

REVIEW ARTICLE

DRUG THERAPY

Advances in H₁-Antihistamines

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MORE THAN 30,000 PEER-REVIEWED ARTICLES ON HISTAMINE AND the H₁-antihistamines have been published since this subject was last reviewed in the *Journal* a decade ago.¹ The role of histamine in neurotransmission,²⁻⁴ allergic inflammation,⁵⁻¹² and immune modulation⁹⁻¹⁹ has been further elucidated since that time. The human H₁-histamine and H₂-histamine receptors were cloned and characterized in the early 1990s,^{20,21} as were the human H₃-histamine and H₄-histamine receptors several years ago.^{22,23}

H₁-antihistamines, historically known as histamine H₁-receptor blockers or antagonists, are specific for the H₁-receptor. In addition, some H₁-antihistamines inhibit transmission through the muscarinic, α -adrenergic, and serotonin receptors and through ion channels (Fig. 1).²⁴⁻²⁶ The H₁-antihistamines have recently been reclassified as inverse agonists, rather than as H₁-receptor antagonists, which is consonant with an increased understanding of their molecular pharmacologic features (Fig. 2).^{24,25} More than 40 H₁-antihistamines are available worldwide — indeed, these agents are among the most widely used of all medications.²⁷ The H₁-antihistamines astemizole and terfenadine, which are associated with cardiac toxic effects,²⁵ are no longer approved for use. New H₁-antihistamines have been developed and introduced.^{26,28} Both health care professionals and consumers generally assume that all approved H₁-antihistamines have been shown to be efficacious and safe, but many medications in this class, in particular those introduced before 1985, have not been optimally studied in randomized, double-blind, controlled trials. This discussion of the differences in the clinical pharmacology and the similarities in efficacy and safety of the H₁-antihistamines^{25,26,29,30} is based on a review of the literature published since 1994.

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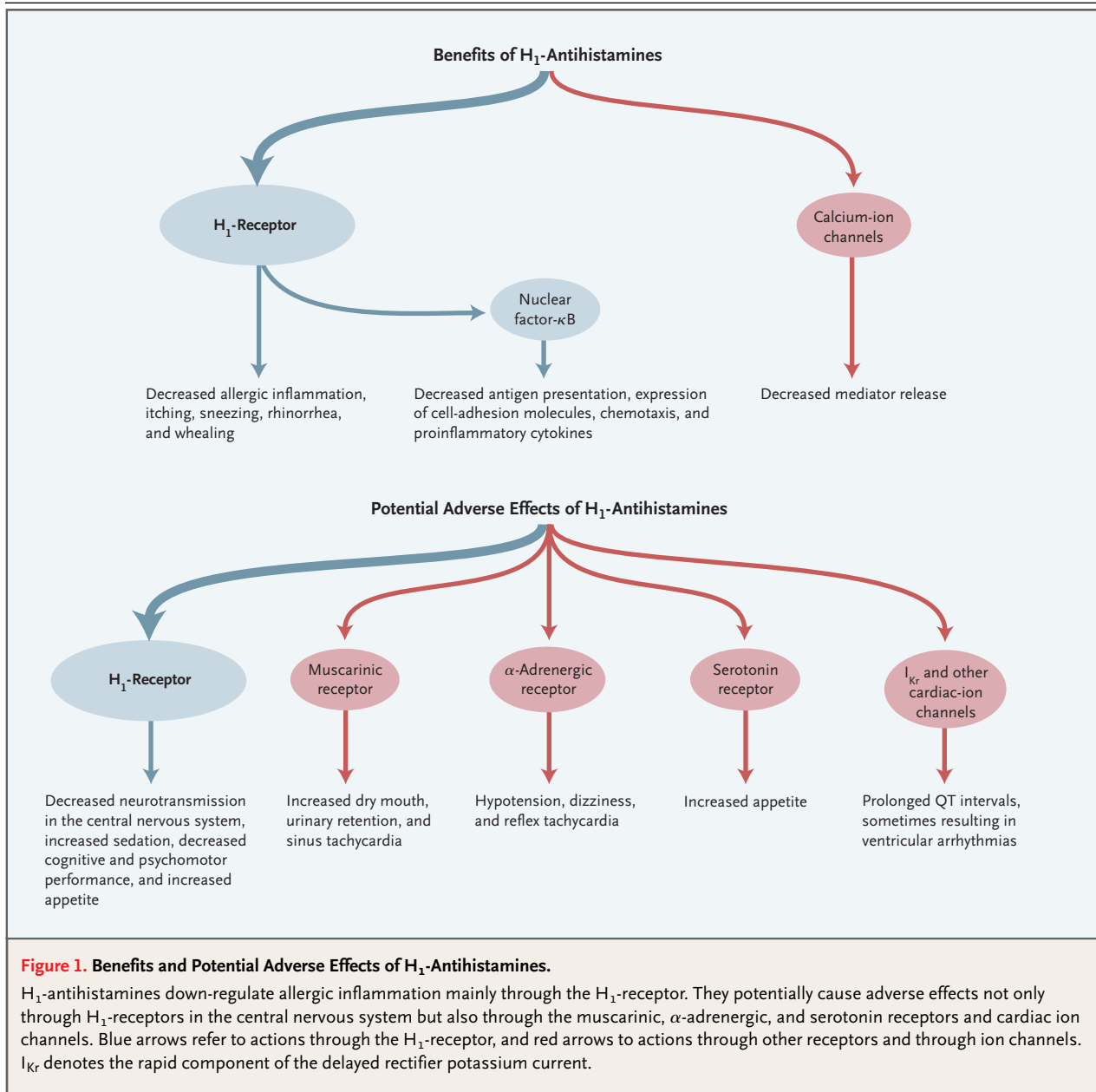
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HISTAMINE

ROLE IN HUMAN HEALTH

Histamine, a natural body constituent, is a low-molecular-weight amine synthesized from L-histidine exclusively by histidine decarboxylase, an enzyme that is expressed in cells throughout the body, including central nervous system neurons, gastric-mucosa parietal cells, mast cells, and basophils. Histamine has an important role in human health, exerting its diverse biologic effects through four types of receptors (Table 1).^{1,10-12,20-23} It is involved in the proliferation and differentiation of cells, hematopoiesis, embryonic development, regeneration, and wound healing. In the mammalian central nervous system, histamine is produced in neurons that have cell bodies located exclusively in the tuberomammillary nucleus of the posterior hypothalamus with axons that transmit histamine to the frontal and temporal cortexes and other regions of the brain. In this phylogenetically “old” neurotransmitter system, histamine is involved in the regulation of basic body functions through the H₁-receptor. These functions include the cycle of sleeping and waking, energy and endocrine homeostasis, cognition, and memory. His-



tamine also possesses anticonvulsant activity.^{2,4} It modulates the release of neurotransmitters through presynaptic H₃-receptors located on histaminergic and nonhistaminergic neurons of the central and peripheral nervous system.²² Histamine facilitates some proinflammatory activities through the novel H₄-receptor, which has a high degree of homology with the H₃-receptor but a unique expression profile.²³

ALLERGIC INFLAMMATION AND IMMUNE MODULATION

Histamine plays a pivotal role in allergic inflammation, which is a complex network of cellular events that involve redundant mediators and signals. Histamine is released from the granules of FcεRI+ cells (e.g., mast cells and basophils) along with tryptase and other preformed mediators, as well as leukotrienes, prostaglandins, and other newly generated

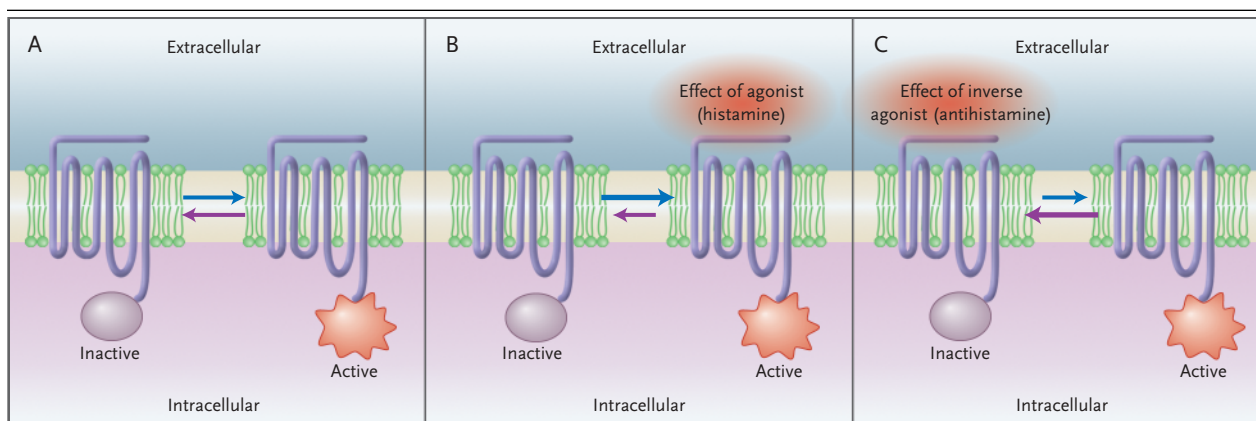


Figure 2. Simplified Two-State Model of the Histamine H₁-Receptor.

In Panel A, the inactive state of the histamine H₁-receptor is in equilibrium with the active state. In Panel B, an agonist, which has a preferential affinity for the active state, stabilizes the receptor in this conformation and consequently causes a shift in the equilibrium toward the active state. In Panel C, an inverse agonist, which has a preferential affinity for the inactive state, stabilizes the receptor in this conformation and consequently causes a shift in the equilibrium toward the inactive state. All known H₁-antihistamines function as inverse agonists. Intracellular and extracellular are defined in relation to the cell membrane. The purple serpentine line denotes the G-protein-coupled receptor, and green the cell membrane. Adapted from Leurs et al.²⁵

mediators, after the cross-linking of surface IgE by allergen or through mechanisms that are independent of IgE. After allergen challenge in sensitized persons, histamine is found locally in relatively large (microgram) quantities per 1 million cells, in contrast to leukotrienes and other mediators, which are found in picogram quantities. Although most of the effects of histamine in allergic disease occur through H₁ receptors^{5,10-12} (Table 1), hypotension, tachycardia, flushing, and headache occur through both the H₁- and H₂-receptors in the vasculature,⁶ whereas cutaneous itch and nasal congestion may occur through both the H₁- and H₃-receptors.^{7,8} In addition to its role in the early allergic response to antigen, histamine acts as a stimulatory signal for the production of cytokines and the expression of cell-adhesion molecules and class II antigens, thereby contributing to the late allergic response.⁹⁻¹¹

Histamine exerts other important immunomodulatory effects through H₁-, H₂-, H₃-, and H₄-receptors⁹⁻¹⁹ (Table 1). The expression of the receptors changes according to the stage of cell differentiation and microenvironmental influences. Depending on the predominance of the type of histamine receptor and on the experimental system studied, histamine may have proinflammatory or antiinflammatory effects. Through the H₁-receptor, histamine has proinflammatory activity and is involved in the

development of several aspects of antigen-specific immune response, including the maturation of dendritic cells and the modulation of the balance of type 1 helper (Th1) T cells and type 2 helper (Th2) T cells. Histamine may induce an increase in the proliferation of Th1 cells and in the production of interferon γ and may block humoral immune responses by means of this mechanism. Histamine also induces the release of proinflammatory cytokines and lysosomal enzymes from human macrophages and has the capacity to influence the activity of basophils, eosinophils, and fibroblasts. In addition, it may play a role in autoimmunity and malignant disease through the H₁-receptor.^{10,18}

TYPES OF HISTAMINE RECEPTORS

The four major types of histamine receptor, H₁-, H₂-, H₃-, and H₄-receptors, differ in their expression, signal transduction, and function^{10-12,20-24} (Table 1). H₁- and H₂-receptors are widely expressed, in contrast to H₃- and H₄-receptors. All types of histamine receptor are heptahelical transmembrane molecules that transduce extracellular signals by way of G proteins to intracellular second-messenger systems. All have constitutive activity, which is defined as the ability to trigger downstream events even in the absence of ligand binding (Fig. 2).^{24,25} The active and inactive states of the receptors exist in equilibrium. H₁-receptor polymor-

Table 1. Characteristics of the Histamine Receptors.*

Characteristic	H ₁ -Receptor	H ₂ -Receptor	H ₃ -Receptor	H ₄ -Receptor
Receptor described, human gene cloned (yr)	1966, 1993	1972, 1991	1983, 1999	1994, 2000
Receptor proteins in humans	487 amino acids, 56 kD	359 amino acids, 40 kD	445 amino acids, 70 kD; splice variants	390 amino acids
Chromosomal location in humans	3p25, 3p14–21	5q35.3	20q13.33	18q11.2
Receptor expression	Widespread, including neurons, smooth-muscle (e.g., airway, vascular), and other types of cells†	Widespread, including gastric-mucosa parietal cells, smooth-muscle, heart, and other types of cells†	High expression in histaminergic neurons, low expression elsewhere	High expression in bone marrow and peripheral hematopoietic cells; low expression elsewhere
G-protein coupling	Gα _{q/11}	Gα _s	G _{i/o}	G _{i/o}
Activated intracellular signals	Ca ²⁺ , cGMP, phospholipase A ₂ , C, and D, NF-κB, cAMP, NOS	cAMP, Ca ²⁺ , phospholipase C, protein kinase C, c-fos	Ca ²⁺ , MAP kinase; inhibition of cAMP	Ca ²⁺ , MAP kinase; inhibition of cAMP
Inverse agonists for clinical use	>40, Including diphenhydramine, cetirizine, desloratadine, fexofenadine, and loratadine	Cimetidine, famotidine, nizatidine, and ranitidine	None to date	None to date
Histamine function (general)	Increased pruritus, pain, vasodilation, vascular permeability, hypotension; flushing, headache, tachycardia, bronchoconstriction, stimulation of airway vagal afferent nerves and cough receptors; decreased atrioventricular-node conduction time	Increased gastric acid secretion, vascular permeability, hypotension, flushing, headache, tachycardia, chronotropic and inotropic activity, bronchodilation, mucus production (airway)	Prevents excessive bronchoconstriction; mediates pruritus (no mast-cell involvement)	Differentiation of myeloblasts and promyelocytes
Histamine function in allergic inflammation and immune modulation	Increased release of histamine and other mediators; increased cellular adhesion-molecule expression and chemotaxis of eosinophils and neutrophils; increased antigen-presenting-cell capacity, costimulatory activity on B cells; blocking of humoral immunity and IgE production; induction of cellular immunity (Th1); increased IFN-γ, autoimmunity	Decreased eosinophil and neutrophil chemotaxis; induction of interleukin-10, suppression of interleukin-12 by dendritic cells; development of Th2 or tolerance-inducing dendritic cells; induction of humoral immunity; suppression of cellular immunity; suppression of Th2 cells and cytokines; indirect role in allergy, autoimmunity, malignant disease, and graft rejection	Probably involved in control of neurogenic inflammation through local neuron–mast-cell feedback loops; pro-inflammatory activity; increased APC capacity	Increased cytosolic calcium in human eosinophils; increased eosinophil chemotaxis; increased interleukin-16 production (H ₂ -receptor also involved)
Histamine function in the central nervous system	Cycle of sleeping and waking, food intake, thermal regulation, emotions and aggressive behavior, locomotion, memory, and learning	Neuroendocrine	Presynaptic heteroreceptor; decreased histamine, dopamine, serotonin, noradrenaline and acetylcholine release	Not yet defined

* The abbreviation cAMP denotes cyclic adenosine monophosphate, cGMP cyclic guanosine monophosphate, IFN-γ interferon-gamma, MAP mitogen-activated protein, NF-κB nuclear factor-κB, NOS nitric oxide synthase, TNF-α tumor necrosis factor α, Th1 type 1 helper T cell, Th2 type 2 helper T cell, and APC antigen-presenting cell.

† Other types of cells include epithelial and endothelial cells, neutrophils, eosinophils, monocytes, dendritic cells, T cells, B cells, hepatocytes, and chondrocytes.

phisms have been described, although it is not yet clear how they influence the clinical response to H₁-antihistamines.³¹ Human H₁-receptors have approximately 45 percent homology with muscarinic receptors. Targeted disruption of the H₁-receptor gene in mice results in the impairment of neurologic functions such as memory, learning, and locomotion and in aggressive behavior. Mice that are H₁-receptor-deficient also have immunologic abnormalities, including impaired antigen-specific responses of T cells and B cells.^{19,32}

BASIC AND CLINICAL PHARMACOLOGY

INVERSE AGONISM AND CLASSIFICATION SYSTEMS

H₁-antihistamines act as inverse agonists that combine with and stabilize the inactive form of the H₁-receptor, shifting the equilibrium toward the inactive state^{24,25} (Fig. 2). Traditionally, these agents have been classified into six chemical groups: the ethanolamines, ethylenediamines, alkylamines, piperazines, piperidines, and phenothiazines. The classification according to function of first-generation H₁-antihistamines, which are sedating, as compared with second-generation compounds, which are relatively nonsedating, is now more commonly used^{1,26} (Table 2). Many of the H₁-antihistamines introduced during the past two decades have been identified by means of the screening of existing compounds, and they are chemically related to older medications in the class. For example, acrivastine is related to triprolidine, cetirizine is a metabolite of hydroxyzine, levocetirizine is an enantiomer of cetirizine, desloratadine is a metabolite of loratadine, and fexofenadine is a metabolite of terfenadine. No currently available H₁-antihistamine is appropriately described as “third” or “new” generation — these terms should be reserved for future H₁-antihistamines that will be designed with the use of molecular techniques.³³

ANTIALLERGIC AND ANTIINFLAMMATORY ACTIVITIES

The antiallergic and antiinflammatory activities of H₁-antihistamines occur through a variety of mechanisms^{15,24,25,34-36} (Fig. 1). Antiallergic activities such as the inhibition of the release of mediators from mast cells and basophils probably involve a direct inhibitory effect on calcium-ion channels that reduces the inward calcium current activated by the depletion of the intracellular store of calci-

um. Antiinflammatory effects such as the inhibition of the expression of cell adhesion molecules and the chemotaxis of eosinophils and other cells may involve down-regulation of the H₁-receptor-activated nuclear factor- κ B, a ubiquitous transcription factor that binds to the promoter and enhancer regions of many genes that regulate the production of proinflammatory cytokines and adhesion proteins.^{24,25}

Pretreatment with an oral H₁-antihistamine reduces the early response to an allergen challenge in the conjunctiva, nose, lower airway, and skin. In patients who receive such pretreatment, the level of proinflammatory cell adhesion molecules (e.g., intercellular adhesion molecules and vascular cell adhesion molecules), cells (e.g., eosinophils and neutrophils), cytokines, and mediators (e.g., histamine, leukotrienes, prostaglandins, and others) is lower in lavage fluid after the challenge than at baseline. Plasma exudation is also diminished, a change that is reflected in decreases in the levels of albumin, fucose, and α_2 -macroglobulin. Physiological changes and relief from symptoms can be measured concurrently. Moreover, pretreatment of the nasal mucosa and the conjunctivae with topical H₁-antihistamines down-regulates the inflammation locally after an allergen challenge.^{26,36}

In order to establish the clinical relevance of the antiinflammatory effects of the H₁-antihistamines to their overall efficacy, further studies conducted during natural exposure to allergens are needed to document that the levels of proinflammatory cell adhesion molecules, cells, cytokines, and mediators decrease in response to the usual doses of these medications. Additional studies comparing the antiinflammatory effects of different H₁-antihistamines are also needed. Glucocorticoids, irrespective of the route of administration, consistently show greater antiinflammatory effects than H₁-antihistamines do.²⁶

PHARMACOKINETICS AND PHARMACODYNAMICS

Clinical pharmacologic studies provide objective information on which to base doses and dose intervals of the H₁-antihistamines, including the modified dose regimens that may be required to treat children and elderly persons, patients with hepatic or renal dysfunction, or those who take other medications concurrently. The pharmacokinetics and pharmacodynamics of the H₁-antihistamines are summarized in Table 3.^{1,28,33,37-41} Many first-generation H₁-antihistamines have never been

Table 2. Chemical and Functional Classification of H₁-Antihistamines.

Chemical Class	Functional Class	
	First-Generation Drugs	Second-Generation Drugs
Alkylamines	Brompheniramine, chlorpheniramine, dimethindene,*† pheniramine,† triprolidine	Acrivastine
Piperazines	Bucizine, cyclizine, hydroxyzine, meclizine, oxatomide*	Cetirizine, levocetirizine*
Piperidines	Azatadine, cyproheptadine, diphenylpyrrolidine, ketotifen†	Astemizole,* desloratadine, ebastine,* fexofenadine, levocabastine,† loratadine,‡ mizolastine,* olopatadine,† terfenadine*
Ethanolamines	Carbinoxamine, clemastine, dimenhydrinate, diphenhydramine, doxylamine, phenyltoloxamine*	—
Ethylenediamines	Antazoline, pyrilamine, tripeleminamine	—
Phenothiazines	Methdilazine, promethazine	—
Others	Doxepin§	Azelastine,† emedastine,† epinastine†

* In the United States, this H₁-antihistamine is either not yet approved, has never been approved, or has had approval withdrawn.

† Topical H₁-antihistamines are applied to the conjunctivae, the nasal mucosa, or both. Some of them are available in oral formulations in some countries.

‡ In the United States, loratadine became available over the counter in 2003, and the change in status had a major effect on physicians' prescribing patterns and on the costs of the medication to patients. Other second-generation H₁-antihistamines are available only by prescription.

§ This medication has H₁- and H₂-antihistamine activities and is also classified as a tricyclic antidepressant.

adequately studied in healthy adults, let alone in special populations or with respect to drug–drug interactions.^{37,38} All first-generation H₁-antihistamines, and some second-generation H₁-antihistamines such as desloratadine and loratadine are metabolized by the hepatic cytochrome P450 (CYP450) system. Cetirizine is excreted largely unchanged in the urine, and fexofenadine is excreted largely unchanged in the feces.

Drug–drug interactions may involve interference with absorption through active transport mechanisms (e.g., P-glycoprotein, organic-anion transporters, and other ATP-binding cassette transporters) in the mucosa of the gastrointestinal tract, or may involve the inhibition or induction of metabolism in the hepatic CYP450 system. Interactions that result in decreased H₁-antihistamine plasma concentrations may be associated with diminished efficacy. Interactions that result in increased plasma concentrations may be more likely to be associated with adverse effects when first-generation H₁-antihistamines are used than when second-generation H₁-antihistamines, which have a wider therapeutic index,^{29,30} are used.

The onset, the amount, and the duration of action of H₁-antihistamine can be studied by measuring the suppression of the symptoms of allergic rhinitis in groups of patients who have been challenged with high doses of allergen indoors and out of season, or who have been challenged naturally outdoors during the peak pollen season.^{42,43} More commonly, the pharmacodynamics of orally administered H₁-antihistamines are investigated by measuring the suppression of the cutaneous histamine-induced or allergen-induced wheal and flare,³⁷⁻⁴¹ which is reported to correlate with H₁-antihistamine concentrations in the skin.^{37,41} Clinically relevant differences in the onset, amount, and duration of action can be identified³⁷⁻⁴¹ (Table 3). After a single oral dose, the onset of action occurs within one to three hours. The duration of action for many oral H₁-antihistamines is at least 24 hours, facilitating once-daily dosing. No tolerance to the suppressive effect on skin-test reactivity to allergens has been found in rigorously controlled, double-blind studies of three months' duration. Residual suppression of skin-test reactivity to allergens lasts for up to seven days after discontinuation of an H₁-anti-

Table 3. Pharmacokinetics and Pharmacodynamics of Oral H₁-Antihistamines in Healthy Young Adults.*

H ₁ -Antihistamine (Metabolite)	T _{max} after a Single Dose†	Terminal Elimination Half-Life	Elimination Unchanged in Urine/Feces	Clinically Relevant Drug-Drug Interaction	Onset, Duration of Action‡	Usual Adult Dose	Conditions That May Require Dose Adjustment
	hr		%		hr		
First-generation drug§							
Chlorpheniramine	2.8±0.8	27.9±8.7	—	Possible	3, 24	4 mg three or four times daily 12 mg (sustained-release formulation) twice daily	
Diphenhydramine	1.7±1.0	9.2±2.5	—	Possible	2, 12	25–50 mg three or four times daily or at bedtime	Hepatic impairment
Doxepin	2	13	—	Possible	—	25–50 mg three times daily or at bedtime	Hepatic impairment
Hydroxyzine	2.1±0.4	20.0±4.1	—	Possible	2, 24	25–50 mg three times daily or at bedtime	Hepatic impairment
Second-generation drug							
Acrivastine	1.4±0.4	1.4–3.1	59/0	Unlikely	1, 8	8 mg three times daily	—
Cetirizine	1.0±0.5	6.5–10	60/10	Unlikely	1, 24	5–10 mg daily	Renal and hepatic impairment
Desloratadine	1–3	27	0	Unlikely	2, 24	5 mg daily	Renal and hepatic impairment
Ebastine¶ (carebastine)	(2.6–5.7)	(10.3–19.3)	(75–95/0)	—	2, 24	10–20 mg daily	Renal and hepatic impairment
Fexofenadine	2.6	14.4	12/80	Unlikely	2, 24	60 mg twice daily or 120 or 180 mg daily	Renal impairment
Levocetirizine¶	0.8±0.5	7±1.5	86/13	Unlikely	1, 24	5 mg daily	Renal and hepatic impairment
Loratadine (descarboethoxy-loratadine)	1.2±0.3 (1.5±0.7)	7.8±4.2 (24±9.8)	Trace	Unlikely	2, 24	10 mg daily	Hepatic impairment
Mizolastine¶	1.5	12.9	0.5/0	—	1, 24	10 mg daily	—

* Unless otherwise indicated, results are expressed as means ±SD or as a range of values. Parentheses denote active metabolites.

† T_{max} denotes time from oral intake to peak plasma concentration.

‡ Onset and duration of action are based on wheal-and-flare studies.

§ Studies were performed decades after some of these drugs were introduced. Empirical dosage regimens persist.

¶ Second-generation H₁-antihistamines were not available in the United States at the time of publication.

|| Fexofenadine should not be administered within 15 minutes after the ingestion of antacids that contain aluminum and magnesium, because these minerals decrease its absorption.

histamine that was in regular use for one or more weeks.³⁷

Although topical intranasal and ophthalmic H₁-antihistamines differ in their pharmacokinetics, most of them need to be administered twice daily because of washout from the nasal mucosa or conjunctivae. Dose adjustment is not required in

special populations. Some systemic absorption, and transient suppression of skin-test reactivity, may occur.

ADVERSE EFFECTS

First-generation H₁-antihistamines such as chlorpheniramine, diphenhydramine, hydroxyzine, and

promethazine bind to H₁-receptors and block the neurotransmitter effect of histamine in the central nervous system (Fig. 1 and Table 4). The ability of these medications to penetrate the blood–brain barrier is related to their lipophilicity, relatively low molecular weight, and lack of recognition by the P-glycoprotein efflux pump that is expressed on the luminal surfaces of nonfenestrated endothelial cells in the vasculature of the central nervous system.^{44–46} Positron-emission tomography (PET) with ¹¹C doxepin as the radioactive ligand has shown that the first-generation H₁-antihistamines occupy 50 to 90 percent of the H₁-receptors in the frontal cortex, temporal cortex, hippocampus, and pons.⁴⁷

Second-generation H₁-antihistamines are specific for H₁-receptors and penetrate the central nervous system poorly, owing to their lipophobicity and affinity for P-glycoprotein that is expressed on vascular endothelial cells in the central nervous system.^{44–46} Their propensity to occupy central nervous system H₁-receptors varies from none for fexofenadine to 30 percent for cetirizine.⁴⁸

Cardiac toxic effects induced by H₁-antihistamines occur rarely and independently of the H₁-receptor^{49–51} and are not a class effect^{25,51} (Fig. 1 and Table 4). First-generation H₁-antihistamines have antimuscarinic and α -adrenergic blockade activity and may cause dose-related prolongation of the QT interval. Two early second-generation H₁-antihistamines, astemizole and terfenadine, which are no longer approved, block the rapid component of delayed rectifier potassium current (I_{Kr}) with 50 percent inhibitory concentrations in the nanomolar range. As a result, these two agents potentially prolong the monophasic cardiac action potential and QT interval, induce the development of early after-depolarizations and dispersion (slowing) of repolarization, and thereby may cause torsades de pointes. New second-generation H₁-antihistamines such as cetirizine, desloratadine, fexofenadine, and loratadine have 50 percent inhibitory concentrations in the micromolar range and have a thousandth of the potency in blocking the I_{Kr} current.^{25,49–51}

EFFICACY

First-generation H₁-antihistamines have not been optimally studied in any allergic disorder. Indeed, most clinical trials of these older medications do not meet current standards with regard to study design (e.g., criteria for randomization, controls,

masking, measured outcomes, number of participants enrolled, reporting of attrition, adherence, and duration). In contrast, the use of second-generation H₁-antihistamines for the relief of symptoms in seasonal and perennial allergic rhinoconjunctivitis and in chronic urticaria is supported by a large number of adequately powered, randomized, double-blind, placebo-controlled clinical trials lasting weeks or months.^{52–54}

H₁-antihistamines are best taken on a regular basis, rather than as needed, in order to reduce allergic inflammation and prevent symptoms.³⁶ Tolerance to doses that achieve clinical efficacy does not develop.^{26,55,56} The dose–response curve for efficacy is flat as compared with that for adverse effects, especially with the use of first-generation H₁-antihistamines. The relief from symptoms may be incomplete, however, because leukotrienes and other mediators also play a role in allergic inflammation.

ALLERGIC RHINOCONJUNCTIVITIS

H₁-antihistamines relieve nasal itching, sneezing, rhinorrhea, and congestion; conjunctival itching, watering, and redness; and itching of the palate, throat, and ears. These agents thus reduce misery and improve the quality of life.^{53,55–62} Various H₁-antihistamines have a similar efficacy for the overall relief of symptoms reported by patients^{53,57–59}; statistically significant differences reported in the relief of individual symptoms are small and inconsistent.^{58,59} Topical intranasal or ophthalmic H₁-antihistamines have a more rapid onset of action than oral H₁-antihistamines, but they require administration several times a day.⁵³ The selection of an H₁-antihistamine for a patient should be based primarily on considerations of safety^{26,53} and the patient's preference for a particular medication, formulation, route of administration, or dose regimen. There are not many comparative data on these drugs, and more head-to-head comparisons among H₁-antihistamines are needed.

Many H₁-antihistamines are available in fixed-dose formulations in combination with pseudoephedrine,⁶¹ which enhances the relief of nasal congestion. The efficacy of H₁-antihistamines is similar to or greater than that of topical cromoglycate or nedocromil and similar to that of the leukotriene antagonist montelukast.^{53,62} An oral H₁-antihistamine administered alone or with a leukotriene antagonist appears to be less effective than an intranasal glucocorticoid.^{63,64}

Table 4. Potential Adverse Effects of H₁-Antihistamines.*

Site of Adverse Effect	First-Generation Drugs	Second-Generation Drugs
Central nervous system Mechanism: interference with neurotransmitter effect of histamine through H ₁ -receptor	After usual doses, may cause drowsiness, fatigue, somnolence, dizziness; impairment of cognitive function, memory, and psychomotor performance; headache, dystonia, dyskinesia, agitation, confusion, and hallucinations May cause adverse effects in newborns if taken by mother immediately before parturition; may cause irritability, drowsiness, or respiratory depression in nursing infants	None with fexofenadine, up to 360 mg total daily dose (off-label); none with desloratadine, 5 mg, or loratadine, 10 mg, although adverse effects may occur at higher doses; cetirizine, 10 mg or higher, may cause sedation in adults No adverse effects reported in newborns or nursing infants
Cardiac Mechanisms: multiple; antimuscarinic effects; α -adrenergic-receptor blockade; blockade of cardiac ion currents (I_{Kr} ; less commonly, I_{Na} , I_{to} , I_{Kl} , and I_{Ks})	Dose-related sinus tachycardia; reflex tachycardia and supraventricular arrhythmias; dose-related prolongation of the QT interval and ventricular arrhythmias reported for cyproheptadine, diphenhydramine, doxepin, hydroxyzine, and others	No major concern in the United States since regulatory approval was withdrawn for astemizole and terfenadine
Other sites Mechanisms: blockade of muscarinic, α -adrenergic, and serotonin receptors	After usual doses, may cause mydriasis (pupillary dilatation), dry eyes, dry mouth, urinary retention and hesitancy, gastrointestinal motility, constipation, erectile dysfunction, memory deficits; peripheral vasodilatation, postural hypotension, dizziness; appetite stimulation and weight gain (cyproheptadine, ketotifen); contraindicated in patients with glaucoma or prostatic hypertrophy	None reported
Toxic effects after overdose Mechanisms: multiple	Central nervous system effects — e.g., extreme drowsiness, lethargy, confusion, delirium, and coma in adults; paradoxical excitation, irritability, hyperactivity, insomnia, hallucinations, and seizures in infants and young children; in adults and children, central nervous system effects predominate over cardiac adverse effects; death may occur within hours after ingestion of drug in untreated patients	No serious toxic effects or deaths reported
Abuse of drug Mechanisms: through H ₁ -receptors in central nervous system and other receptors	Euphoria, hallucinations, and “getting high” reported for diphenhydramine, dimenhydrinate, and others	None reported
Teratogenicity after use in pregnancy	FDA category B (chlorpheniramine, diphenhydramine) or C (hydroxyzine, ketotifen)	FDA category B (cetirizine, emedastine, loratadine) or C (azelastine, epinastine, desloratadine, fexofenadine, olopatadine)

* Food and Drug Administration (FDA) category B denotes drugs for which studies in animals have shown no adverse effects but data in humans are not available, or those for which studies in animals have shown adverse effects but studies in humans have not. Category C denotes drugs for which studies in animals have shown adverse effects but data in humans are not available, or those for which no data are available from studies in humans or animals. I_{Kr} denotes rapid component of the delayed rectifier potassium current, I_{Na} sodium current, I_{to} transient outward potassium current, I_{Kl} the inward-rectifying current, and I_{Ks} the slow component of the delayed rectifier potassium current.

OTHER AIRWAY DISORDERS

Although the H₁-antihistamines are widely used to relieve symptoms in upper respiratory tract infections, otitis media, and sinusitis, the published evidence does not support this practice.^{53,65,66} Similarly, current evidence does not support the use of

H₁-antihistamines in persistent asthma.^{53,67} However, in patients with allergic inflammation throughout the upper and lower airways that results in concurrent symptoms of allergic rhinitis and asthma, the use of H₁-antihistamines is reported to result in a significant decrease in the symptoms of both rhi-

nititis and asthma as well as a decrease in the use of β_2 -adrenergic-agonist medications, and the H_1 -antihistamines may even improve pulmonary function.^{55,61,68} Among these patients, desloratadine and montelukast appear to have similar effects.⁶⁸ Treatment with cetirizine over a period of 18 months is reported to delay the onset of asthma in some young children with atopic dermatitis who are at high risk for the disease,⁶⁹ but this observation requires confirmation.

URTICARIA

H_1 -antihistamines reduce the number, size, and duration of wheals and decrease itching. They are efficacious in relieving and preventing acute urticaria,^{54,70,71} although there is considerably less published evidence in support of their efficacy in this disorder as compared with chronic urticaria,^{54,72-76} in which the second-generation H_1 -antihistamines cetirizine, desloratadine, fexofenadine, and loratadine have been well studied. Both first-generation and second-generation H_1 -antihistamines appear to have similar efficacy in chronic urticaria,⁷⁴ but additional comparative studies are needed. Although the sequential use of two different H_1 -antihistamines within the same day (i.e., one medication in the morning and another at bedtime) has been recommended,⁷² this strategy has not been adequately tested in randomized, double-blind, placebo-controlled trials. H_1 -antihistamines appear to be effective in treating dermatographism and physical urticarias, including cholinergic, cold, and pressure-induced urticarias, but they do not seem to be effective in treating either urticarial vasculitis or hereditary angioedema.^{54,73} In some patients with chronic urticaria, an H_2 -antihistamine such as cimetidine administered concurrently with an H_1 -antihistamine may give added relief and appears to be worth a trial of a period of three to four weeks.^{54,72,73} A recent study showed that the simultaneous administration of the leukotriene antagonist montelukast did not appear to offer an advantage over the H_1 -antihistamine desloratadine alone.⁷⁶

OTHER ALLERGIC AND IMMUNOLOGIC DISORDERS

H_1 -antihistamines should not replace epinephrine in the treatment of severe acute systemic allergic reactions (anaphylaxis). However, administered as an ancillary treatment, alone or with an H_2 -antihistamine, these agents may relieve flushing, itching,

urticaria, and rhinorrhea.⁷⁷ Furthermore, they are used, often in combination with other medications, to prevent idiopathic anaphylaxis, reactions to allergen-specific immunotherapy, and reactions to radiocontrast agents.^{77,78}

H_1 -antihistamines are used both for relief of itching and for their glucocorticoid-sparing effects in atopic dermatitis, but the evidence in support of their efficacy in this disorder is not convincing.⁷⁹⁻⁸¹ They are also administered to treat symptoms in disorders such as mastocytosis and local allergic reactions to insect bites.^{26,82,83}

DISORDERS OF THE CENTRAL NERVOUS SYSTEM AND VESTIBULAR DISORDERS

Although they are not the medications of choice, the first-generation H_1 -antihistamines diphenhydramine, doxylamine, and pyrilamine are widely used in the treatment of insomnia,^{84,85} and diphenhydramine, hydroxyzine, cyproheptadine, and promethazine remain in use for perioperative sedation⁸⁶ and for analgesia,⁸⁷ akathisia,⁸⁸ serotonin syndrome, anxiety, and other conditions affecting the central nervous system.²⁶ Dimenhydrinate, diphenhydramine, meclizine, and promethazine block the histaminergic signal from the vestibular nucleus to the vomiting center in the medulla and are thus administered for antiemetic effects⁸⁹ and for the prevention and treatment of motion sickness, vertigo, and related disorders.²⁶ The unfavorable risk:benefit ratio associated with the use of first-generation H_1 -antihistamines to treat disorders of the central nervous system and vestibular disorders has been noted,^{84-86,90} and their use is contraindicated in the treatment of pilots, ships' captains, drivers, and others who must remain alert.

POTENTIAL ADVERSE EFFECTS

The first-generation H_1 -antihistamines, in the usual doses, have potential adverse effects (Table 4). Although some of these medications have been in clinical use for six decades, no long-term safety studies have been published. These older medications have the potential to lead to depression of the central nervous system, have been associated with fatalities in accidental or intentional overdose, and are potential agents of suicide and of homicide of infants.^{51,91-96} Some first-generation H_1 -antihistamines are drugs of abuse.⁹⁷

In contrast, second-generation H_1 -antihistamines are relatively free of adverse effects^{29,30,38,40}

and appear to have relatively few toxic effects in the setting of overdose.⁹⁸⁻¹⁰⁰ The results of a prospective safety study of the use of cetirizine in the treatment of infants¹⁰¹ and an 18-month safety study of cetirizine in young children^{100,102} are available. Additional safety studies in infants, the elderly, and other vulnerable populations and additional long-term safety studies are needed.

CENTRAL NERVOUS SYSTEM TOXICITY

There are few regulations to protect consumers from potential toxic effects on the central nervous system from H₁-antihistamines (Table 4). Indeed, people purchasing over-the-counter first-generation H₁-antihistamines are on their own with regard to reading and comprehending the warnings and the abbreviated list of potential adverse effects on the labels of the packages. Moreover, neither standardized objective testing nor the precise quantification of symptoms related to the central nervous system is required by regulatory agencies during the preclinical and clinical development of new H₁-antihistamines.

People may fail to recognize or may underestimate the adverse effects on the central nervous system resulting from the use of H₁-antihistamines—a situation analogous to that with other sedating medications and with chemicals such as ethanol. Lapses and errors may be documented when patients who do not report symptoms undergo objective testing of the functioning of the central nervous system after ingestion of an H₁-antihistamine.^{29,30}

In the more than 80 randomized, double-blind, placebo-controlled, comparative crossover studies that have been performed, statistically significant and clinically relevant differences between the effects of first-generation and second-generation H₁-antihistamines have been consistently documented.^{29,30,40,103-107} In addition to the PET scans described earlier,^{47,48} multiple tests of sleep latency, evoked potentials, and other electroencephalographic studies, as well as tests of psychomotor performance, have been conducted. The tests range from simple tasks (e.g., critical flicker-fusion tests or digit-symbol substitution) to complex sensorimotor tasks (e.g., simulated flying or driving and actual on-the-road driving).^{29,30,40,103-107} The interpretation of most of these studies is complicated by the fact that they were conducted in healthy young adults rather than in persons with allergic rhinoconjunctivitis or urticaria—conditions that are associated with the daytime seda-

tion due to nocturnal symptoms and sleep deprivation.

Small body mass and the consequent large dose for size of H₁-antihistamine, hepatic or renal dysfunction leading to accumulation in the central nervous system, and the concomitant use of drugs or chemicals such as alcohol that impair the function of the central nervous system may increase the risk of adverse effects, especially with regard to the use of first-generation H₁-antihistamines.^{29,30,105,106} Driving performance is reported to be impaired more by diphenhydramine than by alcohol.¹⁰⁶ In a randomized, placebo-controlled trial with the use of a driving simulator, a 50-mg dose of diphenhydramine impaired driving performance to a greater extent than alcohol; the alcohol dose produced an estimated blood alcohol concentration of 0.1 percent (21.7 mmol per liter).¹⁰⁶ The use of potentially sedating H₁-antihistamines is a particular concern in the treatment of elderly persons¹⁰⁷ and anyone with obvious or subclinical cognitive impairment. This is also true for those with jobs that require constant alertness.¹⁰⁸ First-generation H₁-antihistamines have been implicated in the loss of productivity by workers,¹⁰⁹ injuries,¹¹⁰ and deaths in aviation and traffic accidents.¹¹¹ Military and civilian pilots are prohibited from using these or any other potentially sedating medications before or during flights. Currently, desloratadine, fexofenadine, and loratadine are the only oral H₁-antihistamines for which pilots can receive a waiver for use from the Federal Aviation Administration.

Taking a first-generation H₁-antihistamine at bedtime may result in a hangover (i.e., impaired cognitive and psychomotor performance with or without perceptible sedation) the following morning.¹¹² Clinical tolerance to the sedating effects of first-generation H₁-antihistamines, which has been reported anecdotally but has not consistently been found on objective testing, is an important issue that deserves further exploration.^{113,114} Additional investigations are also needed in people with allergic rhinitis or urticaria, the elderly, elite athletes, and children, about whom there are conflicting data regarding the effects of H₁-antihistamines on performance tests.^{115,116}

CARDIAC TOXICITY

There is an increased risk of cardiac toxic effects from the use of any H₁-antihistamine that prolongs the QT interval in women and in patients with pre-existing organic heart disease (e.g., ischemia or car-

diomyopathy), cardiac arrhythmias (congenital or acquired, including bradycardia), or electrolyte imbalance (i.e., hypokalemia, hypocalcemia, and hypomagnesemia). Also at an increased risk are persons who take overdoses or ingest foods, medications, or herbal formulations that inhibit the elimination of H₁-antihistamines and increase their concentrations in cardiac tissue. In addition, persons concomitantly taking another drug that blocks the I_{Kr} current are at increased risk.^{26,49-51}

During the preclinical and early clinical development of new drugs, regulatory agencies worldwide now aim to identify all new medications, including H₁-antihistamines, that may block the I_{Kr} current, prolong the QT interval, and potentially cause polymorphic ventricular arrhythmias. Second-generation H₁-antihistamines such as cetirizine, desloratadine, fexofenadine, and loratadine appear to be relatively free of cardiac toxic effects as compared with astemizole and terfenadine^{26,49,50,100,101,117} (Table 4). The human ether-a-go-go-related gene (HERG) encodes for the alpha subunit of the I_{Kr} current, and if a medication is implicated in triggering ventricular arrhythmias in a given person, it may now be possible to confirm or rule out causality by performing in vitro tests involving variants of cloned HERG I_{Kr} current.¹¹⁸

OTHER ADVERSE EFFECTS AND CONCERNS

In rare cases, both first- and second-generation H₁-antihistamines are reported to cause adverse effects, the mechanisms for which are incompletely understood.²⁶ These effects include fixed-drug eruption, photosensitivity, urticaria, fever, elevation of liver enzymes and hepatitis, and agranulocytosis. First-generation H₁-antihistamines such as diphenhydramine or doxepin, applied topically to abraded or excoriated skin, may cause systemic adverse effects or contact dermatitis. Topical intranasal or ophthalmic H₁-antihistamines may cause stinging or burning. Azelastine and emedastine may cause dysgeusia (bitter taste). No H₁-antihistamines currently approved for use in the United States are con-

sidered to have carcinogenic or tumor-promoting effects in humans.¹¹⁹ First-generation H₁-antihistamines, particularly those in the phenothiazine class, have been associated with the sudden infant death syndrome, although causality has never been proved. Some oral H₁-antihistamines, including cetirizine and loratadine, are considered relatively safe for use during pregnancy (Food and Drug Administration category B) (Table 4).¹²⁰

FUTURE DIRECTIONS

Through the H₁-receptor, histamine has an important role as a chemical messenger in physiologic responses, including neurotransmission, and in allergic inflammation and immunomodulation. Health care professionals and people who are attempting to make a rational selection from among the large number of H₁-antihistamines available should be aware that many medications in this class have never been optimally investigated. Most H₁-antihistamines have similar efficacy in allergic rhinoconjunctivitis and chronic urticaria; however, there are clinically relevant differences in their pharmacologic characteristics and their safety profiles. Additional within-class comparative studies of their efficacy and safety are needed. To protect people from the toxic effects of H₁-antihistamines on the central nervous system, regulatory agencies should consider developing guidelines for measuring the penetration of the blood-brain barrier and its clinical sequelae, analogous to those being developed to protect people from cardiac toxic effects. In the future, on the basis of improved knowledge of ligand-receptor interactions, clinically advantageous H₁-antihistamines designed with the use of molecular techniques, perhaps with intrinsic H₂-, H₃-, or H₄-antihistamine or antileukotriene properties, may be developed.

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