REVIEW

Evaluation of the Optimal Oral Antihistamine for Patients With Allergic Rhinitis

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Because of its bothersome symptoms, allergic rhinitis (AR) is 1 of the top 10 reasons for patient visits to primary care physicians. This highly prevalent disease also results in loss of productivity, both at work and in school. Oral antihistamines are one of the most frequently prescribed medications for the management of AR and, with several agents available, it is important to discern the specific benefits and detriments of each. To assess the differences in efficacy and safety factors among antihistamines, the individual therapeutic window of each agent can be used as a comparative reference tool because it defines the dose range over which an antihistamine is efficacious and free of adverse effects. As such, the therapeutic window includes both undesired effects, such as sedation, and desired properties, such as rapid onset of action, long duration of efficacy, broad age range of applicability, and potential to improve quality of life. Therefore, agents with broad therapeutic windows, based on both efficacy and safety, are expected to be more favorable; this therapeutic window should be understood by the primary care physician when prescribing a medication.

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AR = allergic rhinitis; ARIA = Allergic Rhinitis and its Impact on Asthma; ICAM = intercellular adhesion molecule; IL = interleukin; PAR = perennial AR; QOL = quality of life; RQLQ = Rhinoconjunctivitis Quality of Life Questionnaire; SAR = seasonal AR; SF-36 = Medical Outcome Study Short-Form Health Survey

Allergic rhinitis (AR) represents a global health problem, affecting 10% to more than 40% of the population worldwide.[1-3] It has been identified as 1 of the top 10 reasons for patient visits to their primary care physicians.[4] However, the prevalence of AR may be underestimated because many patients self-medicate without consulting a physician and thus are not included in official surveys.

Allergic rhinitis is clinically defined as a symptomatic disorder of the nose induced by IgE-mediated inflammation after allergen exposure. Symptoms include rhinorrhea, nasal obstruction, nasal itching, and sneezing.[5] Patients are affected differently and at variable times by their symptoms. Patients also can experience decreased quality of life (QOL), which can cause sleep disturbance and affect school and work performance.[6,7] Substantial costs can be incurred.[8] Furthermore, AR is often associated with numerous comorbidities, such as asthma, conjunctivitis, and rhinosinusitis.

Traditionally, AR has been subdivided into seasonal AR (SAR) or perennial AR (PAR); SAR is triggered by numerous outdoor allergens, such as pollens and molds, whereas PAR is induced most frequently by indoor allergens, such as dust mites, molds, and animal dander. However, because SAR can be protracted and SAR and PAR often coexist in individual patients, new AR subdivisions have been proposed. The new terms, *intermittent AR* and *persistent AR*, were introduced in the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines, developed by an expert panel in collaboration with the World Health Organization. The ARIA guidelines were created to update specialty and primary care clinicians on the current knowledge of AR, provide recommendations for the use of available treatments, and propose a stepwise approach to disease management.[5] The ARIA guidelines define AR on the basis of the duration of symptom presentation with severity classified as mild or moderate to severe[5] (Table 1).

Numerous classes of pharmacological agents are available for treatment of AR. Given the multiple populations of patients with AR, treatment needs to be tailored specifically to the individual. Treatment choices need to be based on both the efficacy and safety of the agent to provide the greatest symptomatic relief with the most convenience and least potential for harm.

Oral antihistamines and intranasal corticosteroids are recommended as first-line therapy for AR, depending on symptom severity.[5,9,10] Oral antihistamines, commonly prescribed by primary care physicians, are very effective at

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controlling the mild-to-moderate symptoms of AR. This evidence-based review describes the available oral antihistamines as a therapeutic class. To assess the differences among oral antihistamines, the therapeutic window for each medication should be considered and evaluated.

PATHOPHYSIOLOGY OF AR

Because of an inherited predisposition to phenotype type 2 helper T (T_H2) cells, atopic patients exhibit exaggerated responses to normal substances.[11] The T_H2 cells initiate the type 1 hypersensitivity reaction seen in AR and typified by pollen-induced rhinitis. During the sensitization phase, the immune system identifies an allergen as foreign and generates specific IgE antibodies in response.[11] Airborne allergens originating from animals, insects, and plants, including fungi, are antigens that induce and react with specific IgE antibodies. On reexposure to the sensitizing allergen, the specific IgE antibodies bound to mast cells are cross-linked, resulting in mast cell degranulation and release of histamine and other chemical mediators, the so-called early-phase response of the allergic reaction. The mediators initiate the AR symptoms of rhinorrhea, nasal itching, sneezing, and nasal obstruction. Although nasal congestion occurs during the early phase of the allergic reaction, it is more prominently a result of the late-phase response, principally involving inflammatory cells including eosinophils, monocytes, and basophils.[12] Basophils and mast cells release histamine during the early-phase reaction, whereas basophils alone are considered the predominant source of histamine in the late-phase response.[13]

Histamine is the major mediator released after immunological challenge by mast cells and basophils.[13] Other important components of the early-phase and late-phase allergic response are cytokines, interleukin (IL) 3, IL-4, IL-5, IL-6, and IL-8, and the cellular adhesion molecules such as intercellular adhesion molecule 1 (ICAM-1) and E selectin, leukotrienes, and prostaglandins.[14-17] Histamine induces the expression and activity of some of these mediators.[14-17]

AVAILABLE ORAL ANTIHISTAMINES

In the United States, several older or first-generation H_1-antihistamines, such as diphenhydramine and chlorpheniramine, are available as over-the-counter preparations, whereas others, such as hydroxyzine, are available by prescription. However, these agents display poor receptor selectivity for the H_1-receptor and block muscarinic receptors, causing substantial anticholinergic effects, such as dry mouth, constipation, urinary retention, and tachycardia, and conferring an overall unfavorable risk-benefit ratio.[9,18,19] Since 1980, pharmacological research has produced additional H_1-antihistamines that have more specific H_1-receptor selectivity and either faster onset of action, longer duration of action, greater potency, or fewer adverse events. The newer, or second-generation, H_1-antihistamines currently available in the United States are summarized in Table 2.

TABLE 1. **Classification of Allergic Rhinitis**

Intermittent symptoms	Persistent symptoms
<4 d/wk	>4 d/wk
or <4 wk	*and* >4 wk
Mild	Moderate to severe (*1 or more items*)
Normal sleep	Abnormal sleep
No impairment of daily activities, sport, leisure	Impairment of daily activities, sport, leisure
Normal work and school	Abnormal work and school
No troublesome symptoms	Troublesome symptoms

Adapted from Bousquet et al,[5] with permission from the Allergic Rhinitis and its Impact on Asthma (ARIA) Expert Panel.

THERAPEUTIC WINDOW

The *therapeutic window*, or therapeutic index, is defined as the safety-to-efficacy ratio or risk-to-benefit ratio of the agent. For antihistamines, the therapeutic window includes both undesired effects, such as sedation and anticholinergic responses, and desired properties, such as rapid onset of action, long duration of efficacy, broad age range of applicability, and potential to improve QOL.[20,21] Therefore, the optimal antihistamine is expected to have a wide therapeutic window. Numerous factors, including the formulation, tissue distribution and metabolism, dose range, disease, and population, can contribute to the therapeutic window. Not surprisingly, the therapeutic window differs across the class of currently available antihistamines (Table 3).[21-49]

ANTIALLERGIC AND ANTI-INFLAMMATORY EFFECTS

Some of the currently available newer-generation oral antihistamines have been shown to have a range of additional anti-inflammatory properties; however, the mechanism of action for these effects remains unclear. For example, desloratadine has been shown to produce anti-inflammatory effects by inhibiting the tumor necrosis factor α–in-

TABLE 2. **Available US Second-Generation Antihistamines and Their Clinically Licensed Adult Dose**

H_1-antihistamine	Clinically licensed dose (mg/d)
Fexofenadine	180
Desloratadine	5
Loratadine	10
Cetirizine	10

TABLE 3. **Antihistamine Characteristics Criteria***

Antihistamine characteristics	Cetirizine	Desloratadine	Fexofenadine	Loratadine
Efficacy				
Controlling symptoms of AR	Yes[22-24]	Yes[25-27]	Yes[22,28-30]	Yes[31,32]
Onset of action within 1 h	Yes [33]	No[34]	Yes[35]	No[33]
24-h symptom control	Yes [22-24]	Yes[25-27]	Yes[22,28-30]	Yes[31,32]
Anti-inflammatory potential	Yes [36,37]	Yes[38]	Yes[39,40]	Yes[39]
Safety				
No significant impairment of performance	Impairment [41,42]	Impairment with high doses [41,42]	No impairment[41,42]	Impairment with high doses[41,42]
Does not prolong QTc interval in overdose or with drug interaction	Yes[43,44]	Yes[45]	Yes[44,46,47]	Yes[43,44,48,49]

*AR = allergic rhinitis.

duced chemokine and regulated upon activation, normal T-cell expressed and secreted (RANTES).[38] Similarly, fexofenadine has been shown to inhibit the tumor necrosis factor α–induced release of IL-8, in the late-phase allergic response, as well as basal ICAM-1 expression on epithelial cells and histamine-mediated induction of IL-6 and β-glucuronidase, a marker of exocytosis.[40,50,51] Cetirizine also has shown anti-inflammatory effects and inhibition of interferon gamma–induced expression of membrane ICAM-1 in cultured keratinocytes.[36]

SAFETY: UNDESIRABLE PHARMACOLOGICAL AND CLINICAL EFFECTS

Drug Interactions

The ability of a drug to work with the intended effector systems may be compromised by its interactions at sites other than the targeted receptors, thereby affecting its bioavailability. Therefore, differences can exist among antihistamines because of variations in their metabolic profiles. For example, the second-generation antihistamines astemizole and terfenadine, which are no longer available in the United States, and loratadine are substrates of the hepatic cytochrome P-450 isoenzymes, a group of enzymes found in the liver and small intestine. Consequently, they are susceptible to interactions with other drugs that are metabolized by this system, such as ketoconazole and erythromycin, which can increase the plasma concentrations of these antihistamines.[21,48]

In contrast, fexofenadine, cetirizine, and desloratadine do not undergo cytochrome P-450 metabolism and therefore do not pose a risk in terms of this mechanism. However, other mechanisms, such as the potential for interaction with the efflux and uptake transporters P-glycoprotein and organic anion transporting peptide, also have been investigated. Various drugs, such as ketoconazole, and foodstuffs, such as grapefruit juice, interact with these proteins and modify the absorption and elimination of many antihistamines, including fexofenadine and desloratadine. For example, coadministration of the antibiotic ketoconazole with desloratadine or fexofenadine increases the plasma concentrations of these antihistamines by 40% and 135%, respectively.[52,53] Similarly, the coadministration of fexofenadine with very large quantities (1.2 L) of grapefruit juice was observed to decrease plasma levels of fexofenadine, possibly from the saturation of organic anion transporting peptide carrier proteins with grapefruit juice.[54-56] However, this decrease is not believed to affect the efficacy of the agent.[20] Cetirizine exhibits no apparent interactions with ketoconazole or erythromycin.[57]

The product insert for desloratadine reports that 6% of the general population and 17% of the African American population are slow metabolizers of this agent.[45] These individuals may have difficulty in converting desloratadine to its active metabolite[45] and are therefore more likely to be susceptible to increased blood levels and to potential associated dose-related adverse events, such as sedation. Further investigations are warranted to rigorously assess this safety aspect of the agent.

When prescribing multiple medications, the therapeutic windows of the agents should be considered to assess the potential effect of drug-drug interactions as well as the likely clinical relevance of increased plasma concentrations. Patients who have been identified previously as slow metabolizers of antihistamines[45] may benefit from an agent with a broad therapeutic window.

Central Nervous System Effects

Undesirable effects of antihistamines include sedation and impairment and depend on the ability of the drug to cross the blood-brain barrier and bind to central H_1-receptors.[58] Such adverse effects can seriously affect work and school performance as well as safety in high-risk jobs such as in the aviation field.

Cetirizine and the first-generation antihistamines have produced sedative effects at recommended therapeutic doses.[41,59-61] The absence of sedative effects at therapeutic doses, but with sedation at higher doses, has been observed

with loratadine and desloratadine[41,42,59-62] (Table 4). In contrast, fexofenadine has been found to be free of sedative effects at clinical doses and even at higher-than-recommended doses[63,64] (Table 4). This difference in potential for sedation may be due to the observed lack of lipophilicity of fexofenadine, resulting in a reduced propensity of the agent to penetrate the blood-brain barrier, compared with diphenhydramine, loratadine, desloratadine, and cetirizine.[58] These clinical and experimental findings have been borne out in a "real-world" scenario: in a postmarketing surveillance study, the risk of drowsiness and sedation was significantly lower for fexofenadine and loratadine than for cetirizine and acrivastine.[65]

The effects of antihistamines on the central nervous system can be measured objectively by using numerous psychometric tests to assess cognition, attention, reaction times, and memory or by using positron emission tomography.[66,67] For example, in driving studies, the performance of participants receiving diphenhydramine was more impaired, including a tendency to lane weave, than that of participants whose blood alcohol levels were above the legal limit for driving in most states in the United States.[68] In contrast, study participants treated with 1 dose of fexofenadine HCl at 60 mg or placebo showed similar driving performance. Similar positive results have been obtained in driving studies that assessed the effects of desloratadine and levocetirizine.[69,70] Subjects who experienced the sedative effects of cetirizine exhibited driving performance impairments similar to those of subjects impaired by alcohol.[71]

Cardiotoxicity

The potential of antihistamines to cause cardiac toxicity is closely related to their plasma concentrations; therefore, drug-drug interactions and overdose are important in this respect.[21] First-generation antihistamines, such as diphenhydramine and hydroxyzine, have been shown to induce QT prolongation at higher-than-recommended doses.[72] The second-generation antihistamines astemizole and terfenadine were withdrawn from the US market because of their cardiotoxic activities at increased plasma concentrations caused by interaction with other drugs.[21]

To date, no clinically relevant effects on cardiac function have been observed with loratadine, cetirizine, fexofenadine, or ebastine, even at high plasma concentrations.[43,44,46-49,73]

EFFICACY: DESIRABLE PHARMACOLOGICAL AND CLINICAL EFFECTS

The effectiveness of the newer antihistamines in AR has been evaluated in both short-term pollen chamber studies and long-term efficacy studies.

TABLE 4. **Antihistamine Sedative Adverse Effects***

Antihistamine	Sedative effects
First generation	
Brompheniramine	++
Chlorpheniramine	++
Clemastine	+++
Diphenhydramine	+++
Second generation	
Cetirizine	+; ++ with HD
Desloratadine	0; + with HD
Fexofenadine	0
Loratadine	0; + with HD

*HD = higher-than-recommended dose; +++ = high effect; ++ = moderate effect; + = low effect; 0 = no effect.

Short-term Studies

Day et al[35] conducted a pollen challenge study to characterize the time to onset of clinically important relief of the symptoms of AR after exposure to ragweed pollen in an environmental exposure unit. The findings from this study revealed that the median time to onset of slight-to-complete clinically important relief was significantly lower for fexofenadine HCl at 120 mg compared with placebo (60 vs 100 minutes, respectively; P=.018). Similarly, in another study, the clinical characteristics of cetirizine and loratadine were characterized in patients with SAR who underwent a controlled ragweed pollen challenge in an environmental exposure unit.[33] Cetirizine at 10 mg showed significantly greater reductions in total symptom complex and major symptom complex severity scores compared with loratadine or placebo ($P \leq .01$).[33] The effects of desloratadine at 5 mg on nasal airflow and nasal obstruction were examined recently in patients with SAR in the Vienna Challenge Chamber allergen exposure unit.[74] Desloratadine treatment was associated with less severe nasal obstruction and reduced the accompanying nasal congestion and the other symptoms of SAR compared with placebo.[74]

Long-term Efficacy Studies

Several clinical studies have shown the clinical efficacy of cetirizine,[23,24] desloratadine,[25-27,74] fexofenadine,[26,28-30] and loratadine[31,32]; however, there have been few direct comparator studies between these antihistamines. In a 7-week study of 90 patients, once-daily cetirizine at 10 mg or loratadine at 10 mg were both found to be significantly superior to placebo. However, cetirizine was shown to be quantitatively superior to loratadine, although the differences were not statistically significant.[75] In a separate 2-week study of approximately 500 patients, once-daily cetirizine at 10 mg and fexofenadine at 180 mg were shown to be statistically equivalent in improving symptoms of AR.[59] In a pan-European comparative study of

fexofenadine and loratadine in more than 600 patients with SAR, both agents were significantly superior to placebo at reducing the mean 24-hour reflective total symptom score from baseline ($P \leq .0001$ for fexofenadine and $P \leq .001$ for loratadine). However, fexofenadine was associated witha significant reduction in nasal congestion compared with placebo and loratadine ($P \leq .05$).[30] In a further study, the clinical efficacy of fexofenadine and desloratadine on the subjective and objective measures of nasal congestion were evaluated in 49 patients with SAR.[76] Once-daily fexofenadine at 180 mg and desloratadine at 5 mg were equally effective in improving peak nasal inspiratory flow and nasal symptoms in patients with SAR.[76]

QUALITY OF LIFE

Allergic rhinitis can disrupt and diminish productivity at work and school, and optimal treatment of AR should attenuate these effects in order to be truly valuable. Quality of life is included now as an outcome measure in clinical trials assessing the overall effectiveness of an intervention. Both disease-specific and general questionnaires have been developed to assess QOL, such as the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ)[77] and the Medical Outcome Study Short-Form Health Survey (SF-36).[78]

Of the evidence-based data available, 3 placebo-controlled studies of patients with AR who received fexofenadine HCl (60 mg twice daily) revealed a significant ($P<.05$) improvement with active treatment, as measured by the RQLQ, in activity, work, and overall work over a 2-week study period.[79-81] Similarly, with use of the SF-36 and RQLQ, once-daily cetirizine at 10 mg was found to improve QOL.[78,82,83] A further study assessed the effect of once-daily fexofenadine at 120 mg, loratadine at 10 mg, or placebo on QOL in patients with SAR. The improvement in the fexofenadine group was found to be significant compared with either loratadine ($P \leq .03$) or placebo ($P \leq .005$).[30] Loratadine also has been compared with triamcinolone in patients with SAR. In this study, triamcinolone was significantly better in maintaining improved QOL than was loratadine.[84] Levocetirizine has significantly ($P<.05$) improved RQLQ scores during a 6-month period, and preliminary data have shown desloratadine to improve QOL.[85-87]

FLEXIBLE DOSING FOR ALL PATIENT TYPES

Oral antihistamines are approved for use by patients with AR over a wide age range, whereas cetirizine is indicated for children aged 6 months and older to treat indoor allergies; desloratadine is indicated for children aged 6 months and older for all allergy symptoms; and fexofenadine is indicated for children aged 6 to 11 years to treat SAR. Safety in children and drug-drug interactions in elderly persons should be considered. Although there is no maximum age indicated for these antihistamines, the adverse effects already reviewed should be considered when prescribing these agents. Moreover, to effectively reduce these risks, a broad therapeutic window is particularly important in elderly persons and in patients who increase their antihistamine dose to obtain sufficient symptom relief.

AVAILABILITY OF LORATADINE AS AN OVER-THE-COUNTER AGENT

A topic of particular relevance with oral antihistamines is the availability of loratadine as an over-the-counter preparation. This has raised several issues. Loratadine is now preferred for treatment of allergies by many insurance companies, reflected in the higher copayments for the other oral second-generation antihistamines,[88] although loratadine may not be as effective as the other preparations for controlling allergy symptoms in all patients.[30,75] However, patients with low incomes may be unable to obtain these other agents.

SUMMARY

Allergic rhinitis is a highly prevalent disorder and a source of major discomfort to patients. The clinical symptoms of AR can decrease patient QOL, affecting sleep, work, and school performance. Oral antihistamines are one of the most frequently prescribed medications for treatment of AR, and with an array of available agents, it is important for the prescribing physician to evaluate these agents individually on the basis of their therapeutic window.

REFERENCES

1. Sibbald B, Rink E. Epidemiology of seasonal and perennial rhinitis: clinical presentation and medical history. *Thorax*. 1991;46:895-901.

2. Meltzer EO. The prevalence and medical and economic impact of allergic rhinitis in the United States. *J Allergy Clin Immunol*. 1997;99(6, pt 2):S805-S828.

3. Wright AL, Holberg CJ, Martinez FD, Halonen M, Morgan W, Taussig LM. Epidemiology of physician-diagnosed allergic rhinitis in childhood. *Pediatrics*. 1994;94(6, pt 1):895-901.

4. Fornadley JA, Corey JP, Osguthorpe JD, et al, Committee on Practice Standards, American Academy of Otolaryngic Allergy. Allergic rhinitis: clinical practice guideline. *Otolaryngol Head Neck Surg*. 1996;115:115-122.

5. Bousquet J, van Cauwenberge P, Khaltaev N, ARIA Workshop Group, World Health Organization. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol*. 2001;108(5, suppl):S147-S334.

6. Bousquet J, Bullinger M, Fayol C, Marquis P, Valentin B, Burtin B. 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(2, pt 1):182-188.

7. Thompson AK, Juniper E, Meltzer EO. Quality of life in patients with allergic rhinitis. *Ann Allergy Asthma Immunol*. 2000;85:338-347.

8. Malone DC, Lawson KA, Smith DH, Arrighi HM, Battista C. A cost of illness study of allergic rhinitis in the United States. *J Allergy Clin Immunol*. 1997;99(1, pt 1):22-27.

9. van Cauwenberge P, Bachert C, Passalacqua G, et al, European Academy of Allergology and Clinical Immunology. Consensus statement on the treatment of allergic rhinitis. *Allergy*. 2000;55:116-134.

10. Casale TB, Blaiss MS, Gelfand E, et al, Antihistamine Impairment Roundtable. First do no harm: managing antihistamine impairment in patients with allergic rhinitis. *J Allergy Clin Immunol*. 2003;111:S835-S842.

11. Kay AB. Allergy and allergic diseases. *N Engl J Med*. 2001;344:30-37.

12. Naclerio RM, Proud D, Togias AG, et al. Inflammatory mediators in late antigen-induced rhinitis. *N Engl J Med*. 1985;313:65-70.

13. Naclerio RM, Creticos PS, Norman PS, Lichtenstein LM. Mediator release after nasal airway challenge with allergen [letter]. *Am Rev Respir Dis*. 1986;134:1102.

14. Jeannin P, Delneste Y, Gosset P, et al. Histamine induces interleukin-8 secretion by endothelial cells. *Blood*. 1994;84:2229-2233.

15. Miki I, Kusano A, Ohta S, et al. Histamine enhanced the TNF-alpha-induced expression of E-selectin and ICAM-1 on vascular endothelial cells. *Cell Immunol*. 1996;171:285-288.

16. Kubes P, Kanwar S. Histamine induces leukocyte rolling in post-capillary venules: a P-selectin-mediated event. *J Immunol*. 1994;152:3570-3577.

17. Asako H, Kurose I, Wolf R, et al. Role of H1 receptors and P-selectin in histamine-induced leukocyte rolling and adhesion in postcapillary venules. *J Clin Invest*. 1994;93:1508-1515.

18. International Rhinitis Management Working Group. International Consensus Report on the diagnosis and management of rhinitis. *Allergy*. 1994;49(19, suppl):1-34

19. Dykewicz MS, Fineman S, Skoner DP, et al, American Academy of Allergy, Asthma, and Immunology. Diagnosis and management of rhinitis: complete guidelines of the Joint Task Force on Practice Parameters in Allergy, Asthma and Immunology. *Ann Allergy Asthma Immunol*. 1998;81(5, pt 2):478-518.

20. Howarth PH. The concept of the therapeutic window in the choice of H_1-receptor antagonist. *Adv Studies Med*. 2004;4:S508-S512.

21. Howarth PH. The choice of an H_1-antihistamine for the 21st century. *Clin Exp Allergy Rev*. 2002;2:18-25.

22. Howarth PH, Stern MA, Roi L, Reynolds R, Bousquet J. Double-blind, placebo-controlled study comparing the efficacy and safety of fexofenadine hydrochloride (120 and 180 mg once daily) and cetirizine in seasonal allergic rhinitis. *J Allergy Clin Immunol*. 1999;104:927-933.

23. Lockey RF, Widlitz MD, Mitchell DQ, et al. Comparative study of cetirizine and terfenadine versus placebo in the symptomatic management of seasonal allergic rhinitis. *Ann Allergy Asthma Immunol*. 1996;76:448-454.

24. Falliers CJ, Brandon ML, Buchman E, et al. Double-blind comparison of cetirizine and placebo in the treatment of seasonal rhinitis. *Ann Allergy*. 1991;66:257-262.

25. Salmun LM, Lorber R. 24-hour efficacy of once-daily desloratadine therapy in patients with seasonal allergic rhinitis [ISRCTN32042139]. *BMC Fam Pract*. 2002;3:14.

26. Wilson AM, Haggart K, Sims EJ, Lipworth BJ. Effects of fexofenadine and desloratadine on subjective and objective measures of nasal congestion in seasonal allergic rhinitis. *Clin Exp Allergy*. 2002;32:1504-1509.

27. Simons FE, Prenner BM, Finn A Jr, Desloratadine Study Group. Efficacy and safety of desloratadine in the treatment of perennial allergic rhinitis. *J Allergy Clin Immunol*. 2003;111:617-622.

28. Bernstein DI, Schoenwetter WF, Nathan RA, Storms W, Ahlbrandt R, Mason J. Efficacy and safety of fexofenadine hydrochloride for treatment of seasonal allergic rhinitis. *Ann Allergy Asthma Immunol*. 1997;79:443-448.

29. Casale TB, Andrade C, Qu R. Safety and efficacy of once-daily fexofenadine HCl in the treatment of autumn seasonal allergic rhinitis. *Allergy Asthma Proc*. 1999;20:193-198.

30. van Cauwenberge P, Juniper EF. Comparison of the efficacy, safety and quality of life provided by fexofenadine hydrochloride 120 mg, loratadine 10 mg and placebo administered once daily for the treatment of seasonal allergic rhinitis. *Clin Exp Allergy*. 2000;30:891-899.

31. Dockhorn RJ, Bergner A, Connell JT, et al. Safety and efficacy of loratadine (Sch-29851): a new non-sedating antihistamine in seasonal allergic rhinitis. *Ann Allergy*. 1987;58:407-411.

32. Skassa-Brociek W, Bousquet J, Montes F, et al. Double-blind placebo-controlled study of loratadine, mequitazine, and placebo in the symptomatic treatment of seasonal allergic rhinitis. *J Allergy Clin Immunol*. 1988;81:725-730.

33. Day JH, Briscoe M, Widlitz MD. Cetirizine, loratadine, or placebo in subjects with seasonal allergic rhinitis: effects after controlled ragweed pollen challenge in an environmental exposure unit. *J Allergy Clin Immunol*. 1998;101:638-645.

34. Day JH, Briscoe MP, Rafeiro E, Hewlett D Jr, Chapman D, Kramer B. Randomized double-blind comparison of cetirizine and fexofenadine after pollen challenge in the Environmental Exposure Unit: duration of effect in subjects with seasonal allergic rhinitis. *Allergy Asthma Proc*. 2004;25:59-68.

35. Day JH, Briscoe MP, Welsh A, et al. Onset of action, efficacy, and safety of a single dose of fexofenadine hydrochloride for ragweed allergy using an environmental exposure unit. *Ann Allergy Asthma Immunol*. 1997;79:533-540.

36. Albanesi C, Pastore S, Fanales-Belasio E, Girolomoni G. Cetirizine and hydrocortisone differentially regulate ICAM-1 expression and chemokine release in cultured human keratinocytes. *Clin Exp Allergy*. 1998;28:101-109.

37. Pestelli E, Floriani I, Fabbri P, Caproni M. Cetirizine modulates adhesion molecule expression in a double-blind controlled study conducted in psoriatic patients [published correction appears in *Int J Tissue React*. 2003;25:79]. *Int J Tissue React*. 2003;25:1-8.

38. Geha RS, Meltzer EO. Desloratadine: a new, nonsedating, oral antihistamine. *J Allergy Clin Immunol*. 2001;107:751-762.

39. Ciprandi G, Tosca MA, Cosentino C, Riccio AM, Passalacqua G, Canonica GW. Effects of fexofenadine and other antihistamines on components of the allergic response: adhesion molecules. *J Allergy Clin Immunol*. 2003;112(4, suppl):S78-S82.

40. Paolieri F, Battifora M, Riccio AM, et al. Terfenadine and fexofenadine reduce in vitro ICAM-1 expression on human continuous cell lines. *Ann Allergy Asthma Immunol*. 1998;81:601-607.

41. Shamsi Z, Hindmarch I. Sedation and antihistamines: a review of inter-drug differences using proportional impairment ratios. *Hum Psychopharmacol*. 2000;15:S3-S30.

42. Hindmarch I, Shamsi Z. Antihistamines: models to assess sedative properties, assessment of sedation, safety and other side-effects. *Clin Exp Allergy*. 1999;29(suppl 3):133-142.

43. Woosley RL. Cardiac actions of antihistamines. *Annu Rev Pharmacol Toxicol*. 1996;36:233-252.

44. Yap YG, Camm AJ. Potential cardiac toxicity of H_1 antihistamines.*Clin Allergy Immunol*. 2002;17:389-419.

45. Clarinex [package insert]. Kenilworth, NJ: Schering Corporation; 2002. Available at: www.spfiles.com/piclarinex.pdf. Accessibility verified July 13, 2005.

46. Pratt C, Brown AM, Rampe D, et al. Cardiovascular safety of fexofenadine HCl. *Clin Exp Allergy*. 1999;29(suppl 3):212-216.

47. Pratt CM, Mason J, Russell T, Reynolds R, Ahlbrandt R. Cardiovascular safety of fexofenadine HCl. *Am J Cardiol*. 1999;83:1451-1454.

48. Brannan MD, Reidenberg P, Radwanski E, et al. Loratadine administered concomitantly with erythromycin: pharmacokinetic and electrocardiographic evaluations. *Clin Pharmacol Ther*. 1995;58:269-278.

49. Hey JA, Affrime M, Cobert B, Kreutner W, Cuss FM. Cardiovascular profile of loratadine. *Clin Exp Allergy*. 1999;29(suppl 3):197-199.

50. Simons FE, Johnston L, Gu X, Simons KJ. Suppression of the early and late cutaneous allergic responses using fexofenadine and montelukast. *Ann Allergy Asthma Immunol*. 2001;86:44-50.

51. Triggiani M, Gentile M, Secondo A, et al. Histamine induces exocytosis and IL-6 production from human lung macrophages through interaction with H1 receptors. *J Immunol*. 2001;166:4083-4091.

52. Hwang K, Correll M, Offord SJ. Evaluation of desloratadine for absorption drug-drug interactions with ketoconazole. *J Allergy Clin Immunol*. 2001;107(2, pt 2):S153.

53. Allegra. Fexofenadine HCl [prescribing information]. Kansas City, Mo: Aventis Pharmaceuticals, Inc; 2003.

54. Hansten PD, Levy RH. Role of P-glycoprotein and organic anion transporting polypeptides in drug absorption and distribution: focus on H_1-receptor antagonists. *Clin Drug Invest*. 2001;21:587-596.

55. Cvetkovic M, Leake B, Fromm MF, Wilkinson GR, Kim RB. OATP and P-glycoprotein transporters mediate the cellular uptake and excretion of fexofenadine. *Drug Metab Dispos*. 1999;27:866-871.

56. Bailey DG, Dresser GK, Munoz C, Freeman DJ, Kim RB. Reduction of fexofenadine bioavailability by fruit juices [abstract]. *Clin Pharmacol Ther*. 2002;69:P21. Abstract PI-82.

57. Zyrtec. Cetirizine HCl [prescribing information]. New York, NY: Pfizer, Inc; 2004.

58. Tejani-Butt S, Yaroslavsky I. Determining the membrane permeability of newer antihistamines: implications for central nervous system function and safety [abstract]. *Proc 22nd EAACI*. 2003;276. Abstract 959.

59. Hampel F, Ratner P, Mansfield L, Meeves S, Liao Y, Georges G. Fexofenadine hydrochloride, 180 mg, exhibits equivalent efficacy to cetirizine, 10 mg, with less drowsiness in patients with moderate-to-severe seasonal allergic rhinitis. *Ann Allergy Asthma Immunol*. 2003;91:354-361.

60. Howarth PH. Assessment of antihistamine efficacy and potency. *Clin Exp Allergy*. 1999;29(suppl 3):87-97.

61. Welch MJ, Meltzer EO, Simons FE. H1-antihistamines and the central nervous system. *Clin Allergy Immunol*. 2002;17:337-388.

62. Simons FE. Advances in H1-antihistamines. *N Engl J Med*. 2004;351: 2203-2217.

63. Hindmarch I, Shamsi Z, Stanley N, Fairweather DB. A double-blind, placebo-controlled investigation of the effects of fexofenadine, loratadine and promethazine on cognitive and psychomotor function. *Br J Clin Pharmacol*. 1999;48:200-206.

64. Hindmarch I, Shamsi Z, Kimber S. An evaluation of the effects of high-dose fexofenadine on the central nervous system: a double-blind, placebo-controlled study in healthy volunteers. *Clin Exp Allergy*. 2002;32:133-139.

65. Mann RD, Pearce GL, Dunn N, Shakir S. Sedation with "non-sedating" antihistamines: four prescription-event monitoring studies in general practice. *BMJ*. 2000;320:1184-1186.

66. Dogan A, Catafau A, Zhou Y, et al. In vivo cerebral histamine receptor occupancy of three antihistamine drugs: a ^{11}C-doxepin pet study [abstract]. *J Nucl Med*. 2001;42:143P-144P. Abstract 537.

67. Tashiro M, Sakurada Y, Iwabuchi K, et al. Central effects of fexofenadine and cetirizine: measurement of psychomotor performance, subjective sleepiness, and brain histamine H1-receptor occupancy using 11C-doxepin positron emission tomography. *J Clin Pharmacol*. 2004;44:890-900.

68. Weiler JM, Bloomfield JR, Woodworth GG, et al. Effects of fexofenadine, diphenhydramine, and alcohol on driving performance: a randomized, placebo-controlled trial in the Iowa driving simulator. *Ann Intern Med*. 2000;132:354-363.

69. Vuurman EF, Rikken GH, Muntjewerff ND, de Halleux F, Ramaekers JG. Effects of desloratadine, diphenhydramine, and placebo on driving performance and psychomotor performance measurements. *Eur J Clin Pharmacol*. 2004;60:307-313.

70. Verster JC, de Weert AM, Bijtjes SI, et al. Driving ability after acute and sub-chronic administration of levocetirizine and diphenhydramine: a randomized, double-blind, placebo-controlled trial. *Psychopharmacology (Berl)*. 2003;169:84-90.

71. Ramaekers JG, Uiterwijk MM, O'Hanlon JF. Effects of loratadine and cetirizine on actual driving and psychometric test performance, and EEG during driving. *Eur J Clin Pharmacol*. 1992;42:363-369.

72. Taglialatela M, Timmerman H, Annunziato L. Cardiotoxic potential and CNS effects of first-generation antihistamines. *Trends Pharmacol Sci*. 2000; 21:52-56.

73. Moss AJ, Chaikin P, Garcia JD, Gillen M, Roberts DJ, Morganroth J. A review of the cardiac systemic side-effects of antihistamines: ebastine. *Clin Exp Allergy*. 1999;29(suppl 3):200-205.

74. Horak F, Stubner UP, Zieglmayer R, Harris AG. Effect of desloratadine versus placebo on nasal airflow and subjective measures of nasal obstruction in subjects with grass pollen-induced allergic rhinitis in an allergen-exposure unit. *J Allergy Clin Immunol*. 2002;109:956-961.

75. Nunes C, Ladeira S. Double-blind study of cetirizine and loratadine versus placebo in patients with allergic rhinitis. *J Investig Allergol Clin Immunol*. 2000;10:20-23.

76. Wilson AM, Haggart K, Sims EJ, Lipworth BJ. Effects of fexofenadine and desloratadine on subjective and objective measures of nasal congestion in seasonal allergic rhinitis. *Clin Exp Allergy*. 2002;32:1504-1509.

77. Juniper EF, Thompson AK, Ferrie PJ, Roberts JN. Validation of the standardized version of the Rhinoconjunctivitis Quality of Life Questionnaire. *J Allergy Clin Immunol*. 1999;104(2, pt 1):364-369.

78. Bousquet J, Duchateau J, Pignat JC, et al. Improvement of quality of life by treatment with cetirizine in patients with perennial allergic rhinitis as determined by a French version of the SF-36 questionnaire. *J Allergy Clin Immunol*. 1996;98:309-316.

79. Tanner LA, Reilly M, Meltzer EO, Bradford JE, Mason J. Effect of fexofenadine HCl on quality of life and work, classroom, and daily activity impairment in patients with seasonal allergic rhinitis. *Am J Manag Care*. 1999; 5:S235-S247.

80. Okubo K, Gotoh M, Shimada K, Ritsu M, Okuda M, Crawford B. Fexofenadine improves the quality of life and work productivity in Japanese patients with seasonal allergic rhinitis during the peak cedar pollinosis season. *Int Arch Allergy Immunol*. 2005;136:148-154.

81. Meltzer EO, Casale TB, Nathan RA, Thompson AK. Once-daily fexofenadine HCl improves quality of life and reduces work and activity impairment in patients with seasonal allergic rhinitis. *Ann Allergy Asthma Immunol*. 1999;83:311-317.

82. Noonan MJ, Raphael GD, Nayak A, et al. The health-related quality of life effects of once-daily cetirizine HCl in patients with seasonal allergic rhinitis: a randomized double-blind, placebo-controlled trial. *Clin Exp Allergy*. 2003;33:351-358.

83. Murray JJ, Nathan RA, Bronsky EA, Olufade AO, Chapman D, Kramer B. Comprehensive evaluation of cetirizine in the management of seasonal allergic rhinitis: impact on symptoms, quality of life, productivity, and activity impairment. *Allergy Asthma Proc*. 2002;23:391-398.

84. Condemi J, Schulz R, Lim J. Triamcinolone acetonide aqueous nasal spray versus loratadine in seasonal allergic rhinitis: efficacy and quality of life. *Ann Allergy Asthma Immunol*. 2000;84:533-538.

85. Bachert C, Bousquet J, Canonica GW, et al, XPERT Study Group. Levocetirizine improves quality of life and reduces costs in long-term management of persistent allergic rhinitis. *J Allergy Clin Immunol*. 2004;114: 838-844.

86. Schmier J, Leidy N, Prasad M. Health-related quality of life outcomes of desloratadine in patients with moderate-to-severe SAR [abstract]. *Ann Allergy Asthma Immunol*. 2001;86:111. Abstract P69.

87. Coren J, Salmun M. Quality of life in patients with seasonal allergic rhinitis is improved by desloratadine. *Allergy*. 2000;55(suppl 63):191.

88. Hoffmann C. Seasonal allergy treatment affected by OTC Claritin. FirstWord, April 21, 2003. Available at: www.firstwordplus.com/Fws.do?articleid=0053C577AEE5A70285256D0F00740323. Accessibility verified July 13, 2005.