

Clinical reviews in allergy and immunology

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Histamine and H₁-antihistamines: Celebrating a century of progress

F. Estelle R. Simons, MD, FRCPC,^a and Keith J. Simons, PhD^b Winnipeg, Manitoba, Canada

In this review we celebrate a century of progress since the initial description of the physiologic and pathologic roles of histamine and 70 years of progress since the introduction of H₁-antihistamines for clinical use. We discuss histamine and clinically relevant information about the molecular mechanisms of action of H₁-antihistamines as inverse agonists (not antagonists or blockers) with immunoregulatory effects. Unlike first (old)-generation H₁-antihistamines introduced from 1942 to the mid-1980s, most of the second (new)-generation H₁-antihistamines introduced subsequently have been investigated extensively with regard to clinical pharmacology, efficacy, and safety; moreover, they are relatively free from adverse effects and not causally linked with fatalities after overdose. Important advances include improved nasal and ophthalmic H₁-antihistamines with rapid onset of action (in minutes) for allergic rhinitis and allergic conjunctivitis treatment, respectively, and effective and safe use of high (up to 4-fold) doses of oral second-generation H₁-antihistamines for chronic urticaria treatment. New H₁-antihistamines introduced for clinical use include oral formulations (bilastine and rupatadine), and ophthalmic formulations (alcaftadine and bepotastine). Clinical studies of H₃-antihistamines with enhanced decongestant effects have been conducted in patients with allergic rhinitis. Additional novel compounds being studied include H₄-antihistamines with anti-inflammatory effects in allergic rhinitis, atopic dermatitis, and other diseases. Antihistamines have a storied past and a promising future. (*J Allergy Clin Immunol* 2011;■■■:■■■-■■■.)

Key words: Histamine, H₁-antihistamine(s), H₂-antihistamine(s), H₃-antihistamine(s), H₄-antihistamine(s), allergic rhinitis, allergic conjunctivitis, urticaria, atopic dermatitis, cetirizine, desloratadine, fexofenadine, levocetirizine, loratadine, rupatadine, bilastine, alcaftadine, bepotastine

Abbreviations used

BBB: Blood-brain barrier
CNS: Central nervous system
PET: Positron emission tomography

In 2010-2011, we celebrate the centenary of the initial description of the physiologic and pathologic effects of histamine. In 2012, we celebrate the 70th anniversary of the introduction of H₁-antihistamines for clinical use. These and other important events related to histamine, histamine receptors, and H₁-antihistamines are shown in Fig 1.¹⁻¹⁸

HISTAMINE AND HISTAMINE RECEPTORS

Histamine, a structurally simple chemical messenger, is a natural body constituent synthesized from the amino acid histidine by L-histidine decarboxylase, an enzyme expressed in many different cell types. Histamine plays an important physiologic role in human health, exerting its diverse effects through 4 subtypes of receptors (Table I).¹¹⁻¹⁸ Through the H₁-receptor, it contributes to regulation of cell proliferation and differentiation, hematopoiesis, embryonic development, regeneration, and wound healing and plays an important role in neurotransmission in the central nervous system (CNS). It is produced in neurons with cell bodies in the tuberomammillary nucleus of the posterior hypothalamus that send their axons throughout the cerebrum, cerebellum, posterior pituitary, and spinal cord. It has anticonvulsant activity and contributes to regulation of vigilance (alertness and attention), cognition, learning, memory, and the circadian sleep-wake cycle, as well as to energy and endocrine homeostasis.^{1,18-20}

Through its 4 receptor subtypes, histamine plays an important role in a complex system of immunoregulation and in acute and chronic allergic inflammation.²¹ Through the H₁-receptor, it increases antigen-presenting cell capacity, increases release of histamine and other mediators from mast cells and basophils, downregulates humoral immunity, and upregulates T_H1 priming, T_H1 proliferation, IFN- γ production, cellular adhesion molecule expression, and chemotaxis of eosinophils and neutrophils (Table I).¹⁸

Histamine receptors are heptahelical transmembrane molecules that transduce extracellular signals by way of G proteins to intracellular second messenger systems. These receptors have constitutive activity, defined as the ability to trigger downstream events, even in the absence of ligand binding. Their active and inactive states exist in equilibrium; at rest, the inactive state

From ^athe Department of Pediatrics & Child Health and the Department of Immunology, Faculty of Medicine, and ^bthe Faculty of Pharmacy and the Department of Pediatrics & Child Health, Faculty of Medicine, University of Manitoba.

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Corresponding author: F. Estelle R. Simons, MD, FRCPC, Room FE125, 820 Sherbrook St, Winnipeg, R3A 1R9 Manitoba, Canada. E-mail: lmcniven@hsc.mb.ca.
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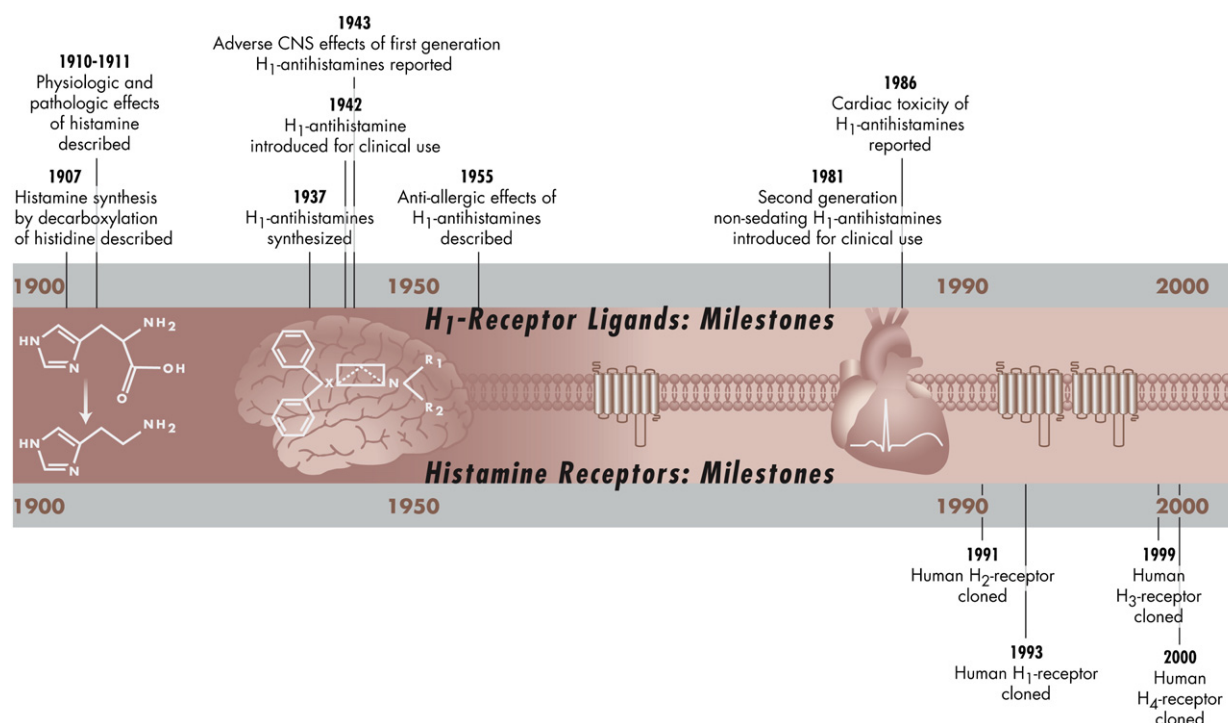


FIG 1. Celebrating a century of progress: timeline featuring historical highlights related to histamine, histamine receptors, and H₁-antihistamines. The physiologic and pathologic effects of histamine were described in 1910-1911. H₁-antihistamines were introduced for clinical use in the 1940s, for example, antergan (1942), diphenhydramine (1946), and chlorpheniramine (1949). In the 1980s, relatively non-sedating second (new)-generation H₁-antihistamines were introduced for clinical use, and histamine-containing neurons were identified in the CNS. Cloning and characterization of human histamine receptors was reported for the H₂-receptor in 1991, the H₁-receptor in 1993, the H₃-receptor in 1999, and the H₄-receptor in 2000.¹⁻¹⁸

isomerizes with the active state and vice versa (Fig 2).^{1,11-16,18,21} The low H₁-receptor selectivity of first-generation H₁-antihistamines has been attributed to direct interaction with tryptophan 428^{6,48}, a highly conserved key residue in G protein-coupled receptor activation.²²

H₁ receptor-deleted mice have neurologic abnormalities, including aggressive behavior and impaired vigilance, learning, memory, and locomotion, in addition to metabolic and immunologic abnormalities.¹⁸

H₁-ANTI-HISTAMINES

More than 45 H₁-antihistamines are available worldwide, comprising the largest class of medications used in the treatment of allergic diseases. New H₁-antihistamines, including bilastine and rupatadine for oral administration and bepotastine and alcaftadine for ophthalmic application, have been introduced. Promising H₁-antihistamine/glucocorticoid nasal formulations are being investigated.²³⁻²⁸

H₁-antihistamines act as inverse agonists that combine with and stabilize the inactive conformation of the H₁-receptor, shifting the equilibrium toward the inactive state. For more than 50 years, they were described as H₁-receptor antagonists or H₁-receptor blockers; however, these out-of-date terms do not accurately reflect their molecular mechanism of action (Fig 2).^{1,15-18,21}

H₁-antihistamines downregulate allergic inflammation directly through the H₁-receptor by interfering with histamine action at H₁-receptors on sensory neurons and small blood vessels. Through the ubiquitous transcription factor nuclear factor- κ B,

they also decrease antigen presentation, expression of proinflammatory cytokines and cell adhesion molecules, and chemotaxis. In a concentration-dependent manner they inhibit mast cell activation and histamine release; although the mechanisms involved have not yet been delineated fully, downregulation of intracellular calcium ion accumulation seems to play a role (Fig 3).^{1,8,16,18,27-30}

H₁-antihistamines are functionally classified into 2 groups. First-generation medications readily cross the blood-brain barrier (BBB) and occupy H₁-receptors located on postsynaptic membranes of histaminergic neurons throughout the CNS. Second-generation H₁-antihistamines do not cross the BBB readily. Use of positron emission tomography (PET) to document H₁-antihistamine penetration into the human brain constitutes a new standard by which CNS H₁-receptor occupancy can be directly related to effects on CNS function (Fig 3 and Table II).^{1,18,31-33}

CLINICAL PHARMACOLOGY OF H₁-ANTI-HISTAMINES

Pharmacokinetic studies provide clinically relevant information about the rate and extent of H₁-antihistamine absorption, metabolism, elimination, and drug interactions. Pharmacodynamic studies provide clinically relevant information about the onset, extent, and duration of H₁-antihistamine action.^{1,18,34-41}

First (old)-generation H₁-antihistamines

Most first-generation H₁-antihistamines were introduced before regulatory agencies existed and before clinical

TABLE I. Histamine receptor subtypes^{17,18}

	GPCR signaling*	Expression	Representative antihistamines	Clinical use/potential use‡
H ₁ -receptor	G _q /G ₁₁ family to phospholipase C stimulation	CNS neurons, smooth muscle cells (vascular, respiratory, and GI), CVS, neutrophils, eosinophils, monocytes, macrophages, DCs, T and B cells, endothelial cells, epithelial cells	Chlorpheniramine, diphenhydramine, hydroxyzine, cetirizine, desloratadine, fexofenadine, levocetirizine, loratadine, and 40 others	Allergic rhinitis, allergic conjunctivitis, urticaria; used in many other allergic diseases and nonallergic diseases, including CNS diseases
H ₂ -receptor	G _s family to adenylate cyclase stimulation and ↑ cyclic AMP	Gastric parietal cells, smooth muscle, CNS, CVS, neutrophils, eosinophils, monocytes, macrophages, DCs, T and B cells, endothelial cells, epithelial cells	Cimetidine, ranitidine, famotidine, nizatidine	Peptic ulcer disease and gastroesophageal reflux disease
H ₃ -receptor	G _{i/o} family to adenylate cyclase inhibition and ↓ cyclic AMP	CNS and peripheral neurons†, CVS, lungs, monocytes, eosinophils, endothelial cells	No agents approved for use to date; those in clinical trials include JNJ 39220675 and PF-03654746 for allergic rhinitis	Potentially useful in allergic rhinitis and neurologic disorders, including Alzheimer disease, attention-deficit hyperactivity disorder, schizophrenia, epilepsy, narcolepsy, and neuropathic pain; also in obesity
H ₄ -receptor	G _{i/o} family to adenylate cyclase inhibition and ↓ cyclic AMP	Neutrophils, eosinophils, monocytes, DCs, Langerhans cells, T cells, basophils, mast cells, fibroblasts, bone marrow, endocrine cells, and CNS	No agents approved for use to date; those in clinical trials have included JNJ 777120 for allergic rhinitis and pruritus, UR 65380 and UR 63825 for pruritus	Potentially useful in allergic rhinitis, atopic dermatitis/eczema, and asthma and in other chronic inflammatory disorders and autoimmune disorders

CVS, Cardiovascular system; DC, dendritic cell; GI, gastrointestinal; GPCR, G protein–coupled receptor.

*The primary signaling mechanism is shown. Additional intracellular signals at the H₁-receptor include phospholipase C, 1,2-diacylglycerol, inositol 1,4,5-triphosphate, phosphatidylinositol 4,5-bisphosphate, protein kinase C, and intracellular calcium. Additional intracellular signals at the H₂-receptor include protein kinase A, cyclic AMP responsive element-binding protein, and exchange protein directly activated by cyclic AMP. At the H₃- and H₄-receptors, stimulation of calcium mobilization from intracellular stores constitutes another important signal.

†The H₃-receptor is a presynaptic autoreceptor on histaminergic neurons in the CNS and on non-histamine-containing neurons in the CNS and peripheral nervous system. It regulates levels of a variety of neurotransmitters, including norepinephrine, acetylcholine, serotonin, and dopamine.

‡Issues in the development of H₃- and H₄-antihistamines include nondisclosure of ligand structure, instability of some of the ligands that have been synthesized, different outcomes in different species, and adverse events in some clinical trials. There is nevertheless considerable optimism that H₃- and H₄-antihistamines will eventually prove effective and safe in the treatment of allergic disorders, not only in patients with allergic rhinitis but also in patients with atopic dermatitis and asthma.

pharmacology studies of new medications were required. Information about pharmacokinetics and pharmacodynamics in healthy adults, elderly people, children, infants, and other vulnerable patients is therefore not available for most of them, and few drug interaction studies have been performed with them (see Table E1 in this article's Online Repository at www.jacionline.org).^{1,18}

Second (new)–generation H₁-antihistamines

For most second-generation H₁-antihistamines, pharmacokinetics have been extensively investigated in healthy adults, patients with impaired hepatic or renal function, and elderly people, children, and infants. Their drug-drug, drug-food, and drug-herbal product interactions, if any, are well characterized and seldom clinically relevant (Table III and see Table E1).^{1,18,34-37}

The pharmacodynamics of most orally administered second-generation H₁-antihistamines have been assessed by measuring suppression of the histamine-induced wheals and flares (erythema), which correlates better with H₁-receptor occupancy by free unbound drug than with H₁-antihistamine concentrations in plasma or even in tissue. Duration of action is at least 24 hours,

facilitating once-daily dosing. Tolerance does not occur during regular use.

After discontinuation of regular daily dosing, residual effects, such as suppression of allergy skin test responses, last from 1 to 5 days (Table III and see Table E1).^{1,34,37-41}

In patients with allergic rhinitis and allergic conjunctivitis, suppression of the response to nasal or conjunctival allergen challenge tests by H₁-antihistamines regardless of route of administration provides clinically relevant information about their onset, extent, and duration of action. Although some systemic absorption of nasal and ophthalmic formulations occurs, no dose adjustments are required in the elderly or other vulnerable populations, and no clinically relevant drug-drug, drug-food, or drug-herbal product interactions have been described. Despite different elimination half-life values (see Table E1), most of these H₁-antihistamine formulations are administered at 8- to 12-hour intervals because of washout by secretions on the nasal mucosa and conjunctivae.^{1,18,26-28}

EFFICACY OF H₁-ANTIHISTAMINES

H₁-antihistamines are widely used in the treatment of allergic and nonallergic disorders (Fig 4).^{1,18,33,42-91}

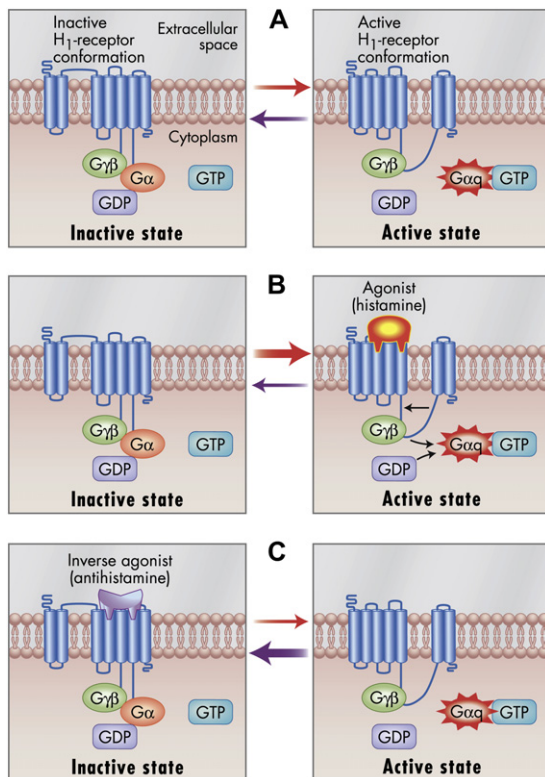


FIG 2. Molecular basis of action of histamine and antihistamines. **A**, The inactive state of the histamine H_1 -receptor is in equilibrium with the active state. **B**, The agonist, histamine, has preferential affinity for the active state, stabilizes the receptor in this conformation, and shifts the equilibrium toward the active state. **C**, An H_1 -antihistamine (inverse agonist) has preferential affinity for the inactive state, stabilizes the receptor in this conformation, and shifts the equilibrium toward the inactive state.^{15,18} GDP, Guanosine diphosphate; GTP, guanosine triphosphate.

Allergic diseases in which H_1 -antihistamines are medications of choice

Few clinical trials of first-generation H_1 -antihistamines in patients with allergic diseases meet current standards. In contrast, use of second-generation H_1 -antihistamines in patients with allergic rhinitis, allergic conjunctivitis, and chronic urticaria is supported by hundreds of well-designed, randomized, placebo-controlled trials lasting for weeks or months.^{1,18,37,42-72} Dosage recommendations for oral, nasal, and ophthalmic H_1 -antihistamine formulations in adults, children, and infants with allergic rhinitis, allergic conjunctivitis, and urticaria are provided in Table E2 in this article's Online Repository at www.jacionline.org.⁴²

Allergic rhinitis. The morbidity and economic impact of allergic rhinitis are widely underestimated. In patients with this disease, oral second-generation H_1 -antihistamines prevent and relieve the sneezing, itching, and rhinorrhea that characterize the early response to allergen, with a small beneficial effect on the nasal congestion that characterizes the late allergic response (Fig 4). Efficacy is documented primarily by standardized symptom scores and quality-of-life assessments.^{1,18,37,42-46,50-56} Some oral H_1 -antihistamines are marketed in fixed-dose combination with the decongestant pseudoephedrine (see Table E2).^{42,53} Oral H_1 -antihistamines are more efficacious than chromones and montelukast; however, all these classes of medications are

less efficacious than nasal glucocorticoids. H_1 -antihistamines are generally ineffective in patients with nonallergic rhinitis.^{56,57}

Nasal H_1 -antihistamine formulations have a more rapid onset of action than oral H_1 -antihistamine formulations (eg, 15 minutes for nasal azelastine vs 150 minutes for oral desloratadine). In patients with seasonal allergic rhinitis, nasal H_1 -antihistamines are reported to be as efficacious or more efficacious than oral H_1 -antihistamines, particularly for relief of nasal congestion. They improve symptoms in patients who are unresponsive to oral H_1 -antihistamines and those with vasomotor rhinitis. Patient preference should be considered when recommending a nasal versus an oral H_1 -antihistamine (see Table E2). Nasal azelastine combined with nasal fluticasone in a single nasal spray delivery device is reported to provide significantly greater improvement of symptoms, including congestion, than either medication alone.^{26,42,56,58-60}

Allergic conjunctivitis. In patients with allergic conjunctivitis, H_1 -antihistamines administered orally or directly to the conjunctivae relieve the itching, erythema, tearing, and edema that characterize the early response to allergen (Fig 4).^{27,28,42,47,61-63} Ophthalmic formulations have a rapid onset of action (3-15 minutes), and some of them are reported to benefit nasal symptoms in addition to conjunctival symptoms. In patients with allergic conjunctivitis, H_1 -antihistamines have a more favorable benefit/risk ratio than all other classes of medications, including ophthalmic nonsteroidal anti-inflammatory drugs, ophthalmic decongestants, and ophthalmic glucocorticoids (see Table E2).^{27,28,42,47,61-63}

Urticaria. In patients with acute urticaria lasting less than 6 weeks or chronic urticaria lasting 6 weeks or more, H_1 -antihistamines decrease itching and reduce the number, size, and duration of wheals and flares (erythema, Fig 4). In patients with acute urticaria, H_1 -antihistamines have not been optimally studied; however, in randomized double-blind placebo-controlled trials lasting 18 months, cetirizine and levocetirizine are reported to reduce acute urticaria in young atopic children.^{1,18,48,49,64}

In patients with chronic urticaria, first-generation H_1 -antihistamines are used despite the absence of satisfactory randomized, placebo-controlled trials to support their efficacy and safety. In contrast, high-quality trials of second-generation H_1 -antihistamines, such as cetirizine, desloratadine, fexofenadine, levocetirizine, loratadine, bilastine, and rupatadine confirm that they decrease symptoms and improve quality of life (see Table E2).^{42,48,65-69} Although many patients respond to standard doses of these medications, more respond to increasing the daily dose up to 4-fold; for example, in one double-blind randomized controlled trial, 13 of 40 patients became symptom free on 5 mg of levocetirizine and 28 of the 40 patients became symptom free on 10 or 20 mg of levocetirizine without experiencing adverse effects at the higher doses. Additionally, in objective tests, such as in patients with acquired cold urticaria, high-dose desloratadine (20 mg) or rupatadine (20 mg) decrease wheal volume and improve cold provocation thresholds significantly compared with standard doses.^{70,71} Treatment guidelines for chronic urticaria now recommend second-generation H_1 -antihistamines as the medications of choice, starting with standard doses and increasing the doses up to 4-fold as needed to provide relief.^{48,72} This approach has not yet been validated in children.⁴⁹

For patients with severe chronic urticaria refractory to non-sedating H_1 -antihistamines, it can be helpful to add an H_2 -antihistamine, montelukast, omalizumab, cyclosporine, or dapsone and treat exacerbations with a glucocorticoid for 3 to 7 days.^{48,72}

Other. Small randomized controlled trials support the use of H_1 -antihistamines to prevent and relieve itching and flushing in

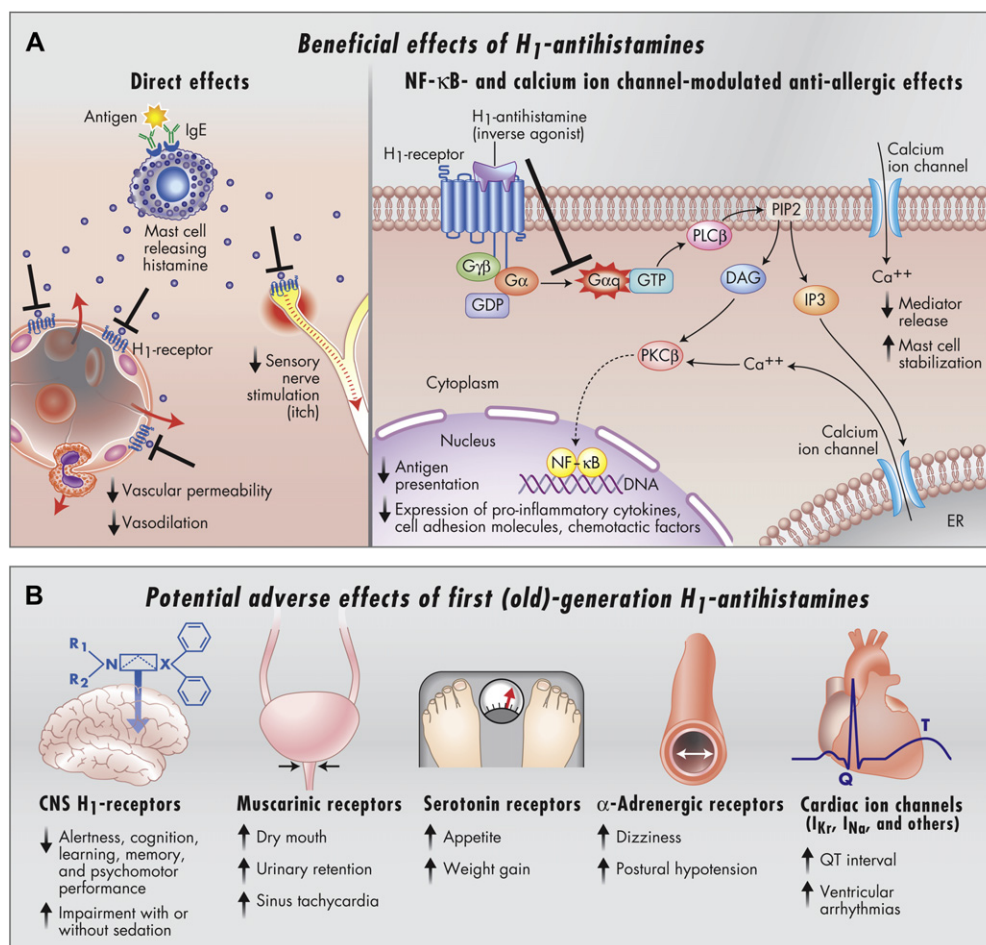


FIG 3. Benefits and risks of H₁-antihistamines. **A**, Beneficial effects: H₁-antihistamines act directly to interfere with histamine action at H₁-receptors on sensory neurons and small blood vessels, mainly post-capillary venules. They also downregulate allergic inflammation indirectly through nuclear factor-κB (NF-κB) and through calcium ion channels. **B**, Potential adverse effects: First (old)-generation H₁-antihistamines cross the BBB and occupy CNS H₁-receptors, as documented by means of PET. High H₁-receptor occupancy correlates directly with impairment of CNS function, with or without accompanying sedation. These medications also potentially cause adverse effects through other mechanisms, such as their antimuscarinic and antiserotonin effects.^{1,7,18,31-33} DAG, 1,2-diacylglycerol; ER, endoplasmic reticulum; GDP, guanosine diphosphate; GTP, guanosine triphosphate; I_{Kr}, rapid component of the delayed outward rectifying potassium channel; I_{Na}, rapid component of the inward rectifying sodium channel; IP3, inositol 1,4,5-trisphosphate; PIP2, phosphatidylinositol 4,5-bisphosphate; PKCβ, protein kinase C β; PLCβ, phospholipase C β.

patients with mastocytosis, prevent and relieve itchy large local allergic reactions to mosquito bites, and reduce adverse reactions and modulate allergen-specific immune responses during stinging insect venom immunotherapy.⁷³⁻⁷⁵

Diseases in which H₁-antihistamines are not medications of first choice

Largely on the basis of tradition, H₁-antihistamines remain widely used in many diseases in which the evidence base for their efficacy and safety is weak and generally not supported by randomized controlled trials that meet current standards (Fig 4).⁷⁶⁻⁹¹

Atopic dermatitis. Histamine acts as a pruritogen through H₄-receptors in patients with atopic dermatitis, and other mediators, including IL-31 and other cytokines, play an important role. No high-quality randomized controlled trials of H₁-antihistamines confirm their efficacy in patients with atopic dermatitis. Despite

the absence of such trials, first-generation H₁-antihistamines are still sometimes used for their sedative effects. Optimal medications for atopic dermatitis include topical glucocorticoids, topical calcineurin inhibitors, agents to restore the skin barrier, and, when needed, antimicrobial agents.^{1,18,76}

Asthma. H₁-antihistamines might provide indirect benefit in patients with concomitant seasonal asthma and allergic rhinitis; however, they are not medications of choice in asthmatic patients. Moderate-to-severe persistent asthma is optimally controlled with an inhaled glucocorticoid with or without a long-acting β-adrenergic agonist (in the same inhalation device) or montelukast, and a short-acting β-agonist to relieve breakthrough symptoms.^{1,18,77}

Anaphylaxis. A Cochrane systematic review of 2070 publications on H₁-antihistamines in the treatment of anaphylaxis did not identify any randomized controlled trials that provided satisfactory evidence for their use in this disease. The onset of

TABLE II. H₁-antihistamines: chemical and functional classification^{1,18}

Chemical class	Functional class	
	First (old) generation	Second (new) generation
Alkylamines	Brompheniramine, chlorpheniramine, dexchlorpheniramine, dimethindene†, pheniramine, triprolidine*	Acrivastine*
Piperazines	Bucizine, cyclizine, hydroxyzine*, meclizine, oxatomide†	Cetirizine* , levocetirizine*
Piperidines	Azatadine, cyproheptadine, diphenylpyraline, ketotifen	Astemizole†, bepotastine, bilastine†, desloratadine* , ebastine†, fexofenadine* , levocabastine†, loratadine* , mizolastine†, rupatadine*†, terfenadine*†, alcaftadine
Ethanolamines	Carbinoxamine, clemastine, dimenhydrinate, diphenhydramine, doxylamine, phenyltoloxamine†	-
Ethylenediamines	Antazoline, pyrilamine, tripeleminamine	-
Phenothiazines	Methdilazine, promethazine	-
Other	Doxepin‡	Azelastine, emedastine, epinastine, olopatadine

*Some of the H₁-antihistamines listed above are related to each other; for example, acrivastine is a derivative of triprolidine, cetirizine is a metabolite of hydroxyzine, levocetirizine is an enantiomer of cetirizine, and desloratadine is a metabolite both of loratadine and rupatadine. Of the H₁-antihistamines currently approved for use in the United States, cetirizine, levocetirizine, desloratadine, fexofenadine, and loratadine (listed in boldface) are the most thoroughly investigated in randomized controlled trials and other prospective studies.

†In the United States these H₁-antihistamines are either not yet approved or have never been approved. Regulatory approval was withdrawn for astemizole and terfenadine in the 1990s.

‡Doxepin has dual H₁- and H₂-antihistamine activities and is classified as a tricyclic antidepressant. The standard dose for urticaria is 25 to 50 mg 3 times daily; yet a considerably lower dose, 1 to 3 mg of doxepin once daily, is effective for insomnia in the elderly.

TABLE III. Orally administered second (new)-generation H₁-antihistamines: clinical pharmacology^{1,18}**Pharmacokinetics***

Absorption: Maximum serum concentrations are reached at 0.8 to 3 hours.

Metabolism: Ranges from minimal (fexofenadine) to extensive (desloratadine and rupatadine).

Elimination: Terminal elimination half-life values range from 6 to 27 hours.

Pharmacokinetics are minimally influenced by age, hepatic dysfunction, and renal dysfunction.

Clinically relevant interactions seldom occur with other drugs, foods, or herbal products.

Pharmacodynamics*†‡§

Studied with suppression of histamine-induced wheals and flares.†

Studied with suppression of symptoms after allergen challenge in allergic rhinitis and allergic conjunctivitis.‡

Onset of action ranges from 0.7 to 2.6 hours.

Extent of action (potency) ranges from 75% to 100%.

Duration of action is typically ≥24 hours.†

Receptor affinity: Studied for some, but not all, second-generation H₁-antihistamines.§

Receptor occupancy by free (unbound) drug: Determined for some, but not all, second-generation H₁-antihistamines.§

*Please see Table E1 for additional information. Despite differences in pharmacokinetics and pharmacodynamics, the doses of many orally administered second-generation H₁-antihistamines are similar or even identical, which is attributable in part to the wide margin of safety of these medications.

†Suppression of wheals and flares and symptoms lasts for hours after serum or plasma H₁-antihistamine concentrations are undetectable. Wheal and flare suppression studies correlate well with the efficacy of orally administered H₁-antihistamines in patients with urticaria but less well in patients with allergic rhinitis or allergic conjunctivitis.

‡Allergen challenge studies are typically conducted in patients with a predetermined symptom score after allergen priming and involve a short duration of exposure and follow-up.

§Those studied include desloratadine, fexofenadine, and levocetirizine.

action of orally administered H₁-antihistamines is slow (0.7-2.6 hours). Although they decrease itch and hives, they do not prevent or relieve laryngeal edema, lower respiratory tract obstruction, or shock and are not life-saving. Epinephrine (adrenaline) is the initial medication of choice.⁷⁸

Nonallergic angioedema. In the absence of itching or urticaria, angioedema is typically nonallergic, not mediated by histamine, and not prevented or relieved by H₁-antihistamines. Treatment of hereditary angioedema types I, II, and III involves C1-esterase inhibitor concentrates, ecallantide, or icatibant. Treatment of angiotensin-converting enzyme inhibitor-associated nonallergic angioedema involves medication substitution, when possible. Treatment of malignancy-associated nonallergic angioedema focuses on definitive treatment of the malignancy.⁷⁹

Other disorders. H₁-antihistamines are used to treat symptoms of upper respiratory tract infections, acute otitis media, otitis media with effusion, sinusitis, nasal polyps, nonspecific cough, and nonallergic, nonspecific itching; however, their efficacy and safety have not been confirmed in high-quality randomized controlled trials in patients with any of these disorders.^{1,18,57,80-85}

Central nervous system and vestibular disorders

The first-generation H₁-antihistamines diphenhydramine, doxepin, doxylamine, and pyrilamine are the most widely used medications in the world for preventing and relieving insomnia, even when given in low doses, such as 25 mg of diphenhydramine or 1 to 3 mg of doxepin once daily at bedtime. In medical settings, diphenhydramine, hydroxyzine, and promethazine are given (often in combination with other medications) for conscious sedation, perioperative sedation, and analgesia. They are also used for treatment of serotonin syndrome, anxiety, acute agitation, akathisia, and migraine headaches.^{1,18,86-88}

Dimenhydrinate, diphenhydramine, meclizine, and promethazine block the histaminergic signal from the vestibular nucleus to the vomiting center in the medulla. They are used for prevention and treatment of nausea and vomiting during pregnancy, chemotherapy, and the postoperative period and for prevention and treatment of motion sickness, vertigo, and related disorders. Commercial airline pilots and military pilots are prohibited from

Conditions currently treated with H ₁ -antihistamines		
Strong evidence base for second (new)-generation H ₁ -antihistamine use	Weak evidence base for H ₁ -antihistamine use	Weak evidence base for first (old)-generation H ₁ -antihistamine use in CNS and vestibular disorders
 Allergic rhinitis	Atopic dermatitis	Insomnia
 Allergic conjunctivitis	Asthma	Conscious sedation
 Urticaria	Anaphylaxis	Perioperative sedation
	Non-allergic angioedema	Analgesia
	Upper respiratory tract infections (colds)	Anxiety
	Otitis media	Serotonin syndrome
	Sinusitis	Akathisia
	Nasal polyps	Migraine
	Non-specific cough	Motion sickness
	Non-allergic, non-specific itching	Vertigo

FIG 4. Science versus reality: evidence-based use of H₁-antihistamines in allergic diseases and other disorders. On the basis of well-designed randomized controlled trials and meta-analyses of such trials, the evidence base for the efficacy and safety of second (new)-generation H₁-antihistamines is strong in patients with allergic rhinitis, allergic conjunctivitis, and urticaria (category of evidence I, strength of recommendation A) but not in those with atopic dermatitis and other diseases (category of evidence II-IV, strength of recommendation B, C, or D, depending on the disease). The evidence base for the efficacy and safety of first (old)-generation H₁-antihistamines remains weak in patients with allergic rhinitis, allergic conjunctivitis, urticaria, atopic dermatitis, and other diseases, including CNS and vestibular disorders (category of evidence II-IV, strength of recommendation B, C, or D, depending on the disease). Their potential adverse effects remain a concern.^{1,18,33,42-91}

using them before or during flights because of their potential CNS-related adverse effects.^{1,18,89-91}

ADVERSE EFFECTS OF H₁-ANTIHISTAMINES

First (old)-generation H₁-antihistamines

First-generation H₁-antihistamines potentially cause adverse effects in multiple body systems (Fig 3). They have poor selectivity for the H₁-receptor. Their antimuscarinic effects include mydriasis, dry eyes, dry mouth, constipation, and urinary hesitancy and retention. Their antiserotonin effects include increased appetite and weight gain. Their anti- α -adrenergic effects include dizziness and orthostatic hypotension.^{1,18,92,93} They have also been implicated in impairing the innate immune response to bacterial infection⁹⁴; however, this is more likely attributable to coadministered H₂-antihistamines.⁹⁵

For 70 years, H₁-antihistamines have been marketed to the medical profession and the general public as safe medications, despite the voluminous medical literature documenting their CNS adverse effects and toxicity (Table IV).^{1,7,18,31-33,96-105} As previously noted, their CNS adverse effects are due to inverse agonism at CNS H₁-receptors, inhibition of neurotransmission in histaminergic neurons, and impairment of alertness, cognition, learning, and memory that is not necessarily associated with sedation, drowsiness, fatigue, or somnolence.

Standard doses. PET studies with ¹¹C-doxepin as the positron-emitting ligand (positive control) confirm that in standard or even low doses, first-generation H₁-antihistamines cross the BBB. In standard doses, they typically occupy more than 70% of CNS H₁-receptors. High H₁-receptor occupancy is

associated with decreased histaminergic neurotransmission and impaired CNS function on objective tests.^{31-33,96-98} Penetration of the BBB is related to lipophilicity, relatively low molecular weight, and lack of substrate recognition by the P-glycoprotein efflux pump expressed on the luminal surfaces of nonfenestrated endothelial cells in the CNS vasculature.

Even in low doses, eg, 2 mg of chlorpheniramine or 25 mg of diphenhydramine, first-generation H₁-antihistamines potentially impair alertness, cognition, learning, and rapid response/waking memory, especially during complex sensorimotor tasks, including divided attention, critical tracking, and attention-switch tasks, and objectively monitored car driving.⁹⁹⁻¹⁰¹ Impairment of CNS function can occur in asymptomatic persons.^{1,18,33,96-98} When taken at bedtime, first-generation H₁-antihistamines increase the latency to onset of restful rapid eye movement sleep and reduce the duration of rapid eye movement sleep (Table IV).^{33,102} In patients who have CNS residual effects the next morning (an antihistamine “hangover”), PET documents residual H₁-receptor occupancy.³² Tolerance to adverse CNS effects might or might not occur with regular daily use.³³ The adverse CNS effects of concurrently ingested ethanol, benzodiazepines, and other CNS-active chemicals are potentially exacerbated.^{1,18,33} Additionally, diphenhydramine and others are documented drugs of abuse.¹⁰⁵

The unfavorable therapeutic index of systemically administered first-generation H₁-antihistamines has been well documented in vulnerable patients, such as those with impaired hepatic or renal function (including patients receiving hemodialysis), elderly people, young children, and infants (see Table E3 in this article's Online Repository at www.jacionline.org).^{1,7,18,33,106-117}

TABLE IV. H₁-antihistamines: potential adverse effects^{1,7,18,33,106-126}

	First (old) generation*†	Second (new) generation†‡
CNS Mechanism: inhibition of the neurotransmitter effect of histamine at CNS H ₁ -receptors	After standard doses, there is potential impairment of alertness, cognition, learning, memory, and performance (especially of complex sensorimotor tasks), with or without drowsiness, somnolence, fatigue, or sedation. Other potential CNS adverse effects include headache, dizziness, confusion, agitation, behavioral changes (children), and, less commonly, dystonia, dyskinesia, and hallucinations.	Minimal or no adverse effects are reported with 5 mg of cetirizine, 5 mg of desloratadine, 360 mg of fexofenadine (off-label), 5 mg of levocetirizine, 10 mg of loratadine, or 10 mg of rupatadine. At higher doses, with the exception of fexofenadine, these H ₁ -antihistamines might cause dose-related CNS effects in some adults with some allergic diseases.
Cardiac Mechanisms: antimuscarinic effects, anti- α -adrenergic effects, and blockade of cardiac ion currents (I_{Kr} , I_{Na} , I_{to} , I_{K1} and I_{Ks})	Dose-related sinus tachycardia; reflex tachycardia, prolonged atrial refractive period, and supraventricular arrhythmias potentially occur. Prolongation of the QTc interval and ventricular arrhythmias have been reported after standard doses but are more likely to occur after overdose (see the "Toxicity after overdose" section).	Concerns are minimal in countries in which regulatory agencies scrutinize second-generation H ₁ -antihistamines for potential cardiac toxicity and do not approve them for use if this is identified.
Other Mechanisms: blockade of muscarinic, serotonin, and α -adrenergic receptors; unknown§	After standard doses, potential antimuscarinic effects include mydriasis (dilation of pupils), blurred vision, dry eyes, dry mouth, urinary retention and hesitancy, constipation, erectile dysfunction, and memory deficits; these H ₁ -antihistamines are contraindicated in persons with glaucoma or prostatic hypertrophy. Antiserotonin effects include appetite stimulation and weight gain (especially with cyproheptadine and ketotifen). Anti- α -adrenergic effects include peripheral vasodilation, orthostatic hypotension, and dizziness.	None
Toxicity after overdose Mechanisms: multiple	In adults potential CNS effects include extreme drowsiness, confusion, delirium, coma, and respiratory depression. In infants and young children paradoxical excitation, irritability, hyperactivity, insomnia, hallucinations, and seizures can precede coma and respiratory depression. Prolongation of the QTc interval and ventricular arrhythmias have been reported after overdose of cyproheptadine, diphenhydramine, doxepin, hydroxyzine, promethazine, and others. Adverse CNS effects typically predominate over adverse cardiac effects. In untreated patients, death can occur within hours.	Up to 30-fold overdoses of cetirizine, fexofenadine, and loratadine have not been causally associated with serious adverse events or fatality.
Drug abuse Mechanisms: through H ₁ -receptors and other receptors in the CNS	Euphoria, hallucinations, and "getting high" are reported for cyclizine, diphenhydramine, dimenhydrinate, and others.	None reported

I_{K1} , Inward rectifying current; I_{Kr} , rapid component of the delayed outward rectifying potassium current; I_{Ks} , slow component of the delayed outward rectifying potassium current; I_{Na} , rapid component of the inward rectifying sodium current; I_{to} , transient outward potassium current.

*Information about adverse effects and toxicity of first-generation H₁-antihistamines is based largely on descriptions in case reports and case series published since the 1940s. Promethazine is no longer recommended because it potentially causes sedation and respiratory depression/arrest. Additionally, through the intravenous route, it can cause vascular irritation, local necrosis, and gangrene. Diphenhydramine or doxepin, applied topically to the skin, potentially cause contact dermatitis; when applied to abraded or thin skin, they can also cause systemic adverse effects and, rarely, fatality.

†Nasal and ophthalmic formulations of H₁-antihistamines are minimally absorbed and seldom cause systemic adverse effects; however, some patients report a transient bitter or unpleasant taste sensation. Ophthalmic H₁-antihistamines can cause stinging or burning on application. These H₁-antihistamines should be applied at least 10 minutes before contact lens insertion because the preservative benzalkonium chloride 0.01% in the formulations can cloud the lenses.

‡Information about relative lack of adverse effects from second-generation H₁-antihistamines is based on information obtained in prospective, randomized, placebo-controlled trials in patients with allergic rhinitis and chronic urticaria and on occasional case reports of overdose with remarkable absence of toxicity.

§Both first- and second-generation H₁-antihistamines are reported to cause rare adverse effects for which the mechanisms are incompletely understood. These include agranulocytosis, anaphylaxis, fever, fixed-drug eruption, liver enzyme elevation/hepatitis, photosensitivity, and urticaria. Rhabdomyolysis has been reported after overdose.

Toxicity after overdose. Accidental or intentional first-generation H₁-antihistamine overdose potentially leads to extreme drowsiness, confusion, delirium, coma, respiratory depression, and, in the absence of supportive treatment, fatality. In infants and young children, paradoxical CNS excitation with irritability, hyperalertness, insomnia, hallucinations, and seizures might precede drowsiness and other CNS symptoms (Table IV).^{1,7,18,33}

Cardiac toxicity of H₁-antihistamines does not occur through the H₁-receptor and is not a class effect. Rather, it is due to blockade of cardiac ion currents, such as the rapid component of the delayed outward rectifying potassium channel (I_{Kr}) and the outward rectifying current or the rapid component of the inward rectifying sodium channel (I_{Na}). After an overdose, some first-generation H₁-antihistamines (eg, 0.5–1 g of diphenhydramine taken by an adult attempting suicide) potentially lead to sinus tachycardia, prolongation of the QT interval, ventricular arrhythmias, and torsade de pointes.^{1,18,33,118–120} Diphenhydramine overdoses are so frequently reported to poison control centers in the United States that validated evidence-based guidelines have been developed for their triage and management.^{121,122} In infants and young children first-generation H₁-antihistamines are causally linked with deaths from accidental overdose and with homicide (Table IV).^{1,7,18,33,115–117,121,122}

Second (new)-generation H₁-antihistamines

In contrast to first-generation H₁-antihistamines, second-generation H₁-antihistamines are relatively free from antihistaminic adverse CNS effects and from antimuscarinic, antiserotonin, and anti- α -adrenergic effects (Table IV and see Table E3).^{1,18,33}

Standard doses. Second-generation H₁-antihistamines cross the BBB to a minimal degree, penetrate poorly into the CNS, and typically occupy fewer than 20% of CNS H₁-receptors, as documented by PET. Fexofenadine is least likely to cross the BBB or occupy CNS H₁-receptors and is consistently nonimpairing and nonsedating, even in a high off-label dose of 360 mg. It is therefore the H₁-antihistamine of choice for airline pilots and others in safety-critical occupations and/or performing activities requiring optimal alertness, cognition, memory, and multi-tasking. Dose-dependent CNS H₁-receptor occupancy has been documented for cetirizine and others. Second-generation H₁-antihistamines do not exacerbate the CNS effects of concurrently used ethanol, benzodiazepines, and other CNS-active substances.^{1,18,31,33,96–98,123}

About 15 years ago, regulatory agencies rescinded their approval for astemizole and terfenadine, the second-generation H₁-antihistamines initially introduced, because they potentially cause QT interval prolongation and torsade de pointes. Subsequently, regulatory agencies have scrutinized all second-generation H₁-antihistamines for their proarrhythmic potential and required studies of their cardiac safety at standard doses and high off-label doses, as well as drug interaction studies and studies in the elderly and other vulnerable patients. H₁-antihistamines that fail this scrutiny are not approved for use (Table IV).^{1,18,124,125}

Long-term safety of the second-generation H₁-antihistamines cetirizine, desloratadine, fexofenadine, levocetirizine, and loratadine has been documented in randomized controlled trials lasting 6 to 18 months in adults and in children as young as 1 to 2 years old.^{1,18,126}

Lack of toxicity after overdose. Massive overdoses of second-generation H₁-antihistamines, such as cetirizine,

fexofenadine, and loratadine, have not been causally linked with seizures, coma, respiratory depression, or fatality (Table IV).^{1,18,33}

FUTURE DIRECTIONS

In the future, H₁-antihistamines will continue to be a cornerstone of pharmacologic treatment in patients with allergic rhinitis, allergic conjunctivitis, and urticaria. Novel agents, such as rupatadine, an H₁-antihistamine/anti-platelet-activating factor agent,^{23,24,66,71,123,125} might play a unique role. H₃-antihistamines lead to an increase in norepinephrine and might have an advantageous decongestant effect in patients with allergic rhinitis administered with or without H₁-antihistamines.^{17,127–131} H₄-antihistamines might play an important role in the downregulation of inflammation in patients with allergic rhinitis, administered with or without H₁-antihistamines, and in patients with atopic dermatitis, asthma, and other chronic inflammatory diseases.^{17,127,128,131–134}

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What do we know?

- At H₁-receptors, the molecular mechanisms of action of histamine and H₁-antihistamines involve inverse agonism.
- H₁-antihistamines are functionally classified into first (old)-generation, potentially impairing, sedating medications and second (new)-generation, relatively nonimpairing, nonsedating medications.
- Use of PET to study H₁-antihistamine penetration in the human brain is a major breakthrough; now CNS H₁-receptor occupancy can be directly related to CNS functional effects.
- Orally administered first (old)-generation H₁-antihistamines are no longer medications of choice in patients with allergic rhinitis, allergic conjunctivitis, and chronic urticaria.
- In patients with allergic rhinitis, orally administered second (new)-generation H₁-antihistamines are among the medications of choice, as are nasal H₁-antihistamines that provide rapid relief of symptoms, including congestion.
- In patients with allergic conjunctivitis, H₁-antihistamines are the medications of choice, either administered orally, or by means of ophthalmic application which relieves symptoms within minutes through antihistaminic and antiallergic (mast cell stabilization) effects.
- In patients with chronic urticaria, second-generation H₁-antihistamines are the medications of choice. With some of these medications, such as levocetirizine, increasing the dose up to 4-fold significantly improves efficacy without compromising safety.
- H₁-antihistamines are not medications of choice for atopic dermatitis, asthma, anaphylaxis, nonallergic angioedema, colds, otitis media, sinusitis, nasal polyps, nonspecific cough, or nonallergic, nonspecific itch, in which their efficacy and safety have not been documented in high-quality randomized controlled trials.

- For insomnia and other CNS disorders and for motion sickness and other vestibular disorders, first-generation impairing, sedating H₁-antihistamines remain in widespread use, despite safety concerns.
- Orally administered first-generation H₁-antihistamines are contraindicated in anyone who requires alertness, intellectual prowess, and ability to perform complex sensorimotor tasks.

What is still needed?

- Additional studies of the molecular mechanisms of action of H₁-antihistamines as inverse agonists (not as antagonists or blockers) at the H₁-receptor, including studies of the molecular basis of their specificity for this receptor
- Additional clinical pharmacology studies and randomized controlled trials of second (new)-generation H₁-antihistamine efficacy and safety in the elderly and in infants and children
- Additional randomized controlled trials in which second (new)-generation H₁-antihistamines are compared with each other in patients with allergic rhinitis, allergic conjunctivitis, and chronic urticaria
- Additional high-quality randomized controlled trials of second-generation H₁-antihistamines for the prevention and relief of mastocytosis-associated itching and flushing and the prevention of allergic reactions
- Additional comparative PET studies of first- and second-generation H₁-antihistamines in order to correlate BBB penetration and CNS H₁-receptor occupancy with CNS functional effects
- Ongoing documentation of the safety of second-generation H₁-antihistamines in pregnancy
- Accelerated investigation of H₃-antihistamines and H₄-antihistamines in allergic diseases, given either alone or with H₁-antihistamines

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TABLE E1. H₁-antihistamines: pharmacokinetics and pharmacodynamics in healthy adults¹⁸

A. Orally administered H₁-antihistamines	Time to maximum plasma concentration (h) after a single dose	Terminal elimination half-life (h)	Clinically relevant drug-drug interactions*	Onset of action (h)†	Duration of action (h)‡
First (old) generation					
Chlorpheniramine‡	2.8 ± 0.8	27.9 ± 8.7	Possible	3	24
Diphenhydramine‡	1.7 ± 1.0	9.2 ± 2.5	Possible	2	12
Doxepin‡	2	13	Possible	NA	NA
Hydroxyzine‡	2.1 ± 0.4	20.0 ± 4.1	Possible	2	24
Second (new) generation					
Bilastine	1.2	14.5	Unlikely	2	24
Cetirizine	1.0 ± 0.5	6.5-10	Unlikely	0.7	≥24
Desloratadine	1-3	27	Unlikely	2-2.6	≥24
Fexofenadine*	1-3	11-15	Unlikely	1-3	24
Levocetirizine	0.8 ± 0.5	7 ± 1.5	Unlikely	0.7	>24
Loratadine (metabolite: descarboethoxyloratadine)	1.2 ± 0.3 (1.5 ± 0.7)	7.8 ± 4.2 (24 ± 9.8)	Unlikely	2	24
Rupatadine	0.75-1.0	6 (4.3-14.3)	Unlikely	2	24
B. Nasal/ophthalmic H₁-antihistamines	Time to maximum plasma concentration (h) after a single dose§	Terminal elimination half-life (h)§	Clinically relevant drug-drug interactions§	Onset of action (h)¶	Duration of action (h)¶
Alcaftadine (ophthalmic)	0.25	8-12	No	0.05	24
Azelastine (metabolite: des-methylazelastine, nasal and ophthalmic)	5.3 ± 1.6 (20.5)	22-27.6 (54 ± 15)	No	0.5	12
Bepotastine (ophthalmic)	1.2	2.5	No	0.25	12-24
Emedastine (ophthalmic)	1.4 ± 0.5	7	No	0.25	12
Epinaestine (ophthalmic)	2	6.5	No	0.1	12
Ketotifen (ophthalmic)	2-4	20-22	No	0.25	12
Levocabastine (ophthalmic)	1-2	35-40	No	0.25	12
Olopatadine (nasal and ophthalmic)	0.5-2	8-12	No	0.25	12-24

Results are expressed as means ± SDs, unless otherwise indicated.

NA, Information not available or incomplete.

*Clinically relevant drug-drug interactions are unlikely with most of the second-generation H₁-antihistamines. Clinically relevant drug-food interactions have been well studied for fexofenadine. Naringin, a flavonoid in grapefruit juice, and hesperidin, a flavonoid in orange juice, reduce the oral bioavailability of fexofenadine through inhibition of OATP 1A2. This interaction can be avoided by waiting for 4 hours between juice consumption and fexofenadine dosing.

†Onset/duration of action is based on wheal and flare studies.

‡Six or seven decades ago, when many of the first-generation H₁-antihistamines were introduced, pharmacokinetic and pharmacodynamic studies were not required by regulatory agencies. They have subsequently been performed for some of these drugs; however, empiric dosage regimens persist. For example, the manufacturers' recommended diphenhydramine dose for allergic rhinitis is 25 to 50 mg every 4 to 6 hours, and the diphenhydramine dose for insomnia is 25 to 50 mg at bedtime. Despite the long terminal elimination half-life values identified for some of the medications (eg, >24 hours for chlorpheniramine), based on tradition, extended release formulations remain in use.

§Nasal and ophthalmic H₁-antihistamines: time to maximum plasma concentration, terminal elimination half-life, and drug-drug interaction information are based on serum levels obtained after oral administration because serum levels after topical application are too low to permit calculation of pharmacokinetic parameters; most of these medications cause minimal or no skin test suppression.

¶Nasal and ophthalmic H₁-antihistamine formulations: onset and duration of action are based on standard adult doses (eg, 1-2 sprays in each nostril or 1 drop in each eye determined in nasal and conjunctival challenge studies, respectively).

TABLE E2. H₁-antihistamines: recommended doses for oral, nasal, and ophthalmic use in adults, children, and infants⁴²

A. Oral second (new)-generation H ₁ -antihistamines*		Formulations	Usual daily adult dosage	Usual daily pediatric dosage
Cetirizine†				
generic	5- or 10-mg chew tabs; 10-mg tabs; 1 mg/1 mL syrup		5 or 10 mg 1×/d	6-11 mo: 2.5 mg 1×/d‡
Zyrtec				12-23 mo: 2.5 mg 1×/d-bid‡
				2-5 y: 2.5 or 5 mg 1×/d or 2.5 mg bid
				6-11 y: 5-10 mg 1×/d
Cetirizine/pseudoephedrine†				
Zyrtec-D 12 hour	5-mg/120-mg ER tabs		1 tab bid	≥12 y: 1 tab bid
Desloratadine				
Clarinx	5-mg tabs; 0.5 mg/mL syrup		5 mg 1×/d	6-23 mo: 1 mg 1×/d§
	2.5- or 5-mg disintegrating tabs			2-5 y: 1.25 mg 1×/d
				6-11 y: 2.5 mg 1×/d
Desloratadine/pseudoephedrine				
Clarinx-D 12 hour, Clarinx-D 24 hour	2.5-mg/120-mg ER tabs		1 tab bid	≥12 y: 1 tab bid
	5-mg/240-mg ER tabs		1 tab 1×/d	≥12 y: 1 tab 1×/d
Fexofenadine†				
generic	30-, 60-, or 180-mg tabs		60 mg bid or 180 mg 1×/d	6-23 mo: 15 mg bid§
Allegra	60- or 180-mg tab; 30 mg/5 mL suspension; 30-mg disintegrating tab			2-11 y: 30 mg bid
Fexofenadine/pseudoephedrine†				
Allegra-D 12 hour, Allegra-D 24 hour	60-mg/120-mg ER tabs		1 tab bid	≥12 y: 1 tab bid
	180-mg/240-mg ER tabs		1 tab 1×/d	≥12 y: 1 tab 1×/d
Levocetirizine				
Xyzal	5-mg tabs; 0.5 mg/mL oral solution		5 mg 1×/d	6 mo-5 y: 1.25 mg 1×/d
				6-11 y: 2.5 mg 1×/d
Loratadine†				
generic	10-mg tabs; 10-mg disintegrating tabs; 1 mg/mL syrup and suspension		10 mg 1×/d	2-5 y: 5 mg 1×/d ^c
Claritin	10-mg tabs; 1 mg/mL syrup;			≥6 y: 10 mg 1×/d
Alavert	5- or 10-mg disintegrating tabs; 10-mg caps			
	10-mg tabs; 10-mg disintegrating tabs			
Loratadine/pseudoephedrine†				
Claritin-D 12 hour, Claritin-D 24 hour,	5-mg/120-mg ER tabs		1 tab bid	≥12 y: 1 tab bid
Alavert-D 12 hour	10-mg/240-mg ER tabs		1 tab 1×/d	≥12 y: 1 tab 1×/d
	5-mg/120-mg ER tabs		1 tab bid	≥12 y: 1 tab bid

Adapted with special permission from *Treatment Guidelines from the Medical Letter* 2010;8:9-18; www.medicalletter.org.⁴²

bid, Twice daily; *ER*, extended release; *FDA*, US Food and Drug Administration.

*Few medications from any class and no H₁-antihistamines are designated FDA Pregnancy Category A. Cetirizine and loratadine are designated FDA Pregnancy Category B (to be used during pregnancy only if the expected benefits to the mother exceed the unknown risk to the fetus). Fexofenadine, desloratadine, and levocetirizine are designated FDA Pregnancy Category C (animal studies negative, human data not available, or animal studies positive, human data negative).

†Available without a prescription.

‡Only approved for treatment of chronic idiopathic urticaria and perennial allergic rhinitis in this age group.

§Only approved for treatment of chronic idiopathic urticaria in this age group.

||Not approved for treatment of seasonal allergic rhinitis in children 2 years or younger.

Continued

TABLE E2. Continued

B. H ₁ -antihistamine nasal sprays*		Formulations	Usual daily adult dosage	Usual daily pediatric dosage
Azelastine				
Astelin 0.1%		Metered-dose pump spray (137 µg/spray)	1-2 sprays per nostril 2×/d	5-11 y: 1 spray per nostril 2×/d
Astepro 0.1%†		Metered-dose pump spray (137 µg/spray)	1-2 sprays per nostril 2×/d	≥12 y: 1-2 sprays per nostril 2×/d
Astepro 0.15%		Metered-dose pump spray (205.5 µg/spray)	1-2 sprays per nostril 2×/d‡	≥12 y: 1-2 sprays per nostril 2×/d
Olopatadine				
Patanase		Metered-dose pump spray (665 µg/spray)	2 sprays per nostril 2×/d	≥12 y: 2 sprays per nostril 2×/d

Adapted with special permission from *Treatment Guidelines from the Medical Letter* 2010;8:9-18; www.medicalletter.org.⁴²

FDA, US Food and Drug Administration.

*Azelastine and olopatadine are designated FDA Pregnancy Category C (animal studies negative, human data not available, or animal studies positive, human data negative).

†FDA approved for the treatment of seasonal allergic rhinitis.

‡Dosage for seasonal allergic rhinitis is 1 to 2 sprays per nostril twice daily or 2 sprays per nostril once daily. Dosage for perennial allergic rhinitis is 2 sprays per nostril twice daily.

C. Ophthalmic H ₁ -antihistamines*†		Formulations	Available sizes	Usual daily dosage	Pediatric use
Alcaftadine					
Lastacaft		0.25% solution	3 mL	1 drop 1×/d	>2 y
Azelastine					
Optivar		0.05% solution	6 mL	1 drop bid	>3 y
Bepotastine					
Bepreve		1.5% solution	10 mL	1 drop bid	≥2 y
Emedastine difumarate					
Emadine		0.05% solution	5 mL	1 drop qid	≥3 y
Epinastine					
Elestat		0.05% solution	5 mL	1 drop bid	≥3 y
Ketotifen fumarate‡					
generic		0.025% solution	5 mL	1 drop every 8-12 h	≥3 y
Zaditor		0.025% solution	5 mL	1 drop every 8-12 h	≥3 y
Claritin Eye		0.025% solution	5 mL	1 drop every 8-12 h	≥3 y
Eye Itch Relief		0.025% solution	5 mL	1 drop every 8-12 h	≥3 y
Olopatadine					
Pataday		0.2% solution	2.5 mL	1 drop 1×/d	≥3 y
Patanol		0.1% solution	5 mL	1-2 drops bid	≥3 y

Adapted with special permission from *Treatment Guidelines from the Medical Letter* 2010;8:9-18; www.medicalletter.org.⁴²

bid, Twice daily; ER, extended release; FDA, US Food and Drug Administration; qid, 4 times daily.

*Except for emedastine, H₁-antihistamine ophthalmic formulations are also designated as antiallergic drugs.

†Alcaftadine and emedastine are designated FDA Pregnancy Category B (to be used during pregnancy only if the expected benefits to the mother exceed the unknown risk to the fetus). Azelastine, bepotastine, epinastine, ketotifen, and olopatadine are designated FDA Pregnancy Category C (animal studies negative, human data not available, or animal studies positive, human data negative).

‡Available over the counter.

TABLE E3. H₁-antihistamines: potential adverse effects in vulnerable patients^{1,7,18,106-126}

	First (old) generation	Second (new) generation
Patients with impaired hepatic or renal function	There are few prospective studies. In patients with impaired hepatic or renal function, including those undergoing hemodialysis, use of first-generation H ₁ -antihistamines in standard doses is potentially associated with adverse effects, including CNS effects such as impaired cognitive function and drowsiness.	The clinical pharmacology (absorption, distribution, metabolism, and elimination) of most of these medications has been studied prospectively in patients with impaired hepatic or renal function. If necessary, specific instructions for reduction in dose or dose frequency are provided.
Elderly people	There are few randomized controlled trials of first-generation H ₁ -antihistamines in the elderly. These medications are commonly used in this population, in which they potentially impair cognition and memory and cause inattention, disorganized speech, falls, incontinence, altered consciousness, and delirium.	The clinical pharmacology of most second-generation H ₁ -antihistamines has been studied prospectively in the elderly. If necessary, specific instructions for reduction in dose or dose frequency are provided.
Pregnant and lactating women	With regard to teratogenicity, first-generation H ₁ -antihistamines are classified as FDA Pregnancy Category B (chlorpheniramine and diphenhydramine) or C (hydroxyzine and ketotifen). In nursing infants they potentially cause irritability or drowsiness.	With regard to teratogenicity, second-generation H ₁ -antihistamines are classified as FDA Pregnancy Category B (alcaftadine, cetirizine, emedastine, and loratadine) or C (azelastine, bepotastine, desloratadine, epinastine, fexofenadine, levocetirizine, and olopatadine). No CNS adverse effects have been reported in nursing infants.
Neonates	When given to the mother immediately before parturition, these medications potentially cause irritability, drowsiness, and respiratory depression in the neonate.	No CNS adverse effects have been reported in neonates.
Infants and young children	For decades, first-generation H ₁ -antihistamines have been assumed to be effective and safe in infants and children with allergies, coughs, and colds, either when given alone or in a mixture containing other drugs; however, they are often associated with adverse effects and occasionally with fatalities.* Regulatory agencies in the United States and other countries have mandated that more than 500 pediatric oral formulations containing first-generation H ₁ -antihistamines be withdrawn from the market.	The long-term safety of cetirizine, desloratadine, fexofenadine, levocetirizine, and loratadine has been confirmed in young children.

*First-generation H₁-antihistamines, particularly in the phenothiazine class, have been associated with sudden infant death syndrome and apparent life-threatening events, although causality has never been proved.