Improved strategies and new treatment options for allergic rhinitis
SANDRA K. WILLSIE, DO

Primary principles relevant to the clinical management of allergic rhinitis include (1) avoidance of allergens and triggering factors, (2) use of appropriate pharmacotherapy, (3) evaluation regarding need for and appropriate use of immunotherapy, and (4) patient education and follow-up. Currently available pharmacotherapeutic options include oral and topical (intranasal) decongestants and corticosteroids, mast cell stabilizers, intranasal anticholinergics, and antihistamines. Future therapeutic options include leukotriene modifiers and anti-IgE antibodies.

(Key words: allergen, allergy, anticholinergics, antihistamines, anti-IgE antibodies, avoidance, corticosteroids, immunotherapy, leukotriene modifiers, mast cell stabilizers, rhinitis, triggers)

Allergic rhinitis, in addition to having an adverse impact on the patient’s quality of life, has potentially serious medical sequelae, including disturbed sleep, exacerbation of asthma, eustachian tube dysfunction with otitis media, and rhinosinusitis (Figure 1).1,2

Therefore, the goals of treating patients with allergic rhinitis are control of symptoms while maintaining function and prevention of sequelae—in general, improvement of the patient’s quality of life. The control of symptoms “while maintaining function” is an important issue that will be discussed in more detail. Essentially, it refers to the idea that treatment should not have side effects that are worse than the disease itself. Using sedating antihistamines to treat patients with allergic rhinitis, for instance, demonstrates treatment’s potential to reduce cognitive function and performance.

There are four general principles for clinical management of allergy:
- avoidance of allergens and triggering factors,
- use of appropriate pharmacotherapy,
- evaluation of need for immunotherapy (allergy vaccine therapy) and use where appropriate, and
- patient education and follow-up.1

Pharmacotherapy
An ideal pharmacologic agent for the treatment of patients with allergic rhinitis—and particularly children with this condition—will maintain quality of life and meet the following criteria:3
- proven safety and efficacy,
- an easy route of administration with rapid absorption,
- rapid onset of action with no side effects, and
- antiallergenic activity.

In addition to the pharmacologic treatment modalities discussed here, patients with allergic rhinitis may also benefit from palliative modes of treatment such as nasal lavage with warm salt water (with or without baking soda) or inhalation of a warm mist through the nose for 10 to 15 minutes, two to four times daily.1

Decongestants
Because nasal congestion is one of the classic yet most problematic symptoms of allergic rhinitis, many patients seek medications possessing decongestant activity. These agents, however, must be used with caution in certain patient populations.

Used orally or as nasal sprays, decongestants have sympathomimetic properties that equate to relief of the symptoms of nasal congestion or blockage by constricting blood vessels in the nasal mucosa.1,4 This constriction reduces the volume of the edematous mucosal tissue and eases blockage of the narrow air passages.1

Oral decongestants include pseudoephedrine and phenylephrine. Practitioners are cautioned against using these agents in patients with heart disease, hypertension, thyroid disease, diabetes, and urinary difficulties due to prostate gland enlargement. Side effects of oral decongestants include agitation, dry mucous membranes, exacerbation of thyrotoxicosis or glaucoma, headache, hypertension (due to nonselective vasoconstriction), insomnia, restlessness, tremor, urinary retention, and cardiovascular effects such as palpitations, tachycardia, and extrasystoles.1

Available intranasal or topical decongestants include oxymetazoline hydrochloride, phenylephrine, and ephedrine. These agents also relieve nasal obstruction via a-adrenergic–mediated vasoconstriction, but, because they are applied directly to the nasal mucosa and have limited systemic absorption, they act more rapidly and effectively than oral agents and have less potential to cause systemic side effects.3

The major limitation to the use of topical decongestants is development of rhinitis medicamentosa. This condition is
A rebound phenomenon that causes an increase in nasal congestion and edema, which can result from several days of continual use. Therefore, the use of topical decongestants should be limited to 3 to 5 days, and it is probably best to be more cautious and limit the use to no more than 3 days. Both adults and children, but especially children, may be susceptible to an intoxication phenomenon, which is another reason to be cautious in using these drugs. This intoxication phenomenon, seen particularly with the imidazoline derivatives (eg, naphazoline hydrochloride) may manifest itself in children and infants as severe central nervous system (CNS) depression or as cardiovascular side effects.

An appropriate short-term use of topical nasal decongestants is for severe airflow obstruction or blockage to “clear the way” for other topical nasal medications (eg, intranasal steroids) to reach the nasal mucosa. When rhinitis medicamentosa occurs secondary to the use of topical decongestants, use of the decongestant should be discontinued and nasal corticosteroid therapy initiated. In severe cases, a short course of oral corticosteroid therapy might be necessary.

**Intranasal corticosteroids**
The development of intranasal steroids revolutionized the treatment of allergic rhinitis. These agents are judged to be most efficacious in alleviating the symptoms of allergic rhinitis, treating the underlying inflammatory disease process in the nasal mucosa. Essentially, antihistamines treat the early-phase reaction caused by immediate release of inflammatory mediators, including histamine, on exposure to allergen. In contrast, repeated dosing of intranasal corticosteroids treats not only the early-phase response but also the late-phase allergic inflammatory reaction caused by infiltration of the nasal mucosa with activated immune cells such as eosinophils and lymphocytes. These agents also reduce endothelial and epithelial permeability, increase sympathetic vascular tone, decrease the response of mucous glands to cholinergic stimulation, and reduce nasal hyperreactivity.

Corticosteroids, which include beclomethasone, budesonide, flunisolide, fluticasone propionate, mometasone, and triamcinolone, are considered first-line therapy for patients with predominant nasal obstruction.

Onset of action may be 4 to 12 hours after the first dose, with a maximal therapeutic effect typically achieved only after regular use for days or weeks. Because corticosteroids target the underlying inflammatory disease process rather than providing immediate symptom relief, they must be taken on a regular basis—even when symptoms are absent—to preserve their effectiveness. Ideally, once the therapeutic effect has been achieved, dosing of the corticosteroid should be tapered to the lowest effective dose for maintenance therapy. Corticosteroids can be given concurrently with antihistamines to patients who continue to have nasal and/or ocular symptoms.

Local side effects of intranasal corticosteroids include burning, dryness, epistaxis (nosebleed), sneezing, and stinging. Although these agents clearly have fewer systemic effects than oral corticosteroids, clinicians and parents may still associate steroid use with possible growth retardation in children, particularly when these drugs are taken long term. Overall, these agents are considered to be safe and effective when used at recommended doses. Although some short-term studies have suggested that intranasal corticosteroids cause a reduction in growth velocity in children, it is not clear whether a child’s ultimate height is affected by corticosteroid use or if some phases of growth are merely suppressed temporarily. In several longer-term studies, although growth rates were reduced during the first years of treatment with intranasal corticosteroid, subjects ultimately attained normal adult height.
Use of topical corticosteroids prophylactically before seasonal allergen exposure has been shown to delay onset of symptoms and may reduce the need for higher-dose therapy when pollen season begins. Specifically, nasal corticosteroid therapy should begin 10 to 14 days before the beginning of the allergen season or at the onset of symptoms, and it should continue for 2 to 3 weeks after the end of the season to reduce nasal hyperreactivity, which may persist after allergen exposure has ended.

Mast cell stabilizers
Cromolyn sodium can be quite effective in some patients with allergic rhinitis. Although the exact mechanism of action is unclear, it is hypothesized that cromolyn inhibits the release of histamine and other inflammatory mediators by stabilizing mast cells.

Intranasal cromolyn, available over the counter, is a topical nonsteroidal anti-inflammatory agent that blocks both early- and late-phase allergic responses. It relieves sneezing, rhinorrhea, nasal congestion, and nasal itching, but not ocular symptoms. It has an excellent safety profile; the most common side effects are local: sneezing and nasal burning.

Overall, cromolyn is not as effective as the nonsedating oral antihistamines or topical nasal corticosteroids; for maximal efficacy, it should be given prophylactically, before the onset of symptoms. The drug is most effective when started before an anticipated allergen exposure and when given 4 to 6 times daily, which is a regimen that can be difficult to maintain consistently.

Antihistamines
Antihistamines remain the mainstay of pharmacotherapy for allergic rhinitis. They are histamine receptor type 1 (H1) antagonists and block the histamine-induced symptoms of allergic rhinitis: rhinorrhea, itching, and sneezing, as well as related symptoms in the eyes and throat. Generally, antihistamines are not considered effective for treating nasal congestion.

**First-generation antihistamines**—The first-generation antihistamines (e.g., chlorpheniramine, diphenhydramine, triprolidine, and demecolchin fumarate) are effective H1-receptor antagonists. Problems associated with their use relate to side effects, which are numerous and can be severe in some patients. The most common and most important side effects are anticholinergic, including dry mouth and eyes, urinary retention, and CNS effects, primarily sedation/drowsiness, and impairment of motor and cognitive functions. Anticholinergic effects may be particularly serious, for example, in older individuals or in men with preexisting urinary retention secondary to prostate enlargement; the elderly may also be more susceptible to sedation and cognitive and motor impairment caused by these drugs.

Central nervous system side effects can be problematic in any patient, particularly those who need to drive motor vehicles or operate complex machinery, or pay attention and learn in school. Often underrecognized are the potentiating effects of alcohol and other CNS-depressing drugs such as sedatives, hypnotics, and antidepressants. First-generation antihistamines are available over the counter and are generally inexpensive; therefore, patients often take these agents without consulting their care provider—preferring instead to take them rather than more costly but nonsedating antihistamines that are available by prescription only (see following discussion).
Side effects of first-generation antihistamines are based on two phenomena: (1) they have poor specificity for the H1 receptor and therefore interact with other receptors such as the cholinergic receptor, and (2) they readily cross the blood-brain barrier and interact with various receptors in the CNS.20

These problems were largely resolved when second-generation antihistamines became available. These agents have good specificity for the H1 receptor and as the result of structural modifications, do not readily cross the blood-brain barrier.21

**Second-generation antihistamines**

The earliest second-generation antihistamine was terfenadine, followed by astemizole and loratadine. These agents are classified as non-sedating because their tendency to cause sedation is no greater than that of placebo. Cetirizine hydrochloride causes significantly less sedation than most first-generation antihistamines but more than the non-sedating properties of second-generation agents.22

After years of use, attention focused on reports of terfenadine and astemizole causing prolongation of the QT interval on electrocardiogram—albeit in rare cases, and primarily at elevated tissue levels.23-26 Prolongation of the QT interval, which reflects delayed myocardial repolarization, can increase the risk for development of potentially lethal ventricular tachyarrhythmias, or torsades de pointes.22,27 Torsades de pointes typically developed in individuals who were taking concomitant erythromycin or ketoconazole.

As a result of their causing arrhythmia, terfenadine and astemizole have been withdrawn from the market in the United States. There is no association of cetirizine and loratadine with similar cardiac effects.

**“Next-generation” antihistamines**

Reports of cardiac toxicity related to terfenadine and astemizole provided the impetus for development of “next-generation” antihistamines. Next-generation antihistamines are typically the structurally modified, active metabolites or isomers of second-generation antihistamines (Figure 2). These agents retain the non-sedating properties of second-generation antihistamines21 while eliminating or limiting the cardiac risks that are associated with some of the second-generation antihistamines.28

Fexofenadine, an active metabolite of terfenadine that does not cause QT prolongation,29 was approved for marketing in the United States in 1996. This agent, like terfenadine, has no associated CNS or anticholinergic side effects and undergoes little or no hepatic metabolism. There has been a single case report of a patient receiving fexofenadine hydrochloride in whom cardiac arrhythmias developed; however, because this patient had numerous predisposing factors for cardiac dysrhythmias, no causal effect was established.30 Indicated for the relief of symptoms associated with seasonal allergic rhinitis, patients received fexofenadine hydrochloride (60 mg, 120 mg, or 240 mg twice a day) or placebo at 12-hour dosing intervals (N = 570).32 At each dosage, fexofenadine provided significant improvement in total symptom score (P ≤ .003) and in all individual nasal symptoms compared with placebo. The frequency of adverse events was similar among fexofenadine-treated and placebo groups, and no dose-related trends were observed. In addition, no sedative effects or electrocardiographic abnormalities—including prolongations in QT intervals—were detected.

Desloratadine, an active metabolite of loratadine, was recently approved for marketing in the United States. Indicated for the relief of the nasal and non-nasal symptoms of seasonal and perennial allergic rhinitis in patients 12 years of age and older, desloratadine is a long-acting tricyclic histamine antagonist with selective H1-receptor histamine antagonist activity.33 Like loratadine, desloratadine is non-sedating and has not demonstrated clinically relevant cardiac effects. Clinical experience in more than 2300 patients has shown the adverse event profile of desloratadine to be similar to that of placebo. In addition, the agent does not impair wakefulness, psychomotor function, or driving performance, and it does not exacerbate the effects of alcohol.20,34

Tecamizole, previously known as norastemizole, is a primary active
metabolite of astemizole. A potent, once-daily, non-sedating antihistamine, teacemizole has shown approximately 13 times more potent binding affinity for H1 receptors than astemizole55 and has an enhanced pharmacokinetic profile. Specifically, it has a faster onset of action, it undergoes little or no hepatic metabolism, and it appears to have no effect on cardiac rhythm.36

Levocetirizine, the active enantiomer (stereoisomer) of cetirizine, is currently approved in Europe and is in clinical development in the United States. In a recently published study of healthy male subjects, levocetirizine was found to be more potent and consistent than other commonly prescribed H1 antihistamines (ebastine, fexofenadine, loratadine, and mizolastine) for blocking the cutaneous response to histamine.37 In a randomized, double-blind, four-way, crossover study, Wang et al38 assessed the effect of treatment with levocetirizine (5 mg), dextrocetirizine (5 mg) and cetirizine hydrochloride (10 mg), and matched placebo on histamine-induced changes in the nasal airways of 24 healthy subjects.38 Following nasal aerosol challenge with increasing concentrations of histamine in both nostrils, the histamine threshold concentration was increased by fourfold (from 8 mg/mL to 32 mg/mL) after treatment with cetirizine (P < .05) or levocetirizine (P < .025). In addition, treatment with either cetirizine or levocetirizine significantly reduced histamine-induced sneezes compared with placebo (P < .01).

To receive approval of the Food and Drug Administration, these agents must demonstrate equivalent or better efficacy, greater safety (ie, absolutely no adverse cardiac effects), and improved convenience (such as once-daily dosing or faster onset of action) than the previous generation of antihistamines.

Leukotriene modifiers
As part of the early-phase allergic response, arachidonic acid is released from cell membrane phospholipids and converted to the eicosanoids: leukotrienes, prostaglandins, and thromboxanes. The cyclooxygenase pathway of arachidonic acid metabolism yields prostaglandins and thromboxanes; the 5-lipoxygenase pathway produces leukotrienes, four of which have proinflammatory effects: leukotriene B4 (LTB4), LTC4, LTD4, and LTE4. The latter three, LTC4, LTD4, and LTE4, each contain a cysteine amino acid residue and are therefore known as the cysteiny1 leukotrienes.39

Leukotriene modifiers include an inhibitor of the 5-lipoxygenase enzyme (zileuton) and three cysteiny1 leukotriene receptor antagonists: pranlukast (investigational), zafirlukast, and montelukast, each of which inhibits bronchoconstriction.40,41 These agents are indicated for the treatment of asthma, but they may also have potential value for the treatment of allergic rhinitis and are being investigated for this purpose. In clinical studies, zileuton,42 zafirlukast,43 and pranlukast have demonstrated efficacy in reducing symptoms of allergic rhinitis.44

Recently, the results of a randomized, double-blind, placebo-controlled, clinical trial demonstrated the efficacy of combination therapy with montelukast and loratadine in patients with seasonal allergic rhinitis.46 In the study, 460 men and women aged 15 to 75 years with seasonal allergic rhinitis were randomly assigned to receive one of the following regimens for 2 weeks, once daily in the evening: montelukast, 10 mg or 20 mg; loratadine, 10 mg; montelukast, 10 mg, plus loratadine, 10 mg; or placebo. The results showed that the combination therapy significantly improved daytime nasal symptoms scores (P < .001), compared with placebo and each agent alone. The combination treatment also significantly improved eye symptoms, nighttime symptoms, results of global evaluations, and quality of life, and was well tolerated, with a safety profile comparable to that of placebo.

Allergen immunotherapy
In 1911, Noon47 first published his system for prophylactic inoculation against hay
fever, and, since then, allergen immunotherapy has been used for the treatment of patients with allergic diseases. This process involves administering repeated doses of allergen-containing substances to the patient with the goal of altering the immune system's responses, i.e., desensitizing the patient to those allergens and reducing symptoms triggered by subsequent exposures. In patients with seasonal allergic rhinitis, immunotherapy blunts the seasonal rise in specific immunoglobulin (IgE) antibody levels.

The allergen extract is given in increasing doses, and protocols may vary considerably. These regimens range from "rush" protocols—in which injections are given several times a day—to relaxed schedules that may last months, a year, or more. In such long-term scenarios, injections might be given once or twice weekly or once every several weeks. Immunoglobulin G antibodies to the antigen are produced, which is considered a sign that the treatment is eliciting a response. However, although the IgG antibodies may participate in the desensitization process, possibly by competing with IgE for binding of the allergen, many immunologic changes occur with immunotherapy that do not involve IgG. Allergy vaccine is thought to work, at least in part, by shifting the allergic response from helper T cells type 2 (TH2) lymphocytes, which predominate in allergic individuals, to helper T cells type 1 (TH1) lymphocytes, to those allergens and reducing symptoms triggered by subsequent exposures.

In a randomized, double-blind, placebo-controlled trial assessing the long-term efficacy of immunotherapy for grass-pollen allergy, investigators reported that immunotherapy for 3 to 4 years continued to reduce symptoms and the need for rescue medication for 3 years after discontinuing immunotherapy injections.

### Anti-IgE antibody therapy

As the early-phase allergic reaction in the respiratory tract mucosa is triggered when allergens bind to IgE antibodies that are bound to receptors on immune cell surfaces, resulting in degranulation and other activation processes, it is logical to assume that blocking the binding of IgE to immune cell surface receptors would block the allergic response. An anti-IgE antibody inhibits production of IgE in B lymphocytes, neutralizes circulating IgE antibodies by binding to them, and prevents IgE antibodies from attaching to immune cell surface receptors. Figure 5 shows the cellular mechanisms involved in airway inflammation and the effects of allergen-bound IgE in the early- and late-phase allergic responses, all of which may be reduced by blockade of IgE-mediated degranulation and activation of immune cells.

A recombinant humanized murine (mouse) monoclonal antibody, omalizumab, has been shown in a randomized clinical trial to reduce nasal symptom scores in patients with seasonal ragweed allergic rhinitis. In this double-blind trial, 536 patients aged 12 to 75 years were randomly assigned to receive one of three doses of omalizumab, or placebo subcutaneously just before the ragweed pollen season and every 3 or 4 weeks (depending on the patients' IgE levels) for a total of three or four treatments. Nasal symptom severity scores in patients who received the highest dose of omalizumab (300 mg) were significantly lower than in those who received placebo ($P = .002$), and IgE reduction appeared to correlate with

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**Figure 5. Effects of IgE in the early- and late-phase allergic reactions, which may be reduced or blocked by anti-IgE therapy.** (Source: National Asthma Education and Prevention Program. Expert Panel Report 2: Guidelines for the Diagnosis and Management of Asthma. Bethesda, Md: National Institutes of Health; 1997. NIH Publication No. 97-4051.)
lower use of rescue antihistamine therapy. The treatment was well tolerated, with similar rates of adverse events in the groups receiving the active treatment and the group receiving placebo.

Comment
The ideal approach to treatment of patients with allergic rhinitis will be individualized, with attention given to the identification and avoidance of triggers in all cases. Responsible practitioners will evaluate the benefit-risk ratio for available agents (Figure 6) before deciding what to prescribe for their patients. Mainstay therapeutic agents that have been proven effective in treating patients with allergic rhinitis—particularly when nasal obstruction plays a role—include the topical, intranasal corticosteroids. Other available agents with proven efficacy include leukotriene modifiers, which are generally considered to be well tolerated, effective in reducing nasal congestion, and, like intranasal corticosteroids, probably work best when combined with an antihistamine.

A variety of new pharmacologic agents are now available for the treatment of patients with allergic rhinitis (Figure 6). These include a number of next-generation antihistamines that provide the benefit of incrementally improved potency, quicker onset of action, and longer duration of action, without evidence of clinically significant cardiac toxicity. In addition, consideration should be given to the use of allergen immunotherapy in selected pediatric cases in which early experimental evidence suggests that control of allergic rhinitis may help prevent the development of asthma. Finally, although further studies are indicated and the potential cost of this therapy may limit its clinical usefulness in some patients, the use of anti-IgE therapy may offer potential benefit for certain individuals with allergic rhinitis by downregulating allergic and inflammatory responses.

References

Checklist

- **Oral decongestants** (Provide no benefit for sneezing, itching, and rhinorrhea; provide modest benefit in relieving congestion.)
  - Pseudoephedrine
  - Phenylephrine
- **Intranasal/topical decongestants** (Provide no benefit for sneezing, itching, and rhinorrhea; provide substantial benefit for congestion.)
  - Oxymetazoline hydrochloride
  - Phenylephrine
  - Ephedrine
- **Intranasal corticosteroids** (Provide substantial benefit in relieving sneezing, itching, congestion, and rhinorrhea.)
  - Beclomethasone
  - Budesonide
  - Flunisolide
  - Fluticasone propionate
  - Mometasone
  - Triamcinolone
  - Intranasal corticosteroids (Provide no benefit for sneezing, itching, rhinorrhea.)
  - Clemastine fumarate
  - Diphenhydramine
  - Chlorpheniramine
  - Cetirizine hydrochloride
  - Loratadine
  - Fexofenadine hydrochloride
  - Desloratadine
  - Montelukast sodium
  - Montelukast sodium
- **Antihistamines** (Oral formulations provide substantial benefit in relieving sneezing, itching, and rhinorrhea and minimal benefit in relieving congestion. Intranasal formulations provide modest benefit in relieving sneezing, itching, and rhinorrhea and minimal benefit in relieving congestion.)
  - First generation
    - Chlorpheniramine
    - Diphenhydramine
    - Triprolidine
    - Clemastine fumarate
  - Second generation (Non-sedating)
    - Terfenadine
    - Astemizole
    - Loratadine
    - Cetirizine hydrochloride
  - Next generation (Non-sedating)
    - Fexofenadine hydrochloride
    - Desloratadine
    - Montelukast sodium
  - Second generation (Non-sedating)
    - Lofexidine
    - Levocetirizine
- **Leukotriene modifiers** (Indicated for the treatment of asthma, these agents are being investigated for efficacy in reducing the symptoms of allergic rhinitis.)
  - Zileuton
  - Montelukast (available in Japan)
  - Montelukast sodium
  - Ipratropium bromide

*Not available in United States because of prolonged QT interval.

Figure 6. Pharmacologic agents available and in clinical trials for the treatment of patients with allergic rhinitis and their effectiveness in relieving specific symptoms.