

Combination therapy in allergic rhinitis: What works and what does not work

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ABSTRACT

Allergic rhinitis and other rhinitis subtypes are increasingly becoming some of the most prevalent and expensive medical conditions that affect the U.S. population. Both direct health care costs and indirect costs significantly impact the health care system due to delays in diagnosis, lack of treatment, ineffective treatment, poor medication adherence, and associated comorbidities. Many patients who have AR turn to over-the-counter medications for relief but often find themselves dissatisfied with the results. Determining the correct diagnosis, followed by initiation of the most-effective treatment(s), is essential to provide patients with better symptomatic management and quality of life. Although there are many options, currently available combination therapies, e.g., azelastine with fluticasone and intranasal corticosteroids with nasal decongestants, offer distinct advantages for the management of complex rhinitis phenotypes. Further research is required to investigate the pathomechanisms and biomarkers for mixed rhinitis and nonallergic vasomotor rhinitis subtypes that will lead to novel targeted therapies for these conditions

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The prevalence of allergic rhinitis (AR) has been well reported, with >60 million Americans having this condition. Allergic diseases, which include AR, are the fifth most prevalent chronic conditions for all ages and the third most common in children, and impact 3 of every 10 adults and 4 of every 10 children in the United States.¹ Recently published prevalence surveys of physician-confirmed diagnoses of AR revealed an increased prevalence in U.S. adults (14%) and children (13%) compared with Latin American (7%) and Asian-Pacific adult (9%) populations.²

ECONOMIC BURDEN

AR has a substantial economic burden on the U.S. health care system. A recent study found that 66% of U.S. adults believed that their nasal allergy symptoms had some sort of impact on their daily life.² As a result, the direct and indirect medical costs for AR are quite substantial, in part, due to a lack of treatment, ineffective treatment, poor medication adherence, and associated comorbidities (e.g., chronic sinusitis, allergic conjunctivitis, otitis media, eustachian tube dysfunction, sleep apnea, nasal polyps, asthma). Headache is an important comorbidity as well, with data that the treatment of chronic rhinosinusitis and chronic rhinitis improves the clinical course of nasal sinus headaches.³

It is estimated that the direct medical costs to treat AR, including prescription medications and physician visits, average ~2–5 billion dollars/year, whereas indirect costs due to missed days from work, presenteeism, lost leisure activities, and overall quality of life range between 5.5 and 9.7 billion dollars/year.⁴ A large questionnaire survey of 1981 employees and students revealed that >90% believed that their work or classroom productivity was negatively affected by AR, with approximately one-fourth missing some work or school due to allergy symptoms in the 7 days before the assessment.⁵ There is no sex predilection for AR, and, given that 80% of patients develop symp-

toms before age 20 years, patients can experience many years of symptoms unless properly diagnosed and treated.² Despite the high prevalence of this condition, surveys in both Europe and the United States found that AR remains undiagnosed in approximately one-third of adult patients.⁶

DISSATISFACTION WITH A MEDICATION REGIMEN

As a result of the significant morbidity associated with chronic rhinitis, many patients resort to over-the-counter (OTC) allergy medications to relieve their symptoms. With health plans that limit access to prescription medications and now easy access to a variety of newly approved OTC allergy products, patients often self treat for months or years before seeking a specialist's help. Although there are many OTC and prescription medications approved to treat AR, a large proportion of patients are dissatisfied with their treatment options. In fact, nearly one-third of patients with allergy are not fully satisfied with their current prescription allergy medication.⁷ This is further compounded because many health care professionals overestimate their patients satisfaction with their medication regimen.⁸

In fact, patient dissatisfaction is quite pervasive, with upward of 80% of patients with allergy indicating that they sometimes (36%) or frequently (44%) felt tired, whereas nearly two-third felt miserable and/or irritable during the allergy season.⁸ A survey of 2500 patients with rhinitis revealed that almost half believed that their nasal allergy medicine did not provide adequate relief, which prompted many to change prescriptions, seek out alternative treatments, or to simply stop taking them.⁸ Another survey, of 510 patients with allergy, was designed to determine the number of prescription and OTC medications that patients typically tried to treat their rhinitis symptoms. The majority of those patients with allergy surveyed reported that they had tried multiple OTC and prescription (oral antihistamines and nasal corticosteroids) medications: 65% of the respondents had tried 6 or more branded medications, and 23% had tried 10 branded medications, with the mean number of branded medications tried being 7.1. These unpublished data further demonstrate patients with poorly controlled symptoms who were trying multiple medications to obtain symptom relief.

PATHOPHYSIOLOGY

A major barrier to appropriate treatment of chronic rhinitis has historically been establishing a correct diagnosis. Therefore, characterizing chronic rhinitis subtypes is an important first step to understanding how to better treat this condition. The differential diagnosis of AR is summarized in Table 1. The three main types of chronic

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Table 1 Differential diagnoses of allergic rhinitis*

Seasonal allergic rhinitis
Perennial allergic rhinitis
Nonallergic rhinitis with eosinophil syndrome
Vasomotor rhinitis (idiopathic or irritant induced rhinitis) with and without triggers
Local allergic rhinitis (also known as entopic rhinitis)
Drug-induced rhinitis
Topical nasal decongestants, oral contraceptives, nonsteroidal anti-inflammatory drugs, antihypertensive medications - β -blockers
Infectious rhinitis
Occupational or work-related rhinitis

*Excluding structural blockages or chronic sinusitis.

rhinitis are AR, non-AR (NAR), and mixed rhinitis (MR). Although NAR consists of a broad category of rhinitis subtypes, vasomotor rhinitis is the most common form and constitutes the majority of cases. The pathogenesis of AR involves a number of effector cell types, cytokines, and bioactive mediators that contribute to the inflammatory process in AR.

Frequently this leads to a biphasic inflammatory reaction characterized clinically as immediate (early) and late-phase clinical symptoms. The early phase is triggered by the interaction of allergen with specific immunoglobulin E bound to high-affinity immunoglobulin E receptors on mast cells, which leads to cell activation and release of preformed and rapidly synthesized newly formed mediators that result in physiologic changes within the nasal mucosa and leads to inflammation and characteristic symptoms of AR, such as nasal congestion, rhinorrhea, sneezing, and itching. The late-phase response, which occurs 4–8 hours after exposure to the inciting allergen, is the result of cellular migration of lymphocytes, eosinophils, and basophils, and activation that leads to further inflammatory changes in the nasal passages manifested as nasal obstruction, rhinorrhea, fatigue, malaise, and increased nasal sensitivity to an allergen, known as priming.⁹

Confirmation of an AR diagnosis requires positive skin-prick or serologic testing that correlates with symptoms on exposure of the sensitizing aeroallergen, whereas confirmation of an NAR diagnosis requires negative skin-prick or serologic testing to aeroallergens. Patients with NAR may exhibit similar symptoms that are exhibited by patients with AR, but their symptoms are triggered by odorants, irritants, and/or weather changes (barometric pressure, temperature) in the absence of underlying structural and/or infectious causes. The most common form of NAR by far is vasomotor rhinitis, and, therefore, these two terms are commonly used interchangeably because no consensus definition for this condition has been agreed on as of yet. The mechanisms involved in this process, although believed to be neurogenic, which leads to autonomic dysfunction, thus far have been poorly elucidated. Evidence *in vitro* and in clinical trials supports a role for transient response potential calcium ion channel activation, which leads to depolarization of A δ nociceptive fibers and antidromic release of neuropeptides, *e.g.*, substance P. Activation of nociceptive nerve fibers also can result in dysautonomia, which results in diminished sympathetic activity and/or parasympathetic overactivity that leads to dilatation of blood vessels and increased mucus secretion responsible for the clinical symptoms exhibited by these patients.^{10,11}

A third and often unrecognized category of chronic rhinitis is referred to as MR, in which patients have clinical rhinitis symptoms that correlate with specific immunoglobulin E sensitization on exposure to seasonal and/or perennial allergens but that also exhibit symptoms in response to nonallergic triggers, such as extreme temperatures, weather or barometric changes, and/or a spectrum of odorants and irritants. The prevalence of rhinitis subtypes reported

Table 2 Rhinitis control assessment test questionnaire**

1. During the past week, how often did you have nasal congestion?
Never (5) Rarely (4) Sometimes (3) Often (2) Extremely Often (1)
2. During the past week, how often did you sneeze?
Never (5) Rarely (4) Sometimes (3) Often (2) Extremely Often (1)
3. During the past week, how often did you have watery eyes?
Never (5) Rarely (4) Sometimes (3) Often (2) Extremely Often (1)
4. During the past week, to what extent did your nasal or other allergy symptoms interfere with your sleep?
Never (5) Rarely (4) Sometimes (3) Often (2) Extremely Often (1)
5. During the past week, how often did you avoid any activities (for example, visiting a house with a dog or cat, gardening) because of your nasal or other allergy symptoms?
Never (5) Rarely (4) Sometimes (3) Often (2) Extremely Often (1)
6. During the past week, how well were your nasal or other allergy symptoms controlled?
Never (5) Rarely (4) Sometimes (3) Often (2) Extremely Often (1)

*Based on the 5-point Likert scale ("Never" to "Extremely Often") with a 1-week recall period for each item; Rhinitis Control Assessment Test scores range from 6 to 30, with any score of ≤ 21 indicating poor control.

#Adapted from Ref. 17.

that ~43% of the respondents had AR, 34% had MR, and 23% had NAR.¹² A subsequent study, which involved 3398 patients with chronic rhinitis who were participating in a seasonal AR (SAR) clinical trial and completed a rhinitis questionnaire that queried symptoms in response to various allergic and nonallergic triggers found that >90% of these patients with SAR reported symptoms in response to at least one nonallergic trigger. Temperature changes (71.4%), tobacco smoke (60.8%), perfumes (56.4%), and cleaning products (37.9%) were the most frequently reported symptoms, which indicated that a high percentage of patients with SAR had a nonallergic component consistent with MR.¹³ In this study, which assessed the clinical efficacy of azelastine in combination with fluticasone (Dymista, Meda Pharmaceuticals Inc., Somerset, NJ), a significant percentage of patients reported incomplete symptomatic improvement with their previous medications used as monotherapies, including intranasal corticosteroids, oral antihistamines, and intranasal antihistamines.¹³

DIAGNOSIS

Given that so many patients with chronic rhinitis and associated comorbidities are dissatisfied with the treatment(s), it is paramount that allergy specialists approach this condition in a more strategic and evidence-based manner. A number of effective tools have been developed to help the allergist to better define chronic rhinitis subtypes so that therapy can be optimally tailored to each patient's condition. For example, it has been demonstrated that patients with a history of late onset symptoms (>35 years of age); no family history of allergies; no symptoms in response to cats, dogs, or furry pets; or seasonality of symptoms and symptoms in response to odorants and irritants such as fragrance and/or perfumes have a >98% likelihood of have a diagnosis of nonallergic vasomotor rhinitis before allergy skin testing. Furthermore, the quantification of inciting nonallergic triggers has been shown to potentially improve the classification of chronic rhinitis subtypes.¹⁴

Thus, a more-thorough clinical history can be very useful for differentiating chronic rhinitis subtypes.¹⁵ Monitoring the severity of symptoms and control over time is another important component in the appropriate physician management of chronic rhinitis. The Rhinitis Control Assessment Test, outlined in Table 2, is a simple patient-completed questionnaire aimed at assessing how well controlled their chronic rhinitis symptoms are.¹⁶ It has been demonstrated that the Rhinitis Control Assessment Test in a clinical setting is a useful tool to

Table 3 Effective environmental control interventions directed at indoor allergens*

Intervention	Reduction in Allergen Level	Reduction in Allergen Level and Symptom
Bedding encasements	Dust mite, cat, mold	Dust mite, cat
HEPA filtration	Cat, dog	Cat, dog
HEPA vacuum cleaner	Dust mite, cat, dog, cockroach	Not studied
Dehumidification	Dust mite, mold, cockroach	Not studied
Thorough cleaning	Cockroach	Not studied

HEPA = High-efficiency particulate air.
 *Based on high-quality evidence in double blinded control trials.
 Adapted from Ref. 27.

help physicians identify patients with uncontrolled chronic rhinitis and facilitate their ability to follow up patients' progress with treatment. The questionnaire is reliable, valid, and responsive to changes in rhinitis control over time.^{16,17} The higher the Rhinitis Control Assessment Test score, the better the patient's control. Scores range from 6 to 30, and any score of ≤ 21 indicates poor control.¹⁷ The minimally important difference was found to be 3 points, and a change of at least 3 points is considered clinically meaningful.¹⁷

AVOIDANCE OF TRIGGERS

Avoidance of triggers is an often overlooked component of the integrative approach to treating chronic rhinitis subtypes. Although avoidance of seasonal pollens and nonallergic triggers can be difficult, a concerted effort to reduce indoor allergens in the home, when applicable, is an invaluable tool to combat allergy symptoms. A number of studies strongly support the relationship between allergen exposure and sensitization, and the development of AR.^{18–26} Research focused on determining the effectiveness of directed environmental control measures provides high-quality evidence that environmental control interventions directed at indoor allergens can be effective at reducing exposure, and, in some cases, clinical symptoms Table 3.

A relative indoor humidity below 50% effectively reduces dust mite (DM) growth and production of allergens, whereas bedding encasements reduce DM allergen levels up to 98%.²⁷ Application of benzyl benzoate, in addition to traditional DM avoidance measures, was also shown to be effective in reducing carpet DM levels for up to 3 months.²⁷ Although removal of pets is the most cost-effective intervention to reduce cat and dog allergens in the home, this suggestion is often not well received by loving pet owners. A more-productive approach is to suggest creating "allergy-free" zones in the house by encouraging patients to keep animals out of the bedroom(s) and main activity rooms and by placing freestanding high-efficiency particulate air filters in these rooms. Contrary to popular belief, washing pets is not an efficient way to reduce allergen levels because the effect is transient and lasts only 24–48 hours.²⁷

TREATMENT

Despite appropriate avoidance measures and validated monitoring tools for assessing control, chronic rhinitis symptoms can be challenging to treat. For many patients, it is difficult to find the right combination of medications that limits adverse effects and that provides effective relief. As with most treatment regimens, adverse effects need to be considered. Common adverse effects, *e.g.*, nose bleeds with nasal sprays, elevated blood pressure with oral decongestants, the bitter taste of azelastine, and the somnolence sometimes associated with cetirizine, need to be discussed. Most adverse reactions associated

Table 4 Pharmacologic options for the treatment of allergic and nonallergic rhinitis

Treatments for SAR or PAR (IgE mediated)	Treatment for NAR (symptomatic)
Avoidance of indoor and, when possible, outdoor allergens; avoidance of irritants that can enhance allergic inflammation	Avoidance measures of indoor and outdoor air pollutants
Second-generation nonsedating antihistamines (<i>i.e.</i> , cetirizine, loratadine)	
First-generation sedating antihistamines (<i>i.e.</i> , diphenhydramine, chlorpheniramine)	First-generation sedating antihistamines
Oral or topical decongestants	Oral or topical decongestants
Intranasal corticosteroids (<i>i.e.</i> , fluticasone) used alone or in combination with intranasal antihistamines	Intranasal corticosteroids (not as effective in NAR without eosinophils)
Intranasal antihistamines (<i>i.e.</i> , azelastine, olopatadine)	Intranasal antihistamines (<i>i.e.</i> , azelastine)
Intranasal cromolyn sodium	
Leukotriene modifying agents (<i>i.e.</i> , montelukast)	
Eye drops (antihistamines...)	Eye drops (ketorolac...)
Immunotherapy (SCIT, SLIT)*	
Nasal irrigation with saline solution	Nasal irrigation with saline solution
	Intranasal anticholinergic agents
	Oral anticholinergic agents (<i>i.e.</i> , methscopolamine)
	Intranasal capsaicin

SAR = Seasonal allergic rhinitis; PAR = perennial allergic rhinitis; IgE = immunoglobulin E; NAR = nonallergic rhinitis; SCIT = subcutaneous immunotherapy; SLIT = sublingual immunotherapy.

*From Refs. 49, 50.

with medicated nasal sprays, *e.g.*, Dymista, include the following: $<2\%$ of subjects with headache, pyrexia, cough, nasal congestion, rhinitis, dysgeusia, viral infection, upper respiratory tract infection, pharyngitis, pain, diarrhea, and epistaxis.^{28,29}

Ultimately, any medication regimen should be tailored to the patient's tolerability, and a risk-benefit analysis should be applied based on known potential adverse effects. To complicate matters, there are overwhelming numbers of OTC and prescription rhinitis medications available. The various treatment options used to treat both allergic and NAR are summarized in Table 4. Although many of these medications are used as monotherapy, they are often combined with additional treatments in an attempt to enhance effectiveness. There is a growing body of evidence that adding oral therapy (antihistamines) to intranasal therapy (corticosteroid or antihistamine) does not always translate into clinical benefit.³⁰ A review of the effectiveness of some of these medication combinations, therefore, is discussed below.

COMBINATION INTRANASAL CORTICOSTEROID WITH ORAL ANTIHISTAMINES

Multiple studies demonstrated a lack of additive benefit when adding oral therapies to intranasal corticosteroid and antihistamine nasal sprays. Ratner *et al.*³¹ examined the efficacy and impact on the

quality of life of fluticasone propionate nasal spray (FPNS) and loratadine, alone and in combination, for the treatment of SAR. Comparison studies showed that FPNS plus loratadine and FPNS monotherapy were comparable in efficacy for almost all evaluations.³¹ Berger *et al.*³² performed similar double-blind trials of azelastine nasal spray monotherapy versus combination therapy with loratadine tablets and beclomethasone nasal spray in patients with SAR. These findings revealed that azelastine nasal spray monotherapy was as effective as the combination of oral loratadine plus intranasal beclomethasone in treating moderate-to-severe symptoms of SAR.³² Two additional studies confirmed a lack of efficacy with the addition of loratadine over the monotherapy, with either azelastine or fluticasone in any of the study efficacy variables.^{33,34} In addition to loratadine, fexofenadine, levocetirizine, and cetirizine were also studied in combination with various nasal sprays, and it was determined that none of these oral agents were any more effective than nasal sprays, which indicated that adding an oral H₁ antihistamine to a nasal corticosteroid or nasal antihistamine regimen does not increase the clinical benefit of therapy.^{35–37}

COMBINATION INTRANASAL CORTICOSTEROID AND MONTELUKAST

Wilson *et al.*³⁸ investigated whether using the leukotriene receptor antagonist (montelukast) with an H₁ antihistamine was any more beneficial than monotherapy with an intranasal corticosteroid (mometasone furoate) for patients with SAR. They found that both treatment regimens were equally effective for improving objective and subjective treatment responses in SAR.³⁸ Di Lorenzo *et al.*³⁷ found that FPNS monotherapy was equally or more effective than either FPNS combined with montelukast or cetirizine combined with montelukast for treating patients affected by AR.

COMBINATION IPRATROPIUM BROMIDE NASAL SPRAY WITH NASAL CORTICOSTEROID SPRAY

In an attempt to address the treatment gap for patients with perennial rhinitis, Dockhorn *et al.*³⁹ enrolled 533 patients with perennial rhinitis to compare the efficacy and safety of the combined use of ipratropium bromide nasal spray (IPNS) nasal spray 0.03% and beclomethasone dipropionate nasal spray versus either active agent alone for the treatment of chronic rhinorrhea. They concluded that the combined use of IPNS with beclomethasone dipropionate nasal spray is more effective than either active agent for the treatment of rhinorrhea.³⁹

COMBINATION INTRANASAL ANTICHOLINERGICS AND ORAL ANTIHISTAMINES

Finn *et al.*⁴⁰ examined the risk-benefit of combined therapy with IPNS 0.03% administered three times daily in conjunction with a non-sedating antihistamine (terfenadine, 60 mg administered twice daily) in comparison with the effects of placebo nasal spray plus terfenadine. The results of this study revealed that IPNS plus terfenadine was more effective for the treatment of rhinorrhea versus monotherapy with terfenadine and was very safe to use long term.⁴⁰

COMBINATION INTRANASAL CORTICOSTEROIDS AND INTRANASAL DECONGESTANTS

In an attempt to address the unmet needs of patients with chronic rhinitis, a number of studies investigated the stigma regarding chronic OTC oxymetazoline (OXY) use. Although this medication offers many patients instant relief of nasal congestion, daily use has been linked to rhinitis medicamentosa or rebound congestion. Vaidy-

anathan *et al.*⁴¹ found that OXY-induced tachyphylaxis and rebound congestion are reversed by intranasal fluticasone and recommended additional studies to further elucidate if this combination is an effective long-term strategy to obviate tachyphylaxis and rebound in rhinitis. An additional study, by Baroody *et al.*,⁴² confirmed the effectiveness of adding OXY to fluticasone furoate for effective treatment of perennial AR. Meltzer *et al.*⁴³ investigated treatment of mometasone furoate nasal spray with OXY in SAR symptoms and found that it provided a faster onset of action than mometasone furoate nasal spray alone, and better sustained efficacy than OXY alone twice a day. Also, Kirtsreesakul *et al.*⁴⁴ found that nasal symptoms of blocked nose, hyposmia, nasal mucociliary clearance, and polyp size were more effectively treated with mometasone furoate nasal spray combined with OXY compared with nasal steroids alone over a 6-week period, with no subsequent rebound congestion.

COMBINATION OF INTRANASAL AZELASTINE AND CORTICOSTEROID SPRAYS

Three pivotal clinical trials demonstrated increased efficacy of azelastine and fluticasone in combination (Dymista) compared with each individual component for the treatment of SAR.^{45,46} With nearly 3400 adult and adolescent patients involved in these three trials, the data presented is among the largest body of evidence comparing the efficacy of various intranasal therapies for allergic rhinitis. Symptoms were scored by using a reflective total nasal symptom score (rTNSS), which included nasal congestion, rhinorrhea, nasal itching, and sneezing. In these trials, use of Dymista provided consistent, statistically significant ($p < .001$) improvement in rTNSS regardless of the allergy season when compared with placebo, with lower spray volume compared with either monotherapy while exerting a rapid onset of action (as early as 30 minutes).^{45,46} Hampel *et al.*⁴⁷ supported the results of these studies demonstrating 90% greater improvement in rTNSS for Dymista relative to commercially available generic fluticasone propionate and an even more impressive 196% difference when compared with azelastine. Thus, Dymista significantly improved the individual rTNSS symptoms of nasal congestion, itchy nose, sneezing, and runny nose compared with azelastine, generic fluticasone, or placebo ($p < .05$).⁴⁷ Another single-blind, crossover study involved 30 patients with persistent AR who were randomized into three treatment groups of azelastine only, budesonide only, and combined azelastine plus budesonide. Effects were measured by using a nasal provocation test and acoustic rhinometry, and showed that combined therapy offered more substantial therapeutic benefits than the medications by themselves.⁴⁸

CONCLUSION

AR and other rhinitis subtypes have significant health impact on patients and a substantial economic burden on society. To complicate matters, this condition can be challenging to diagnose correctly, which is essential for proper treatment. Despite the saturated rhinitis medication market, patients can remain symptomatic despite being treated with both mono- or multiple-therapy regimens if they are not prescribed or used correctly. Therefore, determining which combination therapies are most effective is important in improved patient quality of life and overall satisfaction. Currently available combination therapies such as azelastine with fluticasone and intranasal corticosteroids with nasal decongestants offer distinct advantages for the management of complex rhinitis phenotypes. Ultimately, treatment response to medications will be most effective when these medications are individualized to the patient's diagnosis.¹⁴ Further research is required to investigate the pathomechanisms and biomarkers for MR and nonallergic vasomotor rhinitis subtypes, which will lead to novel targeted therapies for these conditions.

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