Evidence Report

Chapter 1. Introduction

Goal of the Report

This report summarizes the scientific evidence for diagnosing and treating allergic and nonallergic rhinitis. This topic was selected by the Agency for Healthcare Research and Quality in response to a request from the American Academy of Family Physicians. The report provides summaries of evidence for use by different groups, including primary care practitioners, specialists, researchers, policy decision makers, and health care financiers. Recognizing the different interests and approaches of these groups, this report focuses on the diagnosis and treatment of allergic and nonallergic rhinitis in the primary care, clinical practice setting. We sought evidence on diagnostic methods that can help differentiate between allergic from nonallergic rhinitis. We summarize the evidence on the efficacy of treatments for these conditions.

Scope of the Problem

Prevalence of Allergic Rhinitis

Twenty to forty million Americans are affected by allergic rhinitis (Dykewicz, Fineman, Skoner, et al., 1998) making it the sixth most prevalent chronic illness (Collins, 1997). The peak prevalence of allergic rhinitis is observed in children and young adults. Estimates range from 10 to 30 percent of adults and up to 40 percent of children suffer with this condition, making allergic rhinitis currently the most common chronic condition found in children (Fireman, 2000). In the past 30 years there has been a dramatic increase in the prevalence of allergic rhinitis in "Westernized" societies, and studies from England, Sweden, and Australia have confirmed a doubling of prevalence over this time (Aberg, 1989; Aberg, Hesselmar, Aberg, et al., 1995; Hopper, Jenkins, Carlin, et al., 1995).

Despite the high prevalence of the disease, there is still insufficient epidemiologic data. Population surveys frequently have relied on physician-diagnosed rhinitis for primary data, which might underestimate the true prevalence of rhinitis (Aberg, 1989; Aberg, Hesselmar, Aberg, et al., 1995; Fleming and Crombie, 1987; Hopper, Jenkins, Carlin, et al., 1995). While population studies have been regularly performed by directly administered questionnaires, followed by telephone contact, which probably provide more accurate information, this approach probably still underrates the true prevalence of disease (Dykewicz, Fineman, Skoner, et al., 1998). In addition, most epidemiological studies have been directed towards estimating the prevalence of seasonal rhinitis because perennial allergies are more difficult to identify since its symptom complex overlaps with chronic sinusitis, recurrent upper respiratory infections, and vasomotor rhinitis (Dykewicz, Fineman, Skoner, et al., 1998).

Biology of Disease, Natural History

Rhinitis encompasses a group of disorders affecting the mucous membranes lining the nasal passages. Typical symptoms of rhinitis include sneezing episodes, nasal itching, rhinorrhea, nasal obstruction, postnasal dripping and occasionally nasal pain. Based on timing or periodicity of symptoms, allergic rhinitis may be classified as either seasonal or perennial. Rhinitis is also classified under etiology as either allergic or nonallergic (Ng, Warlow, Chrishanthan, et al., 2000).

The symptoms of allergic rhinitis result from exposure to allergens in a susceptible (sensitized) individual (Kay, 2001). Allergens include pollen, grass, tree, weed, house-dust mite etc., and symptoms are triggered by the interaction of an allergen with IgE molecules bound, through the high affinity IgE receptor, to the surface of mast cells in the nasal mucosa or circulating basophils. Recognition of the allergen by the IgE antibody leads to activation of the mast cell or basophil causing the release of preformed granule-associated mediators (including histamine), membrane derived lipid mediators (including leukotrienes), as well as cytokines and chemokines which are responsible for attracting inflammatory cells from the peripheral circulation to the site of degranulation. This orchestrated chain of events results in the characteristic clinical features of allergic rhinitis (Fireman, 2000; Kay, 2001). Clinically, allergic rhinitis may be associated with "early phase" symptoms occurring within minutes of allergen exposure (due to the release of preformed mediators) and "late phase" symptoms, seen at 4-8 hours after exposure due to synthesis of newly formed mediators and infiltration of inflammatory white blood cells from the circulation (Bellanti and Wallerstedt, 2000; Skoner, 2001). Nasal itching is a prominent symptom during the early phase; sneezing, congestion and rhinorrhea are seen in both early and late phases, but nasal congestion dominates the late phase reaction.

Genetic factors probably play an important role in the development of allergic rhinitis (Fireman, 2000). It has been suggested that if both parents are atopic, chances of allergic disease risk in the offspring are 50 percent or higher, a number that increases to 72 percent if parents are afflicted with the same atopic disease (Fireman, 2000). While the precise details of the determinants of allergic sensitization and subsequent development of clinical symptoms remain poorly understood, the paradigm in modern allergy teaching is that the tendency to develop atopic disease is a heritable one but that the specific allergic sensitivities exhibited by an individual relate to specific allergen exposures.

Nonallergic rhinitis is characterized by sporadic or persistent perennial nasal symptoms that do not result from IgE-mediated immunopathologic events (Dykewicz, Fineman, Skoner, et al., 1998). The diagnosis of non-allergic rhinitis is frequently a diagnosis of exclusion when an allergic etiology can be substantiated by diagnostic testing. There is no universally accepted classification of non-allergic rhinitis. The symptoms can be similar to allergic rhinitis, but with a decrease in the amount of nasal itch and in the number of sneezing episodes and conjunctival complaints (Jones, 1988; Settipane and Lieberman, 2001). Examples of nonallergic rhinitis include infectious rhinitis, vasomotor rhinitis (noninfectious) and nonallergic rhinitis with eosinophilia syndrome (NARES), overuse of topical-adrenergic agonists/nasal decongestants (rhinitis medicamentosa) and structural or anatomic abnormalities in the nose (including septal deviation or nasal polyposis). Other less common causes of this problem include: endocrine changes of hypothyroid and hyperthyroid disease, pregnancy or damage to sympathetic nerves (Dykewicz, Fineman, Skoner, et al., 1998). Nonallergic rhinitis with eosinophilia is characterized by the presence of nasal eosinophilia without evidence of allergic sensitization. Typical symptoms include perennial symptoms of sneezing, nasal itching, rhinorhoea, nasal obstruction and occasionally loss of sense of smell. It has been associated with non-specifc bronchial hyper-reactivity (Teodoro, Pelucchi, Mastropasqua et al.). It has been suggested that NARES may be linked to aspirin sensitivity (Moneret-Vautrin, Hsieh, Wayoff et al.). The distinction between allergic and nonallergic rhinitis can be difficult clinically. The presence of concurrent symptoms in the eyes or upper respiratory tract such as ocular itching, scratchiness, tearing or redness, palatal itching, or asthma symptoms such as coughing, chest tightness, wheezing and shortness of breath are more likely to suggest allergic rhinitis. The presence of comorbid conditions, such as allergic eczema or asthma, also point toward a diagnosis

of allergic rhinitis. Recognition by the patient of trigger factors for symptoms, such as exposure to dusty environments, exposure to cats, dogs or other domestic animals, association of the symptoms with specific seasons, especially spring (tree and grass pollens) or fall (ragweed pollens), all point towards an allergic etiology. In contrast, the symptoms of vasomotor rhinitis are often exacerbated by exposure to nonspecific irritants (non-allergens) such as strong odors, fragrances, perfumes or other volatile chemicals such as exhaust fumes, cigarette smoke or solvents, or by exposure to changes in air temperature or humidity. Additionally, symptoms such as fever, sore throat, generalized malaise or achiness, might point to infectious causes of the rhinitic symptoms (Jones, 1988; Settipane and Lieberman, 2001). While no formal diagnostic criteria have been formulated for distinguishing allergic from vasomotor rhinitis, detailed history taking plays a crucial role in diagnosis.

The exact prevalence of nonallergic rhinitis is not known but estimates indicate that up to 50 percent of patients with rhinitis actually have nonallergic causes (Jones, 1988). Vasomotor rhinitis is more likely to affect adults, and it is more prevalent in women (Settipane and Lieberman, 2001).

Burden of Illness

In addition to the physical symptoms of allergic rhinitis, such as sneezing, rhinorrhea, nasal pruritus, sufferers from allergic rhinitis also experience symptoms such as significant fatigue, headache, and cognitive impairment. These symptoms in turn are often associated with psychosocial problems, ranging from public embarrassment and diminished physical and emotional well being due to lack of sleep and diminished participation in recreational activities. All told, this can have negative effects on their physical, psychological, and social aspects of their lives significantly because of continued symptoms of allergic rhinitis (Thompson, Juniper, and Meltzer, 2000). Accordingly, the human cost of rhinitis (allergic and nonallergic) is assessed in terms of symptoms, medication needs, interference with sleep, and activities of daily living, work impairment, absences from work and school, impaired learning efficiency, and interference with social commerce.

In a recent pooled analysis of two parallel health outcomes (Tanner, Reilly, Meltzer, et al., 1999) 70 percent of 1,948 patients with moderate-to-severe allergic rhinitis reported embarrassment and/or frustration with allergy symptoms. More that 90 percent believed that their ability to perform daily activities was impaired by allergies, and also reported that their work or classroom performance was negatively affected.

The comorbidities that complicate undertreated allergic rhinitis, typically including asthma, sinusitis and otitis media, add further to the economic and psychosocial burden of disease (Spector, 1997).

Estimated Costs of Health Care: Individual and Societal

Allergic rhinitis is responsible for at least $1.8 billion annually for the direct cost of physician visits and medication expenses (McMenamin, 1994), or nearly 2.5 percent of the $47 billion annual direct cost for respiratory treatment in the United States (Levit, Lazenby, Cowan, et al., 1991; McMenamin, 1994; Rice, Hodgson, and Kopstein, 1985). Furthermore, nearly $3.8 billion was the estimated value of lost productivity to employers and society resulting from allergic rhinitis (Ross, 1996). In the mid-1990s the resulting total annual cost for allergic rhinitis amounted to $5.6 billion.

Retail sales of over-the-counter allergy relief products exceed $140 billion per year, yet only about 12 percent of those affected seek treatment from a doctor, implying that all the other allergic

rhinitis sufferers probably self-treat. Because of the significant cost of treatment, it is important that a good method exists for determining resource allocation.

Defining Allergic Rhinitis

Allergic rhinitis is defined as the clinical expression of tissue changes in the upper airway and adjacent structures following interactions of IgE and specific allergens, characterized by the symptoms of nasal congestion, rhinorrhea, postnasal drainage, sneezing, nasal itching, and occasionally impaired sense of smell (and taste). Allergic rhinitis can be seasonal, usually indicative of pollen-allergen sensitivity, or it can be year-round, frequently related to sensitivity to perennial, indoor aeroallergens. Nonallergic rhinitis is characterized by chronic nasal symptoms, often identical to those of allergic rhinitis but without allergic causation. Nonallergic rhinitis is distinguished by the lack of identifiable triggers in the patient's history, making detailed history taking essential.

Diagnosing Patients with Allergic Rhinitis

The typical findings on physical examination in the patient with allergic rhinitis include pallor of the nasal mucous membranes, which are often engorged. In addition, they often have a bluish tint and frequently exhibit clear watery secretions. There is often enlargement of the inferior turbinates visible by anterior rhinoscopy. The identification of venous engorgement in the infraorbital tissues (allergic shiners), erythema of the conjunctivae, scleral injection, especially when bilateral, adds further evidence to suggest an allergic etiology for the nasal findings.

Absences of fever, oropharyngeal erythema or exudate, or lymphadenopathy in the cervical or submental areas also imply a diagnosis of allergic rhinitis. A history of allergy or atopy in first-degree relatives is also likely to be helpful in forming an opinion as to whether allergic rhinitis is the etiology of the nasal symptoms.

Documenting the presence of IgE antibodies against known aeroallergens substantiates the diagnosis of allergic rhinitis. This can be accomplished either by allergy skin testing with representative aeroallergens or by radioallergosorbent testing (RAST). Skin testing identifies the presence of allergen specific IgE antibodies on tissue bound mast cells in the skin, whereas RAST measures these same antibodies circulating in peripheral blood. In clinical practice, skin testing is generally preferred over RAST testing. Several methods of skin testing are available. Prick - puncture skin tests are considered the most reliable as they show a high degree of correlation with clinical symptoms and provocative allergen challenges. Scratch tests have been shown to be associated with poor reproducibility and possible systemic reactions. They are infrequently used. Intradermal tests, which employ a weak allergen solution, are more sensitive than prick-puncture tests. They can induce false positive reactions (Reid, Lockey, Turkeltaub, et al., 1993) and overall tend to correlate less well with symptoms (Dreborg, Backman, Basomba, et al., 1989). It has been suggested that the availability of standardized extracts may obviate the necessity for intradermal tests (Demoly and Bousquet, 1998; Nelson, Oppenheimer, Buchmeier, et al., 1996; Wood, Phipatanakul, Hamilton, et al., 1999). RAST testing in general correlates closely with the results of skin testing but has a higher cost than does skin testing. RAST tests can yield quantitative results but the titre of specifc IgE measured is frequently not correlated to clinical symptoms.

Because nasal symptoms that occur in nonallergic rhinitis are often indistinguishable from perennial allergic rhinitis, nonallergic rhinitis is often diagnosed by excluding allergic disease by an absence of positive allergy skin tests or negative results by RAST. The use of nasal cytology to evaluate mucosal cellular patterns has the potential to distinguish inflammatory from non-inflammatory nasal conditions, following the course of disease and response to treatment. There is evidence that nasal biopsy is superior to nasal smear for finding eosinophils (Ingels, Durdurez, Cuvelier, et al., 1997)

Rationale for Differentiating Allergic from Nonallergic Rhinitis

Antihistamines are an integral component in the treatment of allergic rhinitis, but they are unlikely to be effective in nonallergic rhinitis. In addition, there is increasing support for the position that the primary therapy in confirmed allergic rhinitis should be anti-inflammatory rather than symptomatic. Treating the allergic inflammation has been shown to significantly decrease all the symptoms of allergic rhinitis, not just those mediated by histamine, and also to significantly diminish the complications such as sinusitis and otitis media that frequently occur in patients with allergic rhinitis (Dykewicz and Fineman, 1998).

In contrast, anti-inflammatory therapies such as intranasally applied corticosteroids are often not helpful in other forms of chronic rhinitis such as vasomotor rhinitis where treatment often ends being merely symptomatic in nature. For example, when the dominant symptom is nasal congestion, oral decongestants are recommended, and when the dominant symptom is rhinorrhea, drying agents such as topical ipratropium bromide are more useful. Thus, from a theoretical standpoint, there would indeed appear to be important, therapeutic benefit in distinguishing allergic from nonallergic rhinitis.

Issues in Management of Allergic Rhinitis

Current Therapies in Allergic Rhinitis

Evaluation of the therapies used in allergic rhinitis and nonallergic rhinitis might reasonably include assessments of symptom relief, use of as-needed medications, numbers of days lost from work and school, and estimates of "quality of life." Recent examples of Health-Related Quality of Life questionnaires (HRQOL) used in studies of rhinitis are the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ), the Rhinitis Outcomes Monitoring System (ROMS), and the Work Productivity and Activity Impairment (WPAI) survey (Meltzer, 2001).

Environmental control measures to decrease exposure to inciting factors, e.g. allergens, irritants and irritant medications, are considered fundamental to the management of rhinitis (Dykewicz, Fineman, Skoner, et al., 1998). While the established treatment modalities of allergic rhinitis consist of allergen avoidance, anti-allergic medication and immunotherapy (desensitization) for specific allergens, avoidance of exposure to identified aeroallergens is the primary long-term therapeutic modality (Corren, 2000). There now exists sufficient clinical and experimental evidence that such measures are effective and result not only in the diminution of symptoms, but also significantly lessen medication needs as well as decrease associated morbidity from the complications of allergic rhinitis (Woodcock and Custovic, 2000). Allergen avoidance measures, such as removal of feather pillows and down comforters, and encasing mattresses in dust-proof covers to decrease dust-mite exposures as well as elimination of carpeting in favor of tile or hardwood floors and high-flow air filtration units like a HEPA cleaner are all recommended strategies for those with perennial symptoms due to indoor allergens (Arlian and Platts-Mills, 2001;

Corren, 2000; Woodcock and Custovic, 2000). Similarly, decreasing exposure in sensitized individuals to domestic animals, especially cats and dogs, has demonstrated efficacy (Chapman and Wood, 2001).

In contrast, outdoor allergens are somewhat more difficult to avoid completely, and recommended measures are to stay indoors and keep windows closed, particularly during periods of the day when certain airborne allergens are at their highest concentration (Corren, 2000).

Current pharmacological treatments for allergic rhinitis include antihistamines (oral and more recently intranasal antihistamines), decongestants (oral and to a lesser extent intra-nasal), and intra-nasally applied anticholinergic agents, all of which are used for symptom relief in rhinitis. Topical nasal corticosteroids and immunotherapy are also useful in suppressing allergic inflammation (Thompson, Juniper, and Meltzer, 2000).

Antihistamines, the most frequently prescribed medication for allergic rhinitis, are usually administered on an intermittent basis for patients with the mildest symptoms. They reduce symptoms of itching, sneezing, and rhinorrhea. Oral antihistamines, which act by competitively inhibiting the binding of histamine to H1 receptors, have arbitrarily been subdivided into first and second-generation categories. Second generation H1 receptor antagonists, such as loratadine, fexofenadine and cetirizine, are less sedating and more pharmacologically selective than earlier antihistamines. In addition, some H1 receptor antagonists have also been reported to inhibit allergen-induced infiltration of tissue by eosinophils, or to actually inhibit release of the mediators, histamine or prostaglandins. These effects are as yet of undetermined clinical relevance and apparently independent of their effects on histamine receptors (Corren, 2000; Kay, 2001; Meltzer, 1995; Nightingale, 1996).

Decongestants, which are sold in either oral or topical form, are often used in combination with antihistamines (Corren, 2000; Meltzer, 1995) and the ineffectiveness of oral antihistamines in relieving nasal obstruction has prompted the subsequent manufacture of agents combining antihistamines and decongestants. By themselves, decongestants help to reduce nasal congestion by their vasoconstrictor properties. Topically applied vasoconstrictor sympathomimetic agents, such as phenylephrine, or imidazoline derivatives, such as oxymetazoline, are effective in inducing nasal capacitance vessel vascular constriction through activation of alpha-adrenergic receptors. Vasoconstriction (nasal decongestion) occurs within five to 10 minutes and may last for six to eight hours with oxymetazoline. These agents are effective for short term use (for example, to assist in physical examination, or to use before air travel, or during the early stages of nasal infections or perhaps during the initiation of treatment with nasal corticosteroids (Beckman and Grammer, 1999; Dykewicz, Fineman, Skoner, et al., 1998; Howarth, 1989; Lund, 1996; Meltzer, 1995).

Oral decongestants (also vasoconstricting agents) include phenylephrine and pseudoephedrine and phenylpropanolamine (The FDA has urged companies marketing phenylpropanolamine to voluntarily withdraw the drug from the market while it initiated regulatory actions to mandate such withdrawals). They cause vasoconstriction by activation of alpha-adrenergic receptors and by indirectly stimulating release of norepinephrine from its storage sites. Although these agents decrease nasal resistance to a lesser degree than do topical agents, their long-term use is somewhat safer because they lack the "rebound" vasodilatation that has been associated with the topical vasoconstrictors. Nasal decongestion occurs within 30 minutes and persists for six to eight hours with oral pseudoephedrine at a dose of 60 mg. Decongestion may last for eight to 12 hours with extended release preparations (Beckman and Grammer, 1999; Dykewicz, Fineman, Skoner, et al., 1998; Howarth, 1989; Lund, 1996; Meltzer, 1995).

Increased cholinergic activity from parasympathetic stimulation is documented in allergic and nonallergic (including infectious) rhinitis (Druce, Wright, Kossoff, et al., 1985; Raphael, Baraniuk, and Kaliner, 1991; White, 1995) resulting in increased nasal secretions and congestion. Anticholinergic medications can cause a reduction in the volume of nasal secretions and some degree of vasoconstriction. Ipratroprium bromide, available as a nasal spray, is a quaternary derivative of isopropyl noratropine and is poorly absorbed by the nasal mucosa and does not cross the blood brain barrier. It has been demonstrated to be effective in reducing rhinorrhea in adults and children with both allergic and nonallergic rhinitis (Bronsky, Druce, Findlay, et al., 1995; Druce, Spector, Fireman, et al., 1992; Georgitis, Banov, Boggs, et al., 1994; Grossman, Banov, Boggs, et al., 1995; Meltzer, 1995; Meltzer, Orgel, Bronsky, et al., 1992).

Intranasal corticosteroids, and to a significantly lesser degree, cromolyn sodium, are anti-inflammatory medications that have been proven effective in treating patients with more pronounced or protracted allergic rhinitis (Weiner, Abramson, and Puy, 1998). The corticosteroids inhibit many of the steps in the cascade of allergic inflammation in allergic rhinitis and are documented to provide excellent symptom relief for all the symptoms of allergic rhinitis, including nasal congestion and blockage (Mygind, Nielsen, Hoffmann, et al., 2001). This has resulted in superior efficacy assessments for intranasal corticosteroids when compared to oral antihistamines in the treatment of allergic rhinitis (Weiner, Abramson, and Puy, 1998). Many formulations of intranasal corticosteroids are currently available. Examples include Nasonex (mometasone furoate), Flonase (fluticasone propionate), Rhinocort (budesonide), Beconase and Vancenase (beclomethasone diproprionate), Nasacort (triamcinolone acetonide), Nasarel and Nasalide (fluniolide) (Allen, 2000; Corren, 1999). The onset of action varies but it is believed that all require three to seven days for optimal effect. There are differences in estimated potency and systemic bioavailablity between the different agents, which might alter the long-term safety profile, but clear differences in clinical efficacy have not been established (Allen, 2000; Corren, 1999). Prophylactic use with initiation of use two weeks in advance of seasonal pollen symptoms has been proposed for maximal symptom reduction. The corticosteroids can inhibit inflammatory responses whether the inciting agent is allergic, chemical or infectious, and there is documented clinical efficacy of these agents in both allergic rhinitis and nonallergic rhinitis (Dykewicz, Fineman, Skoner, et al., 1998).

Cromolyn sodium requires frequent dosing (four times a day) for efficacy, and is also best used prophylactically since its postulated mechanism of action is to prevent mast cell degranulation rather to treat the symptoms of an established allergic reaction in the nose. It may require up to two weeks of continuous usage for maximal clinical effect. Its efficacy in treatment of allergic rhinitis is generally considered to be somewhat less than the antihistamines and significantly less than the intranasal corticosteroids (Brogden, Speight, and Avery, 1974; Dykewicz, Fineman, Skoner, et al., 1998; Meltzer, 1995).

Oral corticosteroids are used for treatment of very severe or intractable nasal symptoms or to treat significant nasal polyposis (Dykewicz, Fineman, Skoner, et al., 1998). They are not recommended for the routine treatment of allergic rhinitis or nonallergic rhinitis

Allergen desensitization immunotherapy is utilized for patients with more severe allergic rhinitis requiring significant amounts of medication or for those who exhibit poor tolerance or non-responsiveness to pharmacological treatment (Kay, 2001). Specific immunotherapy consists of administering increasing concentrations of extracts of allergen over a long period. A typical course of therapy consists of three or more years of subcutaneous injections of the highest or maintenance level of extract at intervals of two to six weeks. Initial therapy requires a series of weekly

injections at escalating doses over a period of four to six months in order to induce clinical tolerance to the effective (maintenance) dose (Adkinson, Jr., 1999). Immunotherapy for allergic rhinitis has been reported to be effective and has significant advantages over anti-allergic drugs in that: a) it remains effective for several years after treatment is discontinued (Durham, Walker, Varga, et al., 1999; Mosbech and Osterballe, 1988; Naclerio, Proud, Moylan, et al., 1997) and b) has the potential for decreasing the frequency or intensity of complications or comorbities of allergic rhinitis (Kay, 2001). Due to the increasing costs associated with pharmacotherapy of allergic rhinitis, allergen immunotherapy has been proposed as a cost-effective alternate treatment for allergic rhinitis (Dykewicz, Fineman, Skoner, et al., 1998).

Pharmacotherapy for nonallergic rhinitis therapy can be prescribed either on an as needed basis or as a long-term course of treatment. Until the pathophysiology of non-allergic rhinitis is more clearly delineated, it is unlikely that specific treatments will be identified. To date, most available pharmacotherapeutic approaches are predominantly aimed at symptom relief and can be prescribed either on an as-needed basis or as a long-term course of treatment. Oral decongestants and/or anticholinergics are generally more efficacious than oral antihistamines. However, clinical trials have shown that Azelastine nasal spray (a topical antihistamine) is effective for "total symptom complex" with no discrimination to type of nasal symptom in the treatment of vasomotor rhinitis (Banov, Lieberman, and Vasomotor Rhinitis Study Groups, 2001; Settipane and Lieberman, 2001). Intranasal corticosteroids have also been recommended for long term therapy in nonallergic rhinitis (Jones, 1988; Settipane and Lieberman, 2001). Since the mechanism of vasomotor rhinitis is poorly understood specific therapies are not available and treatments aimed at symptom relief in this syndrome are often not very satisfactory.

Therapies for Seasonal vs. Perennial Allergic Rhinitis

Pharmacologic therapies for seasonal and perennial allergic rhinitis do not differ substantively. However, antihistamines for symptom relief are probably more useful in treating seasonal allergic rhinitis (Howarth, 1989; Meltzer, 1995; Scadding, Richards, and Price, 2000), while immunotherapy is more effective in treating seasonal, rather than perennial allergic rhinitis (Adkinson, Jr., 1999). Immunotherapy is effective for perennial allergic rhinitis, but to a lesser extent (Bousquet, Lockey, and Malling, 1998; Kay, 2001). It is unclear whether the difference in efficacy observed with immunotherapy relates more to the constant nature of the allergen exposure in perennial versus seasonal allergic rhinitis or to the nature of the allergens. It should be noted that in the climates of certain geographic locales, perennial symptoms could be pollen-related. On the other hand, intranasal corticosteroids show a significant benefit in treatment for both seasonal and perennial allergic rhinitis (Corren, 1999; Corren, 2000; Howarth, 1989; Weiner, Abramson, and Puy, 1998), but trials have been unable to identify a meaningful difference in efficacy between the different intranasal corticosteroids for seasonal versus perennial allergies (Corren, 1999; Corren, 2000; Dykewicz, Fineman, Skoner, et al., 1998; Howarth, 1989; Weiner, Abramson, and Puy, 1998).

Therapy Questions Which Remain

Antihistamines, decongestants, and anticholinergics, which are used primarily for symptom relief in allergic and nonallergic rhinitis, are usually taken on an as-needed basis. In contrast, intranasal corticosteroids are recommended for use on a continuous basis (weeks to months at a time). Because of issues of patient non-compliance with these recommendations, studies are currently underway to determine whether that usage of intranasal corticosteroids on an as-needed

basis will prove as effective as regular dosing. One recent study suggests that this might indeed be the case (Jen, Baroody, de Tineo, et al., 2000). As our understanding increases concerning differences in systemic bioavailability of the different preparations of intranasal corticosteroids, further efficacy and relative safety profiles will be warranted (Allen, 2000).

The role of leukotriene modifying drugs in the management of rhinitis (possibly including nonallergic rhinitis), initially developed for use in asthma, is under active investigation. Indeed there are plans to formulate a combination product containing both a second-generation antihistamine and a leukotriene modifying agent (Howarth, 2000; Meltzer, 2000; Mygind, Dahl, and Bisgaard, 2000).

Given the benefits of intranasally applied Azelastine in nonallergic rhinitis (Banov, Lieberman, and Vasomotor Rhinitis Study Groups, 2001), further study of this modality of therapy is warranted. It is unclear whether the benefit in nonallergic rhinitis relates to the antihistaminic activity or associated vasoconstrictor properties of the intranasally applied preparation.

Alternative agents may herald a new era of treatments in rhinitis. As the pathophysiology of allergic rhinitis is becoming elucidated (Kay, 2001), newer biological modifiers are being identified as therapeutic agents or as potential targets of therapy (Kay, 2000). Several of these agents including a soluble recombinant humanized IL4 receptor called altrakincept, anti-IL5, and anti-IL-12 have already undergone clinical study in asthma (Borish, Nelson, Corren, et al., 2001; Bryan, O'Connor, Matti, et al., 2000; Leckie, ten Brinke, Khan, et al., 2000) and studies are planned or underway in allergic rhinitis, nonallergic rhinitis and nasal polyposis. Further evaluation of the promising role of anti-IgE monoclonal antibodies (i.e. omalizumab) in treatment of seasonal and perennial allergic rhinitis (Adelroth, Rak, Haahtela, et al., 2000) are already underway. Strategies directed against adhesion molecules have been considered but it might prove difficult to find targets specific for allergic inflammation that are not intimately involved in other aspects of normal immune functioning (Gundel, Wegner, and Letts, 1993; Wegner, Gundel, Reilly, et al., 1990). The recent discovery of soluble chemo-attractant proteins (chemokines) has provided a molecular basis for many of the observations concerning cellular infiltration in inflammatory processes. The development of antagonists to chemokine receptors offers another strategy for prevention and treatment of inflammation in allergic and possibly nonallergic rhinitis (Frew and Plummeridge, 2001).

Side-effects/Adverse Events

The main drawback of antihistamines is their sedative effect, which negatively affects quality of life (Nolen, 1997). Older antihistamines readily cross the blood-brain barrier and bind not only to H1 receptors, but in many cases, also to dopaminergic, serotinergic, and cholinergic receptors (Corren, 2000), which helps account for a host of adverse central nervous system effects (e.g. sedation, fatigue, dizziness, impairment of cognition and performance (Kay, 2000) and anticholinergic effects (e.g. dryness of the mouth and eyes, constipation, inhibition of micturition etc). The newer or second-generation antihistamines such as loratadine, cetirizine and fexofenadine are more pharmacologically selective than earlier antihistamines and are significantly less able to cross the blood brain barrier. Administration of recommended doses of some second-generation antihistamines (fexofenadine and loratadine) results in no greater incidence of sedation than seen with placebo. The reduced incidence of these side effects in second generation antihistamines has greatly improved the usefulness of this category of drug (Kay, 2000). Notably, however, in second-generation antihistamines, reports of sedation and performance impairment increase with upward titration of dosage (Bradley and Nicholson, 1987; Falliers, Brandon, Buchman, et al., 1991;

Hindmarch and Shamsi, 1999). Furthermore, some older, nonsedating second-generation antihistamines, such as astemizole and terfenadine may have adverse cardiac effects due to pharmacologic effects on repolarization in cardiac tissue (These 2 agents are no longer available in the United States).

Oral decongestants often produce stimulatory side effects in the central nervous system, causing insomnia, tremor, dizziness, loss of appetite or excessive nervousness, and in the cardiovascular system, resulting in tachycardia, palpitations and hypertension (Dykewicz, Fineman, Skoner, et al., 1998; Meltzer, 1995). These agents should be avoided or used with caution in patients with coronary artery disease, hypertension, hyperthyroidism and elderly patients (Corren, 2000).

The foremost problem with using topical decongestants is its rebound effect. If used longer than three to five days, patients might experience rebound congestion with withdrawal of drug. Continual use over months might even cause development of a form of rhinitis, rhinitis medicamentosa, characterized by persistent nasal congestion which will be difficult to treat effectively (Corren, 2000; Meltzer, 1995).

Intranasal corticosteroid sprays or aqueous forms occasionally have local side effects such as nasal irritation and bleeding. However, these events can be kept to a minimum if the patient is carefully instructed as to the use of the drug. Additionally, there is some concern that systemic corticosteroids might have negative side effects on children including growth retardation, hypothalamic-pituitary-adrenal suppression, and behavioral disturbances (Fireman, 2000; Pedersen, 2001). A recent study (Skoner, Rachelefsky, Meltzer et al, 2000) reported on the suppressive effect of belcomethasone nasal spray on bone growth in children and all nasal steroid preparations in the United States now warn of this adverse event. Agents with less systemic bio-availability may be devoid of these risks (Allen, 2000).

Immunotherapy can cause potentially fatal anaphylaxis, with risks being higher during initial dose escalation phase. Therefore, immunotherapy should only be prescribed after careful specialist evaluation and should only be administered under specialist guidance. While systemic reactions are uncommon, physicians administering allergen immunotherapy should be well acquainted with the procedure, and have facilities to administer treatment for acute allergic reactions if they occur. The risk of systemic reactions represents a general limitation in the use of immunotherapy. Risk factors for systemic allergic reactions in allergen immunotherapy have been identified and in addition to dosage escalation, include symptomatic rhinitis and asthma (Fireman, 2000; Lockey, 1995).