown quality-of-life improvements with an anti-leukotriene agent.^{78,79} In a literature review, leukotriene receptor antagonists were no more effective than second-generation (nonsedating) antihistamines, and less effective than intranasal corticosteroids.⁸⁰ The combination of montelukast and antihistamine was superior to monotherapy with either agent,⁴³ although this has not been a consistent finding.⁷⁸

Anticholinergic agents. Cholinergic hyperreactivity has been observed in allergic patients.⁸¹ There also appears to be a cholinergic basis to histamine- and antigen-induced secretion.^{82,83} Rhinorrhea due to allergies and other causes can be safely and effectively alleviated with intranasal anticholinergic agents, such as ipratropium bromide, which inhibit parasympathetic transmission to submucosal glands.⁸⁴ They are muscarinic receptor antagonists with low lipid solubility, resulting in poor absorption across membranes (eg, blood-brain barrier). The most extensively studied anticholinergic agent in allergic rhinitis patients, intranasal ipratropium bromide, exerts its effects locally in the nasal mucosa. Efficacy of ipratropium bromide has been demonstrated in rhinorrhea associated with allergic or nonallergic rhinitis, either alone or in combination with an antihistamine or nasal corticosteroid.⁸⁵⁻⁸⁸ In a study of 533 patients with allergic or nonallergic perennial rhinitis, ipratropium nasal spray and beclomethasone dipropionate nasal spray were both superior to placebo in reducing the severity

and duration of rhinorrhea, with the combination of agents more effective than either one alone.⁸⁸ Of note, however, topical anticholinergics have little effect on other symptoms of allergic rhinitis (eg, postnasal drainage, pruritus, sneezing, nasal congestion).^{84,88}

Immunotherapy

Allergen immunotherapy (also known as allergy shots) is an appropriate approach to treatment for patients whose rhinitis is allergic in etiology (IgE mediated) and due to allergens for which a potent extract is available; symptoms are sufficiently severe to justify the time, expense, and risk of immunotherapy; and exposure to allergens is unavoidable.⁶ The patient's age, co-morbidities, duration and progression of illness, and prior experience with pharmacotherapy should also be considered.

Specific immunotherapy improves recipients' quality of life.⁸⁹ There is also evidence that immunotherapy reduces symptoms and medication reliance,⁹⁰⁻⁹⁴ with clinical benefit sustained on a long-term basis after discontinuation of specific immunotherapy.^{6,95} In a study by Durham et al, continuous specific immunotherapy (for 3 to 4 years) was associated with clinical remission of seasonal allergic rhinitis as well as diminished immunologic activity for up to 3 years after discontinuation.⁹⁶ Immunotherapy for patients with allergic rhinitis may decrease their risk of developing asthma.⁹⁷⁻¹⁰⁰ Specific immunotherapy has also been shown to prevent the onset of new sensitizations.¹⁰¹⁻¹⁰³

A patient's decision to initiate immunotherapy is accompanied by a commitment to frequent office visits, which are required for administration of injections. In addition, the low but serious risk of anaphylaxis is also a concern.¹⁰⁴ Nevertheless, immunotherapy can be an effective therapeutic intervention for suitable patients with seasonal and perennial allergic rhinitis.

Potential Future Therapeutic Options

Sublingual immunotherapy. While the customary (and only reimbursed) route of immunotherapy administration in the U.S. is subcutaneous injection, sublingual delivery is popular in Europe. Since native allergen is undetectable in blood after sublingual administration, drainage into regional lymph nodes is suspected. The efficacy of sublingual immunotherapy (SLIT) is supported by controlled clinical trials performed in Europe in patients with asthma and rhinitis, using single allergen extracts that are not available in the U.S.^{105,106} For example, in a study by Clavel et al, patients with rhinitis, with or without mild asthma, were randomized to SLIT or placebo once daily for 7 months.¹⁰⁷ SLIT significantly ($P < 0.02$ each) improved symptoms and reduced the need for ocular or oral mast cell stabilizers, oral antihistamines, and oral corticosteroids. The side effect profile of SLIT was similar to that of placebo. SLIT is under

investigation in the U.S. and does not currently have F.D.A. approval.

Anti-IgE. Another new therapeutic paradigm is the use of recombinant humanized monoclonal IgE antibody for the treatment of allergic rhinitis. The basis for this area of research is the important role that immune responses mediated by IgE have in the pathogenesis of allergies. The monoclonal antibody to IgE inhibits binding of IgE to high-affinity IgE receptors on the surface of mast cells and basophils, which limits the degree of release of allergic response mediators. Efficacy vs placebo has been demonstrated in patients with asthma¹⁰⁸ and seasonal allergic rhinitis.¹⁰⁹ In a 12-week study, Casale et al documented decreased serum-free IgE levels, which were related to a dose-dependent decrease in nasal severity scores and decrease in antihistamine use in seasonal allergic rhinitis patients treated with the recombinant humanized monoclonal IgE antibody omalizumab.¹¹⁰

The addition of anti-IgE antibody to specific immunotherapy may confer additional benefits. Kuehr et al compared the efficacy of combined specific immunotherapy and anti-IgE therapy in polysensitized patients with seasonal allergic rhinitis.¹¹¹ Patients were treated during sequential pollen seasons, one birch pollen and one grass pollen. They began immunotherapy to either birch or grass; anti-IgE or placebo was started before and maintained during the pollen seasons (total of 24 weeks). Combination therapy reduced symptom load over the two pollen seasons by 48% compared to specific immunotherapy alone ($P < 0.001$). The investigators found that anti-IgE therapy conferred a protective effect that was independent of the allergen type. Additional benefit was observed in both pollen seasons, whether covered by specific immunotherapy or not.

Olopatadine. On the research front is olopatadine, a second-generation (nonsedating) antihistamine that has been shown to reduce secretion of pro-inflammatory cytokines (TNF- α , IL-1 β) from stimulated monocytes.¹¹² In an in vitro experiment using human nasal epithelial cells, Graziano et al also observed a statistically significant decrease in histamine-stimulated release of IL-8 (dose-dependent) and GM-CSF.¹¹² Olopatadine is currently available in an ophthalmic formulation for the treatment of allergic conjunctivitis (U.S., Canada, and Europe) and in an oral formulation for the treatment of allergic rhinitis and other allergic conditions (Japan), and is under clinical development in the U.S. as a nasal spray for allergic rhinitis.

The pharmacodynamic profile of olopatadine nasal spray was evaluated in a randomized, double-blind, placebo-controlled study in which patients with a history of seasonal allergic rhinitis were exposed to ragweed allergen in an environmental exposure chamber and then treated with a single dose (two sprays) of study drug (olopatadine 0.2%, 0.4%, or 0.6%, or placebo nasal spray).¹¹³ They then self-evaluated their nasal symptoms using a four-point scale over the next 12 hours. Response, as measured by reduction

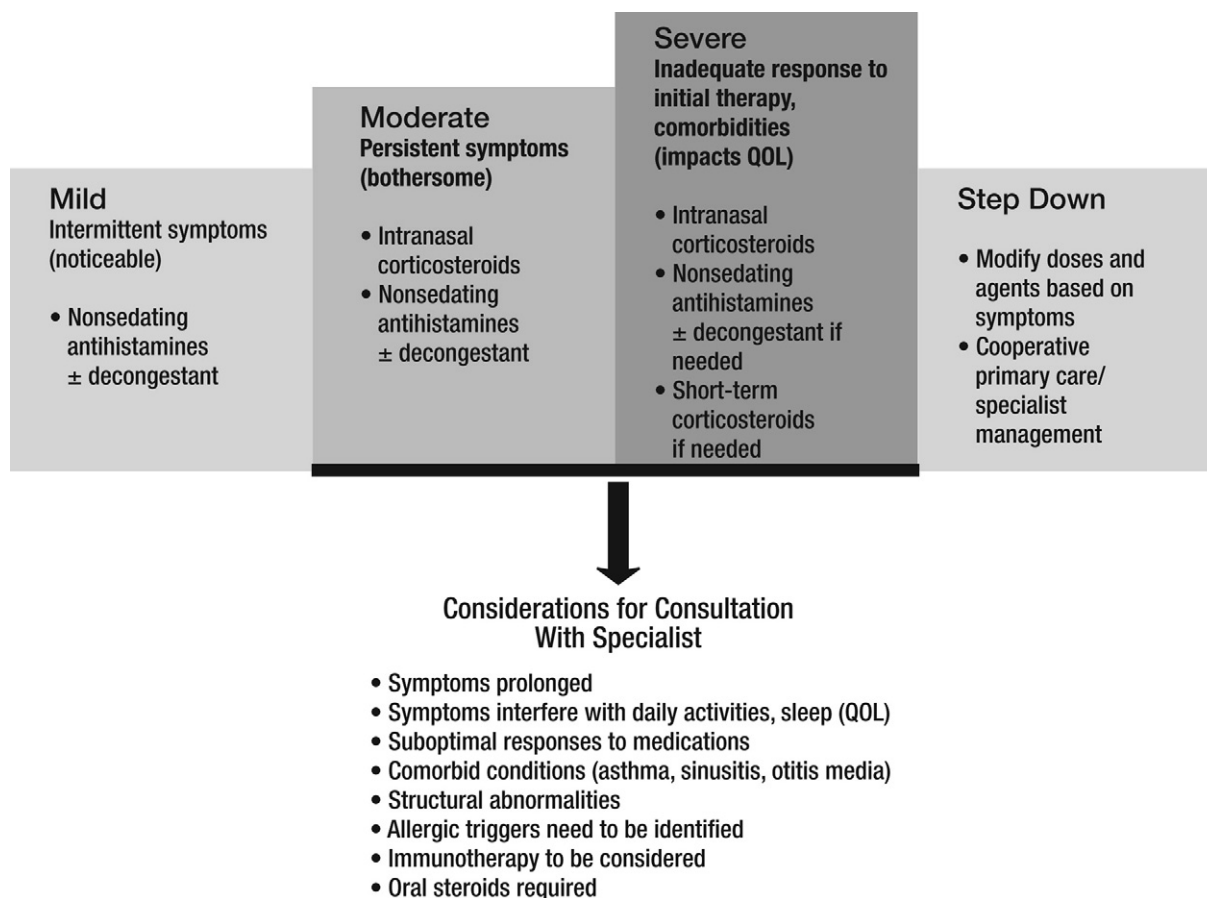


Figure 8 A stepwise treatment approach for allergic rhinitis.³⁴

in TNSS (the sum of scores for runny nose, stuffy nose, itchy nose, and sneezing), was rapid and sustained with olopatadine nasal spray. A beneficial effect was observed within 30 minutes of olopatadine inhalation, with the difference vs placebo reaching the level of statistical significance at 90 minutes and at all time points thereafter.¹¹³

Clinical efficacy with olopatadine nasal spray (0.4% and 0.6%) was assessed in two large, multi-center, double-blind, randomized, placebo-controlled studies in which study drug was administered for 2 weeks.^{114,115} A significant treatment effect was observed based on overall reduction in TNSS in an intent-to-treat population, as well as all the individual rhinitis symptoms. Quality-of-life improvements were also seen.¹¹⁵

Ciclesonide. Also in clinical development is ciclesonide, a corticosteroid that is inhaled as the parent compound and then converted locally in the airways by esterases to an active metabolite, desisobutyryl ciclesonide. The metabolite has 100-fold greater glucocorticoid receptor-binding affinity than does the parent. Furthermore, the active metabolite is both 99% protein bound and extensively metabolized by hepatic oxidases, thus resulting in extremely low systemic exposure.¹¹⁶ Efficacy was assessed by Ratner et al in a double-blind study in which 726 patients with seasonal allergic rhinitis were randomized to ciclesonide 25, 50, 100,

or 200 µg, or placebo nasal spray, each administered each morning for 2 weeks.¹¹⁷ A statistically significant difference ($P = 0.04$) between the active and placebo groups was observed for mean change in TNSS from baseline for the 100 µg and 200 µg dose groups.

Conclusion: Therapeutic Options are Plentiful but Effective Treatment Remains Elusive

With proper management and patient education, allergic rhinitis can be controlled, and affected people can lead normal and productive lives. Treatment for allergic rhinitis should focus on: rapid onset and convenience; safety and cost effectiveness; immune tolerance; improving patient adherence; and recognizing and treating co-morbidities.

A treatment guideline published by the Allergic Rhinitis and its Impact on Asthma (ARIA) Initiative Workshop Expert Panel (Fig 8³⁴) is useful, but refinements to it are in order given the need for a more targeted treatment approach based on an individual's specific allergic rhinitis symptoms and treatment needs. The use of such a treatment algorithm would likely have a positive impact on patient care and, thus, satisfaction. Algorithms should help match a treatment's therapeutic benefits with specific patient symptoms to increase patient relief and satisfaction.

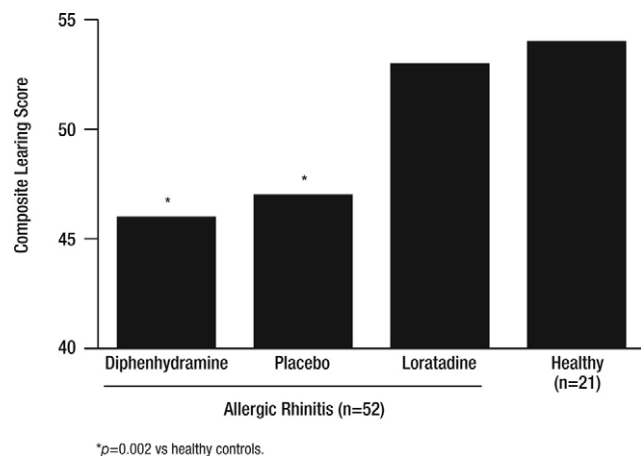


Figure 9 Allergic rhinitis impairs learning. (Adapted and reprinted with permission.²¹)

COMPLIANCE AND ADHERENCE FROM THE ALLERGIC RHINITIS PATIENT'S PERSPECTIVE

Patients Consider Allergic Rhinitis Debilitating

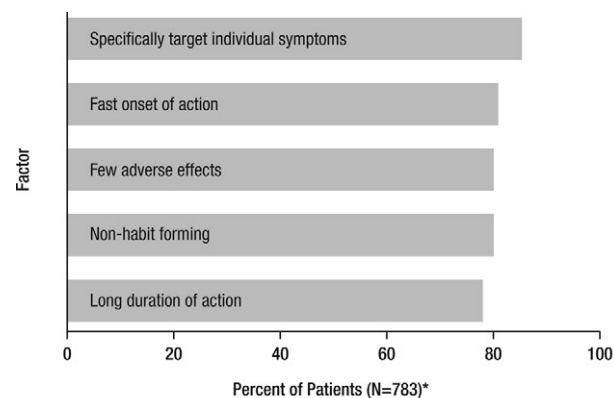
The impact of allergic rhinitis on patient well-being and functioning is far reaching. The illness impairs quality of life (eg, vitality, psychological and social aspects of patients' lives),¹¹⁸ energy and behavior of children,¹¹⁹ cognitive functioning and mood,²² and school/work performance (eg, attendance, productivity).^{25,119,120} Tanner et al documented these consequences in a survey (RQLQ) of almost 2000 patients (1425 employed and 556 students) between the ages of 11 and 68 with moderate-to-severe seasonal allergic rhinitis.²⁵ The majority of survey respondents indicated their ability to participate in daily activities (96%) and classroom productivity (93%) was negatively affected, as was work productivity (91%), underscoring the significant burden of illness. Furthermore, approximately three in four reported being embarrassed by allergy symptoms and troubled by frustration, and one in four, missing work or class time.

Children with symptomatic allergic rhinitis are sometimes described as inattentive, absent-minded, irritable, preoccupied, and/or having impaired learning and school performance. Vuurman et al reported that children aged 10 to 12 years had significantly deficient learning retention as compared to untreated normal controls.²¹ The deficiency was exaggerated by the use of a sedating antihistamine and partially mitigated by the use of a nonsedating antihistamine (Fig 9).²¹ Given this spectrum of behaviors displayed by allergic children, they may be asked to leave the classroom because they are disruptive and they may be misdiagnosed as having attention deficit/hyperactivity disorder (ADHD). The distraction of allergic rhinitis may be further complicated by increased absenteeism, which may result in diminished academic performance.

Occupational injury and impaired driving performance are other consequences of allergic rhinitis. In an observational case-control study of 1223 acute traumatic injury cases (compared to 1202 persons with chronic back injury), the use of oral antihistamines and high pollen exposure in employees with allergic rhinitis increased acute, work-related injury risk by almost threefold (OR 2.41).¹²¹ The effects of allergic rhinitis and its treatment on automobile driving performance were evaluated by Weiler et al in a double-blind, crossover study in which 40 patients were randomized to single doses of a sedating antihistamine, a nonsedating antihistamine, alcohol (to a blood alcohol concentration of 0.1%), and placebo.¹²² The poorest driving performance, based on coherence, drowsiness, lane keeping, and response to another blocking vehicle during a driving simulator test, was observed following ingestion of the sedating antihistamine, more so than alcohol; the nonsedating antihistamine had an effect similar to placebo.

Patients Want Fast-Acting and Long-Lasting Symptom Relief

The collective deleterious effects of allergic rhinitis symptoms on quality of life—which exceed those of asthma, a chronic, debilitating, and sometimes fatal disease^{20,123}—prompt affected persons to seek effective and safe treatment (Table 1). According to the 2005 Gallup Study of Allergies, including responses from a targeted national sample of 783 past-year users of prescription and OTC allergy medications, the most important factors for selecting an allergy medicine include (in decreasing order of importance): its effect in specifically targeting individual symptoms, rapid onset of effect, few adverse effects, not habit forming, and long duration of effect (Fig 10).⁷ Of these factors, time to onset and duration of action are reported by allergic patients as having a substantial bearing on their adherence to a course of treatment. Available formulations (the number of daily doses required), comfort and ease of use, tolerability, side effect profile, and patients' knowledge about their disease also affect adherence.^{7,124}



*Allergy medication users. Top side effects experienced were dry mouth, drowsiness, and inability to sleep.

Figure 10 2005 Gallup poll findings: most important selection factors for allergy medication.⁷

Effective Communication Needed between Providers and Patients

In the AAFA survey of allergic rhinitis patients, an appreciable number were not satisfied with the care they were receiving from their health care provider, with about half (48%) of the discontented patients indicating that the practitioner was not spending enough time talking with them about their condition. Furthermore, nearly a third of the allergic rhinitis patients taking a prescription allergy medication admitted they don't know what class of medication they are taking (29%) or how the medication relieves their symptoms (28%). These findings suggest a need for open dialogue between health care providers and their patients about the patients allergies and the specific allergy medications they are taking, including not only their mechanism of action, but also potential side effects and interactions with other medications. While almost all (92%) of the survey respondents expressed being comfortable discussing their disease with a health care provider, it is important for physicians to initiate such conversations since patients often assume a passive role when speaking with their physician about available allergic rhinitis treatment options.

Health care providers must gain a greater understanding of patient expectations to increase medication adherence and patient satisfaction and confidence. Effective communication between health care providers and their allergy patients fosters increased patient knowledge about allergic rhinitis and its treatment and will lead to clinicians' better understanding of patient expectations. A clinician must allocate enough time during an office visit to discover the patient's preferences for treatment (ie, which attributes/side effects matter most to him/her) as well as his/her prior experiences with allergy medications. For instance, for patients who have used a nasal spray, problems associated with taste/smell, nosebleed, headaches, dripping/burning sensation, and the like should be determined. A clinical decision about treatment can then be made based on the best available evidence, with the clinician selecting from the vast array of available medications one that matches the patient's clinical profile and medication attribute preferences. Such a discussion allows a clinician to select a medication that is tailored to a patient's needs rather than being arbitrary (eg, from samples in the cabinet).

Emerging templates for the office visit advocate evidence-based choice and decision making that is shared with the patient; this approach emphasizes respect for patients who want to be involved in their own health care deci-

Table 4
Communication model to discuss evidence with patients¹²⁶

Step 1	Understand the patient's and family members' experience and expectations
Step 2	Build a partnership using active listening and empathy, and pausing to check for patient understanding
Step 3	Provide evidence, including a balanced discussion of uncertainties
Step 4	Present recommendations informed by clinical judgment and patient preferences
Step 5	Check for patient's understanding and agreement with recommendation

sions.^{125,126} To increase the likelihood of a favorable outcome, allergy patients should also receive information about their condition and instruction on the correct way to use medication, and then be monitored for satisfaction during a follow-up contact/office visit. The patient's access to the prescribed medication (ie, availability/coverage by their health plan) should also be considered in treatment choice. Out-of-pocket costs (co-pay vs cost of drugs not within a health plan's formulary) directly influence how adherent a patient will be to treatment for a chronic disease.

Epstein et al recently published an evidence-based clinical decision and treatment model.¹²⁶ The authors recommend that health care providers follow five steps in communicating decisions with their patients (Table 4), which will advance the likelihood for improved adherence and outcomes. As a practical matter, however, physicians typically spend an average of less than 1 minute during an office visit discussing treatment and planning with their patients.¹²⁷ They incorporate informed decision making in 9% of office visits,^{128,129} and ask patients if they have any questions in less than half of outpatient visits.^{128,129} These findings highlight the lack of an optimal communication pattern. Health care providers can involve nonphysician practice personnel in patient communication and education efforts.

In summary, there is a lack of effective communication between the health care provider and patient, which is a crucial element for optimal treatment. There is evidence to suggest this lack of effective communication leads to poor disease control, poor compliance, and unhappiness in a significant portion of patients.

Appendix 1

Pharmacologic therapy for rhinitis^{6,32-34}

Class of medication	Clinical efficacy	Side effects	Other issues/comments
Oral antihistamines (OA) (1st generation) Diphenhydramine† (Benadryl) Hydroxyzine† (Atarax, Vistaril) Chlorpheniramine†	↓ pruritus ↓ sneezing ↓ rhinorrhea ↔ nasal congestion ↓ ocular symptoms of allergic conjunctivitis	Sedation Motor and cognitive performance impairment, even without obvious sedation Blurred vision, dry mouth, urinary retention, constipation Decreased work/school performance	In most states, patients taking these drugs are legally “under the influence of drugs”; caution in driving Patients don’t perceive their own performance impairment Although effective on a PRN basis, most effective when taken 2-5 hours before allergen exposure or on a regular basis
Oral antihistamines (2nd generation) Loratadine (Claritin) Cetirizine (Zyrtec) Fexofenadine (Allegra) Desloratadine (Clarinex) Acrivastine, with pseudoephedrine (Semprex-D)	Same benefits as 1st-generation oral antihistamines	Older 2nd-generation agents (ie, terfenadine, astemizole) caused QTc prolongation and arrhythmias, causing them to be removed from the U.S. market Cetirizine causes minimal sedation	More expensive than 1st-generation agents 2nd- vs 1st-generation agents mandated in some segments of transportation industry Excluding cetirizine and fexofenadine, agents undergo hepatic metabolism via CYP450, making drug-drug interaction with other CYP450 metabolized agents possible Although effective on a PRN basis, most effective when taken 2-5 hours before allergen exposure or on a regular basis
Intranasal antihistamines Azelastine (Astelin)	↓ nasal congestion ↓ itching ↓ sneezing ↓ rhinorrhea	Bitter taste (20%) Sedation (11%)	
Oral/intranasal decongestants Oral agents: Pseudoephedrine Phenylephrine Intranasal agents: Ephedrine Epinephrine Phenylephrine Oxymetazoline Xylometazoline Tetrahydrozoline	↓ nasal congestion No effect on itching, sneezing, or nasal discharge The onset of activity with topical (intranasal) agents is more rapid than with oral agents	Oral agents: Nervousness, excitability, restlessness, dizziness, insomnia CV effects, including elevated blood pressure, palpitations, tachycardia, arrhythmias Intranasal agents: - burning, stinging, sneezing, local dryness - rhinitis medicamentosa after 5-10 days of treatment	Use with caution in patients with arrhythmias, angina, hypertension, hyperthyroidism, glaucoma, diabetes, and urinary problems Intranasal decongestants better for short-term relief (2-3 h) Oral agents effective when used in combination with antihistamines (eg, Allegra-D, Claritin D, Zyrtec-D)
Intranasal corticosteroids Beclomethasone (Beconase) Budesonide (Rhinocort) Flunisolide (Nasarel, Nasalide) Fluticasone (Flonase) Mometasone (Nasonex) Triamcinolone (Nasocort)	↓ nasal congestion ↓ pruritus ↓ sneezing ↓ rhinorrhea Most effective class in controlling symptoms of allergic rhinitis, particularly more severe forms Time to onset of effect (up to 12 hours) and to maximum effect (days to weeks) is longer than with other classes	Nasal irritation, stinging, burning, dryness, bleeding, epistaxis, altered smell/taste Systemic adverse events less likely than with an oral/parenteral formulation	Pretreatment with a decongestant may be necessary to open nasal airway for delivery of these drugs Septal perforation is rare; spray away from the nasal septum Should be used judiciously in children due to concerns about effects on growth Use in pregnant women should be considered carefully Must be administered regularly, even in the absence of symptoms, to maintain efficacy

**Appendix 1
(Continued)**

Class of medication	Clinical efficacy	Side effects	Other issues/comments
Systemic corticosteroids Prednisone Methylprednisolone	↓ nasal congestion ↓ pruritus ↓ sneezing ↓ rhinorrhea Most effective class in controlling symptoms of allergic rhinitis, particularly more severe forms Last resort when other therapies prove ineffective Reach all parts of the nose and paranasal sinuses vs intranasal corticosteroids	Oral formulation safe for short-term use Parenteral corticosteroid use discouraged because of side effects (eg, hypothalamic-pituitary-adrenal [HPA] axis suppression)	A short oral course (3-7 days) may be appropriate to treat patients with severe symptoms or to control symptom exacerbations Should be used judiciously in children due to concerns about effects on growth
Mast cell stabilizers Cromolyn (Nasal crom)	Prevents allergic reaction (does not alleviate symptoms once the reaction has begun) ↓ pruritus ↓ sneezing ↓ rhinorrhea ↔ nasal congestion Generally less effective than intranasal corticosteroids	Because of its favorable safety profile, it should be considered in children and pregnant women Side effects include: sneezing (10%), nasal stinging or burning (5%), nasal irritation (<3%), and epistaxis (<1%)	Protective effect lasts 4-8 hours; requires multiple doses each day Effect usually noted in 4-7 days, but can take 2 weeks or more for maximum effect Pretreatment with a decongestant may be necessary to open nasal airway for delivery of cromolyn Appropriate patient selection is critical; best for those whose exposure can be anticipated and those with high serum IgE levels
Oral anti-leukotriene agents Montelukast (Singulair)	Has indication for allergic rhinitis in patients 2 years of age and older ↓ nasal congestion ↔ pruritus ↓ sneezing ↓ rhinorrhea No more effective than 2nd-generation (nonsedating) antihistamines, and less effective than intranasal corticosteroids	Side effect profile similar to placebo in placebo-controlled studies	New cases of Churg-Strauss syndrome (vasculitic angiitis), primarily in asthmatics Extensively metabolized by CYP 3A4 and 2C9, with an associated potential for drug-drug interactions
Intranasal anticholinergics Ipratropium (Atrovent)	↓ rhinorrhea No effect on any other symptoms of rhinitis	Minimal side effects (dose related) including: nasal dryness, burning, and irritation; bloody nasal discharge	Use in combination with intranasal corticosteroid or antihistamine in patients with rhinorrhea as the predominant symptom or for those with rhinorrhea who are not fully responsive to other therapies
Immunotherapy	Most appropriate for patients with IgE-mediated rhinitis and severe symptoms from exposure to a well-defined and unavoidable allergen(s) Potential for long-term prevention of allergic rhinitis and the development of lower airway disease	Acute anaphylactic reaction	Frequent office visits; compliance is essential for efficacy Relatively expensive

↓, decrease; ↔, negligible, debated, or highly variable inter-patient response; PRN, taken on an as needed basis.

†Examples of 1st-generation agents

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