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A Focus on the Pharmacologic Management of Allergic Rhinitis

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LEARNING OBJECTIVES

After completing this continuing education program, the pharmacist should be able to:

1. Describe the prevalence of allergic rhinitis and its impact on quality of life.
2. Explain the pathophysiology, risk factors, clinical presentation, and diagnosis of allergic rhinitis.
3. Discuss the role of lifestyle modification in the prevention and treatment of allergic rhinitis.
4. Describe the pharmacologic therapies used to treat allergic rhinitis and distinguish efficacy, adverse effects, and appropriateness among medications.

ABSTRACT: Allergic diseases account for a significant amount of disability than are generally realized. Allergic rhinitis is responsible for over 100 million lost workdays among adults and approximately 1.5 million missed school days among children annually. This manuscript reviews the pathogenesis, clinical presentation, and management of allergic rhinitis, with a focus on pharmacotherapy. Several drug therapies are effective for the management of allergic rhinitis. However, the adverse effect profiles of these drugs differentiate them from one another. The clinical application of various drug therapies, such as first- and second-generation antihistamines and nasal corticosteroids, are discussed with special consideration given to clinically significant adverse effects of these agents.

OVERVIEW

Rhinitis is the inflammation of the mucous membranes lining the nasal cavities. There are different etiologies of rhinitis. Allergic rhinitis is the most common type of rhinitis, affecting approximately 5% to 22% of Americans.[1,2] This may be an underestimate, given that this disease is commonly underreported and treated without a diagnosis. It increases in prevalence among children and adolescents, and declines thereafter among older adults. About 70% of patients with allergic rhinitis develop symptoms of the disease before the age of 30 years.[1]

Allergic rhinitis greatly hinders quality of life by causing fatigue, headache, cognitive impairment, and respiratory complications. Besides the increased morbidity, patients with allergic rhinitis have inhibited normal activity. In fact, it accounts for approximately 1.5 million missed school days in children each year and about 100 million missed workdays in adults annually.[1] Consequently, the direct costs of allergic rhinitis were estimated at $5.9 billion per year in 1996.[3]

Patients with allergies may have a genetic predisposition. Patients who have a parent with a history of atopic disease are 20% to 30% at risk of developing the disorder, and those who have 2 parents with the disease are at 60% to 80% risk.[4]

DEFINITION AND CLASSIFICATION

Rhinitis is classified as either allergic or nonallergic. While allergic rhinitis is the most common type of rhinitis, non-allergic factors must be ruled out prior to introducing therapy (see table 1).

Table 1. Types of Rhinitis and Conditions that May Mimic Rhinitis.[5]

Allergic Rhinitis	Non-allergic Rhinitis	Conditions with Rhinitis-like Symptoms
Seasonal	Infectious	**Anatomical/mechanical factors**
Perennial	NARES syndrome	Septal wall abnormalities
Episodic	(Nonallergic rhinitis with	Foreign bodies
Occupational	eosinophilia syndrome)	Nasal tumors
	Vasomotor rhinitis	**Inflammatory/immunologic factors**
	Hormonally induced	Systemic lupus erythematosus
	Exercise induced	Sjogren's syndrome
	Drug induced	Nasal polyps
	Occupational	

Allergic rhinitis is defined as seasonal, perennial, episodic, or occupational. Of these, seasonal allergic rhinitis is the most prevalent. Seasonal allergic rhinitis occurs at a defined period of time in the year, and it is likely to be associated with outdoor allergens. The onset and duration of seasonal allergic rhinitis depend on the time in which allergens are most abundant in the air. This will also depend on the geographic location in which different seasonal airborne allergens appear. Seasonal allergic rhinitis is commonly associated with the pollinating season of the major trees, grasses, and weeds.[4]

On the contrary, perennial allergic rhinitis occurs throughout the year, and may possibly be secondary to indoor allergens. Perennial allergic rhinitis is associated with environmental allergens such as dust mites, molds, animal dander, and even pollen that may be present all year in certain geographic regions such as the Southwest.[6] Hence, there is a greater ability to modify allergic triggers of perennial rhinitis than seasonal rhinitis.

Some patients experience episodic allergic rhinitis. This type of rhinitis occurs with an allergen that is not typically present in an individual's regular environment. Some episodic allergens include cat or dog dander, pollen, and cigarette smoke.[6]

PATHOPHYSIOLOGY

Patients with allergic rhinitis tend to be more hypersensitive to allergens than normal subjects. This hypersensitivity is characterized as atopy. Atopic patients inherit the tendency to develop various chemical mediators responsible for the many symptoms associated with allergic rhinitis.[5]

Allergic rhinitis is an inflammatory disease that is characterized by an early- and a late-phase allergic response. Symptoms of sneezing and rhinorrhea predominate in the early phase, while nasal congestion predominates in the late phase.[5]

Early phase response
Prolonged exposure to allergens such as dust mites, animal dander, and pollen induces the production of IgE-coated mast cells. With continued allergen exposure or in the early phase, IgE mast cells degranulate and release various chemical mediators. These inflammatory mediators include histamine, prost-aglandins, kinins, and leukotrienes. Of these chemical mediators, scientific evidence suggests that histamine is the major contributor to the etiology of this disease. These chemical mediators are responsible for vasodilation, vascular permeability, and other mechanisms stimulating the typical symptoms associated with allergic rhinitis.[7] Some of these symptoms of allergic rhinitis include

pruritus, sneezing, rhinorrhea, and nasal congestion.[5]

Late phase response
A few hours after the early response phase, symptoms begin to improve as chemical mediators are metabolized and diminish. In the meantime, these mediators recruit other inflammatory cells, including neutrophils, basophils, eosinophils, and later, T-cells and macrophages. These cells then become activated and secrete mediators similar to those in the early phase response, maintaining the inflammatory response. Nasal congestion predominates in this phase as the nasal mucosa is thickened, reducing nasal airflow with little change in other nasal symptoms. In addition, these cells secrete proteins that promote tissue damage in patients with chronic allergic rhinitis. Also during the late phase response, cytokines may travel to the hypothalamus, leading to systemic effects such as fatigue and irritability that lead to cognitive impairment.[5]

Priming response
When an atopic patient is repetitively exposed to allergens, the amount of allergen required to induce an allergic response is reduced. This priming response is secondary to accumulation of inflammatory cells from repetitive late phase responses. The priming effect is important because initial exposure to one allergen may promote an exaggerated response to a later allergen. Hence, it is necessary to identify all allergens that a patient is susceptible to and the seasons in which these allergens are present, to avoid the exaggerated allergic response, when a patient is reexposed to an allergen.[5,6]

CLINICAL PRESENTATION

The symptoms associated with allergic rhinitis vary among individuals and range from mild to seriously debilitating. Some common symptoms of allergic rhinitis include nasal congestion, rhinorrhea, sneezing, nasal pruritus, and postnasal drainage. Other symptoms that may accompany allergic rhinitis include itchy, watery eyes; palatal pruritus; cough; wheezing; and fatigue.

DIAGNOSIS
Diagnosis of allergic rhinitis is primarily based on the patient's past medical history. This includes inquiry about the onset and duration of developing symptoms of allergic rhinitis. A complete medication history, especially with the use of over-the-counter (OTC) agents is prudent. This will provide the clinician information about agents that may or may not have been helpful for treating symptoms for the patient. The medical history should also include questions about the patient's home and work environment, and any changes in those environments that may have triggered the onset of allergic symptoms. The patient's age is important in the patient history, since the majority of patients develop the disease before the age of 30 years.[5]

Obtaining a family history of the disease will also help clarify the diagnosis. The prevalence of allergic rhinitis increases with a family history of the disease. A patient with no family history of rhinitis has a 17% risk of developing the disease. Conversely, a patient with 1 or 2 parents with allergic rhinitis is 26%, and 52% more likely to develop the disease, respectively.[8]

MANAGEMENT
The goals of managing allergic rhinitis focus on regaining the patient's quality of life and resuming normal activities of daily living. Management of allergic rhinitis involves

non-pharmacologic and pharmacologic therapies. The therapeutic plan should be individualized to the patient, involving environmental control measures and addition of drug therapy, if needed.

Prevention and Environmental Control

All measures to prevent the development of allergic rhinitis or an exacerbation of symptoms in a patient with existing disease are worth consideration. The cause of allergic rhinitis is not very well understood; however, there appears to be an increased risk among children who are exposed to risk factors early in life. These risk factors include early introduction of foods or formula, heavy maternal smoking in the first year of life, and exposure to indoor allergens.[5] Therefore, it is important to provide public education about possible preventive measures in the development of allergic rhinitis.

Furthermore, educating patients about avoiding triggers of allergic rhinitis is as important as the drug therapy that is used to prevent or treat symptoms of the disease. Recognizing indoor and outdoor allergens is the first and main step in the treatment of allergic rhinitis. Knowledge of the spectrum of allergens that a patient is susceptible to will help the patient to possibly avoid or eliminate these allergens from his or her environment or, at least, to prepare for exposure to expected seasonal or episodic allergens. This is acc-omplished by obtaining a comprehensive medical history to identify any correlation between the onset of allergic symptoms and exposure to environmental allergens.

There are several sources of aeroallergens in the home that can be reduced. When the clinician has identified the allergens that the patient is susceptible to, the patient can take several steps to avoid or eliminate further exposure.

One of the most common indoor allergens for atopic patients are dust mites. Many individuals who complain of being allergic to dust are actually allergic to dust mite waste matter. Mites live on scales of dead skin of humans and animals.[6] Hence, they live in places that trap such matter such as soft furniture and carpets. When the clinician believes that the patient is allergic to dust mites, several measures can be used to reduce exposure. Table 2 provides recommendations for reducing some of the most common indoor allergens.

Table 2. Steps to Minimize Allergens in the Household.[6]

Allergen	Action
Pollen	Keep doors and windows closed. Use an air conditioner. Stay indoors, if possible, when pollen levels are high.
Mold spores	Use a dehumidifier in damp rooms. Keep plants out of the bedroom.
Dust mites	Remove as many "dust collectors" from the bedroom as possible. Wash all bedding in hot water every two weeks. Rugs and carpets should be removed, if possible. If not, special cleaners are available to kill mites.
Animal dander	Keep pets out of the bedroom and out of the house, when possible.
Cigarette smoke	Avoid and eliminate smoke from the environment.

In addition to minimizing indoor allergens, there are several outdoor allergens that can induce allergic rhinitis. There are several resources for patients about monitoring levels of aeroallergens and how they can minimize their exposure to these allergens. Local weather reports on television, the radio, or the newspaper may be helpful. In addition, several patient education materials are available on the Internet. Below is a sample of web sites that provide educational material on allergic rhinitis for patients and/or providers. Patients should be warned that not all websites provide unbiased and correct information.   Thus, it is always important that patients consult their provider or pharmacist about the validity of a website or information obtained from a website.

- American Academy of Allergy, Asthma, and Immunology (AAAAI) provides definitions and facts about different allergic conditions, a "just for kids" section, and health eHeadlines that are updated daily. http://www.aaaai.org/
- National Pollen Network provides condition information, allergy forecasts, and treatment resources. http://www.allernet.com/
- AllAllergy provides access to asthma, allergy, and intolerance information on the web. This site includes articles, organizations, books and journals, events, products, and an allergen database. http://www.allallergy.net/

Pharmacologic Therapy

There are several classes of drugs that can be helpful in the treatment of allergic rhinitis. Although there is no cure for this disease, various drugs have demonstrated efficacy in the prevention and treatment of allergic rhinitis symptoms in well-designed trials.   Products available for the management of allergic rhinitis include corticosteroids, antihistamines, anticholinergic agents, decongestants, and combinations of these agents.

Prior to providing drug therapy, it is important to identify the type of allergic rhinitis that a patient has. If the individual is allergic to identifiable allergens, the patient may have adequate control of his or her allergies using environmental control alone. If the allergens are unidentifiable or if the

patient fails environmental control measures, then drug therapy can be initiated.

An individual may require chronic or acute drug therapy depending on the type of allergic rhinitis s/he has. For example, an individual with episodic allergic rhinitis will require a relatively quick acting therapeutic agent (e.g., antihistamine), which can be taken prior to a brief exposure to a known allergen (e.g., cats), instead of an agent that requires a longer onset of action such as a nasal corticosteroid. Hence, it is important to individualize the drug therapy to the patient.

Intranasal Corticosteroids

Intranasal corticosteroids are the preferred agents to treat allergic rhinitis because they have been shown to be superior in efficacy as monotherapy in providing control of the majority of allergic rhinitis symptoms. This recommendation is supported by a recent meta-analysis of 16 randomized controlled trials comparing intranasal corticosteroids and first- or second-generation antihistamines for the treatment of allergic rhinitis.[9] The intranasal corticosteroids studied included beclomethasone dipropionate, budesonide, fluticasone propionate, and triamcinolone acetonide. The oral antihistamines studied were dexchlorpheniramine, terfenadine, astemizole, loratadine, and cetirizine. The results of the meta-analysis demonstrated that intranasal corticosteroids produced significantly greater relief from the majority of allergic rhinitis symptoms including nasal blockage, nasal discharge, sneezing, nasal itch, and postnasal drainage than the oral antihistamine agents.[9] The studies included in the meta-analysis also demonstrated that intranasal corticosteroids were as effective as oral antihistamines in the treatment of nasal discomfort, nasal resistance, and eye symptoms. See table 3 for a summary of these results.

Table 3. A Comparison Between Intranasal Steroids and Oral Antihistamines in the Treatment of Allergic Rhinitis[9]

Symptom	No. of Studies Reported	Efficacy	Confidence Interval (95%)
Nasal blockage	14	Significantly greater relief with steroids	(-0.729 to -0.527)
Nasal discharge	14	Significantly greater relief with steroids	(-0.601 to -0.401)
Sneezing	14	Significantly greater relief with steroids	(-0.588 to -0.387)
Nasal itch	11	Significantly greater relief with steroids	(-0.485 to -0.273)
Postnasal drainage	2	Significantly greater relief with steroids	(-0.417 to -0.059)
Nasal discomfort	1	No significant difference	(-0.162 to 0.348)
Total nasal symptom score	9	Significantly greater relief with steroids	(-0.531 to -0.315)
Ocular symptoms	11	No significant difference	(-0.157 to 0.072)

Safety

Intranasal corticosteroids are relatively safe medications that incur minimal side effects when used properly. Unlike oral steroids, intranasal steroids produce few, if any, systemic adverse effects.[5]

The most common side effects associated with nasal steroids are local in nature, including nasal burning or stinging. This is usually attributed to certain additives that are used in particular preparations of nasal steroid products. Polyethylene glycol and freon propellants are examples of these additives that have been associated with nasal irritation with frequent application. Nasal bleeding and nasal septal perforations are rare adverse effects associated with intranasal corticosteroids.[5]

Adverse effects associated with nasal steroids may be minimized when patients are appropriately instructed on administering the different types of preparations. For example, nasal sprays containing aqueous solutions are less likely to cause irritation, and may be pointed directly into the nasal septum. However, with nasal inhalers containing freon propellant, the tip of the applicator should be directed toward the outside nostril to avoid irritation to the septum. Additionally, patients may try saline irrigation prior to administering the nasal spray to help minimize the stinging associated with these agents.[5]

The risk for clinically significant systemic adverse effects including adrenal suppression, osteoporosis, growth retardation in children, cataracts, and glaucoma from topical corticosteroids has been debated. Systemic absorption of

topically administered corticosteroid agents has occurred with older agents, and may be irrelevant with newer preparations. Several factors contribute to the extent of absorption of topical corticosteroid drugs, including the dose, form of delivery, interpatient variability, and the severity of the underlying disease.[10] Fortunately, with intranasal corticosteroids, the dose required to treat allergic rhinitis is much less than that required to treat asthma in inhaled corticosteroid products. Hence, the potential for severe systemic adverse effects of intranasal corticosteroids is far less than that reported with inhaled corticosteroids.

Adrenal Suppression

The most significant systemic adverse effect associated with nasal steroids was with dexamethasone, the first nasal steroid used to treat allergic rhinitis.[5] Although an effective agent, it was absorbed systemically and was reported to produce adrenal suppression. However, these adverse effects have not been reported with the use of other nasal steroids when given at recommended doses.[5]

Osteoporosis

There is minimal evidence for the risk of osteoporosis in adults using intranasal corticosteroids. One study identified that intranasal fluticasone proprionate and budesonide at 200 μg or 400 μg daily significantly reduced serum osteocalcin levels after one week of therapy at lower doses.[11] Bone mineral density, a surrogate marker for osteoporosis, was not used in this study. Additionally, no studies are published on the effects of bone metabolism in children.

Growth Suppression

Two recent well-designed, randomized controlled trials of at least one year in length have evaluated the effects of intranasal corticosteroids on growth suppression in children. Both studies followed approximately 100 children on nasal steroid therapy for one year. One study demonstrated growth suppression of 0.9 cm in children taking beclomethasone, while no evidence of growth suppression was detected in the other study using mometasone.[12-13] Further, since height was not monitored for greater than one year of therapy, it is unclear whether the effects of nasal steroids on childhood growth will result in reduced final adult height. In general, practitioners agree that more studies are needed to confirm the effects of these agents on growth suppression. Other agents, such antihistamines and cromolyn, are available for children with allergic rhinitis; however, nasal steroids remain the most effective therapy for allergic rhinitis. Also, some practitioners will argue that the benefits of adequately treating a child with allergies far outweigh the risk for growth suppression. Since this issue is still unclear, it is important to educate parents about the risks and benefits of the different nasal steroids, so that they can make informed decisions for their children with allergic rhinitis.

Ocular Complications

In terms of cataract or glaucoma adverse effects with nasal steroid use, no concrete evidence is available to support these effects. This is contrary to the evidence supporting a direct association of cataracts and glaucoma with oral steroids and high doses of inhaled steroid therapy.[10,14]

Onset of Action

The onset of action of intranasal steroids is longer than that of oral antihistamines. In general, oral antihistamines take into effect within hours of administration, while nasal steroids take about two weeks to obtain optimal effects.[5] However, a number of

studies may suggest a quicker onset of action of nasal steroids than commonly believed. These studies demonstrate an improvement in allergic rhinitis symptoms within 24 hours of therapy versus placebo.[15-18] However, these studies were limited by their methodologic design to assess onset of efficacy of the nasal steroids on treating allergic rhinitis symptoms. In summary, it may be worth recognizing that nasal steroids may have a potential for improving allergic rhinitis symptoms within 24-72 hours of therapy, but, at this time, it is still important to recommend initiating nasal steroids a few weeks prior to anticipated exposure to allergens to obtain maximal benefit.

Oral Steroids
Systemic steroids, such as prednisone, are reserved for severe cases and exacerbations of allergic rhinitis. Short-term therapy of not more than 5 to 7 consecutive days is usually indicated for these patients. Chronic oral steroid therapy is discouraged because of the risk for serious, long-term adverse effects that include adrenal suppression, cataracts, glaucoma, and growth suppression in children.[5,6]

Antihistamines
Oral antihistamines, including first- and second-generation agents, are effective in the treatment of allergic rhinitis, as demonstrated in the meta-analyses conducted by Weiner and colleagues. On the contrary, as dis-cussed previously, oral antihistamines are less effective than nasal steroids as monotherapy in treating most nasal symptoms, and they are equivalent to nasal steroids in treating ocular symptoms.[9] Antihistamines are effective agents because they inhibit a major mediator, histamine (H_1), which is involved in the proliferation of symptoms associated with allergic rhinitis.[5]

First-generation Antihistamines
First-generation antihistamines were the first antihistamines available for the treatment of allergic rhinitis. They are the most accessible agents for patients experiencing allergic symptoms, given that most agents are available over the counter (OTC) and they are relatively inexpensive. Therefore, it is common to see that many patients have already tried a first-generation antihistamine by the time they are seen by their provider for allergic rhinitis.

There is little information demonstrating significant differences in efficacy among various first-generation antihistamines. One report suggests that chlorpheniramine and hydroxyzine have greater efficacy than other first-generation antihistamines.[19] On the contrary, first-generation antihistamines differ in their degree of adverse effects. Sedation is the most common side effect of these agents, limiting their use in many individuals. In fact, some agents are used for their sedative qualities in a number of OTC preparations. It is important to note that the level of sedation varies among agents, it is dose-dependent, and it is subjective.[5] Table 4 illustrates the relative sedation associated with various oral antihistamine agents.

Table 4. Level of Sedation Associated with Oral Antihistamines[5,20]

Agent	Availability	Adult dose	Level of Drowsiness[a]
First-generation Antihistamines			
Diphenhydramine (Benadryl®)	OTC	25-50 mg q 6-8 hr	+++
Promethazine (Phenergan®)	Rx	25 mg HS or 12.5 mg q 8 hr	+++
Clemastine (Tavist®)	OTC	1.34-2.68 mg q 8-12 hr	++
Hydroxyzine (Atarax®)	Rx	25 mg q 6-8 hr	++
Brompheniramine (Dimetane®)	OTC	4-8 mg q 4-6 hr or 8-12 mg SR q 12-24 hr	+
Chlorpheniramine (Chlor-Trimeton®)	OTC	2-4 mg q 4-6 hr or 8-12 mg SR q 12-24 hr	+
Triprolidine (Actidil®)	OTC	2.5 mg q 4-6 hr	+
Cyproheptadine (Periactin®)		4 mg q 8 hr	+
Second-generation Antihistamines			
Cetirizine (Zyrtec®)	Rx	5-10 mg qd	+/-
Fexofenadine (Allegra®)	Rx	60 mg bid	+/--
Loratadine (Claritin®)	Rx	10 mg qd	+/--
[a] **Incidence +++ = high; ++ = moderate; + = low; +/- = very low; +/-- = very low to none OTC = over-the-counter Rx = prescription required**			

Although there is great interpatient variability among oral antihistamine agents in causing sedative adverse effects, one trial suggests that these subjective reports do not accurately measure performance impairment.[21] Researchers claim that subjective reports of sedation may not be reliable measurements of safety with oral antihistamines.[5] Also, in many of these studies the more sedating antihistamine agents, such as hydroxyzine, were used. This agent is not considered first line for allergic rhinitis, and would not be an accurate representation of most first-generation antihistamines. Nonetheless, since there is a weak correlation between subjective reports of sedation and performance, patients should still be advised to take caution when using first-generation antihistamines, especially when driving or operating heavy machinery.

First-generation antihistamines may also cause anticholinergic side effects such as dry mouth, blurry vision, and urinary retention. The anticholinergic properties of these antihistamines may also complicate coexisting diseases such as diabetes, hypertension, and prostatic hypertrophy.

Second-generation Antihistamines
Second-generation antihistamines were developed in 1987 in response to the sedative limitations with older antihistamine agents. The newer drugs are favored over first-generation agents not for their increased efficacy, but for their favorable adverse effect profile.[22,23] These agents differ chemically from first-generation

antihistamines in that they have weaker CNS penetration and preferential binding to peripheral receptors, causing less somnolence, and less anticholinergic side effects.[5]

The first agents in this class were terfenadine and astemizole, which were discontinued after 10 years of marketing. Post-surveillance data demonstrated an increased risk for cardiac dysrhythmia with these agents, particularly in patients taking concomitant medications that interfered with their metabolism. Loratadine, cetirizine, and fexofenadine followed these drugs, lacking the cardiac complications associated with terfenadine and astemizole. These "newer" second-generation antihistamines maintain the reduced sedative and anticholinergic characteristics associated with first-generation antihistamines, without the cardiac risk factors of the "older" second-generation agents.[5]

While no difference in efficacy has been demonstrated among the second-generation antihistamines, differences may exist in sedative effects. Cetirizine has been shown to cause significantly more sedation than placebo. [5] There are no significant differences in sedative effects with loratadine or fexofenadine when compared to placebo.[5] This difference in sedation among second-generation antihistamines is even recognized by the Federal Aviation Administration (FAA). The FAA prohibits the use of cetirizine along with first-generation antihistamines for pilots because of their increased potential to cause somnolence. The use of loratadine and fexofenadine is permitted with a physician's letter indicating lack of sedative adverse effects when using these agents.[6] It is important to note, however, that all agents are not devoid of adverse effects. Interpatient variability also applies with

second-generation agents causing sedation in certain individuals.

Second-generation agents are currently offered by prescription only, making them relatively expensive agents when compared with their counterpart OTC agents, and they are slightly more expensive than intranasal corticosteroids (see table 5). Unfortunately, many patients pay out of pocket or very high co-pays for branded prescription drugs, making these agents unaffordable. In fact, a citizen petition from Blue Cross of California/Wellpoint is asking the FDA to review switching second-generation antihistamines to OTC status, despite resistance from manufacturers. A recent review from the FDA concluded that second-generation antihistamines are safe for OTC use, although no decisions have yet been made to switch them to OTC status.[24]

A.M./P.M. Antihistamine Dosing
In general, second-generation antihistamines are preferred over traditional antihistamines for their lower sedative properties.[5] But, managed care organizations have researched the plausibility of implementing an "a.m./p.m." dosing regimen that may provide an effective regimen for the patient while minimizing cost. This practice involves using a "non-sedating" second-generation agent dosed once daily in the morning (e.g., fexofenadine), and a less sedating first-generation agent dosed at night. Guidelines developed by national experts from the Joint Task Force on Practice Parameters in Allergy, Asthma and Immunology discourage this practice, suggesting that even bedtime dosing of traditional antihistamines may cause daytime sedation, decreased alertness, and performance impairment.[5] The studies cited in these guidelines had small sample sizes and used agents and doses that were inappropriate for bedtime use.[25-29] Two of

these studies used hydroxyzine, one of the more sedating first-generation antihistamines.[25-26] In fact, hydroxyzine is FDA-approved for anxiety, and it is least appropriate for treating allergic rhinitis because of its sedative effects. The other studies used sustained-release chlorpheniramine 8-12 mg and brompheniramine 12 mg, which may have more sedating side effects than the doses of the immediate-release forms.[27-29] None of the studies cited in the guidelines by the Joint Task Force provide any clinical evidence that less sedating, immediate-release agents, such as chlorpheniramine,

cause daytime sedation, decreased alertness, or performance impairment.

Intranasal antihistamine
Azelastine (Astelin®), is FDA-approved for the treatment of symptoms of rhinorrhea, sneezing, and nasal pruritus associated with allergic rhinitis. Studies demonstrate that the efficacy of azelastine is at least equal to that of oral antihistamine agents. Up to 20% and 12% of patients taking azelastine have reported long-lasting bitter taste and somnolence, respectively.[30]

Table 5. Cost Comparison Among Intranasal Corticosteroids, First-generation Antihistamines, and Second-generation Antihistamines Used for Allergic Rhinitis in 2001[31]

Agent	*Dose and Frequency for Adult*	*AWP Cost for 1-Month Supply*
Intranasal Corticosteroids		
Budesonide (Rhinocort®),	2 sprays per nostril bid	$39.50
(Rhinocort Aqua®)		$49.92
Flunisolide (Nasarel®)	2 sprays per nostril bid-tid	$43.51
Fluticasone (Flonase®)	2 sprays per nostril qd	$56.03
Mometasone (Nasonex®)	2 sprays per nostril qd	$55.85
Triamcinolone (Nasacort®),	2-4 sprays per nostril qd	$45.82
(Nasacort AQ®)		$44.46
Second Generation Antihistamines		
Cetirizine (Zyrtec®)	10 mg qd	$59.40
Fexofenadine (Allegra®)	60 mg bid	$62.03
Loratadine (Claritin®)	10 mg qd	$74.65
OTC Antihistamine		
Brompheniramine	8 mg qid	$7.08
Chlorpheniramine	12 mg bid	$6.75
Diphenhydramine	50 mg tid	$6.30

Intranasal Steroid/Antihistamine Combination Therapy
There is limited literature regarding the efficacy of combining nasal steroids and oral antihistamines for patients inadequately

controlled on either agent alone for allergic rhinitis. The Joint Task Force guidelines cite 1 study suggesting that at least 50% of patients need to take both a nasal corticosteroid and an oral antihistamine to

adequately control symptoms.[5] This non-blinded study measured the rhinoconjunctivitis between the nasal steroid, fluticasone, and the antihistamine, terfenadine.[32] Patients were either assigned to fluticasone 200 µg or terfenadine 60 mg, as needed. Patients who were not controlled on the initial medication were allowed to add a rescue medication: the antihistamine if initiated on the nasal steroid, or the nasal steroid if initiated on the antihistamine. Because this study was not blinded, a larger limitation of the trial was that patients were taking baseline medications as needed, not as scheduled. This does not allow for an appropriate assessment of baseline therapy, since intranasal corticosteroids and antihistamines are most effective when taken as scheduled. Nonetheless, the study demonstrated that 52% of patients in the fluticasone group versus 13% of patients in the terfenadine group did not require rescue therapy.

In 3 other double-blinded, randomized, controlled trials, adding a second-generation antihistamine to a nasal steroid offered no significant benefit in treating symptoms of allergic rhinitis therapy.[33-35] In addition, all 3 trials demonstrated that nasal steroid monotherapy was more effective than taking the second-generation antihistamine alone. The study by Ratner and colleagues also compared the effect of combination therapy with antihistamines taken alone. Their findings indicate that the combination of fluticasone and loratadine was significantly more effective than taking loratadine alone.[34]

Decongestants
Oral decongestants, such as pseudoephedrine, are effective OTC agents for relieving nasal congestion associated with allergic rhinitis.[5] In fact, the combination of these agents with antihistamines have demonstrated superior efficacy over either agent alone.[36-39] However, the adrenergic agonist properties of decongestants may cause mild to severe adverse effects. Insomnia, loss of appetite, and nervousness are some of the common but less serious adverse effects associated with decongestants. These agents may also exacerbate existing complications in patients with certain comorbidities such as angina, diabetes, arrhythmias, hyperthyroidism, urinary dysfunction, and uncontrolled hypertension.[5]

The combination of a decongestant and antihistamine is commonly used in treating allergic rhinitis. There are several antihistamine/decongestant combination products available OTC, which may provide additional symptomatic relief. All second-generation antihistamines are also available in combination with pseudophedrine. Of possible benefit, the combination with pseudophedrine may counteract the sedative effects associated with the antihistamine.

Besides oral decongestants, nasal or topical decongestants, such as oxymetazoline and xylometazoline, are also effective for rapid relief of nasal congestion. These agents are also available OTC. They may be useful in clearing the nasal passageways prior to intranasal steroid administration to obtain optimal benefit from the nasal steroid. Nasal decongestants produce effective nasal vasoconstriction by decreasing nasal edema associated with allergic rhinitis.[5] The most common mistake patients make when using topical decongestants, though, is chronically using them for more than 3 to 5 consecutive days, resulting in rebound nasal congestion. This is secondary to downregulation of alpha adrenoreceptors in the nasal cavity, thus making it less sensitive to the decongestant.[5] It is important for pharmacists to educate patients that topical

decongestants are indicated for short-term use only: no more than 3 to 5 consecutive days. If the patient has insufficient relief with 5 days of use, then the drug should be discontinued for 1 week, then restarted, to avoid rebound congestion.

Intranasal Cromolyn

Intranasal cromolyn sodium or NasalCrom® was introduced in 1983 in the United States for the treatment of allergic rhinitis. The starting dose of this OTC agent is 1 spray in each nostril every 4 hours when awake. The dose may be reduced after a few weeks of therapy, when symptomatic relief is achieved.

Cromolyn works by inhibiting the degranulation of sensitized mast cells preventing the inflammatory response in allergic rhinitis. Therefore, like intranasal corticosteroids, these agents are most effective when given a few weeks prior to allergen exposure with seasonal allergic rhinitis or given chronically with perennial rhinitis. Patients may need to use a topical decongestant to clear the nasal passages prior to application of the nasal spray. The treatment is continued as long as the patient is exposed to the inflicting allergen. The treatment may be reduced to whatever maintenance dose that is effective for the patient.[5]

Few comparative studies are available on the efficacy between cromolyn and other agents used to treat allergic rhinitis. In general, cromolyn is an effective agent in treating some allergic symptoms, but it is significantly less effective than intranasal corticosteroids, especially for nasal congestion.[5,40]

Intranasal cromolyn is appealing in pediatric and pregnant patients because of its favorable safety profile. In fact, NasalCrom® was recently approved for use in children as young as 2 years old. The most common side effects associated with cromolyn include sneezing (10%) and nasal stinging or burning (5%). No septal perforations have been reported with its use, and teratogenicity has not been detected in animal studies.[5] Medication adherence may be hindered with this agent, since it requires frequent drug administration, and has an unpleasant taste.

Intranasal Anticholinergics

Intranasal anticholinergics are limited in their efficacy in treating most nasal symptoms associated with allergic rhinitis. But, they have demonstrated moderate efficacy for relieving rhinorrhea.[6] Theoretically, these agents reduce cholinergic stimulation of histamine in patients with allergies. Ipratropium bromide (Atrovent®) is the most frequently studied agent and it is the most commonly used agent in the United States. The 0.03% ipratropium nasal spray is typically used for relief of rhinorrhea associated with perennial allergic rhinitis.[5] The starting dose of the ipratropium bromide nasal spray is 2 sprays per nostril 2 to 3 times daily. Ipratropium bromide is poorly absorbed systemically. The most common adverse effects include nasal dryness and epistaxis.

Leukotriene Inhibitors

Leukotrienes have been shown to be important pro-inflammatory mediators in the pathophysiology of allergic rhinitis.[4] Hence, there is interest in determining the role of these agents in the treatment of this disease. Currently, the two leukotriene receptor antagonists available by prescription only are montelukast (Singulair®) and zafirlukast (Accolate®), and the leukotriene formation inhibitor available is zileuton (Zyflo®).

A few trials have investigated the use of leukotriene receptor antagonists as monotherapy or in combination with a second-generation antihistamine. A recent multicenter, randomized, controlled trial tested the efficacy of montelukast 10 mg or 20 mg daily, loratadine 10 mg daily, and the combination of these agents in the treatment of seasonal allergic rhinitis.[41] Results of the study demonstrated that the combination of loratadine and montelukast was superior in improving nasal symptoms than either agent taken alone. In another trial, Pullerits and colleagues compared the efficacy of zafirlukast, beclomethasone dipropionate, and placebo on patient symptom scores and on eosinophilic inflammation. Patients receiving beclomethasone significantly reported lower allergic symptom scores and fewer activated nasal eosinophils than zafirlukast or placebo. Unfortunately, these studies had limitations in methodologic design, including a small sample size (33) and an invalid scoring system to assess allergic symptoms.[42] There is little information available about the efficacy of zileuton in the treatment of allergic rhinitis, though some preliminary research may support its use in the future.[43]

In summary, additional studies with larger sample sizes are needed to identify the role of leukotriene inhibitors in the treatment of allergic rhinitis. Currently, these data suggest that these agents may be beneficial as adjunctive therapy with first-line agents.

Immunotherapy
Allergen immunotherapy works by desensitizing the individual to the inflicting antigens. This involves gradual administration of an increasing concentration of allergen(s) to increase the patient's tolerance or immune response to the allergen. Immunotherapy can be very effective for patients with complicated allergic rhinitis. Since immunotherapy is not a convenient method of treatment and requires frequent office visits, it is important to choose appropriate candidates for therapy. Candidates for immunotherapy include patients with moderate to severe symptoms that are persistent or progressive who are not adequately controlled with conventional therapy. Patients with comorbidities may also be good candidates for immunotherapy.[6] Limitations to using immunotherapy include the risk for anaphylaxis and the cost of therapy.

A patient started on immunotherapy requires an extensive workup, which includes a comprehensive medical history and allergy skin testing or in vitro testing. This workup helps identify the allergens that are causing the patient's allergic reactions. Once the allergens are identified, an immunotherapy extract of these allergens is administered regularly to the patient at the clinic.

Periodic assessment is necessary to determine continuation of therapy. In general, indefinite therapy is not appropriate because of the nature by which this therapy works to increase the immune response. Theoretically, the patient should develop an adequate immune response to the inflicting allergen(s) in 3 to 5 years.[5] Patients who do not benefit from 1 year of therapy should be discontinued.

SUMMARY
Allergic rhinitis is a manageable disease that can affect up to 20% of Americans. It is an inflammatory disease that not only affects the nasal passageways, but also has systemic effects. This respiratory disorder is responsible for impaired quality of life, loss of work productivity, school absenteeism, and increased medical costs. An understanding of the pathophysiology of this disease will improve the therapeutic

management of this disorder. Recognizing that allergic rhinitis involves a complicated immunologic response to allergens will help for early identification and appropriate management of this disease.

Both environmental control and pharmacologic therapies for allergic rhinitis are pivotal in the management of this disorder. Preventive measures involve identifying the inflicting allergens and taking measures to remove and/or avoid environmental allergens. Drug therapy is used to prevent the onset or reduce the severity of symptoms associated with allergic rhinitis.

Several pharmacologic agents are available for the treatment of allergic rhinitis. Intranasal corticosteroids have demonstrated superior efficacy as monotherapy over all other agents for the treatment of seasonal and perennial allergic rhinitis, while possessing an excellent safety profile for most patients. To obtain the optimal effects from intranasal steroids, they must be used prior to allergen exposure to prevent the anti-inflammatory cascade associated with allergic rhinitis. Oral antihistamines are also effective agents; they are preferred for treating episodic allergic rhinitis because of their relative quick onset of action.

No difference in efficacy exists among oral antihistamine agents, but they differ in their safety profile. Second-generation antihistamines are the least sedating agents but are not devoid of adverse effects. In addition, these agents can be very expensive to patients and health care systems. The role of low doses of less sedating first-generation antihistamines still needs to be determined. These agents may be safe and effective for patients with mild allergic rhinitis.

An understanding of the pharmacologic basis of allergic rhinitis stresses the importance of preventive measures and the appropriate use of drug therapy. Educating patients about the appropriate management of this disease will not only reduce health care expenditures but will enhance their quality of life.

References

1. Fireman P. Allergic rhinitis. In: Atlas of allergies. Fireman P and Slavin RG, eds. London: Mosby-White, 1996.

2. Shoenwetter WF. Allergic rhinitis: epidemiology and natural history. *Allergy Asthma Proc*. 2000;21:1-6.

3. Ray NF, Baraniuk JN, Thamer M, Rinehart CS, Gergen PJ, Kaliner M, Josephs S, Pung YH. Direct expenditures for the treatment of allergic rhinoconjunctivitis in 1996, including the contributions of related airway illnesses. *J Allergy Clin Immunol*. 1999;103:401-7.

4. Bellanti JA, Wallerstedt DB. Allergic rhinitis update: epidemiology and natural history. *Allergy and Asthma Proc*. 2000;21:367-70.

5. Dykewicz MS, Fineman S. Executive summary of Joint Task Force Practice Parameters on Diagnosis and Management of Rhinitis. *Ann Allergy Asthma Immunol*. 1998;81:478-518.

6. Ledgerwood GL, Luskin AT, Nuckolls JG, Prenner BM, Scherger JE. Allergic rhinitis: the goals of therapy 2000. *Patient Care*. 2000 (Fall suppl):1-28.

7. Frieri M. Treatment update for allergic rhinitis. *Allergy and Asthma Proc*. 2000;21:377-9.

8. Gerrard JW, Vickers P, Gerrard CD. The familial incidence of allergic

disease. *Ann Allergy*. 1976;36:10-15.

9. Weiner JM, Abramson MJ, Puy RM. Intranasal corticosteroids versus oral H_1 receptor antagonists in allergic rhinitis: systematic review of randomized controlled trials. *BMJ*. 1998;317:1624-9.

10. Cave A, Arlett P, Lee E. Inhaled and nasal corticosteroids: factors affecting the risks of systemic adverse effects. *Pharmacol Therapeutics*. 1999;83:153-179.

11. Knuttson U, Sderna P, Marcus C, Carlstedt-Duke J, Calrstrom K, Bronnegard M. Effects of intra-nasal corticosteroids on endogenous glucocorticoid peripheral and central function. *J Endocrinol*. 144, 301-10.

12. Skoner DP, Rachelefsky GS, Meltzer EO, Chervinsky P, Morris RM, Seltzer JM, Storms WW, Wood RA. Detection of growth suppression in children during treatment with intranasal beclomethasone dipropionate. *Pediatrics*. 2000;105:e23.

13. Schenkel EJ, Skoner DP, Bronsky EA, Miller SD, Pearlman DS, Rooklin A, Rosen JP, Ruff ME, Vandewalker ML, Wanderer A, Damaraju CV, Nolop KB, Wicki BM. Absence of growth retardation in children with perennial allergic rhinitis after one year of treatment with mometasone furate aqueous nasal spray. *Pediatrics*. 2000;105:e22.

14. Öztürk F, Yuceturk AV, Kurt E, Unlu HH, Ilker SS. Evaluation of intraocular pressure and cataract formation following the long-term use of nasal corticosteroids. *Ear Nose Throat J*. 1998;77:846,848,850-1.

15. Day JH, Briscoe MP, Rafeiro E, Ellis AK, Pettersson E, Akerlund A. Onset of action of intranasal budesonide (Rhinocort Aqua) in seasonal allergic rhinitis studied in a controlled exposure model. *J Allergy Clin Immunol*. 2000;105:489-94.

16. Day JH, Buckeridge DL, Clark RH, Briscoe MP, Phillips R. A randomized, double-blind, placebo-controlled, controlled antigen delivery study of the onset of action of aerosolized triamcinolone acetonide nasal spray in subjects with ragweed-induced allergic rhinitis. *J Allergy Clin Immunol*. 1996;97:1050-7.

17. Munk ZM, LaForce C, Furst JA, Simpson B, Feiss G, Smith JA. Efficacy and safety of triamcinolone acetonide aqueous nasal spray in patients with seasonal allergic rhinitis. *Ann Allergy Asthma Immunol*. 1996;77:277-81.

18. Selner JC, Weber RW, Richmond GW, Stricker WE, Norton JD. Onset of action of aqueous beclomethasone dipropionate nasal spray in seasonal allergic rhinitis. *Clin Therapeutics*. 1995;17:1099-109.

19. Sue MA, Tamasky PR, Abernathy SB, Klaustermeyer WB. A comparison of six antihistamine drugs in the treatment of perennial allergic rhinitis. *Immunol Allergy Pract*. 1986;8:193-8.

20. Hebel SK. *Drug Facts and Comparisons*. St. Loius: Wolters Kluwer, 2001;698.

21. Gengo FM, Manning C. A review of the effects of antihistamines on mental processes related to automobile driving. *J Allergy Clin Immunol*. 1990;186:1034-9.

22. Kemp JP, Bahna SL, Chervinsky P. A comparison of loratadine, a new

nonsedating antihistamine, with clemastine and placebo in patients with fall seasonal allergic rhinitis. *Am J Rhinol*. 1987;1:151-4.

23. Mann RD, Pearce GL, Dunn N, Shakir S. Sedation with "non-sedating" antihistamines: four prescription-event monitoring studies in general practice. *BMJ*. 2000;320:1184-7.

24. "Zyrtec-D is labeled 'Rx-Only' pending antihistamine OTC switch decision." *The Green Sheet*. 20 Aug. 2001:2.

25. Alford C. Acute effects of hydroxyzine on nocturnal sleep and sleep tendency the following day: a C-EEG study. *Hum Psychopharmacol*. 1992;7:25-35.

26. Goetz DW, Jacobson JM, Apaliski SJ, Repperger DW, Martin ME. Objective antihistamine side effects are mitigated by evening dosing of hydroxyzine. *Ann Allergy*. 1991;67:448-54.

27. Klein GL, Littlejohn T 3rd, Lockhart EA, Furey SA. Brompheniramine, terfenadine and placebo in allergic rhinitis. *Ann Allergy Asthma and Immunol*. 1996;77:365-70.

28. Kay GG, Plotkin KE, Quig MB, Starbuck VN, Yasuda S. Sedating Effects of AM/PM Antihistamine Dosing with Evening Clorpheniramine and Morning Terfenadine. *Am J Man Care*. 1997;3:1843-8.

29. Starbuck VN et al. Functional magnetic resonance imaging shows evidence of daytime sleepiness following evening dosing with chlorpheniramine (CP). *J Allergy Clin Immunol*. 1998;101:abstract 408.

30. Astelin (azelastine HCl) package insert. Cranbury, NJ: Wallace Laboratories; 2001.

31. Red Book. 2001 ed. Montvale: Medical Economics Company, Inc., 2001.

32. Juniper EF, Guyatt GH, Ferrie PJ, Griffith LE. First-line treatment of seasonal (ragweed) rhinoconjunctivitis. A randomized management trial comparing a nasal steroid spray and a nonsedating antihistamine. *CMAJ*. 1997;156:1141-3.

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

34. Ratner PH, van Bavel JH, Martin BG, Hampel FC Jr, Howland WC, Rogenes PR, Westlund RE, Bowers BW, Cook CK. A comparison of the efficacy of fluticasone propionate aqueous nasal spray and loratadine, alone and in combination, for the treatment of seasonal allergic rhinitis. *J Fam Pract*. 1998;47:118-25.

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

36. Falliers CJ, Redding MA. Controlled comparison of a new antihistamine-decongestant combination to its individual components. *Ann Allergy*. 1980;45:75.

37. Georgitis JW. Meltzer EO. Kaliner M. Weiler J. Berkowitz R Onset-of-

action for antihistamine and decongestant combinations during an outdoor challenge. *Ann Allergy Asthma Immunol*. 2000;84:451-9.

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

39. Hebert J, Bedard P-M, Del Carpio J. Loratadine and pseudoephedrine sulfate: a double-blind, placebo-controlled comparison of a combination tablet (SCH 434) and its individual components in seasonal allergic rhinitis. *Am J Rhinol*. 1988;2:71-5.

40. Welsh PW, Stricker WE, Chu C-P, Naessens JM, Reese ME, Reed CE, Marcoux JP. Efficacy of beclomethasone nasal solution, flunisolide, and cromolyn in relieving symptoms of ragweed allergy. *Mayo Clin Proc*. 1987;62:124-34.

41. Meltzer EO, Malmstrom K, Lu S, Prenner BM, Wei LX, Weinstein SF, Wolfe JD, Reiss TF. Concomitant montelukast and loratadine as treatment for seasonal allergic rhinitis: a randomized, placebo-controlled clinical trial. *J Allergy Clin Immunol*. 2000;105:917-22.

42. Pullerits T, Praks L, Skoogh BE, Ani R, Lotvall J. Randomized placebo-controlled study comparing a leukotriene receptor antagonist and a nasal glucocorticoid in seasonal allergic rhinitis. *Am J Respir Crit Care Med*. 1999;159:1814-8.

43. Knapp HR. Reduced allergen-induced nasal congestion and leukotriene synthesis with an orally active 5-lipoxygenase inhibitor. *N Engl J Med*. 1990;323:1745-1748.