Pharmacotherapy for allergic rhinitis

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Background: **Pharmacotherapy for allergic rhinitis is a mainstay of treatment for patients with mild to severe nasal allergy symptoms. A wide array of medical treatment options is available for both episodic relief and prevention of symptoms. Treatment regimens can be tailored to individual patients based on nasal symptoms, severity, and associated atopic disorders. The purposes of this review are to identify available pharmacotherapies for allergic rhinitis, to discuss the benefits and limitations of each treatment option, and to help guide practitioners in providing optimal medical treatment for patients with allergic rhinitis.**

Methods: **A comprehensive review of pharmacotherapies for allergic rhinitis was performed using a PubMed search. Secondary sources within indexed studies were also compiled to review current medication options for patients with allergic rhinitis. The benefits and limitations of each class of allergy medication were reviewed to provide information on selecting the optimal treatment regimen for patients with allergic rhinitis.**

Results: **Pharmacotherapies for allergic rhinitis that are currently used in clinical practice include antihistamines, corticosteroids, leukotriene modifiers, mast cell stabilizers, expectorants, and decongestants. Symptoms of nasal congestion, itching, sneezing, and rhinorrhea can be targeted with specific therapies that modulate the acute-phase or late-phase allergic reactions. Associated atopic disorders, including conjunctivitis and asthma, can help guide medication selection.**

Conclusion: **Pharmacotherapies for allergic rhinitis offer numerous options that are safe, effective, and readily available to target specific nasal symptoms. Symptom-based selection of allergy medications can result in optimal treatment for patients with allergic rhinitis.** © 2014 ARS-AAOA, LLC.

Key Words:
allergy rhinitis; pharmacotherapy; nasal allergies; allergy medication; atopy

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Pharmacotherapy remains a mainstay of treatment for patients with allergic rhinitis. Numerous allergy medication options are readily available for both symptomatic relief and prevention of symptoms, which commonly include nasal congestion, nasal itching, sneezing, and rhinorrhea. The first medications for allergic rhinitis were introduced in the 1940s[1] with the discovery of antihistamines, followed by numerous other medication treatment options over the past 70 years. Current allergy medications have excellent safety profiles and accessibility, and limited interactions with each other, allowing for patient-specific regimens that are tailored to symptom quality, location, and severity.

The clinical variation in symptoms, seasonal worsening, ranges of severity, and associated comorbid conditions, such as asthma or conjunctivitis, often determine the medication regimens that are optimal for each patient. Additional factors in medication selection include compliance with daily treatment schedules, prior success or failure with treatments, tolerance to or side effects of particular medications, patient age, and costs.

Targets for medical therapies are directed at blocking symptoms from either the histamine-mediated early-phase response within the target tissue or the late-phase response that occurs several hours later when infiltrating immune cells are recruited to the site of early-phase response and release proinflammatory molecules. The early-phase response results from an immediate release of histamine from mast cells into the local tissue, leading to neural stimulation that causes pruritis and sneezing. A histamine-mediated increase in vascular permeability and glandular secretions results in clear rhinorrhea and congestion from engorged capillaries

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in the nasal mucosa. A late-phase response is the release of additional inflammatory substances which propagate the tissue edema that patients experience as congestion and obstruction.

This review provides an overview of pharmacotherapy options for allergic rhinitis. Practitioners should be aware of benefits and limitations of each medical therapy so that regimens can be tailored to individual patient symptoms for improved treatment outcomes.

Antihistamines

Histamine is one of the primary chemical mediators involved in the inflammatory response in allergic rhinitis. Upon activation by an antigen binding to an immunoglobulin E (IgE) receptor, basophils and mast cells release histamine, which binds with various histamine receptors in glandular, neurogenic, and vascular target cells. Histamine release results in vasodilation, increased vessel permeability and glandular secretion, sensory nerve stimulation, and subsequent parasympathetic activity.[2] These physiologic responses lead to the common nasal allergy symptoms of pruritus, sneezing, rhinorrhea, and congestion, and form the basis behind antihistamine therapy.

Antihistamines block the binding of histamine to the H1 histamine receptor that is involved in the early phase of the allergic reaction.[3] Antihistamines are safe and effective for episodic control because they have a short onset of action, or as a preventive measure taken on a daily basis for persistent symptoms.[4]

The early antihistamines (first generation) provide rapid and effective blockage of the H1 receptor, resulting in relief of pruritis, sneezing, rhinorrhea, and allergic conjunctivitis, but have little effect on nasal congestion.[5] There are 6 classes of first generation antihistamines, including ethanolamines (diphenhydramine: Benedryl), alkylamines (chlorpheniramine: Chlor-Trimeton), piperazines (hydroxyzine: Atarax), and phenothiazines (promethazine: Phenergan). These early antihistamines are lipophilic and readily cross the blood-brain barrier resulting in central nervous system (CNS) side effects, including sedation and decreased cognitive abilities,[5] motor performance,[6] and ability to drive.[7] First-generation antihistamines are also limited by adverse effects due to anticholinergic stimulation, resulting in blurry vision, dry mouth, and increased mucous viscosity. The sedation side effects from early antihistamines can be tolerated in some patients if taken at night before sleep, but it is important to note that paradoxical stimulation of the CNS can also occur in children.[8]

Second generation antihistamines include cetirizine, desloratadine, fexofenadine, levocetirizine, and loratadine. The major improvement of these medications include less permeability through the blood-brain barrier and thus decreased CNS side effects, with perhaps the exception of cetirizine, which can still cross the blood-brain barrier and cause sedation in a dose-dependent manner.[3] These medications also work on the H1 receptor but are more lipophobic and preferentially bind to the peripheral antihistamine receptors over the central receptors.[3] The anticholinergic side effects seen in earlier antihistamines are not as prevalent with second-generation medications. The second-generation oral antihistamines appear to have similar efficacy.[6]

Of the primary symptoms associated with allergic rhinitis, nasal congestion is less well-controlled with oral antihistamines.[6] Nasal congestion can be due to both the histamine release causing increased permeability in the early-phase response and the other cellular and soluble inflammatory mediators involved in the late-phase response. If the late-phase response has already been initiated, oral antihistamines may not be of as much value in blocking the immune response and alleviating nasal congestion. Oral decongestants or intranasal steroid sprays are often taken in combination therapy with antihistamines to specifically address the symptom of nasal congestion.

More recently, introduction of topical intranasal antihistamine sprays, azelastine and olopatadine, have shown to be effective first-line agents for the treatment of allergic rhinitis.[9] Intranasal antihistamines allow for delivery of a higher concentration of the medication to the site of reaction, although there is systemic absorption with potential sedation as a side effect.[10] Topical antihistamines offer improved efficacy for nasal symptoms, including nasal congestion, compared to systemic anthistamines.[9–11] Intranasal antihistamines have a fast onset of action allowing for symptomatic use. Additional anti-inflammatory properties of azelastine and olopatadine may be responsible for additional benefit over oral antihistamines in addressing nasal congestion.

Combination therapy with oral and intranasal antihistamines did not show added benefit[12]; however, combination therapy with intranasal antihistamine and intranasal corticosteroids may have an additive effect.[13]

Corticosteroids

Allergic rhinitis is a Th2 inflammatory disorder. Corticosteroids are anti-inflammatory medications that are thought to downregulate immune responses in allergic rhinitis and decrease mediators in the late phase of the allergic reaction. Corticosteroids are lipid-soluble and bind to cytoplasmic receptors, which are then transported to the nucleus to effect transcription of immune molecules that downregulate the inflammatory response.[14]

Intranasal corticosteroids have the greatest efficacy at relieving all 4 primary symptoms of allergic rhinitis and are considered a first-line treatment for allergic rhinitis in patients who have moderate to severe disease.[10,15] Nasal corticosteroid sprays have less side effects and associated risks in comparison to oral corticosteroid use, while decreasing the local influx of inflammatory cells and mediators that propagate the allergic response in the nasal mucosa. Although intranasal corticosteroids are effective for allergic rhinitis and serve as a first-line treatment for

moderate to severe disease, their slow onset of action requires daily use to achieve maximal effectiveness.[16] The onset of action of these medications is slower than that of antihistamines and maximal benefit occurs if used prior to onset of symptoms and for at least 7 to 10 days continuously.[17] Intranasal corticosteroids appear to be safe in both children and adults at recommended dosages. Additionally, technique of administration is important for deposition of medication onto the nasal mucosa and turbinates rather than along the nasal floor or septum.[17] Patients should be instructed to aim the spray nozzle toward the lateral eye or ear for proper deposition toward the lateral nasal structures.

There are many intranasal corticosteroids available for prescription use, including beclomethasone dipropionate, budesonide, ciclesonide, flunisolide, fluticasone furoate, fluticasone propionate, mometasone furoate, and triamcinolone. Triamcinolone is also available without a prescription. Intranasal corticosteroid sprays offer improved efficacy over other classes of medications for allergic rhinitis and there is no direct evidence of superiority of any particular nasal corticosteroid preparation over another.[15,16] Patients may have individual preferences of an aqueous or aerosol preparation (ciclesonide, beclomethasone dipropionate). All intranasal steroids have U.S. Food and Drug Administration (FDA) approval for treatment over age 6 years and FDA pregnancy category C safety rating, with the exception of budesonide, which has an FDA pregnancy category B safety rating.

Local adverse effects of long-term topical intranasal steroid use can result from mucosal irritation that causes discomfort, mild bleeding, dryness, or rarely septal perforation.[18] Patients should be counseled to direct sprays away from the nasal septum to avoid these potential side effects. More serious risks of glaucoma exacerbation or cataracts limit their use in patients with these conditions.[19] Initial concerns of risks associate with systemic corticosteroid use, including hypothalamic pituitary suppression, growth suppression in children, bone loss do not seem to be significant concerns.[10] Studies with intranasal beclomethasone demonstrate no effect on the hypothalamic-pituitary-adrenal axis function in adults.[20] Studies with fluticasone propionate, mometasone furoate, and triamcinolone acetonide demonstrate no growth retardation in children when compared to placebo.[21–23]

Oral corticosteroids have greater potency than topical corticosteroids and may provide relief of nasal allergy symptoms but should be limited in long-term use for allergic rhinitis due to side effects and potential complications associated with their prolonged use.[10] Patients who have systemic or long-term exposure with systemic dosing often require bone density monitoring, blood glucose monitoring, and ophthalmic examinations. A short burst (5 to 7 days) of oral corticosteroid is helpful for acute, severe symptoms, but should be limited to sporadic use. There is no consensus on the appropriate dosing and regimen. Clinicians and patients need to weigh the risks and benefits of oral corticosteroid steroid use in deciding systemic dosing frequency and amount.

Decongestants

Decongestants are sympathomimetic alpha-adrenergic agonists that cause nasal vasoconstriction and subsequent reduction of the nasal mucosal edema which is responsible for congestion.[24] Nasal decongestants have limitations for long-term use, but are useful for short-term treatment until the underlying acute process resolves or another acceptable long-term treatment option, such as intranasal corticosteroid spray, becomes effective. Topical decongestants such as oxymetazoline, xylometazoline, and phenylephrine directly stimulate sympathetic alpha receptors in the nasal mucosa resulting in rapid relief of nasal congestion and rhinorrhea. The potential for abuse is seen with topical decongestants, which is why they are only indicated for no more than 3 to 5 days of consecutive use. Prolonged use can cause dependence due to rebound nasal congestion, termed rhinitis medicamentosa, which occurs due to downregulation of alpha-adrenergic receptors. This leads to baseline increased congestion and a decreased efficacy of exogenously applied topical vasoconstrictors.[25]

Oral decongestant agents include pseudoephedrine and phenylephrine. Oral decongestants stimulate both alpha and beta adrenergic receptors, resulting in additional risks and side effects with systemic absorption. Adverse effects of palpitations, irritability, nasal dryness, hypertension, tremor, sleep disturbance, loss of appetite, urinary retention, dizziness, and tachycardia may be seen with short-term use of systemic decongestants. Their use is contraindicated in patients with hypertension, closed angle glaucoma, hyperthyroidism, cardiovascular diseases, urinary retention, and cerebrovascular disease. The drying of the nasal cavity is usually more significant in the winter months when there is less humidity in heat-conditioned environments. Long-term decongestant use is often limited by adverse effects.[10] Studies do show that decongestants in combination with antihistamines are more efficacious in symptomatic control of allergic rhinitis.[26]

Expectorants

Normal functioning of the nasal airway epithelium requires mucous secretion for mucociliary clearance of particulates, allergens, and bacteria from the sinonasal passages. Increased viscosity of the mucous can lead to stasis of immunogenic particulates (allergen epitopes) that contribute to the inflammatory response in allergic rhinitis. Expectorants such as guaifenesin are thought to decrease mucous viscosity and allow for improved mucociliary clearance. Although not FDA-approved for rhinitis, patients with difficulty clearing thick secretions may have benefit from guaifenesin.[27]

Nasal saline

Nasal saline irrigations have been shown to provide significant symptom relief without significant side effects.[28] Nasal saline works by direct thinning and clearance of mucous and allergy particles from the nasal mucosa. The onset of the allergic response is dependent upon contact of allergens with immune cells in the nasal mucosa. A simple cleaning of the nasal cavity can decrease immune exposure to airborne allergen triggers that are filtered and trapped by the nasal mucosa. Infectious contamination of irrigating solution can be avoided with use of clean water sources and delivery devices.

Leukotriene modifiers

Leukotrienes are inflammatory mediators released from white blood cells that partake in both the early-phase and late-phase allergy responses.[29] Leukotrienes have significant contribution to the pathogenesis of asthma by causing bronchoconstriction and mucous secretion in the lungs. Leukotriene D4 receptor antagonists such as montelukast and zafirlukast block cysteinyl leukotriene D4 receptor, which reduces the inflammatory response in nasal tissue. Montelukast has indications for both the treatment of allergic rhinitis and asthma, whereas zafirlukast is only indicated for the treatment of asthma. Comparison of leukotriene receptor antagonists to oral antihistamines and intranasal corticosteroids have shown inferior efficacy for leukotriene receptor antagonists making them a second-line treatment; however, they may enhance the effects of other treatments for allergic rhintis.[30,31] For patients with concurrent asthma and allergic rhinitis, montelukast can improve both conditions. Oral leukotriene receptor antagonists are recommended for adults with seasonal allergic rhinitis; however, their benefit for persistent allergic rhinitis has not been established in adults.[32] The leukotriene inhibitor, zileuton, blocks 5-lipoxegenease in the leukotriene pathway, but is currently only indicated for the treatment of asthma. There have been concerns associated with montelukast, such as behavioral changes; however, no large study has been performed to validate these studies.[33]

Anticholinergics

Anticholinergic medications decrease parasympathetic tone, which results in less secretion of mucous from glandular mucosa and less watery rhinorrhea in patients with rhinitis.[10] Ipratropium, the only available topical intranasal anticholinergic spray, is often used for nonallergic vasomotor rhinitis to decrease mucous secretion. For patients with allergic rhinitis who have a primary symptom of clear rhinorrhea, ipratropium nasal spray can be used to decrease nasal secretions.[34] The onset of action is rapid but dosing needs to occur 3 times daily to achieve maximal effect. Although ipratropium has an excellent safety profile, anticholinergic side effects limit their use in patients with prostate hypertrophy and narrow angle glaucoma. Anticholinergic medication does not address nasal congestion, sneezing, or pruritis.

Cromolyns

Cromolyns are mast-cell stabilizers that block the acute-phase reaction by preventing mast cell degranulation and release of histamine. Intranasal cromolyns are available over the counter and have an excellent safety profile.[35] Cromolyns require continuous use because they are primarily effective at preventing the allergic response rather than blocking the cascade once mast cell degranulation has occurred. The inferior efficacy of cromolyns compared to other first-line medications for allergic rhinitis[36] and the short half-life requiring 4 times daily dosing limits their effectiveness in treating allergic rhinitis. The favorable efficacy and safety profile makes their use an acceptable option for patients who are seeking a preventative measure for nasal allergy symptoms.

Selecting a medication regimen

Many patients with allergic rhinitis suffer from symptoms of both the acute-phase and the late-phase response. Treatment of both phases is often needed to address different pathways that lead to nasal symptoms. Additionally, medications are not intended to be curative and patients often do not have complete relief of symptoms with a single therapy. The use of combination therapy for allergic rhinitis is commonplace and safe when medications from different classes are used.[13,15] The side effects seen with antihistamines are dose-dependent, which limits the maximal safe doses for these treatments. There are no severe cross-reactions between classes of allergy medications, allowing for the concurrent use of multiple classes of medication for allergic rhinitis.

Many patients with allergic rhinitis experience incomplete response to a single medication or ongoing symptoms despite multiple medications. It is common for patients to have tried several medications before seeking specialty care. With numerous medication options readily available, patients often are confused about the appropriate or optimal medication regimen.

For patients with intermittent symptoms, antihistamines used on an as-needed basis are appropriate (Fig. 1). For persistent symptoms, daily use of intranasal corticosteroid spray or daily antihistamine are first-line therapies for treatment.[2] Using both a topical nasal corticosteroid and a topical antihistamine resulted in improved symptoms compared to each medication alone,[13] and faster and more complete symptom improvement compared to each medication individually or placebo.[37] Patient preference, individual efficacy, and tolerability of medications often dictate whether an antihistamine or intranasal corticosteroid spray is used for daily therapy. Antihistamines have the advantage of a quick onset of action and blocking of the acute phase

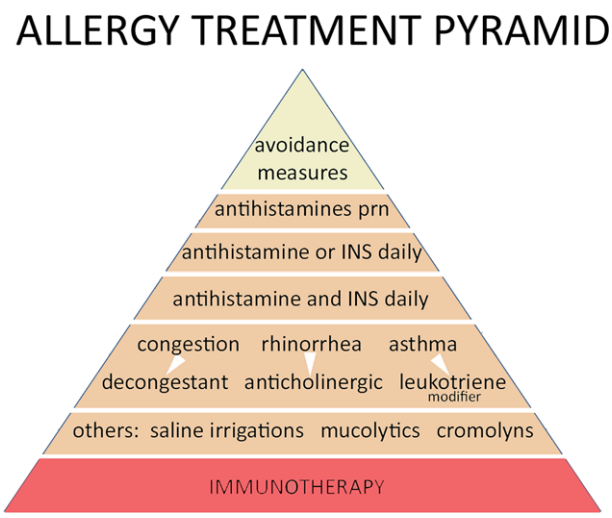

FIGURE 1. Treatment options for patients with allergic rhinitis. A general schema for treatment includes avoidance measures, medications (orange), and immunotherapy. First-line medications include antihistamines and INSs. Refractory symptoms of congestion, rhinorrhea, or asthma can be addressed with the respective medications (white arrows). INS = intranasal corticosteroid spray.

reaction, whereas intranasal steroid sprays require daily use for maximal effectiveness but are able to block the late-phase reaction that causes ongoing nasal congestion. For persistent symptoms, a combination of an oral or topical nasal antihistamine and an intranasal corticosteroid spray are appropriate. The choice of antihistamine route, oral or intranasal, is often determined by individual preferences regarding comfort, cost, availability, prior effectiveness, and tolerability.[38]

The addition of nasal saline irrigations to treatment regimens should routinely be considered given the favorable risk/cost-benefit analyses.[28] Addition of a leukotriene modifier is safe and can be helpful for seasonal symptoms in adults or persistent symptoms in children and adults, especially if there is concurrent asthma for which it is independently FDA-approved. If symptoms are persistent despite use of a daily antihistamine and intranasal corticosteroid spray, the use of decongestants, cromolyns, anticholinergics, and expectorants can be added to target specific symptoms in certain clinical scenarios; however, each of these treatments has limitations in the treatment of allergic rhinitis.

Many patients suffer from polysensitization that includes both intermittent and persistent allergens. The use of prophylactic pharmacotherapy for intermittent (seasonal) allergic rhinitis can be performed with either intranasal corticosteroids or antihistamines, although administration of antihistamines at the onset of symptoms may provide comparable symptom relief to preventative therapy.[39] For patients who have improved symptoms between allergy seasons, step-down therapy can be performed by first removing all medications other than the intranasal corticosteroid and antihistamines. For patients on combination therapy, the decision to stop either an antihistamine or intranasal corticosteroid spray should consider the onsets of action. Restarting an antihistamine can result in maximal efficacy in a short time period, whereas intranasal corticosteroid sprays need a longer time period to reach maximal effectiveness when restarted.

Emerging therapies

Improved understanding of the pathways involved in allergic rhinitis has led to development of specific therapies that target immune dysfunction. Omalizumab, a monoclonal anti-IgE antibody has been FDA-approved for treatment of severe asthma. Based on immunologic principles of allergic rhinitis, blocking of IgE antibodies would be expected to provide a significant relief of allergy symptoms. Clinical trials have shown efficacy in intermittent[40] and persistent allergic rhinitis.[41] The lack of direct comparison to other treatments, high costs of this medication, and need for intravenous therapy are current limitations of anti-IgE therapy.

Interleukin 5 (IL-5) has a well-established role in mediating the Th-2 response and activating eosinophils in the allergy response. An anti–IL-5 antibody has been developed for use in eosinophilic diseases[42] such as asthma; however, its efficacy for allergic rhinitis has not yet been demonstrated. As seen with other classes of directed medications, blocking a specific molecule within a complex pathway may not be sufficient to alter the course of the disease. Conversely, side-effect profiles are greatly improved by the improved specificity of targeted therapies.

The role of the innate immune system in allergic rhinitis has received attention recently.[43] Toll-like receptors (TLRs) use pattern-based recognition to initiate an immune response. A new bioactive molecule that stimulates TLR8 has been proposed for the treatment of allergic rhinitis.[44] A theoretical improvement would be expected with a shift in the Th1/Th2 balance that is seen with response to allergen-specific immunotherapy.

A novel formulation of botulinum toxin (Botox) has been studied in animal models with promising results for reducing the signs of allergic rhinitis by blocking the acetylcholine pathways.[45] Current formulations of botulinum toxin are not approved for intranasal use and introduction of a new gel formulation would allow for easier application. A longer-acting anticholinergic would be beneficial compared to the current anticholinesterase treatment, ipratropium, which requires 3 times daily dosing.

Conclusion

Pharmacotherapy is 1 of 3 pillars of treatment for allergic rhinitis. Intranasal corticosteroids and antihistamines are first-line treatments with established efficacy and favorable safety profiles. Combination therapy is often used to target both early-phase and late-phase responses for optimal relief, in addition to refractory or severe symptoms that

require multimodality therapy. Emerging therapies that are directed as specific pathways in the allergic response offers promise to addressing gaps in treatment and continued symptoms despite maximal pharmacologic therapy.

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