EXHIBIT 1

MEDICINE CABINET

How to treat allergic rhinitis

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INTRODUCTION

Allergic rhinitis is an IgE-mediated inflammatory disease of the nasal mucosal membranes characterized mainly by sneezing, rhinorrhea, nasal pruritis, and congestion. It is the most common form of rhinitis, affecting 20 to 40 million Americans annually, and it is considered one of the most prevalent chronic diseases in the United States.[1] It is also well documented that allergic rhinitis can negatively impact the quality of life and contribute significantly to loss of work productivity.[2]

Allergic rhinitis may be categorized as seasonal "hay fever" or perennial (when symptoms persist year-round). Often, patients may react to multiple allergens and have seasonal exacerbation of symptoms in addition to perennial rhinitis. Tree, grass, and weed pollens are common seasonal allergens because they become airborne in large concentrations during a particular season of the year. Important perennial allergens include house dust mites, indoor molds, animal dander, and occupational allergens.

MANAGEMENT OVERVIEW

Treatment options for allergic rhinitis include allergen avoidance, use of pharmacological agents for prevention and control of symptoms, and allergen immunotherapy for desensitization of patients in whom avoidance strategies and pharmacotherapy have failed to produce a satisfactory response.

ALLERGEN AVOIDANCE

Whenever possible, environmental control measures should be emphasized as a fundamental part of the treatment plan. For instance, patients with pollen or outdoor mold allergies should remain in closed environments whenever possible. Patients sensitive to dust mites should enclose all mattresses and pillows with allergen-proof casings and eliminate carpeting, if possible, to reduce exposure; bedclothes should be frequently laundered in hot water to remove allergens. Although not always feasible, patients with animal allergies should consider removal of pets from home.

Antihistamines

Antihistamines (H1-antagonists) are typically prescribed as first-line agents for allergic rhinitis. They exert their actions by competitively antagonizing histamine at the H1- receptor sites and thereby suppress symptoms attributable to histamine. Antihistamines, however, are generally not effective in alleviating nasal congestion.

First-generation antihistamines

Various 1st-generation antihistamines are widely available with and without prescription. Although effective and economical, the usefulness of these agents is limited by their sedative and anticholinergic properties due to penetration of the central nervous system and poor receptor specificity.

All 1st-generation antihistamines are sedating to some degree and may cause performance impairment in 10% to 40% of users.[3,4] In general, the ethanolamines (e.g., diphenhydramine) and phenothiazines (e.g., promethazine) are the most sedating. The ethylenediamines (e.g., pyrilamine) cause moderate sedation, and the alkylamines (e.g., chlorpheniramine, brompheniramine) are considered the least sedating. The use of 1st-generation antihistamines at bedtime, which are less expensive, and newer nonsedating agents during the day has been advocated as a cost-saving strategy. This therapeutic approach may not be cost-effective, however, as residual effects of the bedtime dose may result in daytime sedation and performance impairment.[1,3]

The anticholinergic effects of 1st-generation antihistamines (dry mucous membranes, urinary retention, blurred vision) may preclude their use in certain patients. Elderly patients are especially sensitive to these adverse effects. These older agents should be used cautiously in patients with narrow angle glaucoma or prostatic hypertrophy or in those taking other medications that may potentiate these side effects.

Although 2nd-generation antihistamines are generally prescribed due to ease of dosing and favorable side-effects profile, clinicians should be cognizant of available nonprescription antihistamines, as many patients may be self-managing with over-the-counter products (see Table 1).

Second-generation antihistamines

The newer antihistamines are devoid of anticholinergic and sedative effects with the exception of cetirizine, which

Table 1 *Selected 1st-generation antihistamines*

Generic	Brand	Usual doses
Brompheniramine	Dimetane, others	4 mg q 6-8 hours Extended Release: 12mg q 12 hours
Chlorpheniramine	Chlor-Trimeton, others	4mg q 6-8 hours Extended Release: 12mg q 12 hours
Clemastine	Tavist, others	1.34-2.68mg q 12 hours

Table 2 *Second-generation antihistamines*

Generic	Brand	Onset	T Ω	Usual doses	Cost per month	Comments
Astemizole *(discontinued June 1999)*	Hismanal	2-5 days	20-24 h (metabolite 10-20 days)	10mg po qd on empty stomach	$68.56	Avoid concomitant use with P450 3A inhibitors & proarrhythmogenic agents
Cetirizine	Zyrtec	Within 1 h	7-9 h	5mg-10mg po qd	$55.80	Also available in syrup (5mg/5ml); may cause drowsiness
Fexofenadine	Allegra	1 h	14-18 h	60mg po bid	$59.30	Active metabolite of terfenadine-devoid of cardiotoxic risk
Fexofenadine/ Pseudoephedrine	Allegra-D			60mg/120mg po bid	$66.71	
Loratadine	Claritin	1 to 3 h	12-15 h	10mg po qd	$65.40	Also available in syrup (5mg/5ml) & rapidly disintegrating tablets
Loratadine/ Pseudoephedrine	Claritin-D 12			5mg/120mg po bid	$73.80	
	Claritin-D 24			10mg/240mg po qd	$72.00	
Azelastine	Astelin	Within 1 h	22-25 h	2 sprays per nostril bid	$53.71	May cause drowsiness

Cost: based on average wholesale prices (AWP), May 1999

may be mildly sedating in some patients. The low incidence of side effects is attributed to their high selectivity for peripheral H_1-receptors and low propensity to cross the blood-brain barrier. Three 2nd-generation antihistamines for oral administration are currently available in the United States: cetirizine, fexofenadine, and loratadine. All appear effective in mitigating the symptoms of allergic rhinitis. Table 2 lists available agents and dosages.

Cardiotoxicity associated with astemizole and terfenadine is the most serious side effect associated with the 2nd-generation antihistamines. Serum accumulation of these agents may deleteriously prolong the QT interval. Serious ventricular arrhythmias (including Torsades de pointes), cardiac arrest, and death have ensued as a result of overdoses and concomitant use of medications that impair the metabolism of terfenadine and astemizole (potent inhibitors of cytochrome P450 3A4 isoenzymes, such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir, indinavir, fluoxamine). These reactions and interactions have not been associated with the currently available agents. (Both terfenadine and astemizole have since been voluntarily withdrawn from the US market; terfenadine has been replaced with its nonarrhythmogenic metabolite, fexofenadine.)

Azelastine is a new topically administered 2nd-generation antihistamine that has demonstrated efficacy in improving both early- and late-phase symptoms of allergic rhinitis.[5] Symptomatic response may be seen as early as 30 minutes after dose.[6] In comparative trials, intranasal azelastine appears equally as efficacious as oral antihistamines but generally less effective than corticosteroids in relieving nasal symptoms.[6] The most commonly reported adverse effects are bitter taste, application site irritation,

Decongestants

Nasal congestion is a common complication of allergic rhinitis. Congestion resulting from initial allergen exposure is usually limited; generation of other inflammatory mediators (e.g., leukotrienes) contributes, however, to the prominence of congestion in the late-phase inflammatory response period.[7,8] Consequently, many patients will require a decongestant in addition to antihistamine therapy. Decongestants are also useful in clearing nasal passages at the onset of intranasal corticosteroid therapy to improve drug delivery.

Decongestants exert their effects by activation of alpha-adrenergic receptors in the vascular smooth muscle of the respiratory mucosa, thereby causing vasoconstriction in the turbinates. Oral formulations such as pseudoephedrine and phenylpropanolamine are available alone or in combination with various antihistamines. Decongestants may produce unwanted side effects, such as excitation of the central nervous system (e.g., insomnia, restlessness, agitation), tachycardia, urinary retention, and elevations in blood pressure. These agents should be administered cautiously in patients with hypertension, hyperthyroidism, diabetes mellitus, cardiovascular disease, or urinary obstructive diseases.

Topical decongestants (e.g., oxymetazoline, xylometazoline) can rapidly improve symptoms with minimal systemic effects. However, overuse may lead to the development of rhinitis medicamentosa (rebound congestion associated with nasal hyperreactivity, mucosal swelling, and tolerance).[9] For this reason, topical decongestants are contraindicated for chronic nasal conges-

Corticosteroids

The use of intranasal corticosteroids is increasingly becoming first-line therapy for many patients with allergic rhinitis, especially those with moderate to severe symptoms or those with perennial allergic rhinitis in which nasal symptoms predominate.[10] Intranasal corticosteroids specifically inhibit the allergic inflammatory processes that contribute to the late-phase response of nasal congestion. When used prophylactically, they can also inhibit the early-phase response to allergens.[11] Overall, they are effective in relieving sneezing, nasal itching, rhinorrhea, and congestion.

Table 3 lists available intranasal corticosteroids, along with dosing information and comparative costs. In general, these agents are considered more cost-effective for use as monotherapy than 2nd-generation antihistamines. A recent meta-analysis found intranasal corticosteroids to be more effective than oral antihistamines in reducing nasal blockage, nasal discharge, sneezing, nasal itch, postnasal drip, and total nasal symptoms.[12] No significant difference was detected for nasal discomfort, nasal resistance, and eye symptoms. No particular product has demonstrated clinical superiority; selection of drug should be based on factors such as response, ease of administration, cost, and formulation.

Application site irritation (e.g., nasal irritation, burning, or sneezing after administration) is the most commonly encountered side effect. Patients complaining of local irritation may be switched to various aqueous formulations. Although rare, mucosal erosion and septal perforations have been reported with long-term use.[13] To minimize septal irritation, patients should be instructed to direct the spray upwards and toward the lateral portion of the nose. Periodic examination of the nasal septum should be performed.[1]

Although systemic effects from intranasal corticosteroids at recommended doses are considered minimal, there are some concerns regarding long-term exposure. Reports of posterior subcapsular cataract formation have been linked with the use of intranasal or inhaled corticosteroids;[14] however, more recent prospective trials did not reveal evidence of posterior subcapsular cataract formation or elevation in intraocular pressure.[15,16]

In 1998, the FDA's advisory committees on pulmonary and allergy drugs and on metabolic endocrine drugs convened to assess data suggesting that intranasal corticosteroids may have an effect on growth velocity in children. Consequently, a new class labeling for pediatric use of inhaled and intranasal corticosteroids was mandated. At this time, the long-term significance of growth velocity reduction on final adult height is unknown. The FDA recommends routine monitoring of growth in pediatric patients using intranasal corticosteroids and titration to the lowest effective dose to minimize systemic risks.

Patient education is essential in ensuring proper use and compliance to intranasal corticosteroid therapy. Patients should be instructed on instillation techniques and informed about the possible delay in symptomatic response. Assessment of maximal response may require a therapeutic trial of several weeks. The drug should be administered regularly on a daily basis, rather than as needed for rescue relief.

For patients with severe disease, the combined use of intranasal corticosteroids and antihistamines may be necessary to control symptoms. The use of oral corticosteroids should be reserved for patients with severe exacerbations or intractable disease due to high risk of systemic adverse effects.

Cromolyn sodium

Cromolyn sodium stabilizes mast cells and thereby prevents the degranulation of chemical mediators upon antigen presentation. Intranasal cromolyn ameliorates symptoms such as sneezing, rhinorrhea, and nasal pruritis but lacks efficacy for nasal congestion. Cromolyn

Table 3 *Intranasal corticosteroids*

Generic	Brand	Usual dose per nostril	Formulation	Inhalations per bottle	Cost per month
Beclomethasone dipropionate	Beconase	1-2 sprays bid	Aerosol	200	$25.85-$51.69
	Beconase AQ	1-2 sprays bid	Aqueous	200	$26.50-$53.00
	Vancenase	1-2 sprays bid	Aerosol	200	$25.56-$51.12
	Vancenase AQ	1-2 sprays bid	Aqueous	200	$34.73-$69.47
	Vancenase DS	1-2 sprays qd	Aqueous	120	$25.30-$50.59
Budesonide	Rhinocort	2 sprays bid or 2-4 sprays qd	Aerosol	200	$21.70-$43.40
Flunisolide	Nasarel	1-2 sprays bid	Aqueous	200	$23.02-$46.03
Fluticasone	Flonase	1-2 sprays qd	Aqueous	120	$24.94-$49.87
Mometasone	Nasonex	1-2 sprays qd	Aqueous	120	$24.96-$49.92
Triamcinolone acetonide	Nasacort	1-2 sprays qd	Aerosol	100	$25.42-$50.83

is generally less efficacious than intranasal corticosteroids.[17] Therapy adherence may be problematic, as it necessitates frequent dosing (3 to 4 times daily). However, cromolyn may be safely administered, even to very young children, with negligible side effects. Intranasal cromolyn is now available without prescription. Patients should be advised to initiate therapy with cromolyn before the start of the allergy season or in anticipation of allergen exposure.

Ipratropium bromide

Ipratropium bromide is a well-tolerated topical anticholinergic agent that is available in a 0.03% nasal formulation. It is indicated for rhinorrhea associated with allergic and nonallergic perennial rhinitis. (A 0.06% formulation is approved for rhinorrhea associated with the common cold.) This agent quickly and effectively reduces nasal hypersecretion but has no effect on other symptoms of rhinitis such as sneezing and congestion. The most commonly reported adverse effects are nasal dryness and epistaxis.[18] The recommended dose of intranasal ipratropium bromide is 2 sprays per nostril 2 to 3 times daily.

CONCLUSION

Pharmacotherapy remains the mainstay of management in patients with allergic rhinitis. Given the wide selection of available agents, the ideal regimen should be individualized to reflect disease severity and specific symptoms. Factors such as the potential for side effects, risk for drug interactions, ease of administration, and cost should also be considered. Most importantly, patients should be routinely followed to assess therapeutic response and to monitor for side effects or complications.

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