

First do no harm: Managing antihistamine impairment in patients with allergic rhinitis

The Antihistamine Impairment Roundtable: Thomas B. Casale, MD,^a Michael S. Blaiss, MD,^b Erwin Gelfand, MD,^c Timothy Gilmore, MD, PE,^d Philip D. Harvey, PhD,^e Ian Hindmarch, PhD, CPsychol, FBPSS,^f F. Estelle R. Simons, MD, FRCPC,^g Dennis L. Spangler, MD,^h Stanley J. Szefer, MD,ⁱ Thomas E. Terndrup, MD,^j Scott A. Waldman, MD, PhD, FCP,^k John Weiler, MD,^l and Dean F. Wong, MD, PhD^m Omaha, Neb, Memphis, Tenn, Santa Monica, Calif, Denver, Colo, Seattle, Wash, New York, NY, Guildford, United Kingdom, Winnipeg, Manitoba, Canada, Atlanta, Ga, Birmingham, Ala, Philadelphia, Pa, Iowa City, Iowa, and Baltimore, Md

Antihistamines are effective medications that have been used for decades in the management of allergic rhinitis; however, they may be administered or selected in an inappropriate fashion and may be the source of drug-related morbidity. Our objective is to present relevant background information and an expert consensus statement on the use of antihistamines in treatment of allergic rhinitis. In July 2002, 14 experts in allergy, clinical immunology, pharmacology, and impairment assessment were invited to participate in a roundtable conference to present current concepts and develop a consensus statement on the clinical management of allergic rhinitis with antihistamines. Many of the antihistamines used to treat allergic rhinitis, as well as the disease itself, may produce sedation, impairment, and reduced quality of life. Allergic rhinitis is more appropriately managed with the relatively nonimpairing second-generation antihistamines (eg, loratadine, desloratadine, cetirizine, and fexofenadine), because older agents (eg, diphenhydramine, chlorpheniramine, and brompheniramine) produce sedation and impairment and worsen sleep architecture.

Although there is some debate surrounding the varying degrees of efficacy of second-generation antihistamines, it is known that some agents may produce varying levels of drowsiness or impairment, especially at higher than recommended doses. The differences with regard to safety among the second-generation antihistamines are smaller than are the differences between the first and second generations. A nonsedating, nonimpairing (even at higher than recommended doses), second-generation antihistamine is preferred for all patients, particularly those with a higher risk for the development of adverse effects. We recommend that primary care and specialist physicians, nurse practitioners, physician assistants, pharmacists, and all other health professionals involved in the diagnosis and treatment of allergic rhinitis follow this consensus document and share this information with patients for whom antihistamine therapy is recommended. In addition, further epidemiologic studies on the effects of antihistamines should be performed. (*J Allergy Clin Immunol* 2003;111:S835-42.)

Key words: Allergic rhinitis, antihistamines, cetirizine, fexofenadine, loratadine, desloratadine, sedation, drowsiness, impairment

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Allergic rhinitis is among the most common diseases, and antihistamines are among the most commonly used medications. Despite the passage of 6 decades since antihistamines were first discovered, however, the manner in which these products are used or in which a particular antihistamine is selected could be improved, as evidenced by the current incidence of drug-related morbidity.^{1,2} The widespread acceptance of a number of incorrect ideas about antihistamines among clinicians and patients often precludes their proper use (Table I).

In July 2002, the authors—with expertise in the areas of allergy, clinical immunology, pharmacology, and impairment assessment—were invited to participate in a roundtable conference on the problems of impairment in people who use antihistamines in the treatment of allergic disorders and to compose a consensus statement that describes the problems and offers concrete recommendations for primary care and specialist physicians. In this article, we present the relevant background information and the consensus statement.

TABLE I. Myths and truths about H₁ antihistamines

Myths	Truths
Antihistamines are active antagonists at H ₁ and other receptors.	Antihistamines are inverse agonists of the H ₁ receptor. Rather than physically blocking the receptor, they stabilize its inactive conformation.
Older H ₁ antihistamines have no anti-inflammatory effects.	Drugs such as chlorpheniramine were shown in the mid 1950s to have anti-inflammatory effects.
Older H ₁ antihistamines are not long acting, but newer ones are.	In fact, chlorpheniramine, brompheniramine, and hydroxyzine have half-lives of 24 hours, whereas some newer agents have short half-lives (eg, acrivastine has a half-life of 1.4 h).
Older H ₁ antihistamines have no cardiotoxicity.	These agents can produce adverse effects on the heart, especially in overdose.
Tolerance to H ₁ antihistamine activity occurs.	No evidence has been demonstrated that the effectiveness of antihistamines declines with time.
	No consistent evidence exists to support that people can become accustomed to the sedative or impairing effects of antihistamines.
FGAs are as safe and effective as newer agents.	Important differences in potency, efficacy, and safety can be demonstrated among both FGAs and SGAs.
All SGAs are the same in terms of efficacy and safety.	Differences have been demonstrated among the SGAs with regard to adverse effects, especially impairment.

Abbreviations used

CNS: Central nervous system
 FGA: First-generation antihistamine
 PET: Positron-emission tomography
 SGA: Second-generation antihistamine

Because several terms used in this article have multiple meanings, some basic definitions are in order:

- *Sedation* is used in this article to refer to both symptoms of drowsiness and overt measures of impairment, as defined here.³ This term is not used to refer to the therapeutic use of medications to produce sleep or reduce anxiety or agitation.
- *Drowsiness* refers to a subjective state of sleepiness or lethargy.
- *Impairment* is used to mean an objectively measured decrease or absence of specific physical or mental abilities, as in an impaired ability to drive or operate cars or other motorized equipment.
- *First-generation antihistamines* (FGAs) are the older antihistamines that are now sold without a prescription in most, if not all, parts of the world. Commonly referred to as *sedating antihistamines*, these include diphenhydramine, chlorpheniramine, and brompheniramine.
- *Second-generation antihistamines* (SGAs) are more recently marketed antihistamines that many clinicians refer to as *nonsedating antihistamines*. These include loratadine, cetirizine, fexofenadine, and desloratadine.

EPIDEMIOLOGY AND SOCIETAL IMPACT

People every day encounter allergens and triggers that produce symptoms of rhinorrhea, sneezing, and nasal

congestion indicative of rhinitis. Although allergic rhinitis is recognized as a global health problem, there are insufficient epidemiologic data with regard to its distribution, etiologic risk factors, and natural history.⁴ It is known, however, that allergic rhinitis affects at least 10% to 25% of the worldwide population and has demonstrated a steady increase in prevalence during the last 40 years.⁴ In the United States, a large percentage of Americans report having one or more upper respiratory diseases: allergic rhinitis (approximately 14% of all Americans), nonallergic rhinitis (18%), and sinusitis (15%, often in conjunction with rhinitis).⁵ According to 2000 National Census figures,⁶ this means that approximately 40 million people in the United States on a daily basis for some or all of the year seek relief from the debilitating symptoms of allergic rhinitis, often by using a confusing medley of nonprescription and prescription medications. Although these medications are generally effective for reducing the symptoms of allergic rhinitis, they have important differences in adverse effects, which can range from sleepiness and impaired psychomotor skills to cardiac toxicity.

Rhinitis and similar conditions cause a decreased quality of life for patients, altering the social life of patients and affecting school performance and work productivity.⁴ In several domains of the Medical Outcomes Study Short Form-36 instrument, patients who live with allergic rhinitis have worse health-related quality of life than do patients with asthma.^{7,8} Productivity losses, a major contributor to the indirect costs of the disease, are large, especially given the number of people with atopic diseases. Recent estimates are that allergic rhinitis affects 19 million employed adults in the United States. A recent study showed a 10% decrease in productivity among employees with allergic rhinitis who were not receiving medication.⁹ In 1997 dollars, direct costs total \$4.5 billion for this disease,

and 3.8 million workdays and school days are lost annually because of allergic rhinitis.^{1,10,11}

In November 2001, the US National Transportation Safety Board and the US Food and Drug Administration held a joint public meeting to assess the potential public health consequences related to sedating or impairing medications. At the time, government representatives requested “real world” data to determine whether the drugs in question cause impairment. Gilmore et al¹² in 1996 found elevated rates for six common injuries in those taking a sedating antihistamine, and other studies have shown similar results with diphenhydramine.¹³ More recently, in 2002, Finkle et al¹³ published a study comparing the risk of injury in patients exposed to diphenhydramine or loratadine. Their data show a strong association between initial use of diphenhydramine and the subsequent occurrence of injuries. Approximately 55% of all injuries in the diphenhydramine group were attributable to use of the drug.¹³ Because an estimated 47% of people with allergies use over-the-counter antihistamines, most containing an FGA, to treat their allergy symptoms, there should be considerable concern about the use of these products, particularly when safer, nonsedating, nonimpairing SGAs are available.

Allergic disorders can have detrimental effects on the psychologic and social aspects of people's lives, causing embarrassment and frustration as well as diminishing cognitive processing, verbal learning, and memory. Disturbed sleep and sedation (drowsiness and impairment) are other important negative impacts on patients' quality of life with allergic rhinitis. Disease-related impairments recognized during the daytime are primarily due to fatigue related to disturbances in sleep.¹⁴ Patients who are taking antihistamines with sedating properties have a 1.5-times increased risk of occupational injury.¹² Physicians attempting to devise appropriate treatment strategies should consider the impact of allergic disorders and antihistamine use on work and school performance, as well as on patients' quality of life.

DIFFERENTIAL DIAGNOSIS

Of the millions of people with upper respiratory tract disorders, only a small portion seek care from a physician. Most patients with allergies turn to nonprescription medications for self-treatment of their symptoms. In fact diphenhydramine—a medication still widely used for insomnia treatment and preoperative sedation and commonly used to control agitated or intoxicated psychiatric inpatients—is the sixth most commonly used medication (considering both prescription and nonprescription drugs) in the United States, and chlorpheniramine is the 12th most commonly used agent.² Because older antihistamines are sedating, they also disrupt the normal sleep process, and patients awake unrested.

To determine appropriate treatment in upper respiratory disease, an accurate diagnosis is required. Even with a comprehensive history and physical examination, these conditions often cannot be accurately and reliably diag-

nosed. Patients should be screened with allergen skin tests or in vitro tests for specific IgE.¹⁵

For patients whose symptoms are confirmed to be the result of IgE-mediated allergy, therapy should begin with avoidance of the allergens. If the patient can reduce the allergen load below the threshold that causes symptoms, drug therapy may not be needed. Allergen exposure does not need to be completely eliminated, because nearly all patients can live with some degree of allergen exposure. Rather, exposure only needs to be lowered below that patient's threshold tolerance for allergens.

ANTIHISTAMINE THERAPY

Antihistamines, decongestants, intranasal corticosteroids, cromolyn sodium, and immunotherapy are the currently available therapeutic options most widely used for patients who require treatment for allergic rhinitis. In this article the impairment issues surrounding allergic rhinitis and the use of antihistamine therapy are evaluated.

Despite common misperceptions, such as those listed in Table I, the clinical pharmacology of the antihistamines is quite well described. Several commonly used FGAs, usually referred to as the *sedating antihistamines*, and SGAs, the so-called *nonsedating antihistamines*, are listed in Tables II and III. Several characteristics can be used to differentiate among the available antihistamines:

- Efficacy, defined in terms of receptor specificity, receptor selectivity, potency, and therapeutic index
- Dosing strategies, specifically how much of and how often medications must be administered, a function of drugs' pharmacokinetics and pharmacodynamics
- Safety concerns
- Effects on quality of life

Efficacy

Potency is often equated with the efficacy of a drug, but the concepts are not interchangeable. Potency measurements are often made in vitro or in vivo in preclinical trials, whereas clinical efficacy judges the therapeutic effectiveness of the drug and reflects all pharmacokinetic and pharmacodynamic properties that determine the concentration of the drug at sites of action. Thus the most potent drug may not be the most clinically efficacious, because it may be the least bioavailable.¹⁶ For example, a recent study found that fexofenadine penetrated the skin to a greater extent than diphenhydramine and was more effective in inhibiting histamine-induced wheal and flare responses in the skin, suggesting that fexofenadine could produce significantly greater suppression of both wheals and flares than diphenhydramine in patients with urticaria.¹⁷

Selectivity and specificity also play an important role in determining the efficacy of an antihistamine. Since the first antihistamines were developed in the 1940s, attention to the agents' structure-activity relationship has resulted in improvements in their specificity and selectivity for the H₁ receptor. However, all FGAs and most SGAs inhibit other receptors as well, including the homologous muscarinic

TABLE II. Key characteristics of commonly used FGAs and SGAs

Agent	Common adult dosage (mg/d)	Relative drowsiness effect*	Relative anticholinergic effect*	Relative effect on impairment*
FGAs				
Diphenhydramine (Benadryl)	25–50 mg every 4–6 h	+++	+++	+++
Chlorpheniramine (Chlor-Trimeton)	4 mg every 4–6 h	++	+++	++
Brompheniramine (Dimetapp)	4 mg every 6 h	++	+++	++
Clemastine (Tavist)	1–2 mg of base 3 times daily	+++	+++	+++
SGAs				
Loratadine	10 mg once daily	0, + (HD)	+	0, + (HD)
Cetirizine	5–10 mg once daily	+/-, + (HD)	+	+/-, + (HD)
Fexofenadine	180 mg once daily or 60 mg twice daily	0	0	0
Desloratadine	5 mg once daily	0, + (HD) ^b	+	0, + (HD)

HD, At high doses.

Adapted from Shamsi Z, Hindmarch I. Sedation and antihistamines: a review of inter-drug differences using proportional impairment ratios. *Hum Psychopharmacol* 2000;15(S1):S3-30 and from Welch MJ, Meltzer EO, Simons FE. *H₁-antihistamines in allergic disease*. 2nd ed. New York: Marcel Dekker; 2002. p. 337-88.

*Key: +++, High effect; ++, moderate effect; +, low effect; 0, no effect; +/-, low to no effect.

TABLE III. Differentiating H₁-receptor antagonists

Agent	Specificity	Onset of action (h)	Peak (h)	Duration (h)	T _{max} (h)	Half-life (h)
Diphenhydramine (50 mg)	Drowsiness; reduces time to fall asleep			6-10	1.7	9.2
Cetirizine (10 mg)	Larger and more lipophobic than FGAs; higher risk of drowsiness than with other SGAs	1	4-8	24	1	7
Loratadine (10 mg)	Larger and more lipophobic than FGAs; low CNS penetration; risk of drowsiness at higher than recommended doses	1-3	4-12	24	1	11
Desloratadine (5 mg)	Larger and more lipophobic than FGAs; low CNS penetration; risk of drowsiness at higher than recommended doses	1-2	3	24	3	27
Fexofenadine (180 mg)	Larger and more lipophobic than FGAs; low CNS penetration; no sedative effect at high doses	1	3-4	24	1-3	14.4

T_{max} Time of maximum concentration. Adapted from product prescribing information and from Simons FE, Simons KJ. Clinical pharmacology of new histamine H₁-receptor antagonists. *Clin Pharmacokinet* 1999;329-52.

M₂ receptors that regulate chronotropy and inotropy of the heart.¹⁸⁻²⁰ For example, in canine models, desloratadine has high affinity for M₂ receptors in cardiac muscle and is only 5-fold more selective for H₁ receptors than for M₂ receptors. In contrast, the selectivity ratio of fexofenadine is 2 orders of magnitude higher, with 600-fold higher selectivity for the H₁ receptor than for the M₂ receptor.¹⁷ Some antihistamines also affect other important groups of muscarinic receptors, including M₁ receptors in the vas deferens, ureter, and prostate and M₃ receptors in ocular, vascular, and gastrointestinal and lung smooth muscle.

Antihistamines that do not discriminate well among the various types of receptors may have adverse effects or toxicity when used to treat human beings, and this relationship can be expressed by the therapeutic index (a ratio of the dose that produces toxicity divided by the dose that produces beneficial effects), as shown in Table IV. In addition, the relationship between selectivity and the risk-benefit of a drug is shown graphically in Fig 1.

The mechanisms of action of FGAs and SGAs have not been completely determined at this time. They are probably

inverse agonists of the histamine H₁ receptor, meaning that they stabilize an inactive conformation of the receptor, thus preventing histamine from causing activation.²¹ Whereas all marketed antihistamines have sufficient effects on the histamine receptor to provide clinical benefits, the SGAs are more specific for the histamine receptor than are the FGAs, and for this reason they possess less potential for adverse effects, including cardiotoxicity. The FGAs are nonselective, reacting with a number of receptors in addition to the H₁ site.¹⁸ In addition, as is discussed in the next section, FGAs distribute into the central nervous system (CNS) more than do SGAs, and their effects on histamine, an important chemical mediator in the brain, produce the high degree of sedation observed with these drugs.

Antihistamines react with H₁ receptors in a variety of organs, including both the upper and lower respiratory tracts. This enhances their therapeutic effects, because the allergens that produce rhinitis also cause symptoms through H₁ receptors in other organs. Antihistamines also have been shown to have anti-inflammatory effects that go beyond their effects on the H₁ receptor.

Histamine is an important chemical mediator in the brain. Positron-emission tomographic (PET) scans demonstrate the differences between antihistamines and the extent to which they penetrate the CNS. PET studies, such as those performed at Dr Dean Wong's research center at Johns Hopkins University, show that those drugs that penetrate the CNS are associated with sedation.²²

In clinical studies, differences have been observed among the SGAs in terms of onset of action (1 hour for cetirizine and fexofenadine, 1-3 hours for loratadine) and efficacy at the end of dosing intervals (efficacy of loratadine is less than that of cetirizine, which is about the same as that of fexofenadine).²³⁻²⁵

Dosing strategies and drug safety

Differences among the available antihistamines are further magnified when their pharmacokinetic and pharmacodynamic differences are assessed. These properties determine the dosing strategies that can be used with each drug and ultimately the safety profile within which clinicians must maneuver in treating allergic rhinitis.

Antihistamines are typically well absorbed, although a large first-pass effect reduces the relative bioavailability of some agents. FGAs distribute into the brain easily, and PET scans, as mentioned previously, have shown a correlation between drug occupancy of histamine receptors and both serum drug concentrations and relative sedative effects of individual agents. Diphenhydramine occupied a significantly greater number of receptors throughout all parts of the cortex. Cetirizine, which produces more drowsiness than do other SGAs, occupied a significantly increased number of receptors in the frontal cortex at doses of 20 mg (twice the recommended dose), whereas fexofenadine at doses of 180 and 360 mg (2 times greater than a single dose) showed little penetration of the central nervous system and no change in binding of central receptors.²² Loratadine was not examined in this study. Although these PET findings are preliminary and only a few products have been studied, the results suggest, on the basis of the pharmacokinetic and pharmacodynamic properties of antihistamines, that there is a lower risk of sedation with fexofenadine and loratadine than with cetirizine and acrivastine.

In a postmarketing surveillance study, several antihistamines were analyzed for their sedative properties. With an odds ratio for sedation arbitrarily set at 1.0 for loratadine, the odds ratios were 0.63 for fexofenadine, 2.79 for acrivastine, and 3.53 for cetirizine.²⁶

Many of the antihistamines have long half-lives, which is problematic if they produce drowsiness at usual clinical doses. For instance, some FGAs that are taken at bedtime have half-lives as long as 24 hours, which may give patients an "antihistamine hangover" the next morning and for a considerable part of the work or school day. Contrary to popular assumption, patients do not necessarily or always acquire a tolerance to these sedative effects.²⁷

Drug interactions involving several of the FGAs and SGAs may be serious. This is particularly true of those metabolized by the hepatic microsomal system of the liver.

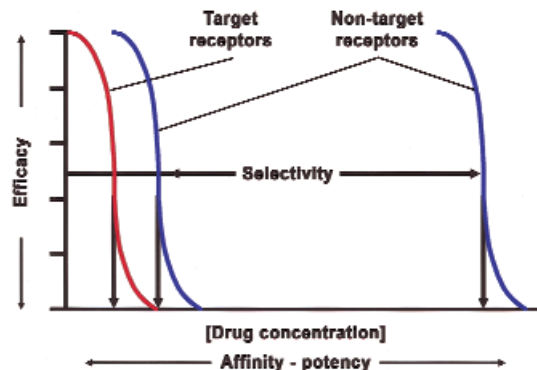


FIG 1. Antihistamine selectivity and risk-benefit relationship. Compared with drug 3 (farthest to the right), drug 1 (farthest to the left) is 1000 times more selective because it provides equivalent pharmacologic effect at 1000 times lower blood level. Compared with drug 2 (middle), drug 1 is 5 times more selective. Adapted from Waldman SA. Does potency predict clinical efficacy? Illustration through an antihistamine model. *Ann Allergy Asthma Immunol* 2002;89:7-11.

TABLE IV. Proportional impairment ratios of selected antihistamines

Antihistamine	PIR*
Fexofenadine (80–360 mg)	0
Cetirizine (2.5–20 mg)	0.18
Loratadine (10–40 mg)†	0.58
Diphenhydramine (25–150 mg)	2.05
Promethazine (10–50 mg)	3.14

PIR, Proportional impairment ratio. From Shamsi Z, Hindmarch I. Sedation and antihistamines: a review of inter-drug differences using proportional impairment ratios. *Hum Psychopharmacol* 2000;15(S1):S3-30. Used with permission.

*This ratio is calculated as follows. Where *a* is the number of instances in which individual psychometric tests have shown impairment with the antihistamine of interest, *b* is the number of such tests that showed no impairment with the antihistamine of interest, *c* is the number of such tests that show impairment with all other antihistamines in a research database, and *d* is the number of such tests that do not show impairment with all other antihistamines in the database, $PIR = [(a/a+b)/(c/c+d)]$.

†Desloratadine was not included in this study.

On the pharmacodynamic side of the equation, SGAs vary in times to onset of action, peak effects, and durations of action (Table III). Because patients often take antihistamines in response to symptoms that have already begun, faster onset of action is particularly desirable. Loratadine has a relatively slow onset of action; its active metabolite peaks later, and antihistaminic effects begin between 1 and 3 hours after an oral dose. Fexofenadine and cetirizine have onsets of action of about 1 hour,²³⁻²⁵ and the combination of fexofenadine plus pseudoephedrine has an onset of action of 45 minutes.²⁸ Similarly, the combination of loratadine and pseudoephedrine has an onset of action of 1 to 3 hours.

Despite their longer half-lives, FGAs are typically administered several times a day or in sustained-release forms. This is necessary because of their low therapeutic indices, underscoring the safety problems of FGAs discussed in the next section.

All currently available SGAs are approved for and can be administered in single daily doses. Some are also available in dosage strengths that permit either once- or twice-daily dosing. According to Food and Drug Administration–approved product labeling, sedation (impairment or drowsiness) may occur with cetirizine, loratadine, and desloratadine when used at higher than recommended doses (Table III).

Overuse of antihistamines is a problem, especially with those sold without a prescription. Certain clinical situations may lead patients to believe that all nonprescription medications are so safe that doses can be increased and that “more is better.”²⁹ Such overcompliance can be a serious problem when FGAs or some SGAs are involved, because sedation or cardiotoxicity may result from higher than recommended doses.

Safety and humanistic concerns

Three adverse effects vary among the available antihistamines and should be considered by clinicians during the drug-prescribing process. According to Food and Drug Administration–approved product labeling, these are cardiotoxicity, drowsiness, and impairment.

Cardiotoxicity, including torsades de pointes in patients taking interacting drugs such as macrolide antibiotics, led to the market withdrawal of terfenadine and astemizole. Among the antihistamines that remain on the US market, cardiotoxicity is most likely with FGAs. Although the relative risk of cardiotoxicity with these drugs is real (patients taking the drugs have an increased risk of the side effect), the absolute risk is small (the side effect occurs in only a small number of people, even when a large number of people take the drug). However, it is important to note that over-the-counter FGAs have been shown to be associated with a higher rate of ventricular arrhythmias than terfenadine.³⁰

Drowsiness is considerable with diphenhydramine, the most widely used antihistamine in the United States. In studies of cognitive function and driving ability, diphenhydramine and other FGAs have been proved to cause sleepiness and drowsiness, whereas SGAs do not produce sedation at usual clinical doses. In some driving tests, patients who were taking diphenhydramine performed as poorly as or more poorly than those with blood alcohol levels above the legal limit for driving in most states.³¹

Patients can readily detect drowsiness, but impairment presents a different challenge. Studies of a wide variety of CNS depressants have shown consistently that patients affected by these drugs cannot reliably or accurately determine how well they are driving or performing other complex tasks. Among SGAs given at doses that do not produce sedation, important indicators of differences in impairment have emerged.^{32,33} These include the following objective measures:

- In objective tests of driving performance, patients taking fexofenadine or placebo drove similarly—drivers matched the velocity of the car ahead, drove farther behind that car, and had better steering con-

trol.³¹ Other driving studies have shown that cetirizine at recommended doses can produce impaired performance (albeit to a lesser degree than FGAs),³⁴ and have similarly demonstrated that both cetirizine and loratadine at double the usual dose impair driving performance.^{35,36}

- Objective psychometric tests show that a small percentage of patients are impaired by recommended doses of loratadine and cetirizine.^{29,31}
- Other objective performance measurements, such as digit symbol substitution, tracking, and visual vigilance, have shown that some SGAs (such as cetirizine) can affect performance, whereas others do not impair task performance.^{37,38}
- Patients who take higher than recommended doses of the SGAs loratadine and desloratadine experience sedation, with measurable impairment seen at twice the recommended dose of loratadine. It is important to note that patients often use higher than the recommended dose.³⁹

An additional analysis of impairment produced by antihistamines is shown in Table IV. The impairment gap between the FGAs and SGAs is striking, and more subtle differences exist among the SGAs as well.⁴⁰

The US Federal Aviation Administration, through independent private agencies, has authorized the use of fexofenadine and loratadine by pilots when needed.^{41,42} In the United States, 32 states including the District of Columbia have special laws that include medication use in defining impaired driving. Patients would be considered impaired under these laws if they operated vehicles while taking any of the FGAs or cetirizine.

CONCLUSION: PRIMUM NON NOCERE

On the basis of these considerations, the following Consensus Statement on antihistamine treatment of allergic rhinitis was developed. We encourage primary care and specialist physicians, nurse practitioners, physician assistants, pharmacists, and all other health professionals involved in the diagnosis and treatment of allergic rhinitis to follow the recommendations made in the statement and to share them with patients for whom antihistamine therapy is recommended.

Consensus statement: Clinical management of allergic rhinitis

Allergic rhinitis can produce compromised physical and mental functioning (including subjective drowsiness and objective impairment) and lowered self-esteem in patients. Even though appropriate differentiation between allergic rhinitis and a host of other conditions with similar symptoms requires medical evaluation, only 20% of patients with allergic rhinitis seek professional care.

Appropriate treatment of allergic rhinitis reduces sedation and impairment caused by the disease itself and thereby improves sleep and quality of life. Inappropriate treatment, especially the use of FGAs such as diphenhy-

dramine, chlorpheniramine, and brompheniramine, may worsen these parameters.

Clinically significant differences in pharmacologic profiles exist among antihistamines. All FGAs are more sedating than are SGAs (such as loratadine, cetirizine, fexofenadine, and desloratadine). More subtle differences exist among the SGAs. There is much debate surrounding the varying degrees of efficacy of SGAs, although it is known that some agents may produce varying levels of drowsiness or impairment, especially at higher than recommended doses. In all cases selection of a nonimpairing, nonsedating SGA is preferred, particularly for those patients at higher risk for the development of adverse events. These include patients with renal or hepatic impairment, those with small body masses (for whom normal adult doses provide a larger than recommended dose on a milligram per kilogram basis), patients with preexisting central nervous system or cardiac disorders, patients who may require higher medication doses, and patients who have shown tendencies to overuse nonprescription or prescription medications.

On the basis of these considerations, it is imperative that allergic rhinitis be treated with a true nonimpairing, nonsedating antihistamine, preferably one with a wide therapeutic index that allows practitioners to safely increase dosing as necessary without the risk of increasing the incidence of potentially hazardous adverse events. Primary care and specialist physicians should do the following:

- Recognize that etiologies of upper respiratory disease are difficult to determine from history and physical examination alone.
- Use objective tests of allergies to support diagnosis of allergic rhinitis and related conditions.
- Recognize that disease- or medication-associated sedation can consist of subjective feelings of drowsiness (sleepiness, lethargy, subtle confusion), objective measures of impairment (slowed reaction time, impaired attention and working memory, and perceptual changes), or both. Not all impaired patients feel drowsy, and not all patients who feel drowsy are necessarily impaired with respect to a particular task.
- Recommend that patients avoid nonprescription FGAs because of their adverse effects, including sedation (impairment and drowsiness) and cardiotoxicity.
- Recommend that patients not self-treat potential allergic symptoms because of the needs for appropriate evaluation during diagnosis, professional selection of a therapeutic agent according to the patient's lifestyle and medical history, and monitoring for impairments that might not be obvious to the patient.
- Educate patients about appropriate antihistamine use, especially the need to avoid self-medicating with higher than physician-recommended doses.
- Consider safety, including sedation (both objective impairment and subjective drowsiness), in selecting

and using an SGA. Avoid medications that have the potential to cause sedation or impairment when taken in excess of recommended doses.

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