

# Antihistamine Therapy in Allergic Rhinitis

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## KEYWORDS

- Antihistamine • Rhinitis • Allergy • Allergic • Therapy
- Histamine

Histamine, one of the key mediators of allergic disease, has been a target of allergic rhinitis therapy for some time. More than 40 oral antihistamines are currently available and can be classified as first-generation and second-generation drugs, depending on their pharmacokinetic and pharmacodynamic properties and their side-effect profiles. Intranasal antihistamines were introduced more recently and have shown promise in their efficacy, rapid onset of action, and minimal side effects. The choice of antihistamine for a given individual should be based on patient characteristics that could affect drug metabolism, the specific symptoms experienced, cost concerns, and patient preference. This article discusses the history and classification of antihistamines as well as their role in the treatment of allergic rhinitis and the evidence supporting this use.

## HISTORY OF HISTAMINE DISCOVERY AND ANTIHISTAMINE DEVELOPMENT

The mast cell, which is the main source of histamine, was first identified by Paul Ehrlich in 1870. It was not until 1910, however, that histamine itself was discovered by British physiologist Sir Henry Dale as a bacterial product contaminating Ergot. Experiments by Dale and his colleagues demonstrated that this substance could produce smooth muscle contraction in isolated guinea pig ileum and respiratory tissue, stimulate cardiac contractility, and lead to vasodepression and a shock-like state when injected into animals.<sup>1,2</sup> Histamine was initially termed *H substance* by Lewis, whose 1924 article described the “triple response” of vasodilation, wheal, and flare that occurred after intradermal injection of this substance into human skin. Lewis’ subsequent experiments demonstrated that other stimuli could produce a similar response,

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Flavia C.L. Hoyte has nothing to disclose. Disclosures for Rohit K. Katial: GSK, TEVA, MEDA, Alcon, MedImmune.

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Immunol Allergy Clin N Am 31 (2011) 509–543

doi:[10.1016/j.iac.2011.05.003](https://doi.org/10.1016/j.iac.2011.05.003)

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suggesting an intrinsic molecule similar to H substance produced by the body in response to these stimuli. H substance was later characterized further as  $\beta$ -aminoethyl-imidazole, also known as 2-(4-imidazolyl)-ethylamine, which is the molecule currently known as histamine. The understanding of histamine's clinical impact grew with the identification of histamine in human liver and lung tissue in 1927<sup>3</sup> and with the identification of histamine as the main mediator of anaphylaxis in 1932.<sup>4</sup>

The first antihistamine was identified in 1937 with the discovery of 933F, also known as adrenolytic benzodioxan or piperoxan, a substance that blocked the effect of histamine on guinea pig ileum. In that same year, Bovet and Staub identified 929F, thymol ether, as a substance that protected guinea pig from histamine-induced anaphylaxis. Having been deemed too toxic, 929F was altered by replacing one of the oxygen groups with an amino group to develop aniline ethylene diamine derivatives. Five years later, in 1942, phenbenzamine/pyribenzamine was developed as the first clinically useful antihistamine,<sup>1</sup> followed by the discovery of diphenhydramine, tripeleminamine, chlorpheniramine, and promethazine. By 1943, central nervous system (CNS) toxicity had been observed and was unfortunately a feature of all of these first-generation antihistamines. It was not until 1985 that terfenadine, the first nonsedating antihistamine approved for use in the United States, was introduced for clinical use, thus expanding the potential benefit of this family of medications.<sup>5</sup> More recently, the introduction of ocular antihistamines and intranasal antihistamines as therapeutic options has furthered the impact of antihistamines by providing an option for local administration of these medications for the treatment of chronic conjunctivitis and rhinitis.

## HISTAMINE BIOLOGY AND HISTAMINE RECEPTORS

Histamine is produced from L-histidine through the action of histidine decarboxylase, an enzyme produced by inflammatory cells, neurons of the CNS, and parietal cells in the gastric mucosa.<sup>6–10</sup> Although most of these cells produce histamine without storing it, mast cells and basophils are capable of storing histamine within their granules and releasing it when these cells degranulate due to various stimuli.<sup>10</sup> Specific to allergic rhinitis, mast cells and basophils in the nasal mucosa release large quantities of histamine after the binding and cross-linking of surface IgE molecules on allergen exposure. Compared with other mediators that are released in picogram quantities when these cells degranulate, histamine is released in microgram quantities with 3  $\mu$ g to 5  $\mu$ g per million mast cells and 1  $\mu$ g per million basophils.<sup>8</sup> Histamine exerts its effect through its interaction with 4 different 7-transmembrane G protein-coupled receptors—H<sub>1</sub>, H<sub>2</sub>, H<sub>3</sub>, and H<sub>4</sub>—which are described in **Table 1**. Because each of these receptors predominates on different cell types throughout the body, they exert different biologic effects. Although the H<sub>1</sub> receptor is the most important regarding rhinitis, all 4 histamine receptors contribute to the pathophysiology of this condition.

H<sub>1</sub> receptors are located on endothelial cells and vascular smooth muscle cells, allowing for histamine-mediated vasodilatation and vasopermeability, which are central hallmarks of the pathophysiology of allergic rhinitis, specifically the symptoms of rhinorrhea and congestion.<sup>9</sup> The histamine-mediated parasympathetic reflex stimulation of glandular secretions also contributes to rhinorrhea.<sup>8,9</sup> In addition, H<sub>1</sub> receptors are present on sensory nerves of the upper airway, contributing to the sneezing and itching of the nose, palate, and throat that are prominent symptoms in rhinitis. Furthermore, the presence of these receptors on inflammatory cells, such as neutrophils, eosinophils, lymphocytes, monocytes/macrophages, and dendritic cells, increases trafficking of these cells to areas of inflammation, thus exerting a delayed proinflammatory effect contributing to the late phase allergic response.<sup>8,9</sup>

The  $H_2$  receptor was the next to be discovered and is now most recognized for its role as a receptor for gastric acid secretion. These receptors are also found on the systemic vasculature, hence their role in the cardiovascular instability sometimes seen during anaphylaxis.  $H_2$  receptors are also found on the submucosal glands and epithelial cells of the nasal mucosa, thereby contributing to rhinitis through increased glandular secretions and vascular permeability.<sup>8,9</sup>

The  $H_3$  receptor is found mainly in the presynaptic nerves of the peripheral sympathetic system, leading to suppression of norepinephrine release. Through this mechanism, activation of the  $H_3$  receptor can lead to increased nasal congestion, which is further enhanced by activation of these receptors on the nasal submucosal glands.<sup>11</sup>

Most recently, in 2000, the  $H_4$  receptor was identified and was found present in multiple areas of the body, including the nerves of the nasal turbinates and on multiple inflammatory cells, including eosinophils and mast cells. As such, the  $H_4$  receptor is thought to play a role in the inflammatory aspect of rhinitis, although further work is needed to fully understand the role of this receptor in rhinitis. Data regarding the localization of the  $H_4$  receptor in the CNS are conflicting, although one recent report demonstrates its presence in both human and rodent CNS while postulating its role in pain and itch.<sup>12</sup>

All 4 histamine receptors alternate between an active and inactive form and have a low level of constitutive activity even in the absence of histamine.<sup>13,14</sup> Histamine acts as an agonist of these receptors, preferentially binding to the active conformation and stabilizing the receptor in this form. Antihistamines act as inverse agonists, preferentially binding to and stabilizing the histamine receptors in their inactive form, thereby inhibiting signal transduction.<sup>13</sup> This inhibition has been tested for many of the  $H_1$  antihistamines available for clinical use using gene reporter assays. In these studies, antihistamines inhibit nuclear factor  $\kappa$ B activation resulting from upstream signaling initiated by the activated  $H_1$  receptor.<sup>15</sup> The antihistamine molecules on binding to the histamine receptor cause a shift from the active to the inactive form. This holds true for all antihistamines, even those lacking an ethylamine side chain that resembles that of histamine, thereby disproving previous theories that antihistamines inhibit the histamine receptor through competitive inhibition of the groove where this side chain of histamine binds. As shown in **Table 2**, there are more than 40 antihistamines available for clinical use, most of which target the  $H_1$  receptor. A handful of antihistamines that target the  $H_2$  receptor are also currently in clinical use, but there are no commercially available antihistamines that target the  $H_3$  and  $H_4$  receptors.

## ORAL ANTIHISTAMINES IN RHINITIS THERAPY

### *First-Generation and Second-Generation Oral Antihistamines*

The antihistamines used in the therapy for rhinitis are those that target the  $H_1$  receptor. There are 2 classes of  $H_1$  antihistamines: first-generation antihistamines and the newer second-generation antihistamines, first developed in the early 1980s. Unlike second-generation antihistamines, first-generation antihistamines readily cross the blood-brain barrier due to their lipophilicity, have a low molecular weight and a positive electrostatic charge, and are often not recognized by the P-glycoprotein efflux pump. These properties of first-generation antihistamines lead to adverse CNS effects, especially sedation, which can impair performance during work, school, or even activities of daily living. The use of these medications is, therefore, often limited to the evening hours, but even bedtime administration sometimes results in sedation and impaired performance the morning after ingestion.<sup>25</sup> Sedation has decreased the use of first-generation antihistamines in favor of second-generation antihistamines,

**Table 1**

**Histamine receptors: expression, function, and available inverse agonists**

| Receptor                | Receptor Expression                                                                                                                                                                                                                                                                                       | General Function                                                                                                                                                                                                                                                                                                   | Function in Allergic Inflammation and Immune Modulation                                                                                                                                                                                                                                                                                                                                         | Inverse Agonists Available Clinically                                                    |
|-------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|
| H <sub>1</sub> Receptor | <ul style="list-style-type: none"> <li>• Nerve cells</li> <li>• Airway and vascular smooth muscle cells</li> <li>• Endothelial cells</li> <li>• Epithelial cells</li> <li>• Neutrophils, eosinophils, monocytes/macrophages, DCs, T and B cells</li> <li>• Hepatocytes</li> <li>• Chondrocytes</li> </ul> | <ul style="list-style-type: none"> <li>• Pruritis, pain</li> <li>• Vasodilation, vascular permeability, hypotension</li> <li>• Flushing, headache, tachycardia</li> <li>• Bronchoconstriction, cough receptor stimulation, airway vagal afferent nerve stimulation</li> <li>• ↓ AV node conduction time</li> </ul> | <ul style="list-style-type: none"> <li>• ↑ Release of histamine and other mediators</li> <li>• ↑ Cellular adhesion molecule expression</li> <li>• ↑ Eosinophil and neutrophil chemotaxis</li> <li>• ↑ APC capacity and costimulatory activity on B cells</li> </ul>                                                                                                                             | More than 40 available for allergic disease and urticaria (see <a href="#">Table 2</a> ) |
| H <sub>2</sub> Receptor | <ul style="list-style-type: none"> <li>• Nerve cells</li> <li>• Airway and vascular smooth muscle cells</li> <li>• Endothelial cells</li> <li>• Epithelial cells</li> <li>• PMNs, eosinophils, monocytes, DC, T and B cells</li> <li>• Hepatocytes</li> <li>• Chondrocytes</li> </ul>                     | <ul style="list-style-type: none"> <li>• Gastric acid secretion</li> <li>• Vascular permeability, hypotension</li> <li>• Flushing, headache</li> <li>• Tachycardia, chronotropic and inotropic activity</li> <li>• Bronchodilation, airway mucus production</li> </ul>                                             | <ul style="list-style-type: none"> <li>• Suppresses T<sub>h</sub>2 cells and cytokines</li> <li>• ↑ Humoral immunity</li> <li>• ↓ Cellular immunity</li> <li>• ↓ IL-12 by DCs</li> <li>• ↓ Eosinophil and neutrophil chemotaxis,</li> <li>• Role in graft rejection, autoimmunity, malignancy</li> <li>• ↑ IL-10 and induced development of T<sub>h</sub>2 or tolerance-inducing DCs</li> </ul> | Cimetidine, famotidine, nizatidine, ranitidine for PUD, GERD, and related disorders      |

|                         |                                                                                                                                                                                                                    |                                                                                                                                                                                |                                                                                                                                                                                                         |                                                                                            |
|-------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------|
| H <sub>3</sub> Receptor | <ul style="list-style-type: none"> <li>• High expression in histaminergic neurons</li> <li>• High expression in eosinophils, monocytes, DC</li> <li>• Low expression in peripheral tissues</li> </ul>              | <ul style="list-style-type: none"> <li>• Pruritis independent of mast cells</li> <li>• Nasal congestion</li> <li>• Controls degree of bronchoconstriction</li> </ul>           | <ul style="list-style-type: none"> <li>• Likely plays a role in neurogenic inflammation through local neuron-mast cell feedback loops</li> <li>• ↑ APC capacity and proinflammatory activity</li> </ul> | Currently being developed for narcolepsy, dementia, schizophrenia, and other CNS disorders |
| H <sub>4</sub> Receptor | <ul style="list-style-type: none"> <li>• Bone marrow and peripheral hematopoietic cells</li> <li>• PMNs, eosinophils, DC, T cells, mast cells, basophils</li> <li>• Hepatocytes</li> <li>• Chondrocytes</li> </ul> | <ul style="list-style-type: none"> <li>• Pruritus independent of mast cells</li> <li>• Nasal congestion</li> <li>• Differentiation of myeloblasts and promyelocytes</li> </ul> | <ul style="list-style-type: none"> <li>• ↑ Calcium flux in eosinophils</li> <li>• ↑ Eosinophil chemotaxis</li> <li>• ↑ IL-16 production with help of H<sub>2</sub> receptor</li> </ul>                  | Currently being developed for allergic rhinitis                                            |

*Abbreviations:* APC, antigen presenting cell; AV, atrioventricular; DC, dendritic cell; GERD, gastroesophageal reflux disease; IL, interleukin; PUD, peptic ulcer disease; T<sub>H</sub>2, helper T cells type 2; ↑, increase; ↓, decrease.

*Data from Refs.*<sup>7-9</sup>

**Table 2**  
Pharmacokinetics and pharmacodynamics of Oral H1 Antihistamines<sup>a</sup>

| H1 Antihistamines     | Onset of Action (h) <sup>b</sup> | Duration of Action (h) <sup>c</sup> | T <sub>max</sub> After a Single Dose (h) | T <sub>1/2</sub> (h); Name and T <sub>1/2</sub> (h) of Metabolite, if Active <sup>16</sup> | Skin Test Suppression Mean (max) in Days <sup>16</sup> | Usual Adult Dose                                           | Dose Adjustment in Renal/Hepatic Impairment <sup>9</sup> |
|-----------------------|----------------------------------|-------------------------------------|------------------------------------------|--------------------------------------------------------------------------------------------|--------------------------------------------------------|------------------------------------------------------------|----------------------------------------------------------|
| First-Generation      |                                  |                                     |                                          |                                                                                            |                                                        |                                                            |                                                          |
| Chlorpheniramine      | 3                                | 24                                  | 2.8 ± 0.8                                | –; 27.9 ± 8.7 for Mono- and didesmethyl chlorpheniramine                                   | 3 <sup>17</sup> (6 <sup>18</sup> )                     | 4 mg TID or QID; 12 mg (sustained-release formulation) TID | Neither                                                  |
| Diphenhydramine       | 2                                | 12                                  | 1.7 ± 1.0                                | –; 9.2 ± 2.5 for Nordophenhydramine                                                        | 2 <sup>17</sup> (5) <sup>17</sup>                      | 25–50 mg TID or QHS                                        | Hepatic                                                  |
| Doxepin <sup>19</sup> | —                                | —                                   | 2                                        | 13; 31 for N-desmethyldoxepin                                                              | 6 <sup>20</sup>                                        | 25–50 mg TID or QHS                                        | Hepatic                                                  |
| Hydroxyzine           | 2                                | 24                                  | 2.1 ± 0.4                                | 20 ± 4.1 <sup>21</sup>                                                                     | 5 <sup>17</sup> (8) <sup>17</sup>                      | 25–50 mg TID or QHS                                        | Hepatic                                                  |
| Second-Generation     |                                  |                                     |                                          |                                                                                            |                                                        |                                                            |                                                          |
| Acrivastine           | 1                                | 8                                   | 1.4 ± 0.4                                | 1.4–3.1 <sup>21</sup>                                                                      | ~3, T <sub>1/2</sub> = 1.7 h                           | 8 mg TID                                                   | Renal/hepatic                                            |
| Cetirizine            | 1                                | 24                                  | 1.0 ± 0.5                                | 7–11 <sup>21</sup>                                                                         | 3 <sup>22</sup>                                        | 5–10 mg QDay                                               | Renal/hepatic                                            |
| Desloratadine         | 2                                | 24                                  | 1–3                                      | 27; 7/8 ± 4.2 for 3-OH-desloratadine                                                       | ~7 (T <sub>1/2</sub> = 31 h) <sup>23</sup>             | 5 mg QDay                                                  | Renal/hepatic                                            |

|                              |        |    |           |                                                         |                    |                            |               |
|------------------------------|--------|----|-----------|---------------------------------------------------------|--------------------|----------------------------|---------------|
| Ebastine <sup>d</sup>        | 2      | 24 | 2.6–5.7   | – ; 10.3–19.3 for<br>Carebastine                        | —                  | 10–20 mg QDay              | Renal/hepatic |
| Fexofenadine                 | 2      | 24 | 2.6       | 14.4–14.6                                               | 2 <sup>22</sup>    | 60 mg TID; 180 mg QDay     | Renal         |
| Levocetirizine               | 1      | 24 | 0.8 ± 0.5 | 7 ± 1.5                                                 | 3–4 <sup>8</sup>   | 5 mg QDay                  | Renal/hepatic |
| Loratadine                   | 2      | 24 | 1.2 ± 0.3 | 7.8 ± 4.2; 24 ± 9.8 for<br>Descarboe<br>thoxyloratadine | 7 <sup>22</sup>    | 10 mg QDay                 | Hepatic       |
| Mizolastine <sup>d</sup>     | 1      | 24 | 1.5       | 12.9                                                    | —                  | 10 mg QDay                 | Neither       |
| Intranasal                   |        |    |           |                                                         |                    |                            |               |
| Azelastine<br>hydrochloride  | 15 min | 12 | 2–4       | 22–25; 52–57 for<br>Desmethylozelastine                 | 2 <sup>22,24</sup> | 1–2 Sprays per nostril BID | Neither       |
| Olapatadine<br>hydrochloride | 30 min | 12 | 0.25–2    | 8–12                                                    | Unknown            | 2 Sprays per nostril BID   | Neither       |

**Abbreviations:** BID, twice a day; max, maximum; QDay, daily; TID, 3 times daily;  $T_{1/2}$ , half-life;  $T_{max}$ , time to peak plasma concentration, measured from the time of oral intake; QID, 4 times daily.

<sup>a</sup> Unless otherwise indicated, results expressed as means ±SD or as a range of values.

<sup>b</sup> In general, onset of action is based on wheal-and-flare studies.

<sup>c</sup> In general, duration of action is based on wheal-and-flare studies.

<sup>d</sup> Second-generation H1 antihistamines were not available in the United States at the time of publication.

Data from Refs. <sup>8,9,16–22,24</sup>

which are able to distribute widely throughout the body, usually with little CNS penetration. Fexofenadine, in particular, is readily recognized by the P-glycoprotein efflux pump in both the gastrointestinal tract and CNS, keeping it out of these regions and thereby theoretically eliminating CNS side effects completely.<sup>26</sup> One of the main benefits of second-generation antihistamines is their increased selectivity for the H<sub>1</sub> receptor compared with first-generation antihistamines that also bind to and inhibit muscarinic cholinergic,  $\alpha$ -adrenergic, and serotonin receptors. The increased selectivity of second-generation antihistamines decreases the anticholinergic side effects of dry mouth, urinary retention, constipation, and tachycardia that can be seen with many first-generation antihistamines.<sup>23,26–29</sup>

Since the discovery of the first clinically useful H<sub>1</sub> antihistamine in 1942, there have been more than 40 such antihistamines discovered, and they have become one of the mainstays of treatment in allergic diseases.<sup>9</sup> All H<sub>1</sub> antihistamines have an ethylamine group, making them structurally similar to each other and to histamine (**Fig. 1**). Many of the newer antihistamines are metabolites or enantiomers of older antihistamines. For example, levocetirizine is an enantiomer of cetirizine, which is a metabolite of the first-generation antihistamine hydroxyzine. Similarly, desloratadine is a metabolite of loratadine, and fexofenadine is a metabolite of terfenadine, although the latter is no longer used in most countries due to cardiotoxicity.<sup>9</sup> Based on their side group, most of the H<sub>1</sub> antihistamines fall into 1 of the following 6 categories: alkylamines, piperazines, piperidines, ethanolamines, ethylenediamines, and phenothiazines. Among the first-generation antihistamines, foxepin is unique in that it has potent H<sub>1</sub> antihistamine activity that is approximately 800 times stronger than diphenhydramine as measured by receptor antagonism as well as significant H<sub>2</sub> antihistamine activity that is approximately 5 times weaker than cimetidine, in addition to its tricyclic antidepressant properties.<sup>30,31</sup>

The pharmacokinetics and pharmacodynamics of oral H<sub>1</sub> antihistamines vary from one drug to the next, as shown in **Table 2**. In general, second-generation antihistamines tend to have more favorable pharmacokinetics than first-generation drugs with rapid and near-complete absorption as well as a relatively long half-life that allows for daily dosing, features that further enhance their use in clinical practice.<sup>27</sup> The following drug-drug interactions are particularly important: fexofenadine binds to aluminum-containing or magnesium-containing antacids taken within 15 minutes of ingestion, decreasing fexofenadine plasma concentrations in a clinically relevant manner; grapefruit juice inhibits the P-glycoprotein pump in vitro and can decrease the plasma concentration of fexofenadine up to 40%<sup>27</sup>; inhibitors of the cytochrome P450 system, such as macrolide antibiotics or imidazole antifungals, increase concentrations of all first-generation H<sub>1</sub> antihistamines and some second-generation antihistamines, such as loratadine, desloratadine, and rupatadine, that use this system for their metabolism.<sup>9,28,32</sup>

The allergic response consists of 2 phases, the early phase and the late phase. The early phase, triggered by the binding of allergen to IgE on mast cells with subsequent IgE cross-linking and mast cell degranulation, is characterized by the release of pre-formed mediators, such as histamine, and the synthesis of newly formed mediators, such as prostaglandin D<sub>2</sub>, cysteinyl leukotrienes, and platelet activating factor. The late phase response, which generally occurs with a several-hour delay, consists of tissue infiltration with eosinophils, basophils, T cells, neutrophils, and macrophages and subsequent cytokine release perpetuating the inflammatory response.<sup>27</sup> In vivo and in vitro studies have demonstrated that second-generation antihistamines decrease both phases of the allergic response, possessing both antiallergic and anti-inflammatory properties. They do so in part by directly inhibiting the calcium ion

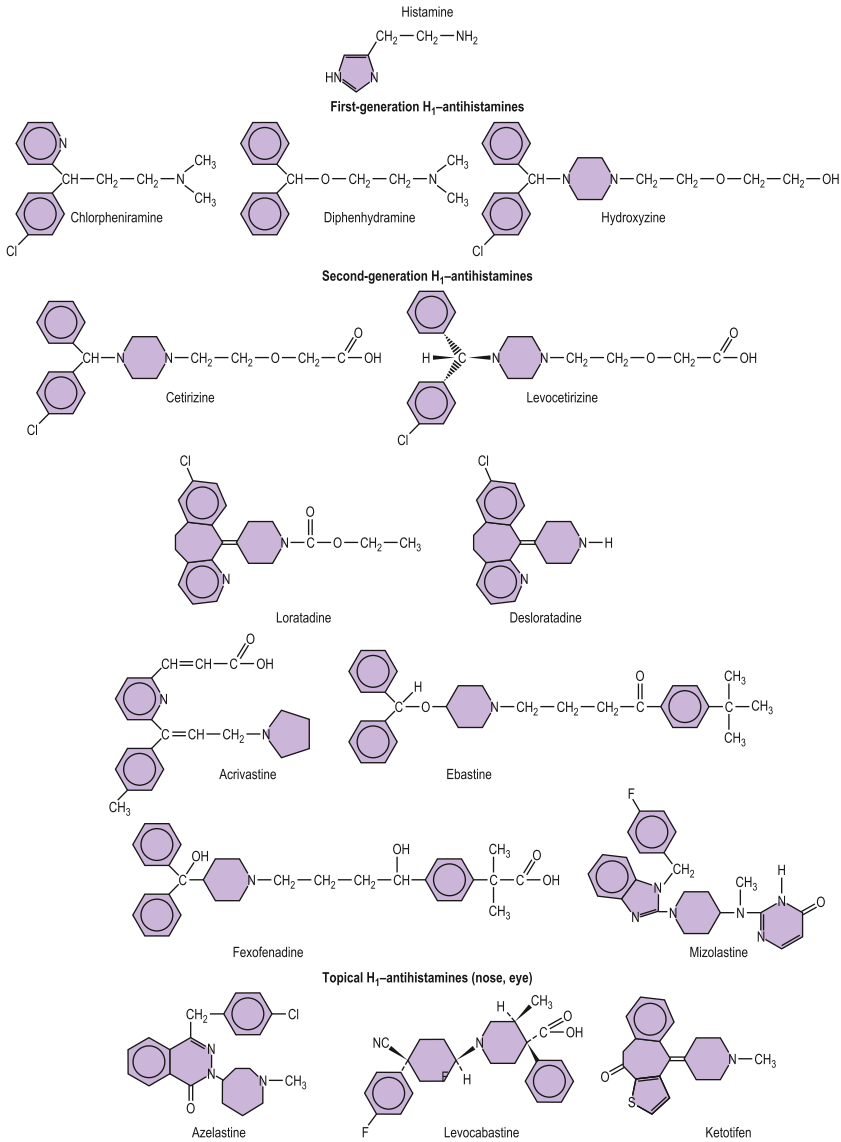


**Fig. 1.** Chemical structures of H<sub>1</sub> antihistamines. All H<sub>1</sub> antihistamines contain an ethylamine group and thus have some resemblance to histamine. In part because of this, many H<sub>1</sub> antihistamines are structurally similar to each other. As shown in the figure, cetirizine and levocetirizine are enantiomers and are thus structurally similar. Metabolites also tend to resemble their parent drug, which is shown here for cetirizine and hydroxyzine as well as desloratadine and loratadine. (From Simons FE, Akdis CA. Histamine and H<sub>1</sub>-antihistamines. In: Adkinson NF Jr, Bochner BS, Busse WW, et al, editors. Middleton's allergy: principles and practice. 7th edition. St Louis (MO): Mosby; 2009; with permission.)

channels of mast cell and basophils<sup>13</sup> as well as by decreasing eosinophil chemotaxis,<sup>3</sup> inhibiting intercellular adhesion molecule 1 expression on nasal epithelium,<sup>33</sup> and curbing inflammation mediated by various other cell types, such as epithelial cells and lymphocytes.<sup>34,35</sup> In clinical trials, H<sub>1</sub> antihistamine administration before allergen challenge has been shown to decrease the levels of cytokines, proinflammatory cell adhesion molecules, and other mediators, such as leukotrienes and prostaglandins, in addition to histamine.<sup>36–38</sup>

### ***Dosing of Oral Antihistamines for Rhinitis Therapy***

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Dosing for most of the first-generation antihistamines has been determined based on clinical experience rather than studies as opposed to the second-generation antihistamines where dose-ranging studies have been performed. As shown in **Table 3**, dosing recommendations for each of the oral antihistamines varies according to the population treated, with special consideration given to the elderly, children, and those with renal or hepatic impairment.<sup>27</sup> Dose-ranging studies performed with cetirizine have shown that higher doses provide greater suppression of the wheal and flare reaction and have greater impact on allergic rhinitis symptoms and quality-of-life (QOL) scores, particularly in patients with higher nasal symptom scores at baseline.<sup>39–42</sup> Such dose increases, however, are also accompanied by increased sedation, hence the current recommendation for 10-mg daily dosing. Similarly, the dosing recommendation of 10 mg daily for loratadine comes from a study comparing this dose with a 40-mg daily dose, which showed an increase in sedation at the higher dose with no added effectiveness.<sup>43,44</sup> Dose-ranging studies for fexofenadine have led to the current United States dosing regimens (60 mg twice daily or 180 mg daily), which were each found significantly better than placebo for the treatment of both rhinitis and conjunctivitis symptoms.<sup>45,46</sup> In Europe, fexofenadine is dosed at 120 mg daily based on these same studies. No benefit was found to increasing the dose of fexofenadine in the twice-daily dosing studies,<sup>45,46</sup> and there was no statistically significant difference in efficacy or QOL between the 120-mg and 180-mg dosages.<sup>47</sup>

### ***Efficacy of Oral Antihistamines in the Treatment of Rhinitis***

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Regarding efficacy in the treatment of allergic rhinitis, few studies have been performed of first-generation H<sub>1</sub> antihistamines.<sup>8,9,48–52</sup> Second-generation H<sub>1</sub> antihistamines, alternatively, have been studied in many rigorous clinical trials (summarized in **Table 3**) that demonstrate the efficacy of these agents in treating both intermittent and persistent allergic rhinitis with minimal adverse effects and good patient acceptance and satisfaction.<sup>8,9</sup>

The currently available second-generation H<sub>1</sub> antihistamines are listed in **Table 2**. Those commonly used in the United States include cetirizine, levocetirizine, loratadine, desloratadine, and fexofenadine. Of these agents, cetirizine and levocetirizine are considered sedating and are, therefore, prohibited for people in certain occupations that demand high psychomotor skills, such as flying airplanes or operating heavy machinery.<sup>53–55</sup> Loratadine, desloratadine, and fexofenadine, alternatively, are considered nonsedating antihistamines if prescribed at their recommended doses.<sup>56,57</sup>

Cetirizine and its enantiomer levocetirizine are zwitterions, molecules with an overall neutral charge despite portions of the molecule having a positive or negative charge, a property that allows for lower serum concentrations, reduced volume of distribution, and less cardiotoxicity due to decreased affinity for the myocardium without compromising efficacy.<sup>53,54,58</sup> As shown in **Table 3**, cetirizine and levocetirizine have proved more efficacious than placebo for the treatment of intermittent and persistent allergic rhinitis in several trials studying symptom relief and QOL. To a lesser degree, both

**Table 3**  
**Recommended daily<sup>a</sup> dosage of second-generation oral antihistamines and intranasal antihistamines in various populations**

| Drug                     | Adults (≥12 y)                                                   | Children                                                                                                                                                             | Elderly        | Adjustment for Renal Impairment                                                                 | Adjustment for Hepatic Impairment                       |
|--------------------------|------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------|-------------------------------------------------------------------------------------------------|---------------------------------------------------------|
| Cetirizine               | 5–10 mg                                                          | 6–12 mo <sup>b</sup> : 2.5 mg<br>12 mo–2 y <sup>b</sup> : 2.5 mg; May increase to 2.5 mg BID<br>2–5 y: 2.5 mg; May increase to 2.5 mg BID or 5 mg<br>6–11 y: 5–10 mg | Same           | <6 y: Not recommended<br>6–11 y: <2.5 mg<br>≥12 y: Depends on creatinine clearance <sup>c</sup> | <6 y: Not recommended<br>6–11 y: <2.5 mg<br>≥12 y: 5 mg |
| Levocetirizine           | 5 mg <sup>d</sup>                                                | 6 mo–5 y <sup>b</sup> : 1.25 mg<br>6–11 y: 2.5 mg                                                                                                                    | 2.5–5 mg       | 6 mo–11 y: Contraindicated<br>≥12 y: Depends on creatinine clearance <sup>e</sup>               | None                                                    |
| Loratadine               | 10 mg                                                            | 2–5 y <sup>f</sup> : 5 mg<br>6–11 y <sup>f</sup> : 10 mg                                                                                                             | Same           | 2–5 y: 5 mg QOD<br>≥6 y: 10 mg QOD                                                              | 2–5 y: 5 mg QOD<br>≥6 y: 10 mg QOD                      |
| Desloratadine            | 5 mg                                                             | 6–11 mo: 1 mg<br>12 mo–5 y: 1.25 mg<br>6–11 y: 2.5 mg                                                                                                                | Same           | Children: not established<br>≥12 y: 5 mg QOD                                                    | 5 mg QOD                                                |
| Fexofenadine             | 180 mg or 60 mg BID                                              | 2–11 y: 30 mg BID                                                                                                                                                    | Start at 60 mg | 2–11 y: 30 mg<br>≥12 y: 60 mg                                                                   | None                                                    |
| Azelastine (intranasal)  | SAR: 1–2 sprays per nostril BID<br>VMR: 2 sprays per nostril BID | 5–11 y: 1 spray per nostril BID                                                                                                                                      | Same           | None                                                                                            | None                                                    |
| Olopatadine (intranasal) | SAR: 2 sprays per nostril BID                                    | Not approved for <12 y                                                                                                                                               | Same           | None                                                                                            | None                                                    |

**Abbreviations:** BID, twice daily; QDay, daily; QOD, every 48 hours; PAR, perennial allergic rhinitis; SAR, seasonal allergic rhinitis; VMR, vasomotor rhinitis.

<sup>a</sup> Unless specified.

<sup>b</sup> Approved down to 6 mo for PAR but only down to 2 y for SAR.

<sup>c</sup> Some adults may respond to 2.5 mg daily.

<sup>d</sup> Creatinine clearance <11 mL/min, not on dialysis: not recommended; 11–31 mL/min or hemodialysis: 5 mg daily.

<sup>e</sup> Creatinine clearance <10: contraindicated; 10–30 mL/min: 2.5 mg every 3 or 4 days; 30–50 mL/min: 2.5 mg every other day; 50–80 mL/min: 2.5 mg daily.

<sup>f</sup> Approved only for SAR in children.

Data from Golightly LK, Greos LS. Second-generation antihistamines: actions and efficacy in the management of allergic disorders. *Drugs* 2005;65(3):341–84; and LexiComp Online drug reference.

cetirizine and levocetirizine have demonstrated efficacy in allergic conjunctivitis symptoms and on nasal congestion, which has traditionally not been a feature of oral antihistamines unless combined with a decongestant.<sup>59,60</sup> QOL can be improved with regular use of either drug,<sup>59,61</sup> and an added benefit has been observed from daily rather than on demand use.<sup>59,62</sup> Higher doses of cetirizine (20 mg daily) improved not only rhinitis symptoms and nasal obstruction but also lower airway symptoms, peak flow measurements, and the need for rescue inhalers in patients with concurrent asthma.<sup>63</sup> In one study of patient preference, the majority of patients who had previously used cetirizine, loratadine, or desloratadine preferred levocetirizine over these other antihistamines.<sup>61</sup>

Loratadine and its metabolite desloratadine are also effective therapies for intermittent and persistent allergic rhinitis, as demonstrated by the studies summarized in **Table 3**. For intermittent allergic rhinitis, loratadine (10 mg daily) helps decrease rhinitis symptoms, with less benefit on nasal obstruction compared with other nasal symptoms.<sup>41</sup> Similar symptomatic relief has been reported for persistent allergic rhinitis, for which one study of loratadine (10 mg daily) demonstrated a gradual increase in symptom improvement over the course of a 28-day treatment period. An additional benefit loratadine is the decrease in both early and late phases of the conjunctival allergic reaction,<sup>37,43</sup> a finding also true for desloratadine.<sup>64</sup>

Fexofenadine, another second-generation antihistamine, has been shown efficacious in various placebo-controlled trials, as depicted in **Table 3**. Like other antihistamines (discussed previously), fexofenadine has an impact on nasal itching, rhinorrhea, and sneezing as well as conjunctival symptoms, with only a small effect on nasal obstruction.<sup>34</sup> Several studies have demonstrated an improvement in QOL for subjects treated with fexofenadine compared with placebo or other antihistamines.<sup>34,47,65</sup> As discussed previously, fexofenadine is unique in that it does not penetrate the CNS due to the effect of the P-glycoprotein efflux pump, translating clinically into less sedation, which was found in comparison trials between fexofenadine and other antihistamines.<sup>66</sup> Unlike its parent drug, terfenadine, fexofenadine does not have cardiotoxic effects.

As shown in **Table 4**, although several studies have compared the second-generation antihistamines, no single drug is considered the best. As such, the decision about which antihistamine to prescribe remains a personalized decision depending on cost and insurance concerns, side-effect profile, and a patient's symptom complex and preference. One placebo-controlled, double-blind study of 688 patients with intermittent allergic rhinitis compared fexofenadine (120 mg daily) with loratadine (10 mg daily) over a 2-week period and demonstrated similar decreases in sneezing, nasal itching, and rhinorrhea but more benefit in nasal congestion and conjunctivitis symptoms in the fexofenadine group.<sup>34</sup> In addition to symptomatic benefit, fexofenadine had a significantly greater improvement in QOL, as measured by the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ), when compared with placebo or loratadine.<sup>34</sup> Another study by Lee and colleagues<sup>105</sup> compared a single dose of levocetirizine, desloratadine, and fexofenadine in a crossover study assessing the ability of each drug to improve nasal peak inspiratory flow in 16 persistent allergic rhinitis patients challenged with adenosine monophosphate. All 3 antihistamines improved nasal peak inspiratory flow to a similar degree, which was higher than for placebo. As shown in **Table 4**, several studies have compared the efficacy of cetirizine and fexofenadine, demonstrating significant benefit of both drugs over placebo but similar efficacy between them.<sup>59,66,94</sup> One finding when comparing the 2 drugs, however, is decreased sedation with fexofenadine compared with cetirizine.<sup>94</sup> A similar conclusion can be drawn from 2 studies that compare standard dosing of desloratadine and fexofenadine in the treatment of intermittent allergic rhinitis.<sup>100,101</sup> Comparison

studies between cetirizine and loratadine, alternatively, demonstrate a fairly consistent benefit in the efficacy of cetirizine over loratadine.<sup>97-99,106</sup> The 2 studies comparing loratadine and fexofenadine showed that either antihistamine is superior to placebo, with 1 study demonstrating equal efficacy between the 2 drugs and the other showing superior efficacy for fexofenadine over loratadine therapy.<sup>34,102,103</sup> In the 2 studies comparing levocetirizine and desloratadine, both drugs demonstrated superior efficacy compared with placebo in decreasing the symptoms of allergic rhinitis, doing so to a similar degree, except for nasal congestion where levocetirizine was overall superior.<sup>60,107</sup>

### ***Oral Antihistamines as Add-on Therapy to Intranasal Corticosteroids in the Treatment of Rhinitis***

Although oral antihistamines are beneficial in the treatment of rhinitis, as discussed previously, several studies have demonstrated that combining an oral antihistamine with intranasal steroid does not provide added benefit to the use of intranasal steroid spray alone.<sup>108-111</sup>

The first of these studies was performed in 1989 and compared intranasal beclomethasone (400 µg daily), astemizole (10 mg daily), and combination therapy. In this 6-week study of 90 adult subjects evaluating nasal symptom scores, intranasal beclomethasone was superior to that of astemizole alone with no added benefit from combination therapy in rhinitis symptoms compared with intranasal beclomethasone alone.<sup>108</sup> A similar study in 1998 compared fluticasone (200 µg once daily), loratadine (10 mg daily), and combination therapy of these 2 agents. This 2-week study of 600 patients showed a similar improvement in RQLQ for the fluticasone only and combination therapy groups.<sup>109</sup> A 2004 study of 100 patients examining intranasal steroid, oral antihistamine, and leukotriene antagonist therapy in various combinations over the course of 6 weeks demonstrated similar results. All groups treated with intranasal steroid (monotherapy with fluticasone [200 µg once daily], fluticasone plus cetirizine [10 mg each morning], and fluticasone plus montelukast [10 mg each evening]) demonstrated similar improvements in nasal congestion, both on awakening and during the day. Again, there was no benefit to adding oral antihistamine to intranasal steroids regarding congestion, and this study demonstrated an advantage in decreasing nasal itching for the fluticasone-only group over combination therapy ( $P = .003$ ).<sup>110</sup> In 2006, 27 patients were treated with fluticasone (200 µg daily) and either levocetirizine (5 mg) or placebo for 2 weeks during allergy season with no benefit to combination therapy over fluticasone therapy alone in any of the following categories: RQLQ; domiciliary peak nasal inspiratory flow; total nasal symptom score (TNSS), which assesses itchy nose, runny nose, stuffy nose, and sneezing; and nasal nitric oxide concentrations.<sup>111</sup> Ocular symptoms were not evaluated in any of these studies and may represent an area of potential benefit for the addition of oral antihistamines to intranasal steroid therapy.

### **INTRANASAL ANTIHISTAMINES IN RHINITIS THERAPY**

A major advance in the treatment of rhinitis has been the development of intranasal antihistamines as a way of delivering antihistamine therapy directly to the nasal mucosa. The advantages of such therapy include attaining higher concentrations of active drug directly to the target tissue with the added benefit of reduced systemic side effects.<sup>112</sup> Since the development of the first intranasal antihistamine, several studies have been performed to determine their proper role in the treatment of rhinitis, and their use has increased considerably. In the most recent practice parameters

**Table 4**  
**Studies evaluating efficacy of second-generation antihistamines**

| Medication     | Dose           | Type of AR | # of Patients | Age Range | Duration (weeks) | Symptom Decrease (%) | Comparative Efficacy | References |
|----------------|----------------|------------|---------------|-----------|------------------|----------------------|----------------------|------------|
| Cetirizine     | CTZ 10 mg      | SAR        | 20            | 19–48     | 4                | 50                   | CTZ > PLA            | 62         |
|                | CTZ 10 mg      | SAR        | 375           | >15       | 4                | 49                   | CTZ > PLA            | 67         |
|                | CTZ 10 mg      | SAR        | 865           | 18–65     | 2                | 29                   | CTZ > PLA            | 68         |
|                | CTZ 10 mg      | SAR        | 403           | 18–65     | 2                | 28                   | CTZ > PLA            | 69         |
|                | CTZ 20 mg      | PAR        | 28            | 13–59     | 26               | 36                   | CTZ > PLA            | 63         |
|                | CTZ 10–20 mg   | PAR        | 220           | 18–70     | 4                | 43                   | CTZ > PLA            | 70         |
|                | CTZ 5 mg       | PAR        | 24            | 18–32     | n/a              | 39                   | CTZ > PLA            | 71         |
|                | CTZ 10 mg      | PAR        | 274           | 18–60     | 6                | 35                   | CTZ > PLA            | 59         |
|                | CTZ 10 mg      | PAR        | 143           | 17–67     | 52               | 33                   | NS                   | 72         |
| Levocetirizine | LEVO 5 mg      | SAR        | 577           | NS        | 2                | NS                   | LEVO > PLA           | 73         |
|                | LEVO 5 mg      | SAR        | 596           | 18–65     | 2                | NS                   | LEVO = PLA           | 74         |
|                | LEVO 5 mg      | SAR        | 1290          | NS        | 4                | NS                   | LEVO > previous AH   | 61         |
|                | LEVO 5 mg      | PAR        | 294           | ≥12       | 6                | 86                   | LEVO > PLA           | 75         |
|                | LEVO 5 mg      | PAR        | 551           | >18       | 4                | NS                   | LEVO > PLA           | 76         |
|                | LEVO 5 mg      | PAR        | 551           | >18       | 24               | NS                   | LEVO > PLA           | 77         |
| Fexofenadine   | FEX 120 mg     | SAR        | 99            | 14–62     | n/a              | 85                   | FEX > PLA            | 78         |
|                | FEX 60 mg      | SAR        | 651           | 12–65     | 2                | 74                   | FEX > PLA            | 79         |
|                | FEX 180 mg     | SAR        | 861           | 12–65     | 2                | 59                   | FEX > PLA            | 80         |
|                | FEX 120 mg     | SAR        | 545           | 12–65     | 2                | 21                   | FEX > PLA            | 45         |
|                | FEX 180 mg     | SAR        | 845           | 12–65     | 2                | 63                   | FEX > PLA            | 47         |
|                | FEX 240 mg     | SAR        | 570           | 12–66     | 2                | 28                   | FEX > PLA            | 46         |
|                | FEX 120–180 mg | PAR        | 31            | Adult     | 4                | 66                   | FEX > PLA            | 81         |
| Loratadine     | LOR            | SAR        | 338           | 12–82     | 1                | 38                   | LOR > PLA            | 82         |

|                        |                         |     |      |       |     |          |                 |     |
|------------------------|-------------------------|-----|------|-------|-----|----------|-----------------|-----|
|                        | LOR 10 mg               | PAR | 14   | Adult | 2   | 36       | NS              | 83  |
|                        | LOR 10 mg               | SAR | 835  | 12–60 | 1   | NS       | LOR > PLA       | 84  |
| Desloratadine          | DES 5 mg                | SAR | 346  | 12–65 | 2   | 44       | DES > PLA       | 85  |
|                        | DES 5 mg                | SAR | 46   | 19–34 | 2   | 43       | DES > PLA       | 86  |
|                        | DES 5 mg, 7.5 mg        | SAR | 677  | 12–72 | 2   | NS       | DES > PLA       | 87  |
|                        | DES                     | SAR | 407  | NS    | 2   | NS       | DES > PLA       | 88  |
|                        | DES 5 mg                | SAR | 331  | 15–75 | 4   | 36       | DES > PLA       | 89  |
|                        | DES 2.5–20 mg           | SAR | 1026 | 12–75 | n/a | 29–38    | DES > PLA       | 90  |
|                        | DES 5 mg                | PAR | 634  | ≥12   | 4   | 38       | DES > PLA       | 91  |
|                        | DES 5 mg                | SAR | 547  | ≥12   | 2   | NS       | DES > PLA       | 92  |
|                        | DES 5 mg                | PAR | 716  | ≥12   | 12  | NS       | DES > PLA       | 93  |
| Comparative<br>Studies | CTZ 10 mg<br>FEX 120 mg | SAR | 39   | 20–36 | n/a | 48<br>47 | CTZ = FEX > PLA | 94  |
|                        | CTZ 10 mg<br>FEX 180 mg | SAR | 722  | 12–66 | 2   | 45<br>45 | CTZ = FEX > PLA | 95  |
|                        | CTZ 10 mg<br>FEX 180 mg | SAR | 495  | 12–70 | 2   | 22<br>19 | CTZ = FEX       | 66  |
|                        | CTZ 10 mg<br>LOR 10 mg  | SAR | 278  | 13–62 | n/a | 57<br>35 | CTZ > LOR > PLA | 96  |
|                        | CTZ 10 mg<br>LOR 10 mg  | SAR | 111  | 14–70 | n/a | 70<br>50 | CTZ > LOR > PLA | 97  |
|                        | CTZ 10 mg<br>LOR 10 mg  | SAR | 360  | 16–65 | n/a | 25<br>11 | CTZ > LOR > PLA | 98  |
|                        | CTZ 10 mg<br>LOR 10 mg  | SAR | 194  | 16–80 | n/a | 37<br>15 | CTZ > LOR > PLA | 99  |
|                        | DES 5 mg<br>FEX 180 mg  | SAR | 49   | NS    | 2   | 24<br>22 | DES = FEX > PLA | 100 |

(continued on next page)

**Table 4**  
(continued)

| Medication | Dose                                  | Type of AR | # of Patients | Age Range | Duration (weeks) | Symptom Decrease (%) | Comparative Efficacy | References        |
|------------|---------------------------------------|------------|---------------|-----------|------------------|----------------------|----------------------|-------------------|
|            | DES 5 mg<br>FEX 180 mg                | SAR        | 722           | NS        | 2                | NS                   | DES = FEX > PLA      | <sup>101</sup>    |
|            | LOR 10 mg<br>FEX 120 mg               | SAR        | 680           | 12–75     | 2                | 32<br>44             | FEX > LOR > PLA      | <sup>34,102</sup> |
|            | LOR 10 mg<br>FEX 120 mg               | SAR        | 569           | ≥12       | 2                | ~79<br>~79           | FEX = LOR > PLA      | <sup>103</sup>    |
|            | DES 5 mg<br>previous AH               | SAR/CIU    | 77            | ≥12       | 5.5              | NS                   | DES > previous AH    | <sup>104</sup>    |
|            | LOR 10 mg<br>EBAS 10 mg<br>EBAS 20 mg | PAR        | 317           | 12–68     | 1                | 32<br>44<br>47       | EBAS > LOR           | <sup>64</sup>     |

**Abbreviations:** AH, antihistamine; AR, allergic rhinitis; CTZ, cetirizine; DES, desloratadine; EBAS, ebastine; FEX, fexofenadine; LEVO, levocetirizine; LOR, loratadine  
n/a, not applicable; NS, not stated; PAR, perennial allergic rhinitis; PLA, placebo; SAR, seasonal allergic rhinitis.

Data from Refs. <sup>9,34,41,45–47,59,61,63,64,66–94,96–104</sup>

released by the American Academy of Asthma Allergy and Immunology in 2008 to help guide rhinitis therapy, nasal antihistamines are considered “efficacious and equal to or superior to oral second-generation antihistamines for treatment of intermittent allergic rhinitis” with a similar role in the treatment of episodic allergic rhinitis given their rapid onset of action.<sup>16</sup> Although the parameters cite evidence that “intranasal antihistamines are generally less effective than intranasal corticosteroids for treatment of allergic rhinitis,” the literature is sparse and at times conflicting on this issue.<sup>113</sup> As such, the parameters conclude that intranasal antihistamines should be considered “first-line treatment for allergic and nonallergic rhinitis” and an “appropriate choice for mixed rhinitis” given the approved indication of azelastine for vasomotor rhinitis. Two unique features of intranasal antihistamines highlighted in these parameters are the “clinically significant effect on nasal congestion” and a potential benefit for ocular allergic symptoms.<sup>16</sup>

### ***Intranasal Antihistamines Available for Clinical Use***

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Azelastine hydrochloride and olopatadine hydrochloride are the 2 antihistamines currently commercially available in intranasal form in the United States (see **Table 2**). Three formulations of azelastine hydrochloride nasal spray have been developed, the original 0.1% aqueous solution and a reformulated solution using sorbitol and sucralose to mask the bitter taste of the original formulation. Two head-to-head comparisons of the original formulation with the sucralose-based 0.1% formulation demonstrated a comparable safety profile and similar pharmacokinetics.<sup>114</sup> Although the reformulated solution originally came in the same 0.1% strength as the original formulation, this strength was recently discontinued and replaced by the same formulation in a new 0.15% strength. A 2009 study by Shah and colleagues<sup>115</sup> comparing the 0.1% and 0.15% strengths of azelastine found that both decreased TNSS scores compared with placebo, but the higher dose did so to a greater degree ( $P < .05$ ) with only a slight increase in somnolence. The other intranasal antihistamine currently available in the United States is olopatadine, which comes only as a 0.6% aqueous solution. The main side effects of intranasal antihistamines are bitter taste and somnolence,<sup>16</sup> both of which are less for olopatadine compared with azelastine. Although somnolence was greater with azelastine nasal spray than placebo in earlier studies, more recent trials of azelastine in the treatment of nonallergic rhinitis have not shown a statistical difference in somnolence between azelastine and placebo groups (3.2% vs 1.0%).<sup>16,116,117</sup>

### ***Efficacy of Intranasal Antihistamines in the Treatment of Rhinitis***

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The efficacy of azelastine and olopatadine nasal sprays has been assessed in various randomized, double-blind, placebo-controlled trials. Azelastine was first evaluated in 1994 through 2 day-in-the-park studies where more than 500 patients were exposed to aeroallergens for 8 hours on 2 consecutive days and then randomized to varying doses of azelastine nasal spray, oral chlorpheniramine, or placebo. In both studies, patients receiving azelastine demonstrated an improvement in rhinitis symptoms compared with the placebo group, as measured by symptom diaries in the first study and by major symptom complex (MSC), assessing nose blows, sneezes, runny nose/sniffles, itchy nose, and watery eyes, and total symptom complex (TSC), assessing those symptoms incorporated in the MSC as well as cough, postnasal drip, and itchy eyes, ears, throat, and palate scores in the second study. Both studies demonstrated duration of action ranging from 12 to 24 hours after a single dose of azelastine, thus supporting a once-daily to twice-daily dosing regimen.<sup>118,119</sup> These studies were followed by two 2-week trials and one 4-week trial of azelastine for the treatment of

intermittent allergic rhinitis. The 2-week trials randomized 498 patients to once-daily or twice-daily azelastine, daily chlorpheniramine, or placebo during pollen season. Azelastine administered twice daily again demonstrated a significant decrease in TSC and MSC compared with placebo ( $P < .01$ ), and once-daily dosing trended toward a similar benefit for azelastine over placebo.<sup>120,121</sup> The 4-week trial evaluated 264 patients randomized to these same treatment arms for 2 extra weeks and demonstrated a statistically significant difference in overall mean percentage of MSC improvement ( $P = .04$ ) with a nonstatistically significant trend in overall mean percentage of TSC improvement for those patients receiving azelastine compared with placebo.<sup>122</sup> Although the standard dosing for azelastine is 2 sprays per nostril twice daily, 2 recent placebo-controlled trials evaluated the efficacy of lowering this dose to 1 spray per nostril twice daily in 554 patients over a 2-week period during the spring pollen season and found a significant reduction in TNSS as well as individual symptom scores compared with placebo, with fewer reports of somnolence or bitter taste than the incidences published for the dose of 2 sprays per nostril twice daily.<sup>123</sup>

The data supporting the use of olopatadine nasal spray in the treatment of intermittent allergic rhinitis come mainly from two 3-week multicenter trials that evaluated 1233 patients randomized to receive olopatadine 0.4%, olopatadine 0.6%, or placebo. The 0.6% strength of olopatadine demonstrated a statistically significant decrease in both reflective TNSS and instantaneous TNSS as well as a decrease in ocular symptoms and nasal congestion, although the latter only reached statistical significance in 1 of the 2 studies.<sup>124,125</sup> When data from these 2 studies were pooled, reduction in TNSS correlated with a beneficial impact on QOL as measured by the overall RQLQ score and correlated with decreased impact on work and daily activities as measured by the Work Productivity and Activity Impairment Questionnaire-Allergy Specific ( $r = 0.45$  to  $0.61$ ,  $P < .001$ ).<sup>125</sup> An improvement in RQLQ with olopatadine treatment was also reported in a trial of 677 patients randomized to treatment with olopatadine 0.4%, olopatadine 0.6%, or placebo. Based on allergen chamber studies, the 0.6% formulation was superior in efficacy and is thus the marketed concentration.<sup>126</sup>

In previous comparisons of olopatadine and azelastine nasal sprays, the 2 medications seem to have similar efficacy. A 2009 study of 544 patients compared olopatadine 0.6%, azelastine 0.1%, and placebo (2 sprays per nostril administered twice daily for 16 days). There was a greater reduction in TNSS for both the olopatadine and azelastine groups compared with placebo, with no difference between the different antihistamine sprays. Although adverse effects were rare for both antihistamine nasal sprays, there were more complaints of bitter taste in the azelastine group ( $P = .05$ ).<sup>127</sup> Comparable efficacy between these 2 medications was also shown in a smaller 2008 study of 20 patients comparing symptom relief from olopatadine 0.1%, olopatadine 0.2%, and azelastine 0.1% (2 sprays per nostril administered before an allergen challenge), with similar benefit from all 3 sprays.<sup>128</sup>

### ***Comparison of Intranasal Antihistamines and Intranasal Corticosteroids***

The contention that intranasal corticosteroids are superior to intranasal antihistamines, as stated in the 2008 practice parameters, is based largely on the results of a meta-analysis published in 2002 and required further consideration. Of the 9 studies incorporated in the 2002 meta-analysis, 3 evaluated intranasal levocabastine, which is currently unavailable in the United States, and the other 6 compared varying doses of azelastine with several intranasal corticosteroids, including beclomethasone, budesonide, and fluticasone. These studies suggested that intranasal corticosteroids were overall more effective than intranasal antihistamines in reducing TNSS and in reducing the symptoms of rhinorrhea and nasal itching, although to a more variable degree than

with overall TNSS. The conclusions drawn from this meta-analysis must be taken with caution because several of the studies of azelastine used subtherapeutic doses of the drug. In addition, intranasal steroids did not prove beneficial for ocular symptoms and nasal congestion when these symptoms were taken alone, whereas intranasal antihistamines have been shown to benefit both.<sup>129</sup>

Since the publication of this meta-analysis, a recent trial has brought the superiority of intranasal corticosteroids into question. In 2009, Kaliner and colleagues<sup>130</sup> published a double-blind, randomized, parallel-group, 2-week noninferiority trial demonstrating no statistically significant difference between olopatadine 0.6% (2 sprays per nostril twice daily) and fluticasone propionate (50 µg, 2 sprays per nostril daily) when analyzing TNSS reduction or individual symptoms of congestion, runny nose, sneezing, itchy nose, and ocular symptoms in 130 symptomatic patients with intermittent allergic rhinitis. The only statistically significant difference between the 2 groups was a faster onset of action of olopatadine compared with fluticasone propionate.

A recent trial by Ratner and colleagues<sup>131</sup> suggests that combination therapy with intranasal corticosteroid and intranasal antihistamine may be the best approach. In this 2-week multicenter trial, the following therapies were compared for their ability to decrease TNSS: azelastine (2 sprays per nostril twice daily), fluticasone (2 sprays per nostril once daily), and combination of the 2. Combination therapy was found superior to each of the monotherapy regimens, with a reduction in TNSS scores of 37.9% in the combined therapy group compared with 27.1% and 24.8% in the azelastine and fluticasone monotherapy groups, respectively.

### ***Onset of Action of Intranasal Antihistamines***

As concluded by Kaliner and colleagues<sup>130</sup> in their 2009 study (referenced previously), one benefit of intranasal antihistamines over intranasal corticosteroids is the more rapid onset of action of the former. This benefit was first demonstrated in the 2007 study by Patel and colleagues<sup>132</sup> that compared olopatadine and mometasone nasal sprays in an allergen exposure chamber, yielding an onset of action of 30 and 150 minutes, respectively, based on TNSS recorded by 425 patients every 30 minutes after spray administration. The 30-minute onset of action was confirmed by another 2007 study demonstrating symptom improvement 30 minutes after administration of olopatadine 0.2%, olopatadine 0.4%, or olopatadine 0.6% with a similar study design.<sup>133</sup> Symptoms were not assessed before 30 minutes in the 2007 or 2009 studies of olopatadine versus intranasal steroids; hence, the possibility exists that the onset of action is more rapid than 30 minutes for olopatadine. Original studies of azelastine, alternatively, began symptom assessments at the 15-minute mark; when compared with mometasone nasal spray, the onset of action of azelastine was 15 minutes compared with mometasone's onset of action of 8 hours, respectively.<sup>134</sup> Azelastine had a faster onset of action than oral desloratadine when both were administered 2 hours after an allergen challenge, with 1 spray of azelastine 0.1% decreasing both MSC and TNSS at 15 minutes compared with 150 minutes for desloratadine.<sup>135</sup> As shown in **Table 2**, the onset of action is faster for intranasal antihistamine compared with all available oral antihistamines, a statement that holds true for all intranasal corticosteroids.<sup>136</sup>

### **COMPARISON STUDIES BETWEEN INTRANASAL AND ORAL ANTIHISTAMINES**

Although intranasal and oral antihistamines are both viable therapeutic options for the treatment of rhinitis in most patients, several studies have demonstrated superior efficacy of intranasal antihistamines over therapy with oral antihistamines. In 2003 and

2004, 2 studies were performed to evaluate the efficacy of azelastine nasal spray in patients inadequately controlled on oral antihistamine therapy. The first study compared twice-daily azelastine to therapy with desloratadine, placebo, or a combination of azelastine and loratadine.<sup>137</sup> The second study compared azelastine monotherapy, fexofenadine monotherapy, and therapy with a combination of these 2 agents.<sup>138</sup> Both studies demonstrated a statistically significant decrease in TNSS for all subjects receiving azelastine spray compared with those receiving placebo therapy or monotherapy with either desloratadine or fexofenadine alone.<sup>137,138</sup> Furthermore, in this subset of patients with inadequate benefit from oral antihistamine monotherapy, there was no added benefit to administering an oral antihistamine concurrent with azelastine nasal spray compared with azelastine monotherapy in either study. Two subsequent trials compared azelastine and cetirizine as a way of directly comparing the efficacy of intranasal and oral antihistamines. The first Azelastine Cetirizine Trial was in 2005 and studied 299 patients,<sup>139</sup> followed shortly by the second Azelastine Cetirizine Trial of 360 patients in 2006.<sup>140</sup> Both studied treatment with azelastine (2 sprays per nostril twice daily) plus a placebo capsule versus a placebo nasal spray plus cetirizine (10 mg capsule daily) over a 2-week period. The azelastine group was superior to the cetirizine group with respect to TNSS in the 2005 Azelastine Cetirizine Trial and regarding RQLQ scores for both trials.<sup>139,140</sup>

## USE OF ANTIHISTAMINES IN SPECIAL POPULATIONS

When using antihistamines in clinical practice, special consideration must be given to children, pregnant women, the elderly, and patients with hepatic or renal dysfunction. Dosing for several of these special populations is shown in **Table 4**. Although caution should be used when choosing an agent during pregnancy and lactation, dose adjustment is generally not necessary unless the mother also has hepatic or renal dysfunction.

### *Antihistamine Use for Rhinitis Therapy in Children*

In children, antihistamines are considered first-line agents for the treatment of allergic rhinoconjunctivitis, urticaria, and atopic dermatitis. First-generation antihistamines approved for use in children as young as 2 years of age include diphenhydramine, hydroxyzine, chlorpheniramine, brompheniramine, and clemastine. The anticholinergic and CNS effects of sedation and impairment that limit the use of first-generation antihistamines in adults can also be seen in children. As such, their use is generally limited to cases of pruritus so severe that sedation is a desired side effect or to cases of anaphylaxis where intravenous antihistamines serve as an adjunct to epinephrine therapy. For the treatment of chronic rhinitis, however, second-generation antihistamines are an attractive choice given their efficacy and favorable side-effect profile. The current pediatric dosing recommendations for the most common second-generation antihistamines are shown in **Table 4**. In general, these recommendations are determined by the Food and Drug Administration (FDA) using the pediatric rule, which allows for extrapolation of efficacy from adults to children as long as the pathophysiology, disease course, and drug effects are similar enough between adults and children, as is the case for allergic rhinitis. Once efficacy is extrapolated, pharmacokinetic and pharmacodynamic data are collected to ensure that it is similar for children and adults, followed by a safety study in younger children.<sup>141</sup>

Pharmacokinetic and pharmacodynamic data have been obtained in small children for most of the second-generation antihistamines in small children.<sup>142–147</sup> Of these agents, cetirizine, levocetirizine, and desloratadine have been approved for children as young as 6 months of age, and loratadine and fexofenadine have been approved

for children as young as 2 years of age. Trials assessing the efficacy and safety of second-generation oral antihistamines are summarized in **Table 5**. In addition to the oral antihistamines, azelastine nasal spray has been shown to provide symptomatic benefit by reducing scores for total rhinitis symptoms, total nasal symptoms, and ocular symptoms in children with allergic rhinitis and is currently approved for use in children 5 years of age and older.<sup>156,157</sup>

One concern particularly relevant to children is the effect that antihistamines may have on academic performance. Allergic rhinitis itself has been shown to affect learning and school performance; therefore, the possible adverse effect of antihistamine therapy on academic performance must be weighed against the potential benefit of these drugs in enhancing academic performance by decreasing rhinitis symptoms. This balance was addressed in a 1999 study by Tanner and colleagues<sup>65</sup> of more than 500 children with allergic rhinitis, 93% of whom reported an effect on classroom productivity, and 23% reporting missed classroom time due to their rhinitis. After treatment with either placebo or fexofenadine (60 mg twice daily for 2 weeks), there was a significant decrease in missed classroom time and in classroom impairment for those children treated with fexofenadine. Taken together, overall impairment decreased by 41% in the fexofenadine group and only 27% in the placebo group after the 2 weeks of treatment. In a 1993 study by Vuurman and colleagues,<sup>158</sup> academic performance was assessed using didactic stimulation, a validated tool that involves acquiring knowledge and subsequently using that knowledge to demonstrate its retention. In this study, atopic patients were pretreated with diphenhydramine, loratadine, or placebo and trained for 1 day, whereas normal controls received no medications but the same training. After 2 weeks of loratadine treatment in the atopic group, both the atopic children and the normal controls were tested about the knowledge taught to them during the training session. In general, the atopic children did worse on this testing compared with the normal controls. Among the atopic children, those treated with diphenhydramine before training had impairment of retention, whereas pretreatment with loratadine seemed to impart a small benefit on learning. In 1996, Vuurman and colleagues<sup>159</sup> performed a similar study on young adults randomized to pretreatment with acrivastine plus pseudoephedrine, diphenhydramine, or placebo and trained for 3 consecutive days instead of just 1 day. The atopic patients were then treated for 2 weeks with the acrivastine/pseudoephedrine combination and compared with a normal control group that received the same training but no medications. Both groups were tested immediately after the 3-day training session as well as at the end of the 2-week treatment period. For each group, test scores improved with each day of training but the amount of improvement differed between groups. Both immediately after training and at the end of 2 weeks, the best results came from the normal control group and the allergic group pretreated with the combination of acrivastine and pseudoephedrine. The allergic patients pretreated with placebo learned less well than these 2 groups, suggesting an inherent impairment in learning from allergic rhinitis itself, and the group receiving diphenhydramine again did significantly worse than all other groups at the end of the training period.

### ***Antihistamine Use for Rhinitis Therapy During Pregnancy***

Allergic rhinitis has been estimated to complicate 20% to 30% of pregnancies, with 10% to 30% of women who have underlying allergic rhinitis describing an increase in symptoms during pregnancy.<sup>160,161</sup> Although prospective studies in pregnancy are few and there are no randomized controlled trials, antihistamines are often used to treat rhinitis symptoms given their extensive clinical experience in pregnant females.<sup>160</sup> First-generation antihistamines have been deemed safe during the first trimester and throughout pregnancy based mostly on epidemiologic data and a

**Table 5**  
**Studies of antihistamine efficacy and safety in the pediatric population**

| Medication | Dose                | Patient Population              | Age Range | Duration | Primary Endpoint    | Study Design | Result                                                                                                           | References     |
|------------|---------------------|---------------------------------|-----------|----------|---------------------|--------------|------------------------------------------------------------------------------------------------------------------|----------------|
| Cetirizine | 5 mg or 10 mg Daily | 209 Children with SAR           | 6–11 y    | 4 wk     | Efficacy (symptoms) | R, DB, PC    | Compared with placebo, cetirizine 10 mg daily but not 5 mg daily significantly improves SAR symptoms             | <sup>148</sup> |
|            | 10 mg Daily         | 544 Children with SAR           | 6–11 y    | 4 wk     | Efficacy (QOL)      | OL, NC       | Cetirizine 10 mg daily led to a significant improvement in QOL                                                   | <sup>149</sup> |
|            | 0.25 mg/kg BID      | 817 Children with SAR/CIU       | 12–24 mo  | 18 mo    | Safety              | R, DB, PG, P | Cetirizine is considered safe in pediatric patients aged 12–24 months                                            | <sup>150</sup> |
|            | 0.25 mg/kg BID      | 85 Infants with previous AH use | 6–11 mo   | 1 wk     | Safety              | R, DB, PC    | Compared with placebo, cetirizine 0.25 mg/kg BID did not cause an increase in adverse events or QTc prolongation | <sup>151</sup> |

|                |                                                                        |                                                    |               |       |                     |                                           |                                                                                                   |
|----------------|------------------------------------------------------------------------|----------------------------------------------------|---------------|-------|---------------------|-------------------------------------------|---------------------------------------------------------------------------------------------------|
| Fexofenadine   | 30 mg BID                                                              | 932 Children with SAR                              | 6–11 y        | 2 wk  | Efficacy (symptoms) | R, DB, PC                                 | Compared with placebo, fexofenadine 30 mg BID significantly reduced symptom scores <sup>152</sup> |
|                | All 3 studies: 30 mg BID; 2 studies also assessed: 15 mg and 60 mg BID | 1810 Children with SAR                             | 6–11 y        | 2 wk  | Efficacy and Safety | Pooled data from 3 studies: R, DB, PC, PG | Fexofenadine is safe, nonsedative, and effective in children ages 6–11 years <sup>153</sup>       |
| Desloratadine  | 1.25 mg daily (2–5 y); 2.25 mg daily (6–11 y)                          | 111 (2–5 y) and 120 (6–11 y) children with SAR/CIU | 2–5 y; 6–11 y | 2 wk  | Safety              | DB, PC, PG                                | Desloratadine is considered safe for 2–11 year-old children <sup>154</sup>                        |
| Levocetirizine | 0.125 mg/kg BID                                                        | 510 Atopic children                                | 12–24 mo      | 18 mo | Safety              | R, DB, PC                                 | Levocetirizine is considered safe in pediatric patients aged 12–24 months <sup>155</sup>          |

*Abbreviations:* AH, antihistamine; BID, twice daily; CIU, chronic idiopathic urticaria; DB, double blind; NC, noncomparative; OL, open label; PC, placebo-controlled; PG, parallel group; QTC, QT interval corrected for rate; R, randomized; SAR, seasonal allergic rhinitis.

*Data from Refs.*<sup>141,148–155</sup>

meta-analysis of more than 200,000 participants, where there was no increase seen in any type of congenital malformation.<sup>162,163</sup>

Several retrospective and prospective studies have been performed to evaluate the safety of cetirizine and loratadine in pregnancy, and both medications are deemed safe as a result of these studies. Loratadine was analyzed in a Swedish registry study of 292 women taking this medication during pregnancy with no increase in the rate of major malformations.<sup>164</sup> A prospective comparative study was subsequently performed on 161 women taking loratadine during pregnancy and 161 pregnant controls, demonstrating similar infant outcomes.<sup>165</sup> In another comparative study, 210 loratadine-exposed pregnant women, 267 women taking other antihistamines during pregnancy, and 929 pregnant women not taking antihistamines had no adverse effects from loratadine ingestion during pregnancy.<sup>166</sup> Although further analysis of the Swedish registry data suggested increased hypospadias risk in male infants exposed to loratadine, a subsequent case-control study using telephone interviews to collect data from the mothers of approximately 2000 male infants demonstrated no significant correlation between first-trimester loratadine exposure and hypospadias.<sup>167</sup> A subsequent meta-analysis of 2694 loratadine-exposed infants and more than 450,000 unexposed controls also refuted this association.<sup>161</sup>

The safety of cetirizine in pregnancy has also been examined through several prospective and retrospective studies. The first of these was a comparative telephone study of 120 women receiving hydroxyzine during pregnancy and 39 women receiving cetirizine (10 mg per day), 37 of whom took the medication during their first trimester. This prospective study showed no difference in pregnancy outcomes for either group.<sup>168</sup> Data from these 39 patients were supplemented with data from 60 other women who also took standard-dose cetirizine early during pregnancy, again with no increase in adverse effects on exposed infants. There was an incidental finding of significantly less pregnancy-induced nausea and vomiting for those women taking cetirizine.<sup>169</sup> The largest study of cetirizine was an analysis of more than 17,000 pregnant females in the Swedish Medical Birth Register from 1995 to 1999, 917 of whom took cetirizine during pregnancy with no increase in malformations or delivery complications when compared with the general population.<sup>164</sup> After this analysis, 144 infants exposed to cetirizine during the first trimester and 196 infants exposed during any trimester were evaluated in a 2004 study by the North Atlantic Treaty Organization<sup>170</sup> and a 2008 analysis of the Berlin teratogen information service, respectively.<sup>161</sup> Neither analysis demonstrated adverse effects on those infants exposed to cetirizine compared with unexposed infants.

Animal studies of cetirizine, levocetirizine, and loratadine have demonstrated safety during pregnancy, yielding an FDA pregnancy category B based on lack of demonstrable risk in animal reproduction studies without well-controlled studies on pregnant women.<sup>53,54</sup> Fexofenadine and desloratadine, alternatively, have been designated pregnancy category C based on adverse effects reported in animal studies without well-controlled studies on pregnant women.<sup>56,171</sup> In animal studies of fexofenadine, animal studies have shown a decrease in pup weight and survival. Limited human data for fexofenadine's parent drug, terfenadine, during pregnancy have not shown an increase in any major malformations for exposed fetuses.<sup>56</sup> Animal studies on desloratadine have been variable, with some showing increased preimplantation loss and a decrease in pup weight and slow righting reflex at doses equivalent to 50 or more times the recommended human dose.<sup>171</sup> Because there have not been any controlled studies examining the safety of antihistamines during human pregnancy, there are no antihistamines that carry an FDA category A rating. Both azelastine and olopatadine intranasal antihistamines are FDA category C for pregnancy due to minor adverse effects on the fetus at high doses in animal studies only.

### ***Antihistamine Use for Rhinitis Therapy During Lactation***

Antihistamines considered safe during lactation include fexofenadine, loratadine, and desloratadine based on studies measuring the actual amount excreted into the breast milk of women taking loratadine or fexofenadine during lactation. A pharmacokinetic study performed on the breast milk of 6 lactating women taking loratadine (40 mg) concluded that the breastfeeding baby would ingest approximately 1% of the weight-adjusted recommended dose for adults when combining breast milk excretion of loratadine and its metabolite, desloratadine.<sup>172</sup> A similar study performed on 4 lactating women taking terfenadine showed that the weight-adjusted fexofenadine dose ingested by the baby was approximately 0.45% of the adult-recommended dose.<sup>173</sup> Because the amount of drug to which breastfeeding infants are exposed is minimal, these 3 antihistamines are currently options available to lactating women. Although similar studies have not been performed on cetirizine, its use is not generally recommended during lactation based on dog studies suggesting higher concentrations of drug excreted in breast milk.<sup>52</sup>

### **SUMMARY**

Histamine, one of the key mediators of allergic disease, functions by binding to 1 of 4 histamine receptors. Antihistamines act as inverse agonists of these receptors to prevent the downstream actions of histamine. More than 40 oral antihistamines are currently available and can be classified as first-generation and second-generation drugs, depending on their pharmacokinetic and pharmacodynamic properties and their side-effect profiles. Intranasal antihistamines, which were introduced more recently, have shown promise as efficacious agents with a rapid onset of action and minimal side effects. Although data are conflicting on how intranasal antihistamines compare with intranasal steroids, several studies comparing intranasal and oral antihistamines point to the intranasal formulation as superior. The role of antihistamines in the treatment of allergic rhinitis is variable from one patient to another depending on an individual's symptom complex, cost concerns, and patient preference. Certain patient populations, such as children, pregnant or lactating women, and those taking medications that could interfere with antihistamine metabolism, require special consideration regarding antihistamine choice and dosing as part of rhinitis therapy.

### **ACKNOWLEDGMENTS**

We would like to thank Diedre Versluis for her assistance in the preparation of this manuscript.

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