Drugs 2006; 66 (18): 2309-2319
0012-6667/06/0018-2309/$44.95/0

Selecting the Optimal Oral Antihistamine for Patients with Allergic Rhinitis

Jeffrey M. Lehman and *Michael S. Blaiss*

Department of Pediatrics, Division of Clinical Allergy and Immunology, University of Tennessee Health Science Center, Memphis, Tennessee, USA

Contents

Abstract

Allergic rhinitis (AR) is now recognised as a global health problem that affects 10–30% of adults and up to 40% of children. Each year, millions of patients seek treatment from their healthcare provider. However, the prevalence of AR maybe significantly underestimated because of misdiagnosis, under diagnosis and failure of patients to seek medical attention. In addition to the classical symptoms such as sneezing, nasal pruritus, congestion and rhinorrhoea, it is now recognised that AR has a significant impact on quality of life (QOL). This condition can lead to sleep disturbance as a result of nasal congestion, which leads to significant impairment in daily activities such as work and school. Traditionally, AR has been subdivided into seasonal AR (SAR) or perennial AR (PAR). SAR symptoms usually appear during a specific season in which aeroallergens are present in the outdoor air such as tree and grass pollen in the spring and summer and weed pollens in the autumn (fall); and PAR symptoms are present year-round and are triggered by dust mite, animal dander, indoor molds and cockroaches. Oral histamine H_1-receptor antag-

onists (H_1 antihistamines) are one of the most commonly prescribed medications for the treatment of AR. There are several oral H_1 antihistamines available and it is important to know the pharmacology, such as administration interval, onset of action, metabolism and conditions that require administration adjustments. When prescribing oral H_1 antihistamines, the healthcare provider must take into account the clinical efficacy and weigh this against the risk of adverse effects from the agent. In addition to the clinical efficacy, potential for improvement in QOL with a particular treatment should also be considered.

Allergic rhinitis (AR) is now recognised as a global health problem that affects 10–30% of adults and up to 40% of children.[1] Each year, there are millions of office visits for AR and its complications, such as sinus disease and otitis media with effusion. However, the prevalence of AR may be underestimated because of misdiagnosis, under diagnosis and failure of patients to seek medical attention.[2-4]

AR is a disorder of the nasal tissue caused by IgE-mediated inflammation and manifests clinically as sneezing, itching, rhinorrhoea and nasal obstruction.[3,5] Ocular symptoms including pruritus, oedema and lacrimation are also commonly associated with AR. In addition to the classical symptoms, it is now recognised that AR has a significant impact on the quality of life (QOL) of those who experience it. A major condition commonly encountered as a result of AR is sleep disturbance. Failure to get a good night's sleep as a result of symptoms of AR can cause significant impairment in daily activities such as work and school.[1,6,7] The vast majority of patients with asthma have AR. Several studies have also shown severe rhinitis symptoms in patients with asthma was associated with worse asthma outcomes.[8-10]

Traditionally, AR has been subdivided into seasonal AR (SAR) or perennial AR (PAR). SAR symptoms usually appear during a specific season in which aeroallergens are present in the outdoor air such as tree and grass pollen in the spring and summer and weed pollens in the autumn (fall); and PAR symptoms are present year-round and are triggered by dust mite, animal dander, indoor molds and cockroaches.[3] The recent Allergic Rhinitis and its Impact on Asthma (ARIA) recommendations, composed of a panel of experts in conjunction with the WHO, have proposed a new classification for AR.[5] These guidelines were intended to educate healthcare providers and aid in the diagnosis and treatment of AR on the basis of symptom duration and severity. However, it was shown that the classic types of seasonal and perennial rhinitis cannot be used interchangeably with the new classification of intermittent/persistent, because they do not represent the same stratum of disease.[4] Furthermore, to date all clinical trials have utilised SAR and PAR.

Treatment of AR includes avoidance of allergic triggers, the use of pharmacological agents and allergen specific immunotherapy. There are numerous pharmacological agents available to help control AR. These include oral first- and second-generation histamine H_1 receptor antagonists (H_1 antihistamines), intranasal antihistamines, intranasal corticosteroids, leukotriene receptor antagonists, mast cell stabilisers, intranasal anticholinergics, and oral and intranasal decongestants. Oral H_1 antihistamines and intranasal corticosteroids are recommended as first-line therapy.[1,2,5,11] This review focuses on oral H_1 antihistamines and helps to guide the healthcare provider in selecting the most appropriate oral H_1 antihistamine based on favourable effects including rapid onset of action, low potential for drug interaction and improvements in QOL and avoidance of undesired side effects such as sedation and dry mouth.

1. Pathophysiology of Allergic Rhinitis

The tendency to develop a T helper type 2 (T_h2) cell immune response is inherited in atopic patients.[3] Sensitisation to specific inhalant allergens

occurs when they are presented by antigen presenting cells to CD4+ T cells that belong to the T_h2 subset, leading to the production of interleukin (IL)-3, IL-4, IL-5, IL-13 and other T_h2 cytokines. These cytokines stimulate B cells to become plasma cells, which produce IgE specific for that allergen. The IgE then binds to high affinity IgE receptors on mast cells and basophils. Upon re-exposure to the specific allergen, it binds to the IgE on mast cells and basophils and starts a cascade of events leading to the symptoms of AR. The allergic response in AR can be subdivided into the acute or early phase and the late phase.

1.1 Early Phase

Allergen binds to IgE on mast cells which causes these cells to degranulate and release pre-formed inflammatory mediators such as histamine, tryptase, chymase, heparin and other enzymes.[3,12] In addition to the preformed mediators, mast cells also synthesise mediators *de novo* such as prostaglandin (PG)D_2, cysteinyl leukotrienes (LTC4, LTD4 and LTE4) and platelet activating factor (PAF).[2,3,13] Histamine is a prominent mediator of the early phase resulting in vascular leakage via H_1 receptors and stimulation of nerve endings, thus resulting in the symptoms of rhinorrhoea, sneezing and nasal pruritus.[2,3]

1.2 Late Phase

The late-phase response occurs several hours after the early phase. It involves cellular infiltration of eosinophils, basophils, T cells, neutrophils and macrophages into the nasal tissue.[14,15] These cells release cytokines and other inflammatory mediators leading to a clinically similar response to the early phase. Eosinophil-derived mediators such as major basic protein, eosinophil cationic protein and leukotrienes have been shown to distort the epithelium ultimately leading to chronic allergic inflammation.[3]

2. Pharmacology

Histamine is primarily produced by mast cells and basophils, and is released upon antigen binding to IgE on the cell surface and crosslinking FcεRI (a high-affinity receptor for IgE).[16] Histamine then acts in the nose to cause vasodilatation and increased vascular permeability, and stimulation of sensory nerves leading to the sensation of itching. This manifests clinically as sneezing, rhinorrhoea and pruritus.[17] There are at least four types of histamine receptors that have been identified. However, the majority of allergic responses are mediated via the H_1 receptor.[16] The second-generation H_1 antihistamines have very high avidity and selectivity for H_1 receptors.[18-21] H_1 antihistamines are inverse agonists that combine with and stabilise the inactive form of the H_1 receptor leading toward a shift in equilibrium to the inactive state.[22,23] In addition to antagonising histamine at the H_1 receptor, the newer second-generation agents have both antiallergic and anti-inflammatory properties. They have been shown to inhibit the release of mediators from mast cells and basophils through a direct inhibitory effect on calcium-ion channels.[24] Pretreatment with an H_1 antihistamine has been shown to decrease the early response to an allergen challenge through decreasing the levels of proinflammatory cell adhesion molecules, cytokines, mediators such as histamine, leukotrienes and prostaglandins.[25-27]

2.1 First-Generation Oral Antihistamines

The older first-generation H_1 antihistamines such as diphenhydramine, chlorphenamine (chlorpheniramine), brompheniramine and hydroxyzine are also referred to as the sedating antihistamines. These agents are effective at controlling the rhinorrhoea, sneezing and pruritus associated with AR. However, because these older agents cross the blood-brain barrier they are associated with significant adverse effects, such as sedation leading to impaired performance at home, work and school.[1,28] Even when first-generation antihistamines are taken at bedtime, they may still cause significant residual daytime sedation, decreased alertness and performance impairment.[28] These agents have poor H_1-receptor selectivity and act on muscarinic receptors causing anticholinergic effects such as dry mouth, urinary retention, constipation and tachycardia.[1,29,30] The

high risk to benefit ratio makes the first-generation H_1 antihistamines a less attractive therapeutic option and they are not recommended as first-line therapy in AR.

2.2 Second-Generation Oral Antihistamines

The newer second-generation H_1 oral antihistamines were first developed in the early 1980s to improve on the sedative and anticholinergic adverse effects in the first-generation agents. The second-generation antihistamines have improved H_1-receptor selectivity, absence or decreased sedation, faster onset and longer duration of action and fewer adverse effects.[13,31] The currently available second-generation H_1 antihistamines are shown in table I. Most second-generation H_1 antihistamines have been shown to have antiallergic and anti-inflammatory properties *in vivo* or *in vitro*.

In general, second-generation antihistamines exhibit favourable pharmacokinetics.[32] They have a relatively quick onset of action, near complete absorption, widespread tissue distribution with minimal CNS penetration, unlike first-generation antihistamines, and relatively long half-life allowing for once-daily administration.[33] The pharmacodynamics and pharmacokinetics of second-generation antihistamines are summarised in table II.[34-40] The second-generation H_1 antihistamines have a similar core moiety, but it is the radicals or side chains adjoining the core which determine the absorption, distribution and elimination of each agent.[41]

It is rather difficult to study the clinical effectiveness of AR treatment because of the variability that is associated with the disorder. Therefore, several standardised methods have been developed to objectively assess the clinical efficacy of AR treatment such as exposure unit and pollen chamber studies and unique outcome measures such as measuring nasal airflow obstruction or patient symptom recording.[42] One method that has become increasingly important in efficacy trials is assessment of QOL.[43] Several controlled trials of second-generation H_1 antihistamines have been published and have shown overall relief of symptoms reported by patients.[42,44-75] Notably, all clinical trials that have been published to date assessing second-generation H_1 antihistamines in the treatment of AR have been on patients with SAR and PAR and not intermittent AR or persistent AR.[5] Examination of these trials has lead to several conclusions: (i) the overall effectiveness of second-generation antihistamines for symptomatic treatment of AR was quite good; (ii) patient acceptance and overall satisfaction was good; and (iii) adverse effects were mild.[62] Several clinical trials assessing QOL in patients with AR have also been reported. Overall, treatment with second-generation antihistamines consistently improves QOL.

Table I. Available second-generation oral H_1 antihistamines

Antihistamine	Usual daily adult dose
Cetirizine	5–10mg
Desloratadine	5mg
Fexofenadine	60mg bid or 120–180mg
Loratadine	5–10mg
Levocetirizine[a]	5mg

a Not available in the US at the time of publication.
bid = twice daily.

2.2.1 Cetirizine

Cetirizine, a metabolite of hydroxyzine, exists mainly as a zwitterion allowing for low volume of distribution, low serum concentration and a decreased affinity for myocardium with decreased risk for cardiotoxicity.[76] Cetirizine is rapidly absorbed and achieves peak plasma concentration in ≈1 hour. In addition to H_1 receptor antagonism, cetirizine was found to inhibit eosinophil chemotaxis during the allergic response and, therefore, blunted the late-phase reaction.[77]

Cetirizine is the only second-generation H_1 antihistamine to cause an increased incidence of sedation at its recommended dose in patients ≥12 years of age.[78] Therefore, cetirizine is classified as mildly sedating and should not be prescribed to patients whose jobs require high psychomotor skills such as pilots.[79] Cetirizine has been shown in numerous clinical trials to be more efficacious compared with placebo in the treatment of both SAR and PAR.[46-50,80] Cetirizine significantly improved QOL measures of general health, physical functioning, vitality, social functioning, and emotional and

Table II. Pharmacodynamics and pharmacokinetics of second-generation H_1 antihistamines[a]

Antihistamine	Usual adult dosage	t_{max} (h)	Onset of action (h)	$t_{½}$ (h)	Duration of action (h)	Elimination renal/faecal (%)	Conditions that require dose adjustment	References
Cetirizine	5–10 mg/day	0.8	1–1.5	7	24	70/10	Renal and hepatic impairment	35-37
Desloratadine	5 mg/day	4	0.5–3	13–30	24	44/44	Renal and hepatic impairment	35,38
Fexofenadine	60mg bid; 120 mg/day; or 80 mg/day	1.2	1–2	12–15	24	12/80	Renal impairment	34,35,37,39
Loratadine	5–10 mg/day	1.5	1.5–2	11–14	24	20/40	Hepatic impairment	35-37
Levocetirizine[b]	5 mg/day	0.8	1	7	24	86/13	Renal and hepatic impairment	35,36,40

a Results are expressed as mean.

b Not available in the US at the time of publication.

bid = twice daily; $t_{½}$ = elimination half-life; t_{max} = time after dose to reach maximum plasma concentration.

mental health within 1 week of treatment and continued up to 6 weeks.[81] In a small but similar study, cetirizine improved QOL measures compared with placebo.[80]

2.2.2 Loratadine

Loratadine has been found to exert protective effects on the early and late phase of conjunctival allergic reactions.[26,82] Loratadine is a nonsedating antihistamine, and psychomotor tests confirm its safety at the recommended dosage (10 mg/day).[83] However, performance studies with higher, off-label loratadine doses of 20 and 40mg showed significant impairment and sedation in some objective performance tests compared with placebo.[84]

Although the placebo-controlled studies with loratadine are limited, two studies[74,75] have shown that loratadine was superior to placebo in the treatment of AR.

2.2.3 Fexofenadine

Fexofenadine, the active metabolite of terfenadine, is a potent H_1 receptor antagonist that does not display cardiotoxicity like its predecessor.[85] In addition to blocking H_1 receptors, *in vitro* and *in vivo* studies have shown that fexofenadine reduces allergic inflammatory responses mediated by mast cells, basophils, epithelial cells, eosinophils and lymphocytes.[71,86] Fexofenadine has proven anti-inflammatory activity and has been shown to inhibit intercellular adhesion molecule 1 expression on nasal epithelium *in vitro*.[82]

Numerous clinical trials have shown fexofenadine to be more efficacious than placebo for the symptoms of SAR.[64-70] Fexofenadine is approved for use in the US for SAR but not PAR.[87] Van Cauwenberge et al.[71] conducted a large, multinational, double-blind, placebo-controlled, 2-week trial of fexofenadine (120mg once daily) versus loratadine (10mg once daily) in patients with SAR. Individual symptoms were self-assessed and no difference in overall symptom scores was observed between fexofenadine and loratadine. However, fexofenadine significantly improved the individual symptoms of nasal congestion and itchy, watery, red eyes compared with loratadine. Fexofenadine was found to decrease work impairment and benefit emotions, sleep and practical problems.[69]

2.2.4 Desloratadine

Desloratadine is the active metabolite of loratadine and is approved for use in children ≥12 years of age for both SAR and PAR.[88] Desloratadine has the greatest avidity for the H_1 receptor, although poor selectivity.[18] Desloratadine has been shown to inhibit IgE mediated and non-IgE mediated release of IL-4 and IL-13 from human basophils *in vitro*.[27] Like loratadine, desloratadine significantly reduces the symptoms of SAR. However, as in the case of loratadine (see section 2.2.2),

somnolence has been noted at higher, off-label doses.[35,84,89,90]

Desloratadine has been shown in several randomised, clinical trials to significantly improve patients symptoms.[60,61] Two, randomised, double-blind, multicentre studies comparing the efficacy of desloratadine with placebo showed a statistically significant reduction in symptoms in patients with SAR over a 2-week study period.[60] Desloratadine treatment of SAR resulted in improvement of social functioning and symptoms.[59] Desloratadine rapidly and safely reduced the symptoms of PAR, and its efficacy did not diminish during 4 weeks of treatment.[91] However, no large clinical trials studying the effect of desloratadine on QOL have been reported.[40]

2.2.5 Levocetirizine

Levocetirizine is the enantiomer of cetirizine. Levocetirizine, like cetirizine, exists as a zwitterion and, thus, has a lower volume of distribution and also has been shown to inhibit eotaxin-induced transendothelial migration of eosinophils *in vitro*.[77,90]

Levocetirizine, like cetirizine, is also considered mildly sedating in placebo-controlled trials.[92] A randomised trial involving >400 patients with SAR found that levocetirizine significantly reduced symptom scores over an 8-week period. A large, multicentre study in children with SAR and PAR found that 4–6 weeks of treatment with levocetirizine significantly improved symptoms and QOL.[93] A multinational, placebo-controlled study recently found that levocetirizine significantly improved QOL over 6 months of treatment.[5]

2.2.6 Comparative Studies

A double-blinded, placebo-controlled, parallel group study comparing fexofenadine, loratadine or placebo in the treatment of SAR showed that both fexofenadine and loratadine were superior to placebo in patient symptom scores; however, fexofenadine decreased the scores for itchy, watery, red eyes and nasal congestion more than loratadine.[71] Lee at al.[94] conducted a crossover study comparing the protective effect of single doses of levocetirizine, desloratadine and fexofenadine against adenosine monophosphate in 16 patients with PAR. All three drugs provided significant improvement in nasal peak inspiratory flow compared with placebo with no differences between them. Several clinical studies have shown that cetirizine and fexofenadine were significantly more efficacious than placebo in the treatment of SAR with no difference between them;[52-54] however, fexofenadine produced less drowsiness.[54] It should be noted that both SAR and PAR often coexist in study participants thus making it difficult to interpret the results of these clinical trials.

3. Adverse Effects

First-generation antihistamines have the greatest potential for serious adverse effects. There are no long-term safety studies on the first-generation antihistamines. These older antihistamines have potential for serious adverse effects such as CNS, depression and cardiotoxicity, and have also been associated with fatalities in accidental and intentional paediatric overdose.[95-97] In contrast, second-generation antihistamines are relatively free of adverse effects and are generally well tolerated. The most prevalent adverse effects associated with second-generation antihistamines reported by the manufacturers from large-scale clinical trials are shown in table III.[78,87,88,92,98]

3.1 CNS 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. The second-generation antihistamines, also referred to as nonsedating, have a decreased tendency to cross the blood-brain barrier.[99] Consequently, second-generation antihistamines are respected for their low potential to cause CNS effects.

Several studies have been conducted to assess the severity and magnitude of CNS depression that these drugs can cause. The majority of these studies focused on subjective and objective measures of sedation such as: sleepiness/wakefulness scores, sleep latency, EEG changes, driving ability, learning/school performance and memory. Studies in-

Table III. Adverse effects with second-generation H_1 antihistamines (% patients/placebo)

Antihistamine (dosage)	Drowsiness	Fatigue	Headache	Dry mouth	Dizziness	GI distress	Dysmenorrhoea	Reference
Cetirizine 10 mg/day	13.7/6.3	5.9/2.6		5/2.3	2/1.2			78
Desloratadine 5 mg/day	2.1/1.8	2.1/1.2		3/1.9			2.1/1.6	88
Fexofenadine 180 mg/day	1.3/0.9	1.3/0.9	10.6/7.5[a]			1.3/0.6	1.5/0.3	87
Loratadine 10 mg/day	8/6	4/3	12/11	3/2				98
Levocetirizine 5 mg/day[b]	5.2/1.4	2.5/1.2	2.6/3.2	2.6/1.6				92

a 60mg twice daily.

b Not available in the US at the time of publication.

GI = gastrointestinal.

volving first-generation antihistamines have consistently shown significantly greater effects on sedation scores, psychomotor test performance and cognitive function compared with second-generation H_1 antihistamines.[89,100-109] Therefore, second-generation antihistamines are generally preferred over first-generation antihistamines especially for people whose jobs require a high level of psychomotor skills.

Multiple studies have evaluated the effects that second-generation antihistamines have on the CNS. Loratadine and desloratadine were found to be comparable with placebo at therapeutic doses, but caused sedation when used off label at higher than recommended doses.[35,42,84,89] Several studies have shown that cetirizine, given at therapeutic doses, causes a slight to moderate increase in sedation, decreased psychomotor function and worsening cognitive function.[102-108] In contrast, fexofenadine has been found to be free of sedative effects even at higher than therapeutic doses.[84,89,110] Memory, attention and tracking performance were unaffected after administration of levocetirizine compared with diphenhydramine and placebo.[111]

3.2 Cardiotoxicity

The potential for H_1 antihistamines to produce cardiotoxicity is directly related to their plasma concentration and, therefore, appropriate administration and drug-drug interactions are important. The first-generation antihistamines have been found to prolong the QT interval at higher than recommended doses.[112] Terfenadine and astemizole, both second-generation antihistamines, were withdrawn from the US market because of their cardiotoxic effects at increased plasma concentrations caused by drug-drug interactions.[35] Currently, no clinically significant cardiotoxic effects have been reported for loratadine, desloratadine, fexofenadine, cetirizine and levocetirizine.[40,81,113]

4. Drug Interactions

Drug-drug interactions usually occur as a result of altered metabolism in the hepatic cytochrome P450 (CYP) system or through interference with absorption via active transport mechanisms such as P-glycoprotein and organic-anion transporters.[13,35] Loratadine and desloratadine undergo CYP metabolism like terfenadine and astemizole, which are no longer on the market.[35,40,42] Therefore, loratadine and desloratadine are more susceptible to altered plasma concentrations when taken in conjunction with other medications that are metabolised via the CYP system. Conversely, fexofenadine, cetirizine and levocetirizine are not metabolised by the CYP450 system, which makes them less susceptible to interactions involving this mechanism.[35,40,42] However, they still remain susceptible to interactions involving P-glycoprotein and organic-anion active transport mechanisms.

Fexofenadine is a substrate for P-glycoprotein, which is a membrane-bound transporter that inhibits absorption and promotes excretion.[114] Grapefruit juice has been found *in vitro* to inhibit P-glycoprotein activity.[115] Therefore, when consumed with grapefruit juice, the plasma concentration of fexofenadine can be decreased by up to 40%.[116] This is thought to be caused by inhibition of the organic

Table IV. Guidelines for the treatment of allergic rhinitis

1. Allergen avoidance if allergen identified via history and/or tests
2. For mild symptoms, start with an oral second-generation H_1 antihistamine; for moderate to severe symptoms or the primary treatment of nasal congestion, use an intranasal corticosteroid
3. For persistent nasal symptoms, a combination of intranasal corticosteroids and a combination oral second-generation H_1 antihistamine/decongestant may be tried
4. Consider an intranasal antihistamine and/or leukotriene-receptor antagonist if symptoms continue
5. For ocular symptoms, add a topical mast cell stabiliser/antihistamine (multi-action) agent, e.g. olapatadine, epinastine, azelastine
6. Consider immunotherapy if relief with medication is inadequate or to prevent further progression of allergic disease

anion transporting polypeptide mediated drug uptake.[116] Rifampin can upregulate P-glycoprotein activity and, thus, when taken in conjunction with fexofenadine, peak plasma concentrations of fexofenadine are decreased.[117] Conversely, when fexofenadine is taken in conjunction with ketoconazole and erythromycin, plasma concentrations of fexofenadine may be increased thus increasing the potential for adverse effects.[87,113] It is important to note that these effects have not been found to be clinically significant and that no serious adverse effects attributable to drug interactions with second-generation H_1 antihistamines have been reported.

5. Conclusions

AR is a common chronic disorder that can significantly interfere with a patient's QOL. The goals of treatment are to provide the patient with symptom relief and improvement in QOL with minimal adverse effects. Oral second-generation antihistamines are considered first-line or second-line therapy (table IV)[5] for the treatment of AR and their use has been supported in numerous clinical trials. Although they are not completely free from adverse effects such as drowsiness or altered cognition, all the second-generation H_1 antihistamines have good benefit with minimal risk compared with oral first-generation antihistamines. These agents can be an important part of the regimen to control the patient's allergy condition.

Acknowledgements

No sources of funding were used to assist in the preparation of this review. Dr Blaiss has acted as a consultant and has received honoraria from Alcon, Alliant, Altana, Astra Zeneca, GlaxoSmithKline, Inspire, King, Merck, sanofi-aventis, Schering Plough and Teva, and has stock or options in Schering Plough. Dr Lehman has no conflicts of interest that are directly relevant to the content of this review.

References

1. Dykewicz MS, Fineman S, Skoner DP, et al. Diagnosis and management of rhinitis: complete guidelines of the Joint Task Force on Practice Parameters in Allergy, Asthma and Immunology. American Academy of Allergy, Asthma and Immunology. Ann Allergy Asthma Immunol 1998 Nov; 81 (5): 478-518
2. Gandhi RK, Blaiss MS. Current concepts and therapeutic strategies for allergic rhinitis. Otorinolaringol 2005; 55 (3): 187-201
3. Skoner DP. Allergic rhinitis: definition, epidemiology, pathophysiology, detection, and diagnosis. J Allergy Clin Immunol 2001 Jul; 108 (1): S2-8
4. Bousquet J, Neukirch F, Bousquet PJ, et al. Severity and impairment of allergic rhinitis in patients consulting in primary care. J Allergy Clin Immunol 2006 Jan; 117 (1): 158-62
5. Bousquet J, Van Cauwenberge P, Khaltaev N. Allergic rhinitis and its impact on asthma. J Allergy Clin Immunol 2001 Nov; 108 Suppl. 5: S147-334
6. Leynaert B, Neukirch C, Laird R, et al. Quality of life in allergic rhinitis and asthma: a population-based study of young adults. Am J Respir Crit Care Med 2000 Oct; 162 (4): 1391-6
7. Craig TJ, McCann JL, Gurevich F, et al. The correlation between allergic rhinitis and sleep disturbance. J Allergy Clin Immunol 2004 Nov; 114 (5): S139-45
8. Huse DM, Hartz SE, Russell MW, et al. Allergic rhinitis may worsen asthma symptoms in children: the international asthma outcomes registry [abstract]. Am J Respir Crit Care Med 1996; 153: A860
9. Corren J, Adinoff AD, Irvin CG. Changes in bronchial responsiveness following nasal provocation with allergen. J Allergy Clin Immunol 1992; 89: 611-8
10. Corren J. Allergic rhinitis and asthma: how important is the link? J Allergy Clin Immunol 1997; 99: S781-6
11. Blaiss M. Current concepts and therapeutic strategies for allergic rhinitis in school-age children. Clin Ther 2004; 26 (11): 1876-89
12. Naclerio RM. Allergic rhinitis. N Engl J Med 1991 Sep; 325 (12): 860-9
13. Meltzer EO. Evaluation of the optimal oral antihistamine for patients with allergic rhinitis. Mayo Clin Proc 2005 Sep; 80 (9): 1170-6
14. Naclerio RM, Proud D, Togias AG, et al. Inflammatory mediators in late antigen-induced rhinitis. N Engl J Med 1985 Jul; 313 (2): 65-70
15. Bascom R, Pipkorn U, Lichtenstein LM, et al. The influx of inflammatory cells into nasal washings during the late response to antigen challenge: effect of systemic steroid pretreatment. Am Rev Respir Dis 1988; 138: 406-12
16. Ash ASF, Schild HO. Receptors mediating some actions of histamine. Br J Pharmacol 1966; 27: 427-39

17. Simons FER, Simons KJ. The pharmacology and use of H_1-receptor-antagonist drugs. N Engl J Med 1994; 330: 1663-70
18. Anthes J, Eckel S, Richard C, et al. Characterization of [^{3}H] desloratadine at the human H_1 receptor [abstract no. 526]. J Allergy Clin Immunol 2001; 107 Suppl. 2: 160
19. Anthes JC, Gilchrest H, Richard C, et al. Biochemical characterization of desloratadine, a potent antagonist of the human histamine H_1 receptor. Eur J Pharmacol 2002; 449: 229-37
20. Snyder SH, Snowman AM. Receptor effects of cetirizine. Ann Allergy 1987; 59 (6 Pt 2): 4-8
21. Weiland K, Ter Laak AM, Smit MJ, et al. Mutational analysis of the antagonist-binding site of the histamine H_1 receptor. J Biol Chem 1999; 274: 29994-30000
22. Bakker RA, Schoonus SB, Smit MJ, et al. Histamine H_1-receptor activation of nuclear factor-kappa B: roles for G beta gamma- and G alpha(q/11)-subunits in constitutive and agonist-mediated signaling. Mol Pharmacol 2001; 60: 1133-42
23. Leurs R, Church MK, Taglialatela M. H_1-antihistamines: inverse agonism, anti-inflammatory actions and cardiac effects. Clin Exp Allergy 2002; 32: 489-98
24. Rimmer SJ, Church MK. The pharmacology and mechanisms of action of histamine H_1-antagonists. Clin Exp Allergy 1990 Aug; 20 Suppl. 2: 3-17
25. Naclerio RM. The effect of antihistamines on the immediate allergic response: a comparative review. Otolaryngol Head Neck Surg 1993 Jun; 108 (6): 723-30
26. Ciprandi G, Passalacqua G, Canonica GW. Effects of H_1 antihistamines on adhesion molecules: a possible rationale for long-term treatment. Clin Exp Allergy 1999; 29 Suppl. 3: 49-53
27. Schroeder JT, Schleimer RP, Lichtenstein LM, et al. Inhibition of cytokine generation and mediator release by human basophils treated with desloratadine. Clin Exp Allergy 2001; 31: 1369-77
28. Kay GG. The effects of antihistamines on cognition and performance. J Allergy Clin Immunol 2000 Jun; 105 (6): S622-7
29. 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: 116-34
30. International Rhinitis Management Working Group. International Consensus Report on the diagnosis and management of rhinitis. Allergy 1994; 49 Suppl. 19: 1-34
31. Passalacqua G, Bousquet J, Bachert C, et al. The clinical safety of H_1-receptor antagonists: an EAACI position paper. Allergy 1996 Oct; 51 (10): 666-75
32. Simons FER, Simons KJ. Clinical pharmacology of new histamine H_1 receptor antagonists. Clin Pharmacokinet 1999; 36: 329-52
33. Baltes E, Coupez R, Giezek H, et al. Absorption and disposition of levocetirizine, the eutomer of cetirizine, administered alone or as cetirizine to healthy volunteers. Fundam Clin Pharmacol 2001; 15: 269-77
34. Simons FER, Simons KJ. Peripheral H_1-blockade effect of fexofenadine. Ann Allergy Asthma Immunol 1997; 79: 530-2
35. Simons FER. Advances in H_1-antihistamines. N Engl J Med 2004 Nov; 351 (21): 2203-17
36. Hindmarch I, Johnson S, Meadows R, et al. The acute and subchronic effects of levocetirizine, cetirizine, loratadine, promethazine and placebo on cognitive function, psychomotor performance, and weal and flare. Curr Med Res Opin 2001; 17: 241-55
37. van Steekelenburg J, Clement PAR, Beel MHL. Comparison of five new antihistamines (H_1-receptor antagonists) in patients with allergic rhinitis using nasal provocation studies and skin tests. Allergy 2002 Apr; 57: 346-50
38. Geha RS, Meltzer EO. Desloratadine: a new nonsedating, oral antihistamine. J Allergy Clin Immunol 2001 Apr; 107: 751-62
39. Simons FER, Silver NA, Gu X, et al. Skin concentrations of H_1-receptor antagonists. J Allergy Clin Immunol 2001; 107: 526-30
40. Passalacqua G, Canonica GW. A review of evidence from comparative studies of levocetirizine and desloratadine for symptoms of allergic rhinitis. Clin Ther 2005 Jul; 27 (7): 979-92
41. Du Buske LM. Clinical comparison of histamine H_1-receptor antagonist drugs. J Allergy Clin Immunol 1996 Dec; 98 (6 Pt 3): S307-18
42. Golightly LK, Greos LS. Second-generation antihistamines: actions and efficacy in the management of allergic disorders. Drugs 2005; 65 (3): 341-84
43. Blaiss MS. Quality of life in allergic rhinitis. Ann Allergy Asthma Immunol 1999; 83: 449-54
44. Day JH, Briscoe MP, Rafeiro E, et al. Comparative clinical efficacy, onset and duration of action of levocetirizine and desloratadine for symptoms of seasonal allergic rhinitis in subjects evaluated in the Environmental Exposure Units (EEU). Int J Clin Pract 2004; 59: 109-18
45. Meltzer EO, Weiler JM, Widlitz MD. Comparative outdoor study of the efficacy, onset and duration of action, and safety of cetirizine, loratadine, and placebo for seasonal allergic rhinitis. J Allergy Clin Immunol 1996; 97: 617-6
46. Ciprandi G, Passalacqua G, Mincarini M, et al. Continuous versus on demand treatment with cetirizine for allergic rhinitis. Ann Allergy Asthma Immunol 1997; 79: 507-11
47. Ciprandi G, Tosca M, Ricca V, et al. Cetirizine treatment of rhinitis in children with pollen allergy: evidence of its antiallergic activity. Clin Exp Allergy 1997; 27: 1160-6
48. Pearlman DS, Lumry WR, Winder JA, et al. Once-daily cetirizine effective in the treatment of seasonal allergic rhinitis in children aged 6 to 11 years: a randomized, double-blind, placebo-controlled study. Clin Pediatr 1997; 36: 209-15
49. Sabbah A, Daele J, Wade AG, et al. Comparison of the efficacy, safety, and onset of action of mizolastine, cetirizine, and placebo in the management of seasonal allergic rhinoconjunctivitis. Ann Allergy Asthma Immunol 1999; 83: 319-25
50. Murray JJ, Nathan RA, Bronsky EA, et al. 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: 391-8
51. 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: 351-8
52. Horak F, Stübner UP, Zieglmayer R, et al. Controlled comparison of the efficacy and safety of cetirizine 10mg od and fexofenadine 120mg od in reducing symptoms of seasonal allergic rhinitis. Int Arch Allergy Immunol 2001; 125: 73-9
53. Howarth PH, Stern MA, Roi L, et al. Double-blind, placebo-controlled study comparing the efficacy and safety of fexofenadine hydrochloride (120 and 180mg once daily) and cetirizine in seasonal allergic rhinitis. J Allergy Clin Immunol 1999; 104: 927-33
54. Hampel F, Ratner P, Mansfield L, et al. 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: 354-61
55. Day JH, Briscoe MP, Clark RH, et al. Onset of action and efficacy of terfenadine, astemizole, cetirizine, and loratadine for the relief of symptoms of allergic rhinitis. Ann Asthma Allergy Immunol 1997; 79: 163-72
56. 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: 638-45
57. Nayak AS, Schenkel E. Desloratadine reduces nasal congestion in patients with intermittent allergic rhinitis. Allergy 2001; 56: 1077-80
58. Salmun LM, Lorber R, Danzig M, et al. Efficacy and safety of desloratadine in seasonal allergic rhinitis [abstract no. 1123]. J Allergy Clin Immunol 2000; 104 Suppl. 1: 384-5
59. Heithoff K, Meltzer EO, Mellars L, et al. Desloratadine improves quality of life in patients with seasonal allergic rhinitis [abstract no. 1121]. J Allergy Clin Immunol 2000; 104 Suppl. 1: 383-4
60. Meltzer EO, Prenner BM, Nayak A. Efficacy and tolerability of once-daily 5mg desloratadine, an H1-receptor antagonist, in patients with seasonal allergic rhinitis: assessment during the spring and fall allergy seasons. Clin Drug Invest 2001; 21: 25-32
61. Berger WE, Schenkel EJ, Mansfield LE, et al. Safety and efficacy of desloratadine 5mg in asthma patients with seasonal allergic rhinitis and nasal congestion. Ann Allergy Asthma Immunol 2002; 89: 485-91
62. Salmun LM, Lorber R. 24-hour efficacy of once-daily desloratadine therapy in patients with seasonal allergic rhinitis. BMC Fam Pract 2002; 3: 14-20
63. Wilson AM, Haggart K, Sims EJ, et al. Effects of fexofenadine and desloratadine on subjective and objective measures of nasal congestion in seasonal allergic rhinitis. Clin Exp Allergy 2002; 32: 1504-9
64. 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: 533-40
65. Wahn U, Meltzer EO, Finn AF, et al. Fexofenadine is efficacious and safe in children (aged 6-11 years) with seasonal allergic rhinitis. J Allergy Clin Immunol 2003; 111: 763-9
66. Sussman GL, Mason J, Compton D, et al. The efficacy and safety of fexofenadine HCl and pseudoephedrine, alone and in combination, in seasonal allergic rhinitis. J Allergy Clin Immunol 1999; 104: 100-6
67. Casale TB, Andrade C, Qu R. Safety and efficacy of once-daily fexofenadine HCl in the treatment of autumn seasonal allergy rhinitis. Allergy Asthma Proc 1999; 20: 193-8
68. Bronsky EA, Falliers CJ, Kaiser HB, et al. Effectiveness and safety of fexofenadine, a new nonsedating H_1-receptor antagonist, in the treatment of fall allergies. Allergy Asthma Proc 1998; 19: 135-41
69. Meltzer EO, Casale TB, Nathan RA, et al. 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: 311-7
70. Bernstein DI, Schoenwetter WF, Nathan RA, et al. Efficacy and safety of fexofenadine hydrochloride for treatment of seasonal allergic rhinitis. Ann Allergy Asthma Immunol 1997; 79: 443-8
71. van Cauwenberge P, Juniper EF, Meltzer EO, et al. Comparison of the efficacy, safety and quality of life provided by fexofenadine hydrochloride 120mg, loratadine 10mg and placebo administered once daily for the treatment of seasonal allergic rhinitis. Clin Exp Allergy 2000; 30: 891-9
72. Mösges R, van Cauwenberg P, Purello-D'Ambrosio F, et al. Fexofenadine and loratadine exhibit rapid relief, but only fexofenadine maintains efficacy over a 2-week period [abstract no. 1005]. Allergy 2000; 55 Suppl. 63: 281
73. Ricard N, Kind P, Christian S, et al. Link between preferences and treatment outcomes in seasonal allergic rhinitis: an empiric investigation. Clin Ther 1999; 20: 268-77
74. Serra HA, Alves O, Rizzo LFL, et al. Loratadine-pseudoephedrine in children with allergic rhinitis, a controlled double-blind trial. Br J Clin Pharmacol 1998; 45: 147-50
75. Druce HM, Thoden WR, Mure P, et al. Brompheniramine, loratadine, and placebo in allergic rhinitis: a placebo-controlled comparative trial. J Clin Pharmacol 1998; 38: 382-9
76. Pagliara A, Testa B, Carrupt P-A, et al. Molecular properties and pharmacokinetic behavior of cetirizine, a zwitterionic H_1-receptor antagonist. J Med Chem 1998; 41: 853-63
77. Best CH, Dale HH, Dudley HW, et al. The nature of the vasodilator constituents of certain tissue extracts. J Physiol 1927; 62: 397-417
78. Zyrtec® (cetirizine hydrochloride) tablets and syrup: package insert. New York: Pfizer Inc., 2002
79. Mohler SR, Nicholson A, Harvey RP, et al. The use of antihistamines in safety-critical jobs: a meeting report. Curr Med Res Opin 2002; 18: 332-7
80. Lai DS, Lue KH, Hsieh JC, et al. The comparison of the efficacy and safety of cetirizine, oxatomide, ketotifen, and a placebo for the treatment of childhood perennial allergic rhinitis. Ann Allergy Asthma Immunol 2002; 89: 589-98
81. Burtin B, Duchateau J, Pignat JC, et al. Further improvement of quality of life by cetirizine in perennial allergic rhinitis as a function of treatment duration. Invest Allergol Clin Immunol 2000; 10: 66-70
82. Ciprandi G, Tosca MA, Cosentino C, et al. Effects of fexofenadine and other antihistamines on components of the allergic response: adhesion molecules. J Allergy Clin Immunol 2003 Oct; 112 (4 Suppl.): S78-82
83. Kay GG, Berman B, Mockoviak SH, et al. Initial and steady-state effects of diphenhydramine and loratadine on sedation, cognition, mood, and psychomotor performance. Arch Intern Med 1997; 157: 2350-6
84. 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: 133-42
85. Bielory L, Lien KW, Bigelsen S. Efficacy and tolerability of newer antihistamines in the treatment of allergic conjunctivitis. Drugs 2005; 65 (2): 215-28
86. Paolieri F, Battifora M, Riccio A, et al. Terfenadine and fexofenadine reduce in vitro ICAM-1 expression on human continuous cell lines. Ann Allergy Asthma Immunol 1998; 81: 601-7
87. Allegra® (fexofenadine hydrochloride) capsules and tablets: package insert. Kansas City (MO): Aventis Pharmaceuticals Inc., 2003
88. Clarinex® (desloratadine) tablets: package insert. Kenilworth (NJ): Schering Corporation, 2002
89. Bower EA, Moore JL, Moss M, et al. The effects of single-dose fexofenadine, diphenhydramine, and placebo on cognitive per-

formance in flight personnel. Aviat Space Environ Med 2003; 74: 145-52

90. Thomson L, Blaylock MG, Sexton DW, et al. Cetirizine and levocetirizine inhibit eotaxin-induced eosinophil transendothelial migration through human dermal or lung microvascular endothelial cells. Clin Exp Allergy 2002; 32: 1187
91. Simons FER, Prenner BM, Finn A. Efficacy and safety of desloratadine in the treatment of perennial allergic rhinitis. J Allergy Clin Immunol 2003; 111: 617-22
92. Xyzal® (levocetirizine) tablets: package insert. Brussels: UCB Pharma Ltd, 2003
93. deBlic J, Wahn U, Billard E. Levocetirizine in children: evidenced efficacy and safety in a 6-week randomized seasonal allergic rhinitis trial. Pediatr Allergy Immunol 2005 May; 16 (3): 267-75
94. Lee DK, Gardiner M, Haggart K, et al. Comaprative effects of desloratadine, fexofenadine, and levocetirizine on nasal adenosine monophosphate challenge in patients with perennial allergic rhinitis. Clin Exp Allergy 2004; 34: 650-3
95. Taglialatela M, Timmerman H, Annunziato L. Cardiotoxic potential and CNS effects of first-generation antihistamines. Trends Pharmacol Sci 2000; 21: 52-6
96. Bockholdt B, Klug E, Schneider V. Suicide through doxylamine poisoning. Forensic Sci Int 2001; 119: 138-40
97. Baker AM, Johnson DG, Levisky JA, et al. Fatal diphenhydramine intoxication in infants. J Forensic Sci 2003; 48: 425-8
98. Claritin® (loratadine) tablets, syrup, and rapidly-disintegrating tablets: package insert. Kenilworth (NJ): Schering Corporation, 2000
99. Timmerman H. Factors involved in the absence of sedative effects by second-generation antihistamines. Allergy 2000; 55 Suppl. 60: 5-10
100. Simons FER, Fraser TG, Maher J, et al. Central nervous system effects of H1-receptor antagonists in the elderly. Ann Allergy Asthma Immunol 1999; 82: 157-60
101. Simons FER, Fraser TG, Reggin JD, et al. Comparison of the central nervous system effects produced by six H1-receptor antagonists. Clin Exp Allergy 1996; 26: 1092-7
102. Scharf MB, Kay G, Rikken G, et al. Desloratadine has no effect on wakefulness or psychomotor performance [abstract no. 1001]. Allergy 2000; 55 Suppl. 63: 280
103. Tashiro M, Sakurada Y, Iwabuchi K, et al. Central effects of fexofenadine and cetirizine: measurement of psychomotor performance, subjective sleepiness, and brain histamine H_1-receptor occupancy using 11C-doxepin positron emission tomography. J Clin Pharmacol 2004; 44: 890-900
104. Ramaekers JG, Uiterwijk MMC, 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: 363-9
105. Vermeeren A, Ramaekers JG, O'Hanlon JF. Effects of emedastine and cetirizine, alone and with alcohol, on actual driving of males and females. J Psychopharmacol 2002; 16: 57-64
106. Gengo FM, Gabos C, Mechtler L. Quantitative effects of cetirizine and diphenhydramine on mental performance measured using an automobile driving simulator. Ann Allergy 1990; 64: 520-6
107. Gengo FM, Gabos C. Antihistamines, drowsiness, and psychomotor impairment: central nervous system effect of cetirizine. Ann Allergy 1987; 59 (6 Pt 2): 53-7
108. Walsh JK, Muehlbach MJ, Schweitzer PK. Simulated assembly line performance following ingestion of cetirizine or hydroxyzine. Ann Allergy 1992; 69: 195-200
109. Vuurman EFPM, Rikken GH, Muntjewerff ND, et al. Effects of desloratadine, diphenhydramine, and placebo on driving performance and psychomotor performance measurements. Eur J Clin Pharmacol 2004; 60: 307-13
110. Hindmarch I, Shamsi Z, Stanley N, et al. 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: 200-6
111. Verster JC, Volkerts ER, van Oosterwijck AW, et al. Acute and subchronic effects of levocetirizine and diphenhydramine on memory functioning, psychomotor performance, and mood. J Allergy Clin Immunol 2003 Mar; 111 (3): 623-7
112. Taglialatela M, Timmerman H, Annunziato L. Cardiotoxic potential and CNS effects of first-generation antihistamines. Trends Pharmacol Sci 2000; 21: 52-6
113. Milne RW, Larson LA, Jorgensen KL, et al. Hepatic disposition of fexofenadine: influence of the inhibitors erythromycin and dibromosulphothalein. Pharm Res 2000; 17: 1511-5
114. Ambudkar SV, Dey S, Hrycyna CA, et al. Biochemical, cellular, and pharmacological aspects of the multidrug transporter. Annu Rev Pharmacol Toxicol 1999; 39: 361-98
115. Tian R, Koyabu N, Takanaga H, et al. Effects of grapefruit juice and orange juice on the intestinal efflux of P-glycoprotein substrates. Pharm Res 2002; 19: 802-9
116. Dresser GK, Bailey DG, Leake BF, et al. Fruit juices inhibit organic anion transporting polypeptide-mediated drug uptake to decrease the oral availability of fexofenadine. Clin Pharmacol Ther 2002; 71: 11-20
117. Hamman MA, Bruce MA, Hachner-Daniels BD, et al. The effect of rifampin administration on the disposition of fexofenadine. Clin Pharmacol Ther 2001; 69: 114-21

Correspondence and offprints: Dr *Michael S. Blaiss*, 7205 Wolf River Blvd, Germantown, TN 38138, USA.
E-mail: wheezemd@gmail.com