

Intranasal antihistamines for allergic rhinitis: Examining the clinical impact

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ABSTRACT

Allergic rhinitis is likely the most common medical complaint to a clinical allergist and immunologist affecting between 10 and 30% of all adults. This disease causes significant impact on quality of life as well as creating a financial burden on society with decreased work productivity and medication costs. Often, many allergy sufferers do not adhere to the medication recommendations provided by their physician most often because these therapies have not provided relief. Although in the past, the mainstay of treatment for allergic rhinitis has been environmental avoidance, immunotherapy, nasal corticosteroids, and oral antihistamines, the most recent rhinitis diagnosis parameters published by the American Academy of Allergy, Asthma and Immunology have also discussed the importance of other often overlooked therapies. More specifically, the new guidelines discuss a place for the use of intranasal antihistamines as first-line therapy as well as potentially providing superior relief to second-generation oral antihistamines. The guidelines also identify the biphasic nature of the allergic response with both phases consisting of nasal pruritus, sneezing, rhinorrhea, and congestion with the late phase predominated by nasal congestion. It is important to understand how intranasal antihistamines fit into these latest guidelines as first-line therapy and to understand how they may be beneficial to the symptoms associated with allergic rhinitis. It is equally important to identify the individuals who have had less success with their current therapies to determine if intranasal antihistamines would be an important adjunct in therapy.

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Since the introduction of antihistamines in the 1940s they have become the mainstay of treatment for allergic rhinitis. Development in the antihistamine class of therapeutics has included more selective receptor antagonism, reduced systemic side effects, and now direct delivery intranasally. Although, the intranasal route of delivery offers increased local drug concentrations and limited systemic bioavailability, the question becomes whether the intranasal antihistamines offer any increased advantage over the oral counterparts or are they “me too” drugs. This article will review the therapeutic impli-

cations of the intranasal antihistamines in hopes of highlighting their unique characteristics.

HISTORY

In 1870 Paul Ehrlich characterized the mast cell that has become the center of investigation for atopic diseases, particularly allergic rhinitis.¹ It was ~30 years later when histamine was first discovered in 1910, by the British physiologist Sir Henry Dale, as a contaminant of ergot generated by bacterial action.¹ In 1924, Lewis described the classic “triple response” to histamine, consisting of vasodilatation, a wheal that was the consequence of increased vascular permeability and flare due to an axon reflex.²

The first compound reported as an antihistamine by Ungar, Parrot, and Bovet was the adrenolytic benzo-dioxan, piperoxan (933F) in 1937, which blocked the effect of histamine on the guinea pig ileum.¹ This was followed shortly afterward by the report by Bovet and Staub (1937) of structurally related aryl ethers such as the thymol ether 929F, which protected the guinea pig from the lethal effects of histamine-induced anaphy-

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laxis.¹ The latter compound proved to be too toxic for clinical development, but replacement of the ether oxygen by an amino group led to the discovery of aniline ethylene diamine derivatives.¹ In 1942, Bernard N. Halpern synthesized the first clinically used antihistamine—phenbenzamine.¹ This was quickly followed by the development of multiple antihistamines such as diphenhydramine (Benadryl), tripeleminamine, chlorpheniramine, and promethazine. After 1945, these antihistamines became widely used in the treatment of various allergic disorders such as allergic rhinitis and urticaria. However, side effects were not uncommon and sedation was a drawback to their use. In the 1990s there was the introduction of nonsedating oral antihistamines, followed by the newer intranasal antihistamines.

PATHOGENESIS OF ALLERGIC RHINITIS

Allergen challenge in individuals with allergic rhinitis establishes the well-described early and late-phase responses both of which contribute to the acute and chronic symptoms seen in allergic patients. Each phase is driven by a spectrum of physiological actions that make them unique with the early phase predominated by the release of preformed mast cell mediators (histamine, tryptase, chymase, kinins, heparins, and others) as well as the release of newly formed mediators from mast cells, eosinophils, basophils, and macrophages (prostaglandin D₂^B, leukotriene C₄^B [LTC₄], LTD₄, and LTE₄).^{3,4} The early phase mediators are responsible for the acute symptoms including nasal pruritus, sneezing, rhinorrhea, and congestion through their direct action on the nasal mucosa.³ The leukotrienes, along with released cytokines, act to recruit inflammatory cells that will ultimately lead to the symptoms associated with the late-phase response.³

The early physiological response to allergic stimuli is not limited to the direct effect of the released mediators but also includes a neurogenic response. Histamine binds to H₁-receptors on nociceptive nerve receptors, leading to the release of substance P, calcitonin gene-related peptide, neurokinin A, and gastrin-releasing peptide, as well as other neurotransmitters contributing to vascular leak and inflammation.³ Parasympathetic neurons also release vasoactive intestinal peptide, acetylcholine, and nitric oxide synthase immediately after an allergen challenge and act collectively to create the early phase response of sneezing, nasal pruritus, rhinorrhea, and congestion.³

The tissue damage and inflammation, predominate features of the late allergic phase, is mediated by the TH₂ cytokines IL-5 and IL-13 as well as an up-regulation of E-selectin and soluble vascular cell adhesion molecule-1 providing a conduit for influx of inflammatory cells such as eosinophils, neutrophils, macro-

phages, and T lymphocytes.⁴ There is also a role for IL-8, eotaxin as well as membrane cofactor protein-1 in attracting eosinophils to the nasal mucosa.⁴

TARGETING TREATMENT

The nasal cavity is separated midline by the nasal septum, which is anteriorly comprised of cartilage and posteriorly the vomer.⁵ From the lateral aspects of the nasal cavities emerge the inferior, middle, and superior turbinates, which are thin bony structures in a c-shape configuration.⁶ They are lined with pseudostratified columnar ciliated respiratory epithelium and their shape creates turbulent airflow that functions to humidify and filter air.⁵ Just posterior to this, the nasal passage narrows to its smallest diameter where the middle turbinate, inferior turbinate, and septum converge to create the nasal valve.^{5,6} Collectively, this allows for filtration and humidification of air to occur with maximal efficiency and inflammation in the nose will impede these functions.

Symptomatic nasal obstruction can occur at many levels in the nasal cavity. Septal deviation can exist causing unilateral nasal obstruction and the presence of polyps or other masses can act to impede the flow of air through the nose.⁵ In the area of the nasopharynx a large adenoid pad can also create nasal obstruction, however, is more often problematic in the pediatric patient. The predominant causes of nasal obstruction in allergic rhinitis are congestion due to vasodilation, capillary leakage, and increased vascular permeability resulting in edema and inflammation of the turbinates, which not only obstructs airflow, but can impede sinus outflow through the middle meatus positioned just lateral to the middle turbinate.⁶

Despite significant progress in available therapeutics for allergic rhinitis, adherence with medications remains suboptimal most often because patients have not found them to be helpful. In fact, the *Allergies in America* survey conducted in 2006 in 2500 allergy sufferers across the country showed that many subjects were less than satisfied with the allergy medications they had used in the past 4 weeks with only 15% of intranasal corticosteroid users having complete control of their symptoms.⁷ Sixty-one percent of patients who participated stated they had discontinued an allergy medication because of an attribute of the medication with 37% of these patients discontinuing the drug because they did not find it effective.⁷

Allergies in America also detailed many of the symptoms seen in allergic rhinitis and reported that the most common symptom was nasal congestion or a sensation of a “stuffed nose” occurring in 60% of patients either most days or every day.⁷ Furthermore, 78% of patients rated their nasal congestion as either extremely bothersome or moderately bothersome during an allergy

Table 1 Differential diagnosis of nonallergic rhinitis

Perennial nonallergic rhinitis (Inflammatory)
Eosinophilic nasal disease
Basophilic/metachromatic nasal disease
Infectious
Nasal polyps
Atrophic rhinitis
Immunologic nasal disease
Noninflammatory, nonallergic rhinitis
Rhinitis medicamentosa
Reflex-induced rhinitis
Vasomotor rhinitis, irritant rhinitis, cold air rhinitis, gustatory rhinitis
Rhinitis sicca
Metabolic (estrogen/hypothyroid)
Structurally related rhinitis
Septal deviation, turbinate deformation, nasal valve dysfunction
Neoplastic and nonneoplastic tumors
Miscellaneous (choanal atresia/stenosis, trauma, foreign body, malformation, cleft palate, adenoid hypertrophy)

Source: Ref. 10.

attack again emphasizing the fact that this symptom should be a focus for target by medications that treat allergic rhinitis.⁷

When considering intranasal antihistamines as a possible treatment of allergic rhinitis, one clear advantage lies with the delivery of the medication to target the nasal passage including the turbinates as well as the inferior, middle, and superior meatus where nasal congestion can be extremely problematic. The ability of the intranasal delivery system provides direct treatment to the source of symptoms as well as rapid onset of action because it does not need to be absorbed systemically for it to function.⁸

RHINITIS SUBTYPES

Allergic rhinitis can be classified as seasonal versus perennial determined by the clinical history of notable triggers, timing of symptoms as well as diagnostic evaluation assessing IgE sensitization to aeroallergens. Clinicians must take care in also identifying the presence of nonallergic causes for rhinitis in those with a lack of specific IgE antibodies because such patients may not respond to traditional therapies specifically indicated for allergic rhinitis. It is estimated that there is a 3:1 prevalence of allergic to nonallergic rhinitis; however, it is also estimated that 44% have a mixed-type rhinitis with both allergic and nonallergic features⁹ (see Table 1).¹⁰

RHINITIS GUIDELINES FOR THERAPY

In 2008, the American Academy of Asthma Allergy and Immunology released its most recent practice parameters for the diagnosis and management of rhinitis. The parameters include outlines for the diagnosis of allergic versus nonallergic rhinitis as well as detailed information regarding the treatment of these diseases. First-line therapy for allergic rhinitis continues to include the identification of any causal triggers and to attempt to remove them from the environment.¹¹ This may include but is not limited to decreasing outdoor exposure when pollen counts are high, reduction of indoor fungal elements, animal avoidance, and cockroach as well as dust-mite control measures. The guidelines also discuss nonpharmacologic modalities such as nasal saline irrigation as beneficial for treatment of chronic rhinorrhea and rhinosinusitis alone or as an adjunct to therapy. The guidelines continue to address immunotherapy as an effective treatment of allergic rhinitis in reducing symptoms. Immunotherapy is also affirmed as useful in reducing or avoiding medication and may prevent the development of new allergen sensitizations and the further development of asthma in patients with allergic rhinitis.¹¹

The guidelines' stance with regards to medications used for control of rhinitis include updates of all current classes including oral antihistamines, intranasal steroids, oral and topical decongestants, intranasal anticholinergics, oral antileukotriene agents, and intranasal cromolyn, as well as intranasal antihistamines. The recommendations on the vast majority of these medications have changed little since the previous guidelines with the exception of discussion regarding the growing number of studies outlining the clinical benefits of intranasal antihistamines (azelastine hydrochloride and olopatadine hydrochloride). These newest recommendations regarding the use of intranasal antihistamines include (1) they may be considered for first-line treatment for allergic and nonallergic rhinitis, (2) they may be more beneficial because of their rapid onset of action, (3) they are efficacious and equal to or superior to oral second-generation antihistamines for treatment of seasonal allergic rhinitis, (4) they have been associated with a clinically significant effect on nasal congestion, (5) they are generally less effective than intranasal corticosteroids, and (6) they may provide added benefit for mixed-type rhinitis when used as combined therapy.¹¹ Other benefits of these drugs not outlined in the guidelines include the ability to achieve higher concentrations of active drug directly to the target tissue as well as minimizing unwanted side effects seen with systemic medications.⁸

CLINICAL BENEFITS OF INTRANASAL ANTIHISTAMINES

To be considered as first-line therapy for allergic rhinitis, the intranasal antihistamines must illustrate that they can be efficacious in treating all or most of the bothersome symptoms associated with allergic rhinitis. A study of 20 subjects treated with lower than marketed doses of either 0.1 or 0.2% olopatadine hydrochloride, 2 sprays in each nostril, before an allergen challenge of either timothy grass or ragweed showed significant inhibition of sneezing, rhinorrhea, pruritus, congestion, and posterior nasal drip when compared with placebo.¹² There was also no significant difference in benefit when comparing the different concentration of drug used on its overall effect on reducing rhinitis symptoms. The study also showed that the benefits of olopatadine 0.1 or 0.2% were not statistically different when compared with azelastine 0.1% using the same study model.¹²

A larger study of 544 patients was performed comparing total nasal symptom scores after administration of olopatadine 0.6%, azelastine 0.1%, or an inactive vehicle, 2 sprays in each nostril twice daily for 16 days, initiated at the start of the allergy season.¹³ This study verified the improvement of nasal symptom scores with a mean reduction of 26.8% for olopatadine, 29.9% for azelastine compared with only 18.4% with placebo. The most common adverse event reported was a bitter taste that was lower with the olopatadine treatment group (12.2%) versus the azelastine treatment group (19.7%) when compared with placebo (1.7%).¹³

In 2005, 677 patients were randomized to 0.4% olopatadine, 0.6% olopatadine, or placebo of 2 sprays in each nostril twice daily for a 2-week period in individuals sensitized to mountain cedar.¹⁴ At the end of the 2 weeks a physical exam and total nasal symptom scores (TNSSs), which assess itchy nose, runny nose, stuffy nose, and sneezing, were obtained and, again, there was a statistically significant reduction in TNSS for both treatment groups with 30 and 27.6% in those receiving 0.6 and 0.4%, respectively, with only a 18.7% reduction of symptoms in those receiving placebo.¹⁴ The same cohort in a more recent publication reported improvements in quality of life (QoL) using the Rhinoconjunctivitis QoL Questionnaire (RQLQ). Mean changes in RQLQ were 1.1 for both olopatadine doses and 0.8 for placebo, which relates to a moderately important difference in QoL.¹⁵

Fairchild *et al.* took this one step further in 2007 in assessing not only RQLQ in allergic individuals treated with olopatadine versus placebo, but also how allergic rhinitis symptoms impacted their work and school function by administering the Work Productivity and Activity Impairment Questionnaire–Allergy Specific (WPAI-AS) before and after a 2-week trial of medica-

tion.¹⁶ Data from 1233 patients were evaluated and improvements in RQLQ were again found to be significantly improved from baseline in both 0.4 and 0.6% olopatadine treatment groups when compared with placebo. There was also a statistically significant improvement in Work Productivity and Activity Impairment Questionnaire–Allergy Specific in both the 0.6% and the 0.4% treatment groups when assessing overall work impairment ($p < 0.001$ and $p < 0.01$, respectively) and activity impairment ($p < 0.01$ and $p < 0.5$, respectively).¹⁶

With regard to evaluating the effectiveness of intranasal azelastine hydrochloride for the treatment of nasal allergy symptoms there are many studies that display the overall benefits of the medication. The first of these publications in 1994 involved a 2-day “park” study where 294 allergic individuals were randomized to either azelastine 0.1% 2 sprays in each nostril once daily, twice daily, oral chlorpheniramine maleate 12 mg twice daily or placebo.¹⁷ The study compared major symptom complex (MSC; nose blows, sneezes, runny nose/sniffles, itch nose, and watery eyes) and total symptom complex (TSC; major plus itchy eyes/ears/throat/palate, cough, and postnasal drip) at baseline and during therapy. The end point analysis for this study showed that both azelastine treatment groups resulted in improvement with once-daily therapy (51% for both MSC and TSC) and with twice-daily treatment regimen (52% for both MSC and TSC).¹⁷ A similar 2-day “park” study dated the same year evaluated 259 patients randomized to azelastine 0.1%, 1 spray in each nostril every 12 hours, 2 sprays in each nostril once daily or twice daily; chlorpheniramine maleate, 12 mg twice daily; or placebo twice daily.¹⁸ The results showed that subjects in all treatment groups rated themselves as improved compared with those in the placebo group. The percent of individuals noting “improvement” were 75% in the 1 spray twice-daily group, 89% for the 2 sprays once-daily group, 83% for the 2 sprays twice-daily group, 77% for the chlorpheniramine group, and only 49% for the group receiving placebo.¹⁸

Several 2-week trials were also performed comparing azelastine 0.1%, 2 sprays once daily, azelastine 0.1%, 2 sprays twice daily; chlorpheniramine maleate, 12 mg twice daily; and placebo. Both studies evaluated baseline MSC and TSC severity scores and then compared these to scores obtained after therapy. The first of these studies performed by Storms showed a statistically significant improvement of all symptom scores when compared with placebo after both weeks observed for the twice-daily azelastine.¹⁹ The end point analysis also confirmed these benefits with the twice daily, with an improvement of TSC of 28% and MSC of 29% over the baseline scores when compared with placebo (8%). Although the once-daily dose showed

clinical improvement superior to placebo, the changes were not statistically significant.¹⁹ The results obtained by Ratner *et al.* revealed a statistical improvement of symptom scores after the 1st week for both the once a day (20% for TSC and MSC) and twice a day dosing (27% for TSC and 30% for MSC) compared with placebo (7% for TSC and MSC); however, after 2 weeks these improvements were only statistically significant for the twice-daily dosing group (34% for TSC and 36% for MSC) when compared with placebo.²⁰

Additionally, a 4-week trial was performed again evaluating TSC and MSC scores when comparing azelastine 0.1%, 2 sprays once daily; azelastine 0.1%, 2 sprays twice daily; chlorpheniramine, 12 mg twice daily; and placebo in subjects with allergic rhinitis.²¹ For this trial 243 subjects completed the study and compared their symptoms at baseline, as well as after weeks 1, 2, 3, and 4. The results of this study showed statistically significant improvement of TSC scores from baseline symptoms at weeks 1, 3, and 4 for once-daily and twice-daily dosing of azelastine when compared with placebo. The MSC scores were clinically and statistically improved at weeks 1 and 3 for both azelastine treatment groups and the overall mean percent improvements in the TSC and MSC severity scores for both azelastine treatment groups were greater than the improvements seen with placebo. At week 2 there was improvement in the MSC and TSC scores approaching but not meeting statistical significance.²¹

The new clinical guidelines report another potential benefit of intranasal antihistamines over other therapies, in regard to the rapid onset of action. In 2007, a randomized, double-blind single-dose, placebo-controlled study was performed of 320 patients comparing olopatadine 0.2, 0.4, and 0.6% doses with 2 sprays in each nostril 2.5 hours after the initiation of a 14.5-hour allergen challenge in an environmental chamber.²² The study patients evaluated their TNSS and individual nasal symptom scores at 30-minute intervals throughout the challenge and found that clinical improvement of these scores was seen as early as 30 minutes after treatment with all concentrations of olopatadine.²² In another study, olopatadine was compared with mometasone furoate monohydrate for determining the onset of action during a 12-hour environmental chamber challenge.²³ Four hundred twenty-five patients were primed with two 3-hour exposures to ragweed in the chamber and then randomized to either olopatadine, 2660 µg total dose; mometasone, 200 µg total dose; and placebo. After dosing, patients recorded their TNSS scores every 30 minutes for the first 4 hours and then every hour for the remaining 8 hours. This study found that olopatadine was superior to mometasone with an onset of action of 30 minutes versus 150 minutes, respectively.²³

Table 2 Onset of action of medications used for allergic rhinitis

Medication	Onset of Action
Intranasal corticosteroids	
Budesonide	3–5 hr ²⁶
Ciclesonide	6 hr ²⁷
Fluticasone propionate	2–4 hr ²⁸
Mometasone	2.5 hr ²³
Triamcinolone	12 hr ²⁹
Oral antihistamines	
Cetirizine	1 hr ³⁰
Loratadine	3 hr ³⁰
Fexofenadine	1 hr ³¹
Levocetirizine	1 hr ³²
Desloratadine	2.5 hr ²⁵
Intranasal antihistamines	
Olopatadine	30 min ^{22,23}
Azelastine	15 min ^{24,25}

Similar results for the onset of action have been shown for azelastine with a publication from 2007 comparing intranasal azelastine 0.1% to mometasone. The individuals randomized to the azelastine group had a significant improvement of their TNSS in as little as 15 minutes when compared with mometasone, which was 8 hours.²⁴ A study in 2006 compared the onset of action of azelastine 0.1% using only 1 spray in each nostril twice daily to desloratadine and placebo.²⁵ The doses were administered 2 hours after the start of an allergen challenge with azelastine 0.1% reducing major nasal symptom score and TNSS at 15 minutes after dosing when compared with desloratadine, which improved scores after 150 minutes. The first measurement of TNSS in the onset of action studies with olopatadine was 30 minutes when compared with 15 minutes in the azelastine studies, thus explaining the difference seen in the two drugs. Overall, the time of onset of action for both azelastine and olopatadine are significantly shorter than that of the oral antihistamine and intranasal steroids as detailed in Table 2.^{22–32}

When compared with oral antihistamines intranasal antihistamines have also been found to be superior in symptom relief in several head to head trials. In 2005, the first Azelastine Cetirizine Trial (ACT I) compared azelastine, 2 sprays in each nostril twice daily, plus placebo tablets against cetirizine, 10 mg, plus placebo saline spray.³³ The study occurred over a 14-day period with 299 patients comparing TNSS obtained immediately before the first dose and then starting at 30, 45, 60, 90, 120, 150, 180, and 240 minutes after the first dose was administered. TNSS and RQLQ were also assessed at the end of 24 hours and again after the 14-day trial. The overall changes in TNSS improved

from baseline in both groups with greater effect seen in the azelastine group (29.3% compared with 23% with cetirizine).³³ The second Azelastine Cetirizine Trial (ACT II) in 2006 performed a similar comparison with 360 participants over a 2-week period. Patients were again given either azelastine and a placebo pill or cetirizine, 10 mg, with a placebo spray and TNSS and RQLQ scores were obtained at baseline and at the end of the 14 days.³⁴ Although not reaching statistical significance the TNSS showed overall improvement favoring azelastine (23.9% improvement) over cetirizine (19.6% improvement); however, when looking at the individual parameters, improvements were statistically significant for nasal congestion and sneezing. Changes in the RQLQ scores were statistically improved from baseline after the 14-day trial ($p = 0.002$).³⁴

Two other studies looked at a population of patients who were taking oral antihistamines with suboptimal effects to see if symptoms would fare better with either azelastine alone or as an adjunct to therapy. The first evaluated 428 individuals who had poor responses to loratadine and randomized them to either azelastine, 2 sprays in each nostril twice daily, plus placebo capsule; desloratadine, 5 mg once daily, plus saline nasal spray; azelastine nasal spray, 2 sprays in each nostril twice daily, plus loratadine, 10 mg; or placebo for both capsule and nasal spray.³⁵ The treatment covered a 2-week period and, again, TNSS were obtained at baseline and at the end of treatment and it was noted that all parameters of the TNSS were statistically superior compared with placebo for both the azelastine group and the combined therapy group; however, these did not differ from each other. The desloratadine group had only an improvement in their sneezing score when compared with placebo.³⁵ Another study showed similar results when comparing monotherapy with azelastine with combined therapy of azelastine and fexofenadine in 334 individuals who had continued with symptoms while on fexofenadine alone. Individuals were randomized to either azelastine, 2 sprays in each nostril twice daily, plus a placebo capsule; azelastine plus fexofenadine, 60 mg twice daily; or a placebo capsule plus a placebo saline spray.³⁶ TNSS and individual symptom scores were obtained at baseline and at the end of a 14-day trial and once again showed a significant reduction of all measurements in both treatment groups with an 18.6% reduction in the azelastine only group, 18.3% in the combination therapy group compared with a 10.5% reduction in the placebo group. These trials suggest that azelastine has efficacy in those failing oral antihistamine therapies and no added benefit was reported with the intranasal/oral combination.³⁶

The most common symptom noted in *Allergies in America* was nasal congestion again rated as occurring

either most days or every day in a majority of individuals and it is well understood that the oral antihistamines provide no benefit on nasal congestion unless combined with an oral decongestant.⁷ With regard to intranasal antihistamine's ability to improve congestion, several studies have outlined this benefit repeatedly when looking at both azelastine and olopatadine used as monotherapy. A study comparing the benefits of azelastine and intranasal fluticasone in 151 patients after 2 weeks of therapy showed a 19.2% reduction in nasal congestion, which was statistically significant when compared with placebo ($p = 0.02$).³⁷ This was also described in the ACT II trial showing an 18% improvement from baseline in congestion with intranasal azelastine compared with only 12.6% with placebo ($p = 0.049$).³⁴ Olopatadine has also had similar effects on nasal congestion with both the 0.6% dose and the 0.4% dose compared with placebo when used daily for 2 weeks. This study showed an improvement of "stuffy nose" symptoms of 17.5 and 17.0% for the 0.6 and 0.4% concentrations of olopatadine, respectively, when compared with 7.7% for placebo.¹⁴ Nasal congestion is an important symptom to target because it is the most problematic symptom in allergic rhinitis. It is also a predominant feature in nonallergic and mixed-type rhinitis where azelastine has indications for both allergic and nonallergic rhinitis.

The practice parameters also state that the evidence supports the concept that intranasal corticosteroids are superior to intranasal antihistamines and base this statement on a systematic review with meta-analysis published in 2002.³⁸ This review included nine studies, three of which evaluated intranasal levocabastine, which is currently unavailable in the United States; the other six compared azelastine with several intranasal corticosteroids including beclomethasone, budesonide, and fluticasone. The review summarizes that intranasal corticosteroids are superior to intranasal antihistamines in reducing TNSS; however, they showed no advantage with regard to ocular symptoms as well as nasal congestion alone. Also, although improvement with symptoms of rhinorrhea and nasal itching did favor corticosteroids, there was more heterogeneity between the studies with reference to these symptoms. One weakness of this review is that several of the studies evaluated did not use the established recommended daily dose for azelastine; therefore, it is difficult to extrapolate these results when considering using azelastine as 2 sprays in each nostril twice daily. With these shortcomings in mind, the cumulative effect in the meta-analysis was in slight favor of the intranasal steroids.³⁸

More recently, there have been additional studies that have evaluated the efficacy of intranasal azelastine when compared with intranasal corticosteroids. In 2008, a 2-week multicenter trial was performed during

mountain cedar season to assess the clinical effectiveness of azelastine nasal spray, 2 sprays in each nostril twice daily, to fluticasone nasal spray, 2 sprays in each nostril once daily, to using combined therapy with both fluticasone and azelastine.³⁷ A total of 151 patients were involved in this study and baseline and daily posttreatment TNSSs were evaluated until the end of the study period. During the study, both monotherapy treatment regimens showed overall improvement of symptoms scores; however, they were not statistically different with a 27.1% improvement in the fluticasone group compared with 24.8% improvement in the azelastine group at the end of the 2 weeks.³⁷ This study suggests that these two classes of medications may be more similar in effectiveness than previously thought.

Several studies have examined the benefit of combining a nasal steroid with an oral antihistamine or leukotriene antagonist in rhinitis with similar results. In 1989 a study analyzing differences in efficacy of intranasal beclomethasone, 400 μ g daily, astemizole, 10 mg daily, to both beclomethasone plus astemizole and showed that the combined therapy provided no better control than beclomethasone alone.³⁹ In 1998, fluticasone, 200 μ g once daily, and loratadine, 10 mg once daily, were compared with combination therapy of both fluticasone and loratadine. During this 2-week trial, an improvement in RQLQ in both the fluticasone and the combination groups was observed.⁴⁰ The combined therapy group showed no significant benefit over the fluticasone-only group. A slightly different study performed in 2004 compared four different treatment arms that included (1) monotherapy with fluticasone, 200 μ g once daily; (2) fluticasone plus cetirizine, 10 mg each morning; (3) fluticasone plus montelukast, 10 mg each evening; and (4) cetirizine, 10 mg each morning, plus montelukast, 10 mg each evening.⁴¹ The results from this study concluded that all groups treated with fluticasone had similar improvements on nasal congestion on waking and for nasal congestion daily when compared with the treatment arm that did not include fluticasone. The fluticasone-only group also seemed to have an advantage over the fluticasone plus cetirizine regarding nasal itching ($p = 0.003$) and again there were no observed benefits on any of the combined therapies over fluticasone alone.⁴¹ Finally, in 2006 a study assessing levocetirizine as potential add-on therapy to fluticasone evaluated 27 patients randomized to either fluticasone, 200 μ g daily, plus levocetirizine, 5 mg, or placebo treated over a 2-week period during allergy season.⁴² RQLQ, domiciliary peak nasal inspiratory flow, TNSSs, and nasal nitric oxide concentrations were evaluated at baseline and after treatment and, again, the add-on therapy with cetirizine showed no added benefit to using fluticasone alone. This study further suggests that there is little to

no evidence that combination therapy with intranasal steroids and oral antihistamines should be implemented in patients with allergic rhinitis; however, the combination may help with controlling ocular symptoms that were not evaluated in these studies.

In 2008 a study evaluating combined therapy with intranasal corticosteroids and azelastine when compared with each agent alone has provided a new direction when considering combined treatment for the allergic patient. The study compared azelastine 0.1%, 2 sprays in each nostril twice daily, to fluticasone, 2 sprays in each nostril once daily, to utilization of both medications simultaneously over a 2-week period.³⁷ As previously mentioned, the fluticasone-only and azelastine-only groups showed no significant differences between the two in improving TNSSs from baseline (27.1 and 24.8, respectively); however, the combined treatment had an even higher percent improvement from baseline than each of the single agents alone at 37.9%.³⁷

Many studies have now displayed the benefits of intranasal antihistamines on allergic rhinitis, but there is now information that these medications may have an equal impact in treating nonallergic and mixed types of rhinitis as well. In 2001 two 21-day double-blind, placebo-controlled trials were performed on a total of 426 patients with vasomotor rhinitis as defined by the lack of skin test positivity, no eosinophils on nasal smears, normal sinus x ray, and without any anatomic abnormalities.⁴³ Patients were randomized to either azelastine, 2 sprays in each nostril twice daily, or placebo and total vasomotor rhinitis symptom scores assessing rhinorrhea, sneezes, nasal congestion, and postnasal drip were obtained at baseline and throughout the study for comparison. The outcome of this trial favored azelastine over placebo in reducing total vasomotor rhinitis symptom scores from baseline (study 1, $p = 0.002$; study 2, $p = 0.005$) and provided impressive results that azelastine may not only be useful in treating allergic rhinitis, but vasomotor rhinitis as well.

Finally, in discussing therapeutic modalities for allergic rhinitis, we must also mention several other medications that may have benefits in treatment. The first of these is ipratropium bromide, an anticholinergic nose spray, not systemically absorbed. This has been shown to have a significant effect on reducing rhinorrhea but has had no observed effect on other nasal symptoms.⁴⁴ Also, montelukast, an LTD₄ receptor antagonist, was Food and Drug Administration approved in January 2003 for allergic rhinitis; however, multiple studies have shown that, overall, leukotriene antagonists are less effective than intranasal steroids.⁴⁵

CONCLUSION

In conclusion it appears that intranasal antihistamines are rapidly being discovered to have earned

their place in the physician's arsenal when treating allergic rhinitis. They have several unique characteristics as compared to other treatments including their rapid onset of action due to their action directly to the target tissue, their ability to improve nasal congestion as well as appearing to meet or exceed all other bothersome symptoms related to allergic rhinitis when compared to oral antihistamines. Intranasal antihistamines may also provide added benefit when using with intranasal corticosteroids and provide an alternative to corticosteroids when patients wish to avoid these types of agents.

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