

Nonallergic Rhinopathy (Formerly Known as Vasomotor Rhinitis)

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- Nonallergic rhinopathy • Vasomotor rhinitis • Allergic rhinitis
- Nasal corticosteroids • Nasal antihistamines

This review focuses on the poorly understood condition of nonallergic rhinopathy (NAR) at a clinical level, with an eye on current optimal treatment. The pathophysiology of this disease is not well understood, and the reader is referred to more comprehensive books and reviews for an extensive discussion of pathophysiology.^{1,2} Nonallergic vasomotor rhinitis (VMR; also referred to as nonallergic rhinitis and/or idiopathic rhinitis) is a term that has been used to describe a common nasal condition of unclear pathophysiology. The term NAR is recommended to replace nonallergic VMR.³ VMR suggests that intrinsic nasal vascular and glandular abnormalities are the principle physiologic causes of inflammation of the nasal mucous membrane. However, current information suggests that NAR is probably caused by neurosensory abnormalities and does not include inflammation as an important component.^{1,2} Thus, it is believed that it is more accurate to term this condition a rhinopathy (a disorder of the nose) rather than a form of rhinitis (inflammation of the nose). The single unequivocal criterion for these patients is that they are not allergic; NAR is a more appropriate term for this disorder.³

DEFINITION OF NAR

NAR is a chronic nasal condition with symptoms that may be perennial, persistent, intermittent, or seasonal and/or elicited by recognized triggers. There is a well-recognized set of clinical exposures that lead to the symptoms, predominantly congestion and rhinorrhea. The clinical characteristics as outlined provide well-defined inclusion and exclusion criteria that should permit precise identification of patients for accurate diagnosis and participation in clinical trials. NAR is defined by

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clinical characteristics, which are summarized below and described in detail in the following sections of this review.³

1. NAR is a chronic disease with some, but not necessarily all, of the following symptoms:
 - Primary symptoms
 - Nasal congestion
 - Rhinorrhea
 - Other associated symptoms
 - Postnasal drip in the absence of a pharyngeal cause of mucous hypersecretion or acid reflux disease
 - Throat clearing
 - Cough
 - Eustachian tube dysfunction (ear pressure/popping/pain)
 - Sneezing
 - Hyposmia
 - Facial pressure/headache
 - Generally no nasal, pharyngeal, or ocular itching.
2. Symptoms of NAR may be perennial, persistent, or seasonal (ie, climatic, see later) and/or elicited by defined triggers. These triggers may include the following:
 - Cold air
 - Changes in climate (such as temperature, humidity, and/or barometric pressure)
 - Strong smells (such as perfume, cooking smells, flowers, and chemical odors)
 - Environmental tobacco smoke
 - Changes in sexual hormone levels
 - Pollutants and chemicals (eg, volatile organics)
 - Exercise
 - Alcohol ingestion.
3. Explanatory details of NAR:
 - Symptoms may be described as perennial, persistent, intermittent, or seasonal
 - Seasonal symptoms occur in response to seasonal climatic shifts in temperature, humidity, and barometric pressure
 - Symptoms may be brought on by 1 or more of the defined precipitants
 - Patients responsive to environmental climate changes as a trigger are not different from those triggered by perfumes or strong smells
 - There is no current information suggesting that patients for whom no specific triggers are identified differ from patients with clearly defined triggers. Thus, NAR may be the clinical diagnosis regardless of the presence or the absence of defined triggers
 - There is a female-to-male incidence ratio for NAR of 2:1 to 3:1
 - NAR presents predominantly with adult onset
 - The nasal mucosa in NAR usually looks normal
 - NAR is associated with negative or irrelevant skin prick tests or antigen-specific IgE tests
 - NAR may present with concomitant conditions, such as the following
 - Food-related rhinorrhea
 - Eustachian tube dysfunction (ear pressure/popping/pain)
 - Senile rhinitis.
4. NAR symptoms are not caused by other known etiologic factors for rhinopathy, such as the following:
 - Chronic rhinosinusitis or nasal polyposis

- Nonallergic rhinitis with eosinophilia syndrome (NARES), with nasal eosinophilia greater than 5%
- Aspirin-related chronic rhinosinusitis, nasal polyps, and asthma, although NAR is one of the clinical characteristics of aspirin-exacerbated respiratory disease
- Infectious rhinitis or rhinosinusitis (eg, viral upper respiratory infections, bacterial/fungal rhinosinusitis, and bacterial rhinitis)
- Anatomic abnormalities
- Adverse reactions to drug usage (eg, adverse effects of systemic medications and/or excess use of topical decongestants)
- Cerebrospinal fluid leak
- Pregnancy.

CHARACTERISTICS OF NAR

Before the extensive and precise identification of the characteristics of NAR summarized herein and elsewhere,³ the diagnosis of this condition was made by exclusion. To establish a definitive diagnosis of NAR as well as NARES, all other nonallergic rhinitis syndromes had to be properly considered and excluded.⁴ A diagnosis of NAR required negative specific IgE responses by skin, serologic, or entopy testing. Differentiation of the nonallergic conditions, NAR and NARES, is defined by the presence or absence of eosinophils in the nasal passages. Therefore, NAR is truly a noninflammatory nonallergic condition, whereas NARES is an inflammatory nonallergic condition. It should be emphasized that symptoms and physical findings alone are not diagnostic of allergic rhinitis (AR) compared with NAR because patients with NAR often manifest similar features.^{5,6} On the other hand, it is now recognized that if patients experience characteristic nasal symptoms in response to environmental triggers as defined earlier, then there is a degree of NAR present, even if allergic testing should prove positive (mixed rhinitis [MR]⁵). Therefore, an accurate history taking and proper diagnostic testing are essential to precisely classify these disorders (see later).

As a way to characterize the clinical symptoms and triggers of patients with rhinitis, Bernstein and coworkers^{7,8} developed a questionnaire survey designed to recognize differences between AR and NAR subtypes. Results from this questionnaire indicate that patients who develop symptoms later in life (older than 35 years); who have no family history of allergies, no seasonal allergy symptoms, or no perennial symptoms induced by cats or other furry pets; and who have symptoms induced by perfumes and fragrances have a likelihood of 95% of having a physician diagnosis of NAR.⁵ Of note, clinical symptoms are not generally sufficiently useful for differentiating chronic rhinitis subtypes.⁷ Data indicate that both AR and NAR have an equally high incidence of congestion and postnasal drip, with AR having slightly more rhinorrhea.⁷

In questioning a group of patients selected to participate in a seasonal AR (SAR) study, symptoms were triggered in 85% (116/136) of patients while outdoors during the spring, summer, or fall; 45% (61/136) by cats; 29% (39/136) by dogs; and 21% (29/136) by furry pets. Also, 54% (74/136) of patients had symptoms triggered by cigarette smoke, 72% (98/136) by weather changes, 49% (67/136) by perfumes, 35% (47/136) by incense, and 40% (54/136) by cleaning products. Thus, most patients enrolled in this SAR study also experienced irritant-induced symptoms in response to perfumes, cleaning products, incense, and smoke, suggesting that they also met diagnostic criteria for a nonallergic component to their chronic rhinitis diagnosis (ie, MR⁷).

Subsequently, the rhinitis questionnaire was distributed to subjects in 2 additional AR studies at baseline. It was found that more than 88% of enrolled subjects in both studies indicated that they experienced significant symptoms in response to

a spectrum of irritant triggers.⁹ Therefore, most patients enrolled in these SAR studies who also experienced irritant-induced symptoms in response to perfumes, cleaning products, incense, and smoke met diagnostic criteria for MR. MR is the condition in which patients have a mixture of allergic and nonallergic rhinitis. The frequency of MR in the population of patients with chronic rhinitis ranges from 22% to 34% depending on the study, with NAR recognized as the causative condition in 23% to 27%.¹⁰

EPIDEMIOLOGY OF NAR

The Task Force on Practice Parameters defines VMR (idiopathic rhinitis) as a “heterogeneous group of patients with chronic nasal symptoms that are not immunologic or infectious in origin and are usually not associated with nasal eosinophilia.”¹¹

Although no studies specifically designed to examine the epidemiology of NAR or VMR have been reported, 9 epidemiologic studies report data regarding the relative prevalence of NAR in comparison with that of AR (Table 1).^{12–20} Of the 9 studies, 7 used skin testing with variable techniques (prick, intradermal, or both or undefined) to distinguish nonallergic rhinitis from AR. These 9 studies, when added in total, are heavily influenced by the enormity of the data from Schatz and colleagues,²⁰ but when analyzed independently of the Schatz data, they reveal a relative prevalence rate of 76% for AR and 24% for nonallergic rhinitis, closely approximating a ratio of 3:1.

ESTIMATED PREVALENCE OF NAR IN THE UNITED STATES AND WORLDWIDE

The data from rhinitis epidemiology studies suggest that the ratio of AR prevalence (pure and mixed combined) to that of pure NAR is 3:1. This ratio can be extrapolated to determine a conservative estimate of the prevalence of NAR in the United States based on established prevalence rates of AR. If the assumption is made that 20% of the population suffers from AR,²¹ then on the basis of current population estimates for the United States of just more than 300 million, the US prevalence of AR is 60 million people. Applying the 3:1 (AR/NAR) ratio, approximately 20 million Americans would be expected to suffer from NAR (or approximately 7% of the total population). Given a current world population of 6.75 billion, similar extrapolation suggests that approximately 450 million people suffer from NAR worldwide. It is not known whether NAR is equally prevalent throughout the world and whether local weather (humidity), climate, air pollution, or genetic factors affect NAR prevalence.

Table 1 Relative rhinitis prevalence: allergic versus nonallergic				
Author	Year	N	AR%	NAR%
Mullarkey et al ¹²	1980	142	48	52
Enberg ¹³	1989	128	64	36
Togias ¹⁴	1990	362	83	17
Leynaert et al ¹⁵	1999	1142	75	25
Mercer et al ¹⁷	2002	278	78	22
Settipane ¹⁶	2003	975	77	23
Bachert et al ¹⁸	2006	743	75	24
Mølgaard et al ¹⁹	2007	1186	77	23
Schatz et al ²⁰	2008	47,894	71	29
—		Total 52,850	71	29

Subtotal without Schatz et al: 76% AR; 24% NAR.

FURTHER CHARACTERIZATION OF NAR

NAR is often described as being characterized by nonallergic symptom triggers, including weather (changes in temperature or relative humidity); alcohol; tobacco smoke; dusts; automotive emission fumes; nonspecific irritant stimuli, such as chlorine; and odors, such as bleach, perfume, or solvents.³ However, no epidemiologic data exist to further categorize NAR based on trigger type. Sex and age demographic data can be extrapolated from NAR data, suggesting a female predominance and an older population for NAR than for AR.^{22,23}

CLASSIFICATION OF NONALLERGIC RHINITIS SYNDROMES

The generally accepted universal clinical characteristics of the diseases classified within the category of chronic nonallergic rhinitis syndromes include only the following¹: nasal symptoms and² no evidence of concomitant allergic disease as determined by negative skin prick testing results for relevant allergens and/or negative allergen-specific antibody test results.¹¹ This classification automatically excludes infectious rhinitis, rhinosinusitis, and mechanical/anatomic abnormalities as causes of the chronic symptoms. There are at least 8 separate clinical entities that can be classified among the disorders that make up the nonallergic rhinitis syndromes (**Box 1**), with NAR being the clinically most common and important one.^{3,23} The cost of care for AR in the United States is estimated at more than \$5 billion to \$6 billion annually.^{24,25} It is estimated that NAR accounts for \$2 billion to \$3 billion. Hard data on the incidence and frequency of rhinitis subtypes are limited. However, it is recognized that NAR is the most prevalent, affecting an estimated 37% to 61% of patients diagnosed with rhinitis.^{26,27} In a survey of US medical practices, a prospective classification of 2500 patients with rhinitis was performed, and it was found that 43% of the patients had pure AR, 23% had pure VMR, and 34% had rhinitis with features of both AR and NAR (sometimes known as MR).^{26,27} These data suggest that at least 57% of patients with rhinitis have some contributions from NAR causing their rhinitis symptoms. Similar European studies have found that approximately 1 in 4 patients complaining of nasal symptoms has pure NAR.²⁸ Recent estimates suggest that 50 million Europeans have NAR, with a total prevalence of more than 200 million worldwide.²⁸

Box 1
Recognized nonallergic rhinitis subtypes

1. Drug-induced rhinitis
2. Gustatory rhinitis (rhinorrhea associated with eating, especially hot and spicy foods)
3. Hormonally induced rhinitis
4. NARES
5. Senile rhinitis
6. Atrophic rhinitis
7. Cerebrospinal fluid leak
8. NAR (formerly known as VMR)

Data from Refs. ^{3,11,29}

There have been several recent attempts at classifying the chronic nasal syndromes not associated with allergic disease.^{11,29,30} The reader is referred to these references for additional approaches to this problem and for a more complete bibliography. The approach taken herein combines the overall recommendations from these 3 sources, combined with input from other experts at a consensus conference held in 2009 and from which several recent references were published in the World Allergy Organization Journal in 2009 and are extensively cited herein. There are at least 8 subtypes that fill the criteria for nonallergic rhinitis (see **Box 1**).³¹

The 2 nonallergic processes, infectious rhinitis (including bacterial rhinitis and chronic rhinosinusitis) and mechanical/anatomic abnormalities, are excluded from this classification. Hormonally induced rhinitis reflects responses to endogenous female hormones. The rhinitis of pregnancy is an extremely common condition, affecting up to 20% to 30% of pregnancies, and is particularly notable during the last trimester. This rhinitis typically resolves spontaneously within 2 weeks of delivery. It is usually assumed that the rhinitis of pregnancy reflects the mucosal engorgement found in the last trimester as a consequence of progesterone stimulation. Thus, the nasal mucosa becomes engorged and congestion ensues because all mucous membranes are affected by the hormonal changes of pregnancy.³² Some patients develop similar symptoms premenstrually on a cyclical basis.³²

Drug-induced rhinitis includes rhinitis medicamentosa, which is the descriptive name for the nasal congestion and rebound rhinitis caused by repeated administration of topical nasal decongestants. The most common cause of rhinitis medicamentosa is the overuse of topical nasal decongestants such as oxymetazoline or phenylephrine. When used briefly (<3–5 days consecutively), these medications provide significant relief of nasal congestion. However, with chronic use, rebound nasal congestion can occur and can be quite severe. The exact mechanism is poorly understood, but theories suggest involvement of recurrent nasal tissue hypoxia and negative neural feedback with chronic decreased α_2 -receptor responsiveness.³³

More broadly, other medications¹¹ can cause chronic nasal symptoms through a host of different mechanisms. Antihypertensive medications, including β -blockers, angiotensin-converting enzyme inhibitors, reserpine, calcium channel blockers, and methyldopa, cause nasal congestion. A very bothersome side effect seen with α -receptor antagonists used for benign prostatic hyperplasia and phosphodiesterase 5 inhibitors for erectile dysfunction is nasal congestion. Aspirin and nonsteroidal anti-inflammatory drugs also may contribute to congestion, especially in patients with a history of nasal polyposis. Oral contraceptive pills also can cause congestion in some women. Personal observations suggest that topical eye drops, such as β -blockers for glaucoma, may also cause nasal symptoms.

Chronic nasal symptoms are found associated with a variety of other medical conditions, the full range of which is beyond the scope of this article. For example, nasal congestion can be seen in distinct diseases such as hypothyroidism and chronic fatigue syndrome. Baraniuk and colleagues³⁴ found that 46% of patients with chronic fatigue syndrome also have NAR and that 76% of these patients have ongoing nasal complaints.

Anatomic anomalies can also contribute to NAR. Adenoid hypertrophy, nasal septal deviation, and idiopathic turbinate hypertrophy or other structural abnormalities can cause chronic nasal obstruction with little relief from medications. Surgical intervention can be curative.

Senile rhinitis is a clinically defined condition most common in the elderly and can lead to persistent watery rhinorrhea that may be worsened by food or environmental irritants. Gustatory rhinitis is the condition that causes anterior rhinorrhea and/or

postnasal drip after eating, especially hot or spicy foods.³⁵ Gustatory rhinitis is more frequent in older individuals and overlaps with senile rhinitis. Both gustatory and senile rhinitis involve excessive secretions and are effectively treated with topical anticholinergic agents.³⁵ These rhinitis can occur concomitantly with NAR.

Atrophic rhinitis may occur as a primary idiopathic syndrome with mucous gland atrophy or as a secondary syndrome after overzealous surgeries, with too many mucus-secreting tissues removed. Because mucus is required to restrict bacterial growth in mucous membranes, these patients have dry mucosa and often contract ozena. A few bacterial diseases (*Pseudomonas ozena* and *Klebsiella rhinoscleromatis*) also can cause atrophic rhinitis.¹¹ Cerebrospinal fluid (CSF) leak in patients with a history of craniofacial trauma or past facial/sinus surgeries must be considered when evaluating persistent rhinorrhea. Increased intracranial pressure can increase the risk of spontaneous CSF leak.

Historically, NAR variants have been divided into 2 groups based on nasal cytology: NARES and non-NARES. However, in this era, nasal cytologic examination is rarely performed in clinical practice. When NARES was described,¹² 20 patients had the same spectrum of symptoms as seen in AR and were noted to have eosinophilia in nasal secretions. However, the results of skin testing and radioallergosorbent testing were negative. Thus, these patients with eosinophilia had the hallmarks of AR except for specific IgE antibodies. Patients with NARES characteristically respond well to topical nasal corticosteroids (NCCS). However, most clinicians no longer do nasal smears, and the relationship of NARES with the other forms of NAR is not known.

Occupational rhinitis is not a separate category but simply designates the location where exposure to nasal triggers is encountered. In practice, many patients complain of occupational rhinitis. Rhinitis from occupation exposures can be caused by irritants and/or allergens. Noxious fumes, odors, and environmental irritants are classic provocateurs of occupational rhinitis, whereas colophony (solder fumes), chemicals, enzymes, and countless other manufacturing by-products can act as allergens to some exposed people.^{11,36} At present, with cleaner more-controlled environments, one might expect fewer occupational diseases, but patients often believe that work-related exposures are still a common cause of rhinitis. A good history taking, combined with inventive provocations (such as exposure to soldering fumes or detergent powder), helps define what condition or exposure is responsible for the patient's problems.³⁶

Chronic rhinosinusitis, with or without nasal polyps, is another cause of chronic rhinitis. The symptoms of nasal congestion, postnasal drip with throat clearing and cough, facial pressure, headache, purulent drainage, and anosmia should lead the astute clinician to examine suspected sinus involvement. Because the inflammation in sinusitis may be infectious or immunologically mediated, these syndromes are usually not considered part of the nonallergic rhinitis syndromes. Bacterial rhinitis refers to a localized nasal infection with *Staphylococcus* or *Streptococcus* species in the anterior portion of the nose. Such patients have recurrent purulent drainage, nasal congestion, and local crusting but retain a normal sense of smell and have normal radiographic study results of the sinuses. Thus, this is a local bacterial infection of the nose, for example, bacterial rhinitis. This condition is effectively treated with topical antibiotics such as mupirocin.

Aspirin-exacerbated respiratory disease usually includes NAR as one of the clinical characteristics, along with sinusitis, nasal polyposis, asthma, and eosinophilia worsened with aspirin or nonsteroidal antiinflammatory drug exposure.¹¹ The NAR seen in aspirin sensitivity is usually a form of NARES and may precede the development of other manifestations of the syndrome.

SOME ADDITIONAL DETAILS ABOUT NAR

The most frequent form of nonallergic rhinitis observed clinically is NAR characterized by persistent or intermittent nasal symptoms that can be triggered by environmental conditions that do not bother normal individuals. The diagnosis can now be made by clinical history taking and exclusion of other known causes. If a patient has appropriate nasal symptoms (usually rhinorrhea, congestion, postnasal drip, headaches, facial pressure, throat clearing, and/or coughing) worsened or triggered by 1 or more of the environmental conditions noted earlier, then NAR is present. Concomitant ocular symptoms tend to be minimal, and the symptoms of nasal and palatal itches and also sneezing spells are not common. Some patients with NAR have persistent nasal symptoms and no other recognized cause. These patients may or may not respond to the environmental conditions that trigger other symptoms in other patients. The clinical characteristics of these patients (predominantly female sex, adult onset, clinical symptoms, and response to treatment) are indistinguishable from those of patients with NAR with recognized triggers. It is proposed that these patients also have NAR.

Unlike AR, NAR is usually adult onset and is not worsened by exposure to classic allergens such as pollen, house dust mite, dogs, or cats. A validated questionnaire has been created to help identify patients with NAR.⁶ Because NAR may be caused by shifts in temperature, humidity, and/or barometric pressure, patients may experience seasonal symptoms associated with changes in these climatic conditions experienced during the spring and fall. Seasonal NAR can, therefore, be confused with SAR.³⁷

The diagnosis of NAR is based solely on the patient's history of symptoms and their triggers, whereas the diagnosis of AR requires an appropriate history taking and confirmatory allergy testing, either positive relevant skin prick test results or allergen-specific IgE test results. These 2 diseases are not mutually exclusive, and at least 60% of patients with AR develop nasal symptoms in response to nonallergic environmental triggers. To have pure NAR, however, the patient must have negative relevant skin test results or in vitro allergen-specific antibody test results.

There are some limited data that histamine can be released from the nasal mucosa after inhaling cold dry air, which elicits cold air-induced rhinitis in some sensitive patients. In a set of cold dry air challenges, in vivo histamine release was observed with cold air-induced rhinitis but not with other forms of NAR.³⁸ The importance of the histamine release in the development of the rhinitis symptoms was considered to be unrelated.

The epidemiologic predominance of women with VMR suggests that female hormones might play some role, but there are little supporting data. One study reported that 71% of patients with VMR were women compared with 62% of those with MR and 55% of those with AR.⁶

TREATMENT OF NAR

Although each form of nonallergic rhinitis should be treated individually, NAR is the most well-studied and clinically important form and the only type for which clinical studies have led to approved treatments. In the following discussion, treatment of nonallergic rhinitis focuses on NAR, but some mention is made of other forms of rhinitis where appropriate. The medications used for treating NAR have been studied less extensively than those for AR, but there are still multiple therapeutic options available.

NCCS

NCCS treat inflammatory conditions regardless of cause. There is substantial evidence that corticosteroids benefit AR; some forms of nonallergic rhinitis, including NAR³⁹; and chronic rhinosinusitis. In a study of 983 patients with NARES and non-NARES, fluticasone propionate (FP) at both 200 and 400 µg significantly improved total nasal symptoms scores when compared with placebo, and no difference was noted between the 2 concentrations.⁴⁰ In the United States, of all the NCCS approved by the Food and Drug Administration (FDA) available at present, only FP is approved for the treatment of both allergic and nonallergic rhinitis.

Although none of the other current NCCS have received the US FDA approval for use in NAR, there are some supportive data for the efficacy of intranasal budesonide and mometasone in some patients with perennial rhinitis.^{41,42} There is also one published study demonstrating that there was no benefit from FP in NAR. In that study, patients with NAR receiving 200 µg of daily FP showed a reduction in inflammatory mediators but no improvement in symptoms as compared with placebo.⁴³ By contrast, clinical experience suggests that all NCCS have some effectiveness in treating NAR. As a class, NCCS treats the broadest spectrum of NAR symptoms and seems to have at least some degree of efficacy in all NAR variants. Thus, for the treatment of NAR, NCCS are considered a first-line therapy.

Antihistamines

It is quite likely that all patients with NAR have tried oral antihistamines, either in the form of over-the-counter medications or as prescribed by physicians who assume that the symptoms are caused by allergies. Histamine release has not been seen in NAR, other than cold air-induced rhinitis.³⁸ Thus, the use of oral antihistamines makes little sense, and these medications have rarely been studied in NAR. A 1982 study does show that first-generation antihistamines can improve NAR symptoms when combined with a decongestant.⁴⁴ It is predictable that first-generation antihistamines might reduce rhinorrhea through anticholinergic actions, whereas second-generation nonседating antihistamines have minimal anticholinergic activity. Typically, second-generation antihistamines are of no benefit in NAR. Oral antihistamines are generally ineffective in reducing congestion in AR and thus are not expected to work in NAR either. The combination of an antihistamine and a decongestant might help reduce the congestion seen in NAR, but no such indication has been approved by the US FDA. Clinical experience suggests that antihistamine/decongestant combinations are somewhat effective in NAR.

By contrast, intranasal antihistamines are very effective in treating AR (both azelastine and olopatadine are approved for treating SAR). Azelastine is also approved by the FDA for treatment of NAR. Although azelastine is primarily a second-generation antihistamine, it is unlikely that its efficacy in NAR is because of histamine receptor blockade. Instead, it is probably azelastine's actions as an antiinflammatory and neuroinflammatory blocker that makes this medication useful in treating VMR/NAR.⁴⁵ Azelastine has been shown to deplete inflammatory neuropeptides in the nasal mucosa; reduce levels of proinflammatory cytokines, leukotrienes, and cell adhesion molecules; and inhibit mast cell degranulation.⁴⁶

In 2 multicenter, randomized, double-blind, placebo-controlled, parallel-group clinical trials, azelastine showed considerable efficacy in the treatment of each of the symptoms of NAR, including congestion.⁴⁷ Treatment for more than 21 days caused a significant reduction in the total VMR symptom score from baseline when compared with placebo ($P = .002$), and every nasal symptom was effectively reduced. Symptom

improvement was rapid with most patients experiencing relief within 1 week. There were no serious adverse events, although a bitter taste was experienced by some in the azelastine group. In studies of AR, onset of effect with nasal azelastine is seen in 15 to 30 minutes.⁴⁶ Based on these clinical studies and extensive clinical experience, nasal antihistamines are considered a first-line therapy for NAR.^{11,45}

A meta-analysis has suggested that NCCS are slightly more effective than nasal antihistamines in the treatment of AR, but no such analyses exist comparing these products in treating NAR. The data from the study by Yanez and Rodrigo⁴⁸ are often quoted to substantiate a claim that NCCS are superior to nasal antihistamines in treating rhinitis, but the data cited do not use the products approved in the United States and involve multiple products used at widely varying doses and using no consistent dose schedule. Thus, the data from Yanez and Rodrigo do not apply to the products used in the United States and should be viewed skeptically unless they are extended to studies with US products.⁴⁹ Several recent studies comparing olopatadine⁵⁰ or azelastine⁵¹ with FP showed equivalence in treating rhinitis.

Olopatadine was recently compared with fluticasone.⁵⁰ In this study, 130 patients were randomized to 2 sprays per nostril per day for a 2-week course of treatment of SAR with olopatadine (0.6%) or fluticasone (50 µg). Both the treatments significantly reduced both reflective and instantaneous assessments of nasal and ocular symptoms over the 2-week study ($P < .05$) and were safe and well tolerated. Both olopatadine and fluticasone nasal sprays reduced SAR symptoms (ocular and nasal) by the same amount, with the only significant difference being that olopatadine provided a greater and faster onset of action.⁵⁰ These current data indicate that both nasal antihistamines are noninferior to NCCS and support their role as a first-line treatment option.

When NCCS and azelastine were combined in the treatment of AR, the effects of the combination were additive. In a randomized double-blind trial comparing FP alone versus azelastine alone versus the 2 in combination for the treatment of AR, the combination produced a further reduction of 40% in total nasal symptom scores as compared with either FP or azelastine alone. The combination of FP and azelastine reduced congestion by 48% compared with the individual components.⁵² Additional studies with azelastine and FP⁵³ as well as olopatadine and FP⁵⁴ support these suggestions. The combination has yet to be studied in NAR, but extensive clinical experience suggests that this combination is highly effective in NAR as well. Based on both published clinical studies and extensive clinical experience, the use of azelastine (and olopatadine) alone and in combination with NCCS is a preferred first-line treatment of NAR as well as AR.^{45,46,49}

Anticholinergics

Ipratropium bromide (IB) is a potent intranasal anticholinergic with utility in the treatment of rhinorrhea in AR and NAR. It has been studied in both adults and children. IB specifically treats rhinorrhea and does little to improve congestion. Intranasal anticholinergics work best for rhinorrhea-predominant NAR variants, such as cold air-induced rhinitis (skier's nose)⁵⁵ and gustatory and senile rhinitis.³⁵ In 28 patients with cold air-induced rhinitis, IB reduced symptoms and the number of tissues required during and after cold exposure ($P = .0007$ and $P = .0023$, respectively).⁵⁶ In children with perennial AR or NAR, the effect of IB was superior to placebo and equivocal to beclomethasone dipropionate (BD) for the treatment of both rhinorrhea and congestion. However, IB was less effective than BD for controlling sneezing.⁵⁷

Similar to the nasal antihistamines, there seems to be an additive effect when IB is used in conjunction with NCCS.⁵⁸ In a study comparing beclomethasone versus IB

versus the 2 combined, the combination group had better symptom control of rhinorrhea. Beclomethasone monotherapy was found to treat sneezing and congestion better than IB monotherapy. Both medications were well tolerated. No study combining IB and nasal antihistamines for the treatment of NAR has been reported, but clinical experience indicates that this combination works well with patients who primarily experience rhinorrhea and postnasal drip.

Oral anticholinergics such as methscopolamine have not been studied in NAR but likely improve symptoms particularly in patients with rhinorrhea as a predominant symptom or in patients with significant postnasal drainage. Many first-generation antihistamines and decongestants also have strong anticholinergic properties. However, side effects such as dry mouth, sedation, and urinary hesitancy limit the usefulness of these drugs. Clinical experience suggests that oral methscopolamine combined with an oral first-generation antihistamine is helpful in treating patients with postnasal drip and that adding this combination to nasal IB, nasal antihistamines, or NCCS is useful.

Decongestants

Both oral and topical decongestants effectively treat congestion regardless of cause; however, none have been studied for NAR. Oral pseudoephedrine is an effective decongestant and can be considered for chronic use. However, side effects such as neurogenic and cardiac stimulations, palpitations, and insomnia affect a significant number of patients. Furthermore, the medication is relatively contraindicated in patients with hypertension. Thus, pseudoephedrine must be used cautiously. Phenylephrine is also an oral decongestant. It has been studied far less than pseudoephedrine and is considered a generally less-potent medication.

Topical decongestants, such as oxymetazoline and phenylephrine, are fast-acting potent local decongestants. These medications cannot be used chronically because continual use for more than 3 to 10 days leads to rhinitis medicamentosa. For patients with NAR with intermittent nasal congestion, a topical decongestant can be used for short-term relief of congestion.

Other NAR Therapies

Even though NAR affects many patients, very few medications have been adequately studied for the treatment of this condition. In patients who do not adequately respond to NCCS, intranasal antihistamines, or IB, other agents can be considered. There are a few limited studies examining intranasal capsaicin in NAR. In theory, repetitive capsaicin application depletes certain neuroinflammatory chemicals. Van Rijswijk and colleagues⁵⁹ did demonstrate decreased nasal symptoms in patients with NAR treated with capsaicin. Similarly, botulinum toxin A injected into the inferior and middle turbinates of patients with NAR has been shown to decrease congestion, sneezing, rhinorrhea, and nasal itch.⁶⁰ In patients with congestion as the predominant nasal symptom who have clinical evidence of turbinate hypertrophy, surgical reduction of the inferior turbinates may be of some benefit.⁶¹ Nasal washing with isotonic or hypertonic saline has a demonstrated benefit particularly in chronic rhinosinusitis and seems to benefit some patients with NAR.⁶² Antileukotrienes have not been studied in NAR, but there is at least some theoretical benefit in patients with aspirin sensitivity and/or nasal polyposis.

SUMMARY

NAR is the new designation for the conditions formerly referred to as VMR or nonallergic idiopathic rhinitis. The clinical characteristics and differential diagnosis are

provided in detail in this review, and the disease should now be characterized sufficiently for clinical studies. The development of acceptable inclusion and exclusion criteria for NAR²³ should facilitate new and much needed clinical studies for this disease to define which medications might be useful in treatment. Moreover, with these precise characteristics, the diagnosis of NAR can be made on clinical grounds rather than as a diagnosis of exclusion. The current treatment of NAR is generally successful and uses nasal antihistamines and NCCS either individually or in combination. As there are a substantial number of patients for whom nonallergic triggers play an important role in their disease, both the recognition and effective treatment of NAR should have a positive effect on their lives.

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