

An overview of current pharmacotherapy in perennial rhinitis

Eli O. Meltzer, MD San Diego, Calif.

Background: Individuals with rhinitis experience significant morbidity due to their disease. Research and clinical care to reduce this suffering are important.

Objective: To review the pharmacological agents that have been developed for the treatment of perennial rhinitis.

Method: Literature review of human studies.

Results: Medication classes include antihistamines, decongestants, anticholinergics, cromolyn sodium, and corticosteroids. These vary in regard to their pharmacology, efficacy, and adverse effects. Compliance and cost issues are also critical components of the therapeutic regimen.

Conclusion: Carefully chosen pharmacotherapy based on an understanding of the pathophysiology of the disease, knowledge of the potential of medications, and commitment to an ongoing patient/physician education and monitoring program can lead to improved well-being for individuals with perennial rhinitis. (*J ALLERGY CLIN IMMUNOL* 1995;95:1097-110.)

Key words: Rhinitis, pharmacotherapy, antihistamines, decongestant, anticholinergic, cromolyn sodium, intranasal corticosteroid, compliance, cost

Nasal diseases have sometimes been regarded as those disorders that are unimportant . . . to those who do not have them. The data support the fact that they are not trivial conditions. Millions of individuals across the world suffer from nasal symptoms, and the majority seek relief. Pharmacologic therapy is an important component of the management of most rhinopathies.

EPIDEMIOLOGY

A classification of nasal diseases is listed in Table I. Many of these are a rhinitis, which is defined as an inflammation of the lining of the nose characterized by one or more of the following symptoms: nasal congestion, rhinorrhea, sneezing, and itching.¹ The prevalence of allergic rhinitis in the U.S. population varies from 10% to 20%.² A more recent community-based study of adults in London determined a minimum prevalence of 16%. Of these, 8% had perennial symptoms, 6% had both perennial and seasonal symptoms, and 2% had seasonal symptoms alone.³ The peak prevalence of allergic rhinitis occurs in children and

young adults, thus affecting 15% to 20% of students.⁴ The prevalence of atopy appears to be growing. Allergic skin test reactivity increased from 39% to 50% in a U.S. community followed for a mean of 8 years,⁵ and reported allergic rhinitis increased from 4.4% in 1971 to 8.4% in 1981 in Swedish army recruits.⁶

The prevalence of nonallergic perennial rhinitis is unknown. Estimates indicate that approximately 50% of rhinitis patients have nonallergic disease.^{7,8} This includes both patients with allergic rhinitis and upper airway hyperreactivity who develop additional symptoms generated by an irritant or reflex mechanism.

Patients with perennial rhinitis are troubled a great deal. Each year Americans with allergic rhinitis are restricted in their activities for 28 million days, miss 2 million days of school, and 10 million days from work.⁹ Rhinitis impacts heavily on health-related quality of life. Patients have impaired sleep, impaired concentration, reduced emotional well-being, impacted social interaction and associated symptoms such as headaches.^{10,11} Both disease-specific and generic quality of life questionnaires have demonstrated the significant morbidity of allergic rhinitis on patients' physical, social, and emotional functioning (Table II¹³).^{10,12,13}

In 1990, the total direct national health expenditure has been calculated at \$589 billion and the

From the Allergy and Asthma Medical Group and Research Center.

Reprint requests: Eli O. Meltzer, MD, Allergy and Asthma Medical Group and Research Center, APC, 9610 Granite Ridge Dr., Suite B, San Diego, CA 92123.

Copyright © 1995 by Mosby-Year Book, Inc.

0091-6749/95 \$3.00 + 0 1/0/64258

TABLE I. Nasal diseases

Allergic rhinitis
Seasonal
Perennial
Nonallergic rhinitis
Eosinophilic
Without nasal polyposis
With polyposis with or without aspirin sensitivity or asthma
Aspirin sensitivity or asthma
Noneosinophilic
Vasomotor (idiopathic)
Metabolic (hypothyroidism, pregnancy)
Rhinitis medicamentosa
Irritants (e.g., cigarette smoke)
Atrophic rhinitis
Infectious rhinitis
Viral (acute nasopharyngitis)
Bacterial (with or without sinusitis)
Anatomic abnormalities
Foreign body
Deviated septum
Polyps, tumors
Cerebrospinal fluid rhinorrhea
Choanal atresia
Adenoid hypertrophy
Defects in host immune defense
Antibody deficiency
T-cell deficiency (acquired immunodeficiency syndrome)
Primary ciliary dyskinesia
Cystic fibrosis
Miscellaneous
Wegener's granulomatosis

total direct cost for respiratory illness as \$47 billion. The total direct for allergic rhinitis for the same period is estimated at \$1.16 billion, with an additional indirect cost (productivity loss) of \$639 million.¹⁴ This total annual cost of \$1.8 billion for allergic rhinitis plus additional expenditures for nonallergic rhinitis may not be relatively high because of lack of hospitalizations or extensive use of health services. Nonetheless, the economic impact on patients themselves may be considerable because of reduced productivity and personal expenses for air filters, air conditioners, home furnishings to reduce mite and mold exposures, and medications not reimbursed by health insurance plans.

As a reflection of the suffering the patients experience from their symptoms, up to 2% of all physician office visits (>8 million) are for allergic rhinitis.¹⁴ At over 90% of these visits, a medication is prescribed.¹⁵

TABLE II. SF-36 quality of life questionnaire

SF-36 health dimensions	Healthy subjects N = 116 adults	Perennial allergic rhinitis patients N = 111	p value
Physical functioning	95.9 ± 6	88.6 ± 14	< 0.0001
Energy/fatigue	71.9 ± 15	54.5 ± 24	< 0.0001
Physical limitations	92.0 ± 18	60.6 ± 38	< 0.0001
Social functioning	91.3 ± 13	73.1 ± 24	< 0.0001
Mental health	73.4 ± 16	64.8 ± 20	< 0.0005
Emotional limitations	86.7 ± 23	64.2 ± 39	< 0.0001
Pain	90.3 ± 17	76.9 ± 26	< 0.0001
General health perception	81.7 ± 12	62.4 ± 21	< 0.0001
Change in health	54.1 ± 14	49.8 ± 20	NS

NS, Not significant.

PHARMACOTHERAPY

Specific pharmacologic agents to control the symptoms of allergic rhinitis and nonallergic rhinitis have long been recommended. Although over the years they have become progressively safer and more effective, they have no cumulative benefits and do not cure the conditions. Consequently, usually within days, or at most, weeks, symptoms will recur if the precipitants and/or the immunologic abnormality are present.

The selection of the medication should consider the pathophysiology of the rhinitis. If possible, it is best to begin treatment prophylactically and prevent the onset of significant symptomatology rather than trying to reduce the ongoing problems. There are five types of pharmacologic agents currently available for perennial rhinitis: They are antihistamines, decongestants, anticholinergics, cromolyn, and corticosteroids.

Antihistamines

Pharmacology. Antihistamines are chemically different groups of compounds with the similar pharmacologic property of competitively antagonizing histamine at its H₁ receptor site due to the core ethylamine moiety. The radicals or side chains adjoining the core determine their absorptions and how they are distributed and eliminated. The classification shown in Table III is based on their chemical structures.¹⁶ However, it does not reflect either efficacy or safety.

Certain antihistamines may also inhibit mediator release such as histamine and prostaglandins from basophils and mast cells and reduce the production of mediators such as leukotrienes and kinins.¹⁷⁻¹⁹ Some antihistamines have also been shown to decrease recruitment of inflammatory cells.²⁰ The clinical benefits of these actions have not been documented. Many of the first-generation antihistamines (available in the United States prior to 1985) also possess anticholinergic effects that can be of further benefit. H₂ antihistamines, which block some vascular dilation, have not been shown to augment the action of H₁ antihistamines in the management of rhinitis.²¹

The antihistamines are both pharmacokinetically and pharmacodynamically diverse. In general, H₁ antihistamines are rapidly absorbed after oral administration, begin to provide symptom relief within 30 minutes (astemizole being a notable exception), and reach their maximum serum concentration within 2 hours. The biologic activity of antihistamines, as reflected by their ability to suppress a histamine-induced skin wheal, is usually longer than their serum levels.^{22,23} This fact supports once, or at most, twice a day dosing with most antihistamines.²³ Antihistamines differ in their potency. In a comparison of the area of histamine-induced wheal suppression by a single dose, cetirizine and terfenadine proved the most potent agents, followed by loratadine, astemizole, and the first-generation antihistamine chlorpheniramine.²⁴ Inhibition of this reaction correlates with relief of symptoms of allergic rhinitis.²⁵

Uses. Since activation of the H₁ receptors stimulates sensory nerves and increases vascular permeability and mucus production, H₁ antihistamines reduce pruritus, sneezing, and rhinorrhea. They have, however, a negligible effect on nasal congestion. The efficacy of oral H₁ antihistamines has been documented in studies of allergic rhinitis.^{26,27} The H₁ antagonists levocabastine and azelastine have been developed for topical application to the nasal mucosa.^{28,29} Since histamine does not appear to play a significant role in non-allergic rhinitis, the value of antihistamines for this condition is considerably less.

Tolerance to the beneficial effects of antihistamines, although described, has not been substantiated. The lack of improvement with these agents more likely represents their limited potency in severe disease and poor patient compliance. In a carefully monitored study, neither the metabolism nor the measured ability of terfenadine to suppress wheal and flare reactions over 56 days was diminished.³⁰

TABLE III. Classification of antihistamines according to chemical class

Chemical class	Generic name	Trade name
Ethanolamine	Clemastine	Tavist
	Diphenhydramine	Benadryl
Ethylenediamine	Tripeleennamine	Pyribenzamine
	Chlorpheniramine	Chlor-Trimeton
Alkylamine	Tripolidine	Actidil
	Acrivastine*	Prolert
Piperazine	Hydroxyzine	Atarax
	Cetirizine*	Reactine
Phenothiazine	Promethazine	Phenergan
Piperidine	Astemizole*	Hismanal
	Cyproheptadine	Periactin
	Ebastine*	Ebastel (Spain)
	Ketotifen*	Zaditen
	Levocabastine*	Livostin
	Loratadine*	Claritin
Miscellaneous	Terfenadine*	Seldane
	Azelastine*	Astelin

*Newer, second-generation antihistamines, usually less sedating.

Adverse effects. The older first-generation antihistamines such as diphenhydramine contain a number of aromatic rings and alkyl substitutes that make them lipophilic. The newer agents are large lipophobic molecules with a charged side chain. They are also bound extensively to protein. Consequently, they have difficulty crossing from the blood into the brain due to a barrier that is the result of tightly fused outer membranes of the endothelial cells lining the brain capillaries.³¹ Radioactive tracer tests in animals confirm the absence of terfenadine, astemizole, and their metabolites in the central nervous system.³² Antihistamines that are able to cross the blood-brain barrier inhibit histamine N-methyltransferase or block central histaminergic receptors. They also can activate central cholinergic serotonergic or α -adrenergic receptors. These actions can produce four types of adverse central nervous system effects: stimulatory, neuropsychiatric, peripheral, and depressive reactions.

The stimulatory effects include appetite stimulation, muscle spasms, seizures, and the anticholinergic responses of insomnia, nervousness, irritability, tremor, and tachycardia.³³ Neuropsychiatric reactions produce anxiety, hallucinations, and psychosis.³⁴ Peripheral neurologic antihistamine adverse effects result in paresthesias and paralysis and, with cholinergic blockade, dilated pupils,

blurred vision, dry eyes, dry mouth, urinary retention, constipation, and impotence.

The most common adverse effect of antihistamines is central nervous system suppression or sedation. The term sedation has been used to include both drowsiness and performance impairment. It can be defined as a global reduction of alertness as well as intellectual and motor performances.³⁵ This presents as sleepiness, fatigue, dizziness, weakness, decreased attention, slowed reaction time, and impaired coordination and cognitive function. In various studies the experience of sedation occurs in 10% to 25% of users of first-generation H₁ receptor antagonists.^{26, 27, 36} This adverse effect is frequently dose related and correlates with the serum drug concentration.²² Unfortunately, there is an inconsistent correlation between the patient's subjective perception of sedation symptoms and objective measures of drowsiness and antihistamine-induced mental impairment.³⁷ Therefore, both should be assessed to determine the potential for adverse central nervous system effects, and patients using the older antihistamines should be cautioned that their ability to perform activities requiring alertness and cognitive skills may be reduced. This occurs even if the dose is only administered at bedtime^{38, 39} and patients do not necessarily become tolerant of the adverse effects.³⁷ With the first-generation antihistamines (Table III), ethanolamines and phenothiazines usually have marked sedative effects. Ethylenediamines cause moderate sedation, and alkylamines typically cause mild sedation.

The newer, second-generation antihistamines are not without adverse effects. Although they appear to cause, in the recommended doses, sedation no different than placebo, sedation can be documented with higher doses, for example, 40 mg of loratadine and 20 mg of cetirizine.^{40, 41} This finding raises some concern about licensing these medications as over-the-counter products. Patients may independently consider "if a little is good, more is better" and self-prescribe a sedating dose.

The second-generation antihistamines astemizole and ketotifen may also, like the older agent cyproheptadine, stimulate the appetite and lead to undesirable weight gain.^{42, 43} Oral and intranasal azelastine is associated with a dose-dependent metallic taste in some patients. This often dissipates over time.⁴⁴

The second-generation antihistamines, terfenadine and astemizole, have been reported to increase a patient's risk for adverse cardiovascular arrhythmias.^{45, 46} These events are caused by the

pharmacologic effects of these compounds on repolarization of cardiac tissue, prolonging the QT interval. QT prolongation predisposes certain patients to fatal or near-fatal episodes of cardiac arrhythmias, including torsades de pointes. Risk factors that raise serum levels of these agents, including overdosage, drug interactions with macrolide antibiotics and oral antifungals and hepatic dysfunction (all of which may compromise the isoenzyme cytochrome P3A4, which is responsible for their metabolism), are areas for concern. Risk factors that prolong cardiac repolarization, such as cardiovascular diseases with prolonged QT interval, hypokalemia, hypomagnesemia, and drugs such as antiarrhythmic agents, should also be monitored. Patients who receive terfenadine or astemizole must be educated about the cardiovascular risks of these drugs. Dose-response studies have revealed no such effects of loratadine or cetirizine on the QT interval.^{47, 48}

Decongestants

Pharmacology. Topically applied vasoconstrictor sympathomimetic agents may be catecholamines (such as epinephrine or phenylephrine) or imidazoline derivatives (such as naphazoline, oxymetazoline, tetrahydrozoline, or xylometazoline). Both types of drugs are effective as nasal decongestants because the nasal capacitance vessels that are responsible for mucosal swelling have both α_1 receptors, responsive especially to catecholamines, and α_2 adrenoceptors, responsive preferentially to imidazoline, exist in the nasal capacitance vessels responsible for mucosal swelling. The result of these medications is reduction in blood flow, edema, and blanching of the nasal mucosa.

Uses. Topical vasoconstrictors are very effective for short-term use to increase nasal airway patency. Indications for perennial rhinitis, both allergic and nonallergic in etiology, would be to assist with physical examination, or to use before air travel to prevent an exacerbation of symptoms or secondary ear or sinus problems, or during the early stages of nasal infections, or during the initiation of treatment with other topical agents such as cromolyn sodium and corticosteroids. After intranasal application, local vasoconstriction usually occurs within 5 to 10 minutes. It lasts less than 1 hour for epinephrine and as long as 6 to 8 hours with oxymetazoline. These vasoconstrictor agents do not improve other symptoms of rhinitis such as rhinorrhea, sneezing, or nasal pruritis.⁴⁹

Nasal solutions are applied to the mucosa as drops or sprays. Drops should be applied to the

dependent (lower) nostril with the patient in the lateral head-low position. The patient should remain in this position for several minutes and then the solution can be applied to the other nostril in a similar manner. Treatment of one of the nasal airways will not influence the contralateral nasal mucosa. Sprays should be squeezed or pumped into the airway with the patient's head erect, avoiding directing the spray toward the nasal septum. In the case of liquid sprays, the lateral head-low position can then be assumed.

Adverse effects. Nasal burning, stinging, dryness, or mucosal ulceration may occur after topical nasal decongestant use. Decreasing responsiveness (tolerance) and rebound congestion characterized by chronic redness and swelling rarely occur when less than 1 week of this type of treatment has been prescribed. However, they frequently occur with prolonged use and may result in rhinitis medicamentosa.⁵⁰

To minimize the risk of spreading infections, droppers, inhalers, and spray dispensers for topical agents should not be used by more than one person, and the tips should be rinsed with hot water after use.

Pharmacology. Oral vasoconstricting agents include phenylephrine, phenylpropanolamine, and pseudoephedrine. They cause vasoconstriction by a direct effect on α -adrenergic receptors and indirectly by releasing norepinephrine from its storage sites.

Uses. Although topical agents decrease nasal airway resistance to a greater degree than oral medications, only the oral preparations can be used continuously for chronic perennial rhinitis because they lack the risk of rebound. Nasal decongestion occurs within 30 minutes and persists for 4 to 6 hours after oral administration of 60 mg of pseudoephedrine. Decongestion may last 8 to 12 hours after a dose of 120 mg from an extended-release form. Phenylephrine at usual doses is probably the least effective because of extensive first-pass metabolism.⁵¹

The ineffectiveness of antihistamines in relieving nasal obstruction has prompted combining them with decongestants. Studies have demonstrated that the efficacy of the combination in the management of allergic rhinitis is superior to the efficacy of either component alone.^{52, 53}

Adverse effects. The central nervous stimulation effects of the oral vasoconstrictor agents may result in nervousness, dizziness, headaches, tremor, and insomnia. Even combining these medications with a first-generation antihistamine does not counter-

balance these adverse events. Patients receiving such a combination often describe a sense of agitated sedation. Tachycardia, palpitations, and increases in blood pressure may also occur due to oral α -adrenergic agents and are usually proportionate to dosage.

Anticholinergics

Pharmacology. Parasympathetic stimulation causes vasodilation and increased glandular secretion. Anticholinergic medications inhibit these effects and produce a reduction in the volume of secretions and some degree of vasoconstriction. They have no influence on sensory nerve endings and, therefore, no effect on nasal itching or sneezing.

Uses. Atropine applied topically in a dose of 8 μ g per nostril has been reported to reduce rhinorrhea in patients with allergic rhinitis.⁵⁴ Ipratropium bromide is a quaternary derivative of isopropyl noratropine. It is poorly absorbed by the nasal mucosa and does not cross the blood-brain barrier. Intranasal ipratropium bromide has also been shown to be effective for perennial allergic rhinitis. Ipratropium in a dose of 21 μ g, and even more so at the dose of 42 μ g per spray, one spray per nostril three times a day, produces a significant decrease in anterior watery rhinorrhea. No significant improvement has been reported for the symptoms of postnasal discharge, congestion, or sneezing.⁵⁵ Ipratropium bromide both by aerosol and intranasal aqueous spray has also been documented to significantly reduce rhinorrhea in patients with nonallergic perennial rhinitis. Other symptoms have not been affected. The aerosol dose has been 80 μ g per dose four times a day,^{56, 57} and the aqueous dose 21 μ g and 42 μ g per nostril twice daily.⁵⁸ Improvement is noted during the first week of treatment, and no tolerance to the clinical benefits develops with either form of perennial rhinitis.⁵⁹

Adverse effects. No long-term adverse effects such as rebound or mucosal damage or systemic effects have been identified with intranasal ipratropium bromide. The only local adverse effects are rare reports of epistaxis, blood-tinged mucus, and a feeling of dryness in the nose. These most often occur with the aerosol formulation and when the dose is too high in relation to the severity of the rhinorrhea.

Cromolyn sodium

Pharmacology. Cromolyn sodium is classified as an antiallergic compound due to its inhibitory action against immunological degranulation of

mast cells.⁶⁰ This compound does not inhibit the binding of IgE to mast cells or the interaction between cellbound IgE and a specific antigen. It also has no discernible antihistaminic, anticholinergic, antileukotriene, antibradykinin, antiserotonin, adrenergic agonist, or corticosteroid-like activity.⁶¹ Despite the recognition of its action on lung mast cells, it is not certain that its clinical benefits in rhinitis relate to similar effects on nasal mast cells. Ultrastructural studies suggest that nasal metachromatic cells resemble blood basophils more than tissue mast cells and cromolyn sodium does not inhibit basophil degranulation. However, cromolyn sodium has been shown to influence granulocyte chemotaxis and cell activation in vitro and reduce mucosal eosinophils in the upper airway.^{62, 63} This action on cell recruitment may be secondary to modulation of cytokine release locally within the nasal mucosa.⁶⁴

In regard to its pharmacokinetics, less than 7% of an intranasal dose of cromolyn sodium is absorbed systemically. The absorbed fraction is rapidly excreted unchanged in urine and bile, with an elimination half-life of 1 to 2 hours. The remainder of the dose is swallowed and, because cromolyn is poorly absorbed from the gastrointestinal tract, excreted in the feces.

Uses. Cromolyn sodium nasal solution is effective for prevention of the immediate and late nasal response associated with allergen challenge in patients with allergic rhinitis.⁶⁵ It has been shown to be effective in the treatment of perennial allergic rhinitis.⁶⁶ Clinical data have suggested that cromolyn sodium is more helpful for sneezing, rhinorrhea, and nasal itching than for nasal obstruction.⁶³ Onset of relief appears during the first week of treatment and symptoms often continue to decrease as the medication is maintained. Without therapy, symptoms usually recur within 1 week of drug cessation.

Nasal cromolyn has been reported to be ineffective in nonallergic rhinitis with eosinophilia syndrome (NARES).⁶⁷ Its efficacy in nonallergic vasomotor rhinitis has also not been documented.

The 4% intranasal solution, available in the United States since 1983, is recommended for adults and children 6 years of age and older. The initial dose is one spray (5.2 mg cromolyn per spray) in each nostril four times a day. The frequency of dosing represents a potential disadvantage because of compliance problems. However, the rinsing accomplished by the spray itself is probably beneficial. Furthermore, when symptomatic relief becomes apparent, a less frequent regimen may be adequate for clinical efficacy.

Adverse effects. Adverse effects reported with intranasal cromolyn sodium occur in less than 10% of patients and most commonly include nasal irritation, sneezing, and unpleasant taste in the mouth. Tachyphylaxis to the effect of nasal cromolyn has not been documented and there is also no evidence of nasal rebound or ciliary damage.

Corticosteroids

Pharmacology. The route that leads to the action of corticosteroids begins when the steroid molecule diffuses across the cell membrane and binds to hormone receptors in the cytoplasm. The steroid receptor complex is then transferred to the nucleus where, after interaction, eventually RNA transcripts are formed. The posttranscriptional proteins mediate the drug effects. The need for transcription and translation account for the time delay between administration and clinical activity.⁶⁸ Of clinical importance in rhinitis, corticosteroids inhibit multiple steps of the inflammatory process. They cause vasoconstriction,⁶⁹ decrease capillary permeability,⁷⁰ decrease glandular response to cholinergic stimulation,⁷¹ interfere with arachidonic acid metabolism, which results in decreased mediator production,⁷² reduce mediator release,⁷³ decrease production of cytokines from TH₂-type lymphocytes, and inhibit influx of eosinophils and basophilic cells to the nasal epithelium.⁷⁴

The corticosteroids can inhibit the inflammatory response, whether the inciting agent is mechanical, chemical, infectious, or immunologic.⁷⁵ In clinical terms, the administration of these medications for their antiinflammatory effects is palliative therapy; the underlying cause of the disease can continue although the inflammatory manifestations are suppressed.

Changes in molecular structure may bring about changes in antiinflammatory activity as a result of alteration in absorption, protein binding, rate of metabolic transformation, rate of excretion, ability to traverse membranes, and intrinsic effectiveness of the molecule at its site of action. The duration of antiinflammatory activity parallels the duration of hypothalamic-pituitary-adrenal axis suppression.

Glucocorticoids are readily absorbed when administered orally or by intramuscular injection. They cross the placenta and may be distributed into breast milk in very low amounts. Metabolism to biologically inactive compounds occurs primarily in the liver.

Several properties of the newer intranasal corticosteroids account for their activity and ability to reduce the risk of adverse systemic glucocorticoid

reactions: they have potent topical activity, which allows for marked reduction in dosage requirements; there is rapid first-pass hepatic degradation to metabolites with little or no glucocorticoid activity; and there is greater inhibition of the early-phase reaction after antigen challenge with intranasal versus systemic corticosteroid treatment.⁷⁶ The approximate relative antiinflammatory potencies of currently available topical agents as determined by the vasoconstrictor assay are shown in Table IV.^{76, 77}

Uses. In the symptomatic treatment of perennial rhinitis, systemic glucocorticoids should generally be reserved for acute, severe exacerbations to reduce nasal and sinus inflammation and polyp size. In acute conditions, a short period of high dosage combined with other therapy is appropriate. An oral dose of 30 to 40 mg per day of prednisone for 7 days and/or a tapered dose over 1 week has been effective for many patients. In rare cases, prolonged oral administration is required and alternate-day therapy at the lowest possible dose should be attempted to minimize adverse reactions.

Although intranasal turbinate injections of corticosteroids have been reported to be useful in the management of allergic rhinitis, vasomotor rhinitis, and nasal polyps,⁷⁸ no prospective double-blind, controlled study exists to document the clinical impressions. In addition, at least 10 cases of loss of vision have been reported as a consequence of inadvertent intravascular infusion of the material and embolization.⁷⁹ Therefore, it seems prudent to recommend oral corticosteroids rather than intraturbinate corticosteroid injections for those perennial rhinitis conditions requiring systemic corticosteroid treatment.

The development of topically active intranasal corticosteroids has reduced the need for the use of systemic steroids. They have increased lipophilic properties and receptor affinity and their therapeutic benefits are derived from their local activity, since oral administration of the equivalent amount of drug produces no benefit.⁸⁰ Their potency exceeds that of antihistamines and cromolyn sodium.^{81, 82}

Modern, highly potent corticosteroids that combine topical efficacy with rapid deactivation in the liver have been available since beclomethasone dipropionate was introduced in 1973. Other members of this class of pharmacological agents developed for intranasal treatment of rhinitis are flunisolide, triamcinolone, acetamide, budesonide, fluticasone propionate, and mometasone furoate.

TABLE IV. Intranasal corticosteroids: topical potencies

Agent	Topical activity*
Hydrocortisone	1
Triamcinolone acetamide	1000
Flunisolide	3000
Beclomethasone dipropionate	5000
Budesonide	10,000
Fluticasone propionate	10,000

Data from Siegel SC. Topical intranasal corticosteroid therapy in rhinitis. *J ALLERGY CLIN IMMUNOL* 1988;81:984-91, and Phillips GH. Structure-activity relationships of topically active steroids: the selection of fluticasone propionate. *Respir Med* 1990;84(suppl A):19-23.

*Vasoconstrictor activity.

They are extremely effective in reducing itching, sneezing, rhinorrhea, and nasal blockage in perennial allergic and nonallergic rhinitis.⁸³⁻⁸⁶ The products differ in their dose per spray. Flunisolide delivers 25 µg per spray, budesonide 32 µg per spray, beclomethasone 42 µg per spray, triamcinolone 55 µg per spray, and fluticasone 50 µg per spray. The recommended frequency of dosing is twice daily for some, but with improvement in symptoms, once daily is usually sufficient with any of these substances.

If the nose is markedly obstructed, temporary use of a topical decongestant may be needed to open up either one or both passages. The patient should blow the nose to clear secretions prior to administering the corticosteroid. Because the therapeutic effects are not immediate, patients should be informed that it takes 24 to 72 hours before symptom improvement should be expected. They should also be taught that intranasal corticosteroids are most beneficial when used regularly and that the dosage should be gradually adjusted to the level of symptom control.

Adverse effects. Prolonged use of the newer topical corticosteroids in recommended doses has not been associated with systemic adverse effects. This includes no ocular changes (e.g., posterior subcapsular cataracts and increased intraocular pressure) and no suppression of the hypothalamic-pituitary-adrenal axis.⁸⁴

The topical corticosteroids are administered by freon-driven aerosols and mechanical pump sprays in aqueous or glycol solutions or as a dry powder. Local side effects are more common with the aerosols and glycol solution. These are irritation in the forms of transient stinging or burning, sneezing, and sore throat. Epistaxis, blood-tinged mu-

cus, septal crusting, and ulceration are occasionally noted, especially when the spray is incorrectly directed toward the septum rather than in the sagittal plane. Rarely, septal perforation has been reported.⁸⁷ There have been no reports of nasal *Candida albicans* colonization and no adverse effects on mucociliary clearance.⁸⁸ There have also been no atrophic or metaplastic changes of the mucous membranes after prolonged treatment.

INDIVIDUALIZATION OF PHARMACOTHERAPY

In the treatment of an individual with perennial rhinitis, many factors contribute to the efficacy of the therapeutic regimen. These include proper diagnosis, patient education, and appropriate treatment selection. Two other issues relevant to perennial rhinitis pharmacotherapy are compliance and cost.

Compliance

Compliance is based on a patient's assurance of the physician's concern for his or her long-term health. The patient also needs to have a personal commitment to their own health care and be thoroughly informed about the cause and course of a rhinopathy and the options and aims of specific forms of treatments. Knowledge alone may not be enough to ensure compliance, but lack of understanding will certainly decrease it. Motivating patients to take medications and taking the extra steps to ensure that they have complied are important parts of treatment.

Compliance with medical recommendations does not correlate with such demographic variables as age, sex, race, religion, marital status, socioeconomic status, or educational level. Compliance with pharmacotherapy is less likely when a patient has either extremely high or low levels of anxiety, when child-resistant "safety" containers are used, and when symptoms abate.⁸⁹ Patients with mild forms of a disease tend to comply less than patients with moderate and moderately severe disease. Patients with extremely severe or even terminal disease usually comply less than the moderate group. This may be because those with severe disease are depressed and have lost hope or the physical ability to take care of themselves. The accuracy of this generalization depends on personality factors, as well as the patient's values, culture, religion, and previous experiences with the disease and the medical establishment.

Measures to promote compliance in the phar-

macotherapy of perennial rhinitis include the following 10 considerations:

Keep it simple. Prescribe a simple, balanced regimen with the least number of medications taken as few times a day as possible and, preferably, all at the same time. Long-acting formulations assist in this aim, as do medications with a protracted duration of action. Medications that need to be taken four times a day have resulted in a compliance rate of 39% (range, 3% to 68%) compared to 77% for three times a day, 81% for twice a day, and 87% for once a day⁹⁰ and the overall percentage of patients failing to take their medications properly ranges from 20% to 82%.⁹¹

Deliver it effectively. Choose the delivery route most compatible with a patient's personal or cultural bias. Some patients will wish to avoid oral medications that might affect other parts of their body. Others do not wish to sniff or spray anything into their nasal airway. This is particularly a problem in young children. For any pharmacotherapy that involves techniques to self-administer the treatment that are not familiar to the patient, it is necessary to demonstrate the technique. The compliance of patients can be enhanced by practicing the administration with nonjudgemental professional staff.

Avoid its problems. Avoid excessive doses or agents that are associated with adverse effects. Medications may cause changes in behavior or physical problems, prompting avoidance of the medication due to the adverse effects. Patients should routinely be asked: Is the medication causing you any problems? Although not a possibility of current rhinitis pharmacotherapy, it would be helpful if an agent's therapeutic effect could be correlated with its concentration in the blood or urine or with some other objective biologic marker. This could allow the dose to be optimized.

Call it medicine. Use the term medication or pharmacologic agent rather than drug. The difference in semantics highlights the difference in intention. Establish a therapeutic goal in conjunction with the patient and assess the patient's progress toward that goal.

Provide it readily. Provide free or starter samples of a medication. This can inexpensively and rapidly point out a patient's tolerance to a medication or establish symptom improvement that will encourage maintaining the treatment. Ease of access to an ongoing supply of required medications also promotes compliance. Compliance is also more frequent in prescriptions that are judged to be useful.⁹²

Review its usage. Use a daily record of symptoms, medications, and their dosages. These records should be reviewed by the physician and the patient together. Pill counts, weighed cannisters, and frequency of prescription refills should not be assumed to be an accurate reflection of compliance because even if accurate, these parameters do not determine if the patient is taking the correct dosage or frequency.⁹⁰ Patients embarrassed about their noncompliance simply discard the number of pills or sprays they think they have missed. In one study of metered dose inhaler adherence, 73% of the participants reported using the inhaler an average of three times daily. However, nebulizer chronolog data showed that only 15% of the participants actually used the inhaler 2.5 or more times a day. The weighing of the inhaler cannister was an equally unreliable measure of adherence to the prescribed regimen.⁹³

It is valuable to have the patient bring in all the medications from all their physicians.⁹⁴ Sometimes the patient will be taking two versions or brands of the same medicine, sometimes the patient will be taking agents that, in combination, might be harmful. Encouraging a patient to always use the same pharmacy reduces the likelihood of these problems occurring. It also helps to document whether the patient ever even picked up the prescription.

It is also important to individualize the treatment program according to the patient's personality. Some patients are dependent/passive and place the responsibility for their medical management on others rather than themselves. They may exaggerate their symptoms and request and use more medication than is really necessary. This can be determined by record reviews.

The contrasting patient personality shows excessive independence or stoical behavior. Symptoms are often disregarded or mislabeled. This pattern is frequent among adolescents. The denial of their disease leads to underreporting of symptoms and underuse of medication. It is important to be proactive in this association between personality and compliance and noncompliance. The patients at either end of the spectrum do better with a regularly reviewed record, but all patients should be encouraged to participate in their own care. Follow-up visits should be arranged at mutually convenient times, and the patient should be ensured of minimal delay in waiting to see the physician or staff.

Patients need to be asked why they did not take their medicines. It may be related to the disease outcome, to adverse reactions, or to personal

factors such as forgetfulness or anger with professionals. A discussion about the topic may improve compliance.

Link it with lifestyle. Organize the regimen to coincide with the patient's lifestyle and routine. Convenience is a major factor in compliance. Medications that can be taken first thing and/or last thing in the day are easier to incorporate. So, too, are those associated with a usual behavior such as tooth brushing, coffee drinking, or a regularly watched TV show. Using a medication carrier that stores one pill for each day or time prescribed works for people who have the patience to load it, but most patients do not. A schedule of pharmacotherapy that must be carried during the day or is affected by meals is also not recommended.

Put it in writing. Write down the medication instructions. Patients often do not understand or remember what they are told, and the number of statements forgotten increases with the number presented. Roughly half is lost within 5 minutes.⁹⁵ Patient compliance was improved by 22% over a 9-day period by giving written instructions for a short course of antibiotics by a physician or a pharmacist.^{96,97} The use of written instructions is probably valuable in starting the correct course and reducing early noncompliance. However, it is unlikely to affect long-term compliance so necessary with chronic diseases. Verbal counseling should be reinforced with written directions containing the name of the medicine(s), the purpose for taking it, the dose frequency and duration for taking it, precautions and potential adverse effect when taking it. When patients do not understand the expected outcome, they are less likely to continue taking a medication. Clear labeling of medicine containers will also enhance compliance, as will the use of tailored reminding systems.

Support it psychosocially. Involve multiple support systems. Parental or spousal concern and sharing of the responsibility of the therapeutic program can be most effective, as can a strong physician-patient relationship, in influencing and maintaining compliance with a treatment regimen. Poor relationships with medical professionals is sometimes a major factor in compliance. This includes both the adherence to a therapeutic regimen and willingness to meet on an ongoing basis. One report determined that patients kept about 75% of clinic appointments they made for themselves but only about 50% of the appointments made for them.⁹⁸ Patients should not be made to feel guilty about poor compliance, and positive feedback should be provided to all patients. Pa-

TABLE V. Cost of oral medications for rhinitis

Drug	Usual adult dose	Wholesale cost/ 30 days/day*
Antihistamines		
Astemizole: Hismanal	10 mg qd	\$53.10/1.77
Brompheniramine	4 mg q 4-6 hr	
Generic		\$ 4.03/0.13
Dimetane		\$15.56/0.52
Chlorpheniramine	4 mg q 4-6 hr	
Generic		\$ 5.25/0.18
Chlor-Trimeton		\$28.80/0.96
Diphenhydramine	25-50 mg q 4-6 hr	
Generic		\$ 8.79/0.29
Benadryl		\$39.77/1.33
Loratadine: Claritin	10 mg qd	\$53.16/1.77
Terfenadine: Seldane	60 mg bid	\$53.16/1.77
Decongestants		
Phenylpropanolamine	20-25 mg q 4 hr	
Generic		\$ 1.46/0.05
Propagest		\$12.15/0.41
Pseudoephedrine	60 mg q 4-6 hr	
Generic		\$ 4.92/0.16
Sudafed		\$23.27/0.76
Antihistamine/decongestant combinations		
Acrivastine/pseudoephedrine: Semprex-D	8 mg/60 mg qid	\$54.73/1.82
Chlorpheniramine/phenylpropanolamine: Allerest, Contact	12 mg/75 mg bid	\$24.26/0.81
Chlorpheniramine/pseudoephedrine: Sudafed Plus	4 mg/60 mg q 4-6 hr	\$19.65/0.66
Clemastine/phenylpropanolamine: Tavist-D	1.34 mg/75 mg bid	\$21.54/0.72
Terfenadine/pseudoephedrine: Seldane-D	60 mg/120 mg bid	\$59.40/1.98
Triprolidine/pseudoephedrine: Actifed	2.5 mg/60 mg q 4-6 hr	\$16.67/0.56

Modified from Med Lett 1994;36:77-88.

*Cost to the pharmacist at highest recommended adult dosage based on average wholesale price (AWP) listings in Red Book 1994 and August Update.

tients may also be given rewards by their families and physicians for complying with medicine taking. This may be particularly useful for children.

Minimize its costs. This is especially an issue when a medication will be needed over a long period of time. Early studies suggest that the expense of treatment (both direct cost and indirect cost, such as loss of work time) appears to have an adverse effect on compliance.⁹⁹ Even insured patients may feel unable to meet deductibles or copayments. A less expensive alternative, although not the newest therapy, may improve compliance.

Cost

The cost of medications for rhinitis must be considered in the context of the cost of untreated disease. Although there is a huge outlay of economic resources by the public each year for pharmacotherapy, millions of days without relief from symptoms affect the well-being and quality of life of the patients.

It has been generally accepted that there are three major elements related to the costs of any illness.¹⁰⁰ These are: direct medical expenditures, indirect costs, and intangible costs.

Direct medical expenditures include all the costs associated with delivery of care such as hospitalizations, doctor's office fees, and medications. Indirect costs are those nonmedical care costs that relate to the value of disease-related morbidity, premature mortality, and productivity loss. Intangible costs reflect the value of psychosocial affliction of the disease for the individual, the family, or the community.¹⁰¹ Without appropriate direct medical expenditures for pharmacotherapy, the indirect and intangible costs for perennial rhinitis might be even greater.

The cost of total direct national health expenditures for the United States in 1990 was \$589 billion.¹⁴ Total direct respiratory illness was \$47 billion, of which it has been estimated that \$3.6 billion was spent for asthma and \$1.16 billion for allergic rhini-

TABLE VI. Cost of intranasal corticosteroids

Drug	Usual adult dose	Wholesale cost/ 30 day/day* Daily dose = 4 sprays
Beclomethasone dipropionate	42 µg	
Beconase aerosol		\$17.23/0.57
Vancenase aerosol		\$17.23/0.57
Beconase AQ		\$18.60/0.62
Vancenase AQ		\$18.60/0.62
Budesonide	32 µg	
Rhinocort		\$16.20/0.54
Flunisolide	25 µg	
Nasalide		\$15.31/0.51
Triamcinolone acetonide	55 µg	
Nascort		\$45.19/1.51

Modified from Med Lett 1994;36:63-4.

*Cost to the pharmacist at the lowest recommended dosage based on average wholesale price listings in First Data Bank Price Alert, June 15, 1994.

tis.^{102, 14} The amount allocated for medications was estimated to be \$1.1 billion for asthma and \$276 million for allergic rhinitis. The U.S. cost of medications for nonallergic rhinitis is not available.

In a recent IMS Drugstore/Hospital Sales survey, the projected sales figures for 1994 for prescription antihistamines would be \$868 million (not all of which would be used for rhinitis); for intranasal corticosteroids, \$435 million; and for prescription oral "cold preparations," \$353 million.¹⁰³ The usage of these agents for rhinitis and colds is reported as approximately 60% for allergic rhinitis, 30% for nonallergic rhinitis, and 10% for common colds.¹⁰⁴ The treatment usage proportions vary depending on the condition: for allergic rhinitis, antihistamines 45%, nasal steroids 37% and prescription oral cold preparations 18%; for nonallergic rhinitis, antihistamines 46%, nasal steroids 32%, prescription oral cold preparations 22%; for common cold, antihistamines 24%, nasal steroids 5%, prescription oral cold preparations 71%.

The cost of individual agents are listed in Tables V and VI.^{105, 106}

There is an emerging literature on the cost-effectiveness of pharmacotherapy. Newer, effective intervention strategies may lead to cost savings. There appears to be significant economic value for the expense of good health.

REFERENCES

1. Lund VJ, Aaronson DW, Bousquet J, et al. International consensus report on the diagnosis and management of rhinitis. *Allergy* 1994;49(suppl 19):5-34.
2. Smith JM. Epidemiology and natural history of asthma,

allergic rhinitis, and atopic dermatitis (eczema). 2nd ed. In: Middleton E Jr, Reed CE, Ellis EF, eds. *Allergy: principles and practice*. St. Louis: C V Mosby Co, 1983: 771-803.

3. Sibbald B, Rink E. Epidemiology of seasonal and perennial rhinitis: clinical presentation and medical history. *Thorax* 1991;46:859-901.
4. Broder I, Higgins MW, Matthews KP, Keller JB. Epidemiology of asthma and allergic rhinitis in a total community. *J ALLERGY CLIN IMMUNOL* 1974;53:127-38.
5. Barbee R, Kaltenborn W, Lebowitz W, Burrows B. Longitudinal changes in allergic skin test reactivity in a community population sample. *J ALLERGY CLIN IMMUNOL* 1987;79:16-24.
6. Aberg N. Asthma and allergic rhinitis in Swedish conscripts. *Clin Exp Allergy* 1989;19:59-63.
7. Jacobs RL. Nonallergic chronic rhinitis syndromes. *Immunol Allergy Clin North Am* 1987;7:93-103.
8. Jones AS. Non-allergic perennial rhinitis. *Biomed Pharmacother* 1988;42:499-503.
9. Young P. Asthma and allergies: an optimistic future. Bethesda, Md.: National Institutes of Health, March 1980; U.S. Department of Health and Human Services, U.S. Public Health Service publication No. (NIH)80-388.
10. Juniper EF, Guyatt GH. Development and testing of a new measure of health status for clinical trials in rhinoconjunctivitis. *Clin Exp Allergy* 1991;21:77-83.
11. Juniper EF, Guyatt GH, Andersson B, Ferrie PJ. Comparison of powder and aerosolized budesonide in perennial rhinitis: validation of rhinitis quality of life questionnaire. *Ann Allergy* 1993;70:225-30.
12. Juniper EF, Guyatt GH, Dolovich J. Assessment of quality of life in adolescents with allergic rhinoconjunctivitis: development and testing of a questionnaire for clinical trials. *J ALLERGY CLIN IMMUNOL* 1994;93:413-23.
13. Bousquet J, Bullinger M, Fayol C, et al. Assessment of quality of life in patients with perennial allergic rhinitis with the French version of the SF-36 Health Status Questionnaire. *J ALLERGY CLIN IMMUNOL* 1994;94:182-8.
14. McMenamin P. Costs of hay fever in the United States in 1990. *Ann Allergy* 1994;73:35-9.
15. Nelson C, McLemore T. The National Ambulatory Medical Care Survey: United States, 1975-81 and 1985 trends. Hyattsville, Md.: National Center for Health Statistics, June 1988; U.S. Department of Health and Human Services publication No. (PHS)88-1754, series 13, No. 93.
16. Meltzer EO. Comparative safety of H₁ antihistamines. *Ann Allergy* 1991;67:625-33.
17. Bousquet J, Lebel B, Chanal I, et al. Antiallergic activity of H₁ receptor antagonists assessed by nasal challenge. *J ALLERGY CLIN IMMUNOL* 1988;82:881-7.
18. Naclerio RM, Kagey-Sobotka A, Lichtenstein LM, et al. Terfenadine, an H₁ antihistamine, inhibits histamine release in vivo in man. *Am Rev Respir Dis* 1990;142:167-71.
19. Naclerio RM, Proud D, Kagey-Sobotka A, et al. The effect of cetirizine on early allergic response. *Laryngoscope* 1989;99:596-9.
20. Charlesworth EN, Kagey-Sobotka A, Norman P, et al. Effect of cetirizine on mast cell mediator release and cellular traffic during the cutaneous late-phase reaction. *J ALLERGY CLIN IMMUNOL* 1989;83:905-12.
21. Naclerio RM. Allergic rhinitis. *N Engl J Med* 1991;325: 860-9.
22. Simons FER, Simons KJ. H₁ receptor antagonist treat-

- ment of chronic rhinitis. *J ALLERGY CLIN IMMUNOL* 1988; 81:975-80.
23. Simons FER. H₁ receptor antagonists: clinical pharmacology and therapeutics. *J ALLERGY CLIN IMMUNOL* 1989;84: 845-66.
 24. Simons FER, McMillan JL, Simons KJ. A double-blind, single-dose, crossover comparison of cetirizine, terfenadine, loratadine, astemizole and chlorpheniramine versus placebo: suppressive effects on histamine-induced wheals and flares during 24 hours in normal subjects. *J ALLERGY CLIN IMMUNOL* 1990;86:540-7.
 25. Watson WTA, Simons KJ, Chen XY, Simons FER. Cetirizine: a pharmacokinetic and pharmacodynamic evaluation in children with seasonal allergic rhinitis. *J ALLERGY CLIN IMMUNOL* 1989;84:457-64.
 26. Kemp JP, Buckley CE, Gershwin ME, et al. Multicenter double-blind, placebo-controlled trial of terfenadine in seasonal allergic rhinitis and conjunctivitis. *Ann Allergy* 1985;54:502-9.
 27. Meltzer EO, Storms WW, Pierson WE, et al. Efficacy of azelastine in perennial allergic rhinitis: clinical and rhinomanometric evaluation. *J ALLERGY CLIN IMMUNOL* 1988; 82:447-55.
 28. Dechant RL, Goa KL. Levocabastine: a review of its pharmacological properties and therapeutic potential as a topical antihistamine in allergic rhinitis and conjunctivitis. *Drugs* 1991;41:202-24.
 29. Meltzer EO, Weiler JM, Dockhorn RJ, et al. Azelastine nasal spray in the management of seasonal allergic rhinitis. *Ann Allergy* 1994;72:354-9.
 30. Simons FER, Watson WTA, Simons KJ. Lack of subsensitivity to terfenadine during long-term terfenadine treatment. *J ALLERGY CLIN IMMUNOL* 1988;82:1068-75.
 31. Timmerman H. Factors involved in the incidence of central nervous system effects of H₁-blockers. In: Church MK, Rihoux J-P, eds. *Therapeutic index of antihistamines*. Lewiston, NY: Hogrefe & Huber, 1992:19-31.
 32. Lesson GA, Chan KY, Knapp WC, et al. Metabolite disposition of terfenadine in laboratory animals. *Arzneimittelforschung* 1982;32:1173-8.
 33. Wyngaarden JB, Seevers MH. The toxic effect of antihistaminic drugs. *JAMA* 1951;145:277-82.
 34. Koppel C, Ibe K, Tenczer J. Clinical symptomatology of diphenhydramine overdose: an evaluation of 136 cases in 1982 to 1985. *J Toxicol Clin Toxicol* 1987;25:53-70.
 35. Passalacqua G, Scordamaglia A, Ruffoni S, et al. Sedation from H₁ antagonists: evaluation methods and experimental results. *Allergol Immunopathol* 1993;21:79-83.
 36. Friedman HM. Loratadine: a potent non-sedating and long-acting H₁ antagonist. *Am J Rhinol* 1986;1:95-9.
 37. Goetz DW, Jacobson JM, Murnane JE, et al. Prolongation of simple and choice reaction time in a double-blinded comparison of twice daily hydroxyzine versus terfenadine. *J ALLERGY CLIN IMMUNOL* 1989;84:316-22.
 38. Goetz DW, Jacobson JM, Apaliski SJ, et al. Objective antihistamine side effects are mitigated by evening dosing of hydroxyzine. *Ann Allergy* 1991;67:448-54.
 39. Alford C, Rombaut N, Jones J, et al. Acute effects of hydroxyzine on nocturnal sleep and sleep tendency the following day: a C-EEG study. *Hum Psychopharmacol* 1992;7:25-35.
 40. Bradley CM, Nicholson AN. Studies on the central effects of the H₁ antagonist, loratadine. *Eur J Clin Pharmacol* 1987;32:419-21.
 41. Falliers CJ, Brandon ML, Buchman E, et al. Double-blind comparison of cetirizine and placebo in the treatment of seasonal rhinitis. *Ann Allergy* 1991;66:257-62.
 42. Janssens MM-L. Astemizole: a non-sedating antihistamine with fast and sustained activity. *Clin Rev Allergy* 1993;11: 35-63.
 43. Grant SM, Goa KL, Fitton A, Sorkin EM. Ketotifen: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic uses in asthma and allergic disorders. *Drugs* 1990;40:412-48.
 44. McTavish D, Sorkin EM. Azelastine: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential. *Drugs* 1989;38:778-800.
 45. Woosley RL, Chen Y, Freiman JP, Gillis RA. Mechanism of the cardiotoxic actions of terfenadine. *JAMA* 1993;269: 1532-6.
 46. Simons FER. H₁ receptor antagonists: comparative tolerability and safety. *Drug Saf* 1994;10:350-80.
 47. Affrime MB, Lorber R, Danzig M, et al. Three month evaluation of electrocardiographic effects of loratadine in humans [Abstract]. *J ALLERGY CLIN IMMUNOL* 1993;91: 259.
 48. Sale ME, Woosley RL, Barby JT, et al. Lack of electrocardiographic effects of cetirizine in healthy humans [Abstract]. *J ALLERGY CLIN IMMUNOL* 1993;91:258.
 49. Malm L, McCaffrey TV, Kern EB. Alpha-adrenoceptor-mediated secretion from the anterior nasal glands of the dog. *Acta Otolaryngol (Stockh)* 1983;96:149-55.
 50. Malm L, Anggard A. Vasoconstrictors. In: Mygind N, Naclerio RM, eds. *Allergic and non-allergic rhinitis: clinical aspects*. Copenhagen: Munksgaard, 1993:95-100.
 51. Hendeles L. Selecting a decongestant. *Pharmacotherapy* 1993;13:129S-34S.
 52. Falliers CJ, Redding MA. Controlled comparison of a new antihistamine-decongestant combination to its individual components. *Ann Allergy* 1980;45:75-80.
 53. Storms WW, Bodman SF, Nathan RA, et al. SCH 434: a new antihistamine/decongestant for seasonal allergic rhinitis. *J ALLERGY CLIN IMMUNOL* 1989;83:1083-90.
 54. Jackson RT, Teichgraber J. Low-dose topical atropine for rhinitis. *Arch Otolaryngol* 1981;107:288-9.
 55. Meltzer EO, Orgel HA, Bronsky EA, et al. Ipratropium bromide aqueous nasal spray for patients with perennial allergic rhinitis: a study of its effect on their symptoms, quality of life, and nasal cytology. *J ALLERGY CLIN IMMUNOL* 1992;90:242-9.
 56. Knight A, Kazim F, Salvatori VA. A trial of intranasal Atrovent versus placebo in the treatment of vasomotor rhinitis. *Ann Allergy* 1986;57:348-54.
 57. Dolovich J, Kennedy L, Vickerson F, Kazim F. Control of the hypersecretion of vasomotor rhinitis by topical ipratropium bromide. *J ALLERGY CLIN IMMUNOL* 1987;80: 274-8.
 58. Druce HM, Spector SL, Fireman P, et al. Double-blind study of intranasal ipratropium bromide in nonallergic perennial rhinitis. *Ann Allergy* 1992;69:53-60.
 59. Milford CA, Mugliston TA, Lund VJ, McKay IS. Long term safety and efficacy study of intranasal ipratropium bromide. *J Laryngol Otol* 1990;104:123-5.
 60. Cos JSG. Disodium cromoglycate (FPL 670 "Intal"): a specific inhibitor of reaginic antigen-antibody mechanisms. *Nature* 1967;216:1328-9.
 61. Brogden RN, Speight TM, Avery GS. Sodium cromoglycate (cromolyn sodium): a review of its mode of action,

- pharmacology, therapeutic efficacy and use. *Drugs* 1974; 7:164-282.
62. Kay AB, Walsh GM, Mogbel R, et al. Disodium cromoglycate inhibits activation of human inflammatory cells in vitro. *J ALLERGY CLIN IMMUNOL* 1987;80:1-8.
63. Orgel HA, Meltzer EO, Kemp JP, et al. Comparison of intranasal cromolyn sodium, 4%, and oral terfenadine for allergic rhinitis: symptoms, nasal cytology, nasal ciliary clearance and rhinomanometry. *Ann Allergy* 1991;66:237-44.
64. Howarth P. Cromoglycate. In: Mygind N, Naclerio RM, eds. *Allergic and non-allergic rhinitis: clinical aspects*. Copenhagen: Munksgaard, 1993:101-4.
65. Orie NGM, Booi-Nord H, Pelikan Z, et al. Protective effect of disodium cromoglycate on nasal and bronchial reactions after allergen challenge. In: Pepys J, Frankland AW, eds. *Disodium cromoglycate in allergic airway disease*. London: Butterworth, 1970:33-41.
66. Cohan RH, Bloom FL, Rhoades RB, et al. Treatment of perennial allergic rhinitis with cromolyn sodium: double-blind study on 34 adult patients. *J ALLERGY CLIN IMMUNOL* 1976;58:121-8.
67. Nelson HL, Jacobs RL. Response of the nonallergic rhinitis with eosinophilia (NARES) syndrome to 4% cromolyn sodium nasal solution. *J ALLERGY CLIN IMMUNOL* 1982;70:125-8.
68. Naclerio RM, Mygind N. Intranasal steroids. In: Mygind N, Naclerio RM, eds. *Allergic and nonallergic rhinitis: clinical aspects*. Copenhagen: Munksgaard, 1993:114-22.
69. Phillips GH. Structure-activity relationships of topically active steroids: the selection of fluticasone propionate. *Respir Med* 1990;84(suppl A):19-23.
70. Sorensen H, Mygind N, Pedersen CB, Prytz S. Long-term treatment of nasal polyps with beclomethasone dipropionate aerosol: morphological studies and conclusions. *Acta Otolaryngol* 1976;82:260-2.
71. Baroody FM, Cruz AA, Lichtenstein LM, et al. Intranasal beclomethasone inhibits antigen-induced nasal hyperresponsiveness to histamine. *J ALLERGY CLIN IMMUNOL* 1992;90:373-6.
72. Jackson RT. Mechanism of action of some commonly used nasal drugs. *Otolaryngol Head Neck Surg* 1992;107: 433-40.
73. Pipkorn U, Proud D, Lichtenstein LM, et al. Inhibition of mediator release in allergic rhinitis by pretreatment with topical glucocorticosteroids. *N Engl J Med* 1987;316:1506-10.
74. Bascom R, Wachs M, Naclerio RM, et al. Basophil influx occurs after nasal antigen challenge: effects of topical corticosteroid pretreatment. *J ALLERGY CLIN IMMUNOL* 1988;81:580-9.
75. Murad F, Hynes RC Jr. Adrenocorticotrophic hormone; adrenocortical steroids and their synthetic analogs; inhibitors of adrenocortical steroid biosynthesis. In: Gilman AG, Goodman LS, Rall TW, Murad F, eds. *The pharmacological basis of therapeutics*. 7th ed. New York: Mac-Millan, 1985:1459-89.
76. Siegel SC. Topical intranasal corticosteroid therapy in rhinitis. *J ALLERGY CLIN IMMUNOL* 1988;81:984-91.
77. Phillips GH. Structure-activity relationships of topically active steroids: the selection of fluticasone propionate. *Respir Med* 1990;84(suppl A):19-23.
78. Mabry RL. Practical applications of intranasal corticosteroid injection. *ENT J* 1981;60:506-10.
79. McCleve B, Goldstein J, Silver S. Corticosteroid injections of the nasal turbinates: past experience and precautions. *Otolaryngology* 1978;86:851-7.
80. Norman PS, Winkenwerder WL, Murgatroyd GW Jr., Parsons JW. Evidence for the local action of intranasal dexamethasone aerosols in the suppression of hayfever symptoms. *J Allergy* 1966;38:93-9.
81. Juniper EF, Kline PA, Hargreave FE, Dolovich J. Comparison of beclomethasone dipropionate aqueous nasal spray, astemizole and the combination in the prophylactic treatment of ragweed pollen-induced rhinoconjunctivitis. *J ALLERGY CLIN IMMUNOL* 1989;83:627-33.
82. Welsh PW, Stricker WE, Chu CP, et al. Efficacy of beclomethasone nasal solution, flunisolide, and cromolyn in relieving symptoms of ragweed allergy. *Mayo Clin Proc* 1987;62:125-34.
83. Meltzer EO, Orgel HA, Bush RK, et al. Evaluation of symptom relief, nasal airflow, nasal cytology, and acceptability of two formulations of flunisolide nasal spray in patients with perennial allergic rhinitis. *Ann Allergy* 1990; 64:536-40.
84. van As A, Bronsky EA, Dockhorn RJ, et al. Once daily fluticasone propionate is as effective for perennial allergic rhinitis as twice daily beclomethasone dipropionate. *J ALLERGY CLIN IMMUNOL* 1993;91:1146-54.
85. Selner J, Banov C, Boltansky H, et al. Fluticasone propionate aqueous nasal spray effectively treats perennial non-allergic rhinitis [Abstract]. *J ALLERGY CLIN IMMUNOL* 1994;93:165.
86. Day JH, Bertil Andersson C, Briscoe MP. Efficacy and safety of intranasal budesonide in the treatment of perennial rhinitis in adults and children. *Ann Allergy* 1990;64: 445-50.
87. Soderberg-Warner ML. Nasal septal perforation associated with topical corticosteroid therapy. *J Pediatr* 1984; 105:840-1.
88. Holmberg K, Pipkorn U. Influence of topical beclomethasone dipropionate suspension on human nasal mucociliary activity. *Eur J Clin Pharmacol* 1986;30:625-7.
89. Sbarbaro JA. The patient-physician relationship: compliance revisited. *Ann Allergy* 1990;64:325-31.
90. Cramer JA, Mattson RH, Prevey ML, et al. How often is medication taken as prescribed? *JAMA* 1989;261:3273-77.
91. Becker MH, Maiman LA. Sociobehavioral determinants of compliance with health and medical care recommendations. *Med Care* 1975;13:10-24.
92. Dekker FW, Dieleman FE, Kaptein AA, Mulder JD. Compliance with pulmonary medication in general practice. *Eur Resp J* 1993;6:886-90.
93. Rand CS, Wise RA, Nides M, et al. Metered-dose inhaler adherence in a clinical trial. *Am Rev Respir Dis* 1992;146: 1559-64.
94. Spector SL. Psychologic factors in patient compliance. *Clin Adv Treatment Allergic Disord* 1989;December:5-9.
95. Ley P. Communication in the clinical setting. *Br J Orthod* 1974;1:173-7.
96. Colcher IS, Bass JW. Penicillin treatment of streptococcal pharyngitis. *JAMA* 1972;222:657-9.
97. Sharpe TR, Mikel RL. Patient compliance with antibiotic regimens. *Am J Hosp Pharm* 1974;31:479-84.
98. Sackett DL, Snow JC. The magnitude of compliance and noncompliance. In: Haynes RB, Taylor DW, Sackett DL, eds. *Compliance in health care*. Baltimore: Johns Hopkins University Press, 1979.

99. Alpert JJ. Broken appointments. *Pediatrics* 1964;34:127-32.
100. Rice DP. Estimating the costs of illness. Washington, DC: U.S. Government Printing Office, 1966; Health Economic Series No. 6, Publication No. 947-4.
101. Weiss K. The impact of pharmacologic therapy on the costs of asthma. *Allergy Proc* 1994;15:189-92.
102. Weiss KB, Gergen PJ, Hodgson TA. An economic evaluation of asthma in the United States. *N Engl J Med* 1992;326:862-6.
103. IMS Drugstore/Hospital Sales-1993; 1994 Estimated.
104. Physician Drug and Diagnosis Audit. Scott Levin MAT, June 1994.
105. *Medical Letter* 1994;36:77-88.
106. *Medical Letter* 1994;36:63-4.