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The therapeutic versatility of antihistamines:

A comprehensive review

Abstract: Antihistamines are common and readily available medications for primary care patients and those seeking over-the-counter treatments. This article provides an overview of available antihistamines, their mechanisms of action, safety concerns in specific populations, and their therapeutic uses in several common conditions.

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Antihistamines are commonly found and easily obtainable medications for patients treated in the primary care setting as well as those seeking over-the-counter (OTC) treatments. This article provides an overview of available antihistamines, their mechanisms of action, safety concerns in specific populations, and their therapeutic use in the following conditions: allergic reactions and anaphylaxis, gastroesophageal reflux disease, motion sickness and vertigo, insomnia, and anxiety. The role of the primary care provider and pharmacist in antihistamine treatment is also discussed.

Histamine and histamine receptor types and locations

Histamine-mediated function, as a therapeutic target, has its origins in the early 1900s. Histamine is a multifaceted biogenic monoamine and neurotransmitter. Depending on the histamine receptor type and location, histamine can have a multitude of effects on the body.[1] For example, when secreted by immune cells, histamine causes flushing and erythema, pruritus, watery eyes, nasal congestion, and bronchospasm. When attached to gastric parietal cells, histamine induces acid production.[2]

Four subtypes of histamine receptors are found in the body: H1, H2, H3, and H4. (See *Comparison of histamine receptors and available therapies targeting specific receptors*.) The H1 receptor, most ubiquitous of the subtypes, is responsible for mediating histamine-stimulated sensory nerve activation leading to sneezing, pruritus, and edema. H1 receptor activation can also contribute to flushing, tachycardia, and hypotension.[3] They are expressed in neurons of the central nervous system (CNS), epithelial and endothelial cells, heart and smooth muscle cells, neutrophils, eosinophils, monocytes, macrophages, dendritic cells, and B and T lymphocytes.[4] Histamine stimulation of the H1 receptor mediates smooth muscle contraction of the respiratory and gastrointestinal (GI) tracts.

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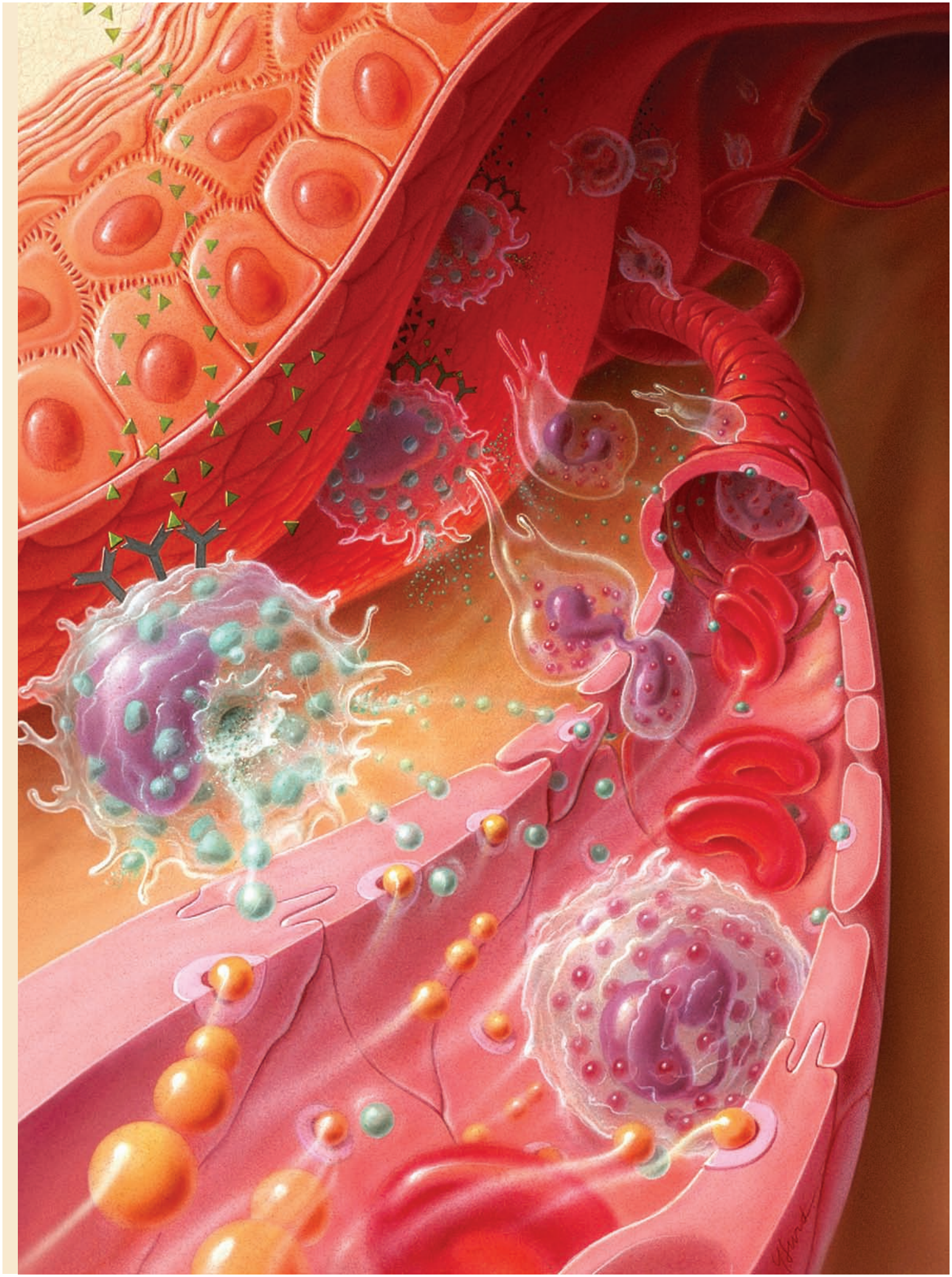
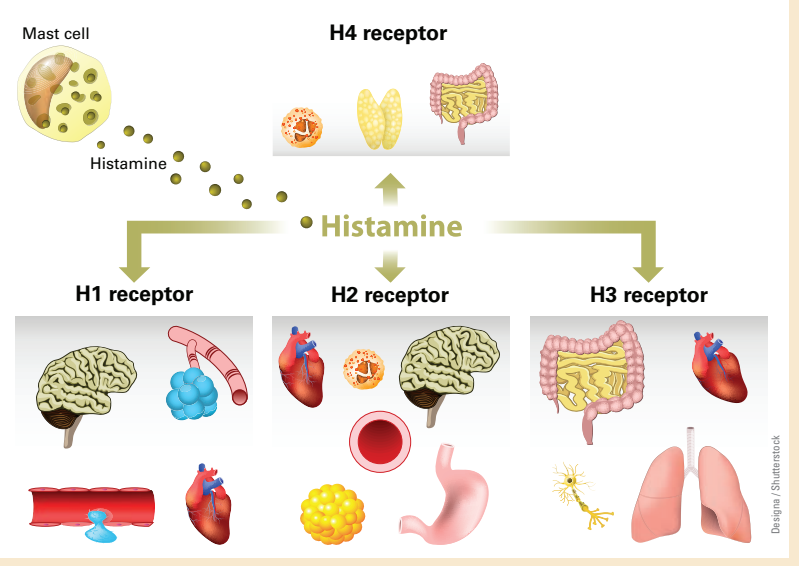
Keywords: allergic rhinitis, anaphylaxis, antihistamine, gastroesophageal reflux disease, generalized anxiety disorder, histamine, insomnia, motion sickness, premedication, urticaria



Histamine receptors



Comparison of histamine receptors and available therapies targeting specific receptors[2]

Distribution/biologic function	Available antihistamines
H1 histamine receptor • Widely distributed in CNS, smooth muscle, heart, immune, epithelial, endothelial, adrenal, and sensory nerve cells. • Mediates postsynaptic effects of histamine in CNS. • Stimulates smooth muscle contraction in GI tract and respiratory tract. • Stimulates sensory nerves causing itching, sneezing, and edema.	**First-generation** • chlorpheniramine • clemastine • diphenhydramine • hydroxyzine **Second-generation** • cetirizine • fexofenadine • levocetirizine • loratadine
H2 histamine receptor • Expressed in gastric mucosa, heart, CNS, immune, airway smooth muscle, endothelial, and uterine cells. • Mediates parietal cell gastric acid secretion. • Relaxes smooth muscles in airway and vasculature. • Increases heart rate and contractility.	• cimetidine • famotidine • ranitidine • nizatidine
H3 histamine receptor • Expressed primarily in the CNS. • Conducts presynaptic regulation of neurotransmitters, such as dopamine, norepinephrine, serotonin, acetylcholine, and histamine. • Relaxes smooth muscles in airway.	**Phase 3 clinical trials** • ciproxifan • pitolisant
H4 histamine receptor • Found in bone marrow, blood, spleen, thymus, lung, GI tract, liver, and CNS. • Mediates calcium function in mast cells. • Mediates mast cell migration.	• alcaftadine

H2 receptors are the second-most abundant histamine receptor type. Although found in the same tissues as H1 receptors (vasculature, airways, and heart), H2 receptors are highly expressed on gastric parietal cells in the stomach.[2] Histamine stimulation leads to increased gastric acid secretion.

The H3 histamine receptor is primarily found in the CNS, with the highest densities in the striatum, hippocampus, and cerebral cortex. H3 receptors are found on both presynaptic and postsynaptic neurons in these areas and are thought to mediate histaminergic activity related to cognition by influencing levels of neurotransmitters such as dopamine, acetylcholine, and serotonin, and even through autoregulation of histamine neurotransmission.[5]

The H4 histamine receptors are located in hematopoietic tissue, such as bone marrow, spleen, blood cells, lungs, and liver, but are also found in neuronal cells.[4] Within these tissues, mast cells, basophils, eosinophils, and T cells have the highest H4 receptor expression. Though still not completely understood, H4-mediated histamine effects include differentiation in hematopoietic cells, mast cell chemotaxis, changes in cytosolic calcium levels, and other immunomodulatory effects.[1,6]

Antihistamine classification and action

Antihistamines, once thought to be pure histamine receptor antagonists, are now understood as inverse agonists of G-protein-coupled histamine receptors.[7] These agents stabilize the inactive conformation, reducing intrinsic histamine activity even beyond a neutralizing blockade. Overall, antihistamines

Comparison of selected first-generation antihistamines and common dosages[24,59,63,66,84*]

Antihistamine	Uses	Oral dosage (adult)	Oral dosage (children)	Effect onset	Elimination half-life
chlorpheniramine	• hay fever • rhinitis • urticaria • food allergy • insect bites	4 mg every 4 to 6 hours (IR) 8 to 16 mg every 8 to 12 hours (ER)	(ages 6 to 11 years) 2 mg every 4 to 6 hours (age 12 years or older) use adult dose	Not available Time to peak = 1 to 4 hours	24 hours
hydroxyzine	• pruritus • urticaria • atopic and contact dermatitis	50 to 100 mg every 6 hours	(younger than age 6 years) 50 mg/day divided (age 6 years or older) 50 to 100 mg/day divided	2 hours	7 to 24 hours
diphenhydramine	• allergic reactions • insomnia • motion sickness • Parkinsonism	25 to 50 mg every 4 to 6 hours	(ages 2 to less than 6 years) 6.25 mg every 4 to 6 hours (ages 6 to 12 years) 12.5 to 25 mg every 4 to 6 hours	1 hour	7 to 12 hours
promethazine	• allergic conditions • preoperative sedation • insomnia • antiemetic	6.25 to 25 mg three times daily	0.125 mg/kg/dose (max 25 mg)	30 minutes	4 to 8 hours
doxylamine	• insomnia • nausea and vomiting of pregnancy	25 mg once daily	(age 12 years or older) 25 mg once daily (ages 2 to younger than 6 years) 2.5 mg every 4 to 6 hours, max 15 mg/24 hours	30 minutes to 8 hours	10 to 12 hours
azelastine • Astelin, Astepro (nasal) • Optivar (ocular)	• allergic and vasomotor rhinitis	(nasal) age 12 years or older, 1 to 2 sprays into each nostril twice daily (ocular) 1 drop into affected eye twice daily	(nasal) (ages 6 months to younger than 12 years) use 1 spray in each nostril twice daily (ocular) age 3 years or older and adolescents same as adult dose	(nasal) 15 to 30 minutes (ocular) 3 minutes	(nasal) 22 to 25 hours (ocular) Dose duration is 8 hours. Plasma levels negligible.

IR = immediate release, ER = extended release
*Common dosages from manufacturers' package inserts—not an exhaustive list

are categorized by the receptor they act on (H1, H2, H3, or H4).

H1-receptor antagonists may be classified by their chemical/pharmacologic structure, which includes, but is not limited to, piperazines, ethanolamines, and phenothiazines. A more clinically useful classification groups H1 antihistamines as first- or second-generation agents, with first-generation agents being significantly more sedating. First-generation antihistamines include chlorpheniramine, diphenhydramine, dimenhydrinate, hydroxyzine, and promethazine, to name a few. (See *Comparison of selected first-generation antihistamines and common dosages.*) Cautious use is recommended with these first-generation agents, especially in older adults, because they also exhibit greater anticholinergic effects and patient psychomotor impairment than the newer second-generation H1 antihistamines.[1,8] The 2019 BEERs

criteria indicate avoidance of first-generation agents in patients over age 65 unless indicated by severe acute allergic reactions.[9]

Second-generation H1 agents include cetirizine, levocetirizine, loratadine, desloratadine, and fexofenadine. (See *Comparison of second-generation antihistamines and common dosages*.) Second-generation antihistamines tend to be more highly selective for peripheral H1 receptors and have minimal anticholinergic properties such as dry mouth, constipation, blurred vision, and urinary retention. These antihistamines are less lipophilic, longer acting, and therefore dosed less frequently. They also have differing affinities to the P-glycoprotein active transport proteins present in the CNS, which may explain differences in sedation levels among and between antihistamine generations. For example, cetirizine is thought by some to be less sedating than diphenhydramine but more sedating than fexofenadine.[3] Studies have shown mixed results on whether cetirizine causes more drowsiness than fexofenadine. Somnolence and drowsiness experienced by patients can vary widely with these antihistamines.[10,11]

H2 antihistamines are drugs that bind to H2 histamine receptors and, like the H1 antihistamines, act as inverse agonists. Gastric acid secretion from the parietal cells can be decreased by H2 antihistamines.[1] Therapeutically, H2 antihistamines such as famotidine, cimetidine, and ranitidine are used for heartburn symptom relief in mild gastroesophageal reflux disease.

Since the 1983 discovery and characterization of the H3 histamine receptor in the brain, research has been progressively highlighting the role of the H3 receptor on wakefulness, attention, learning, and cognition. Animal studies are being done with the H3 antihistamine ciproxifan, and human clinical trials are underway studying the H3 antihistamine pitolisant for potential use in diseases such as narcolepsy, attention-deficit hyperactivity disorder, schizophrenia, dementias, and other illnesses.[12] Pitolisant was approved by the FDA in August 2019 to treat excessive daytime sleepiness in adult patients with narcolepsy.[13]

H4 antihistamines target the most recently discovered H4 histamine receptors found on mast cells, basophils, eosinophils, and T lymphocytes. Due to H4 receptor expression on hematopoietic cells that regulate immune function and inflammatory processes, newly developed H4 antihistamines may enhance future treatment options for allergic conditions and asthma.[14] Alcaftadine, an FDA-approved antihistamine for allergic conjunctivitis, is an example of an H4 antihistamine that also has activity against H1 and H2 receptors. Animal studies have demonstrated initial beneficial effects of H4 antagonists in asthma, dermatitis, pruritus, arthritis, and inflammatory pain and colitis. There are limited reports of findings from clinical trials.[15]

Antihistamine pharmacotherapy for specific disease complaints or indications

Allergic rhinitis. Up to 30% of adults and 40% of children suffer from symptoms of allergic rhinitis. Typical symptoms include sneezing, clear nasal discharge, watery eyes, nasal and ocular pruritus, and fatigue.

Comparison of second-generation antihistamines and common dosages[26,38,80,81]*

Antihistamine	Oral dosage (adult)	Oral dosage (children)	Effect onset	Elimination half-life
loratadine (Claritin, Alavert)	10 mg once daily	(ages 2 to 5 years) 5 mg once daily (age 6 years or older) adult dosing	1 to 3 hours	12 to 15 hours
desloratadine (Clarinex, Rx only)	5 mg once daily	(younger than age 12 years) once-daily dose ranges from 1 mg to 2.5 mg, see product info	1 hour	27 hours
cetirizine (Zyrtec)	5 to 10 mg once daily	(younger than age 6 years) 2.5 mg once daily[81]	1 to 3 hours	7 to 11 hours
levocetirizine (Xyzal)	5 mg once daily in the evening	(ages 6 months to 11 years) 1.25 mg to 2.5 mg[82]	1 hour	8 hours
fexofenadine (Allegra)	60 mg twice daily or 180 mg once daily	(ages 6 months to younger than 2 years) 15 mg twice daily (ages 2 years to younger than 12 years) 30 mg twice daily (age 12 years or older) adult dosing	2 hours	14 hours

*Common dosages from manufacturers' package inserts—not an exhaustive list

Individuals affected with allergies often report diminished quality of life, increased sinus infections, otitis media, asthma exacerbations, sleep apnea, and high financial burdens because of missed work and lost productivity.[16]

Pharmacotherapy for allergic rhinitis is often required and includes first- and second-generation H1 antihistamines, intranasal glucocorticoids (INCS), and leukotriene-receptor antagonists (LTRAs). Intranasal steroids are first-line drugs of choice for allergic rhinitis and are more effective than antihistamines, especially for patients with diminished quality of life due to significant symptom improvement; however, they have a slower onset of action than antihistamines.[17] Histamine suppression with oral antihistamines (OAHs) can occur within hours, whereas intranasal corticosteroids may not reach their full effect for days. The two medication classes can be used concurrently, if needed.

Oral H1 antihistamines are effective for patients with the primary complaints of sneezing and itching.[18] Because the oral first-generation H1 agents cause significant adverse reactions, oral second-generation nonsedating H1 antihistamines are preferred.[19,20] When selecting a second-generation OAH, evidence suggests cetirizine, levocetirizine, loratadine, and fexofenadine share similar efficacy profiles for allergic rhinitis. These agents are readily available OTC. Compared with other agents in this class, cetirizine and levocetirizine may have higher incidence of drowsiness (up to 10% of patients), but are still well below that of older first-generation antihistamines.[21] Uniquely, fexofenadine absorption relies on a transport protein in the gut (organic anion transporting polypeptide). This protein is inhibited by a variety of fruit juices including orange, grapefruit, and apple juice. Consumption of juice within 4 hours of taking fexofenadine can reduce its absorption by up to 40%.[22]

Intranasal antihistamines are another option to treat allergic rhinitis and may be a reasonable alternative to oral agents. Azelastine and olopatadine deliver high concentrations to the nasal mucosa and demonstrated symptom improvement in clinical trials. While exhibiting fewer systemic adverse reactions than oral first-generation agents, these agents can cause bitter taste, headache, somnolence, and nasal burning.[23,24] It is important to consider minimizing use of antihistamines in older adults because of increased incidence of sedation and anticholinergic adverse reactions with this class of medications.[25]

Key points

- Although INCSs are first-line agents for allergic rhinitis, oral second-generation antihistamines can help relieve as well; they exhibit quick onset, good efficacy, and minimal adverse reactions, and are widely available at reasonable prices.
- Nasal antihistamines are acceptable alternatives to OAH agents.
- Combination therapy with INCS can be offered to patients with inadequate response to monotherapy. Combining LTRAs with antihistamines may provide added benefit for patients with the comorbidity of allergic rhinitis and asthma.
- Counsel patients using fexofenadine on the interaction with fruit juice.

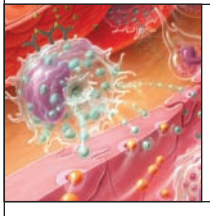
Urticaria. Urticaria is a common condition characterized by hives, flares, and/or wheals resulting from mast cell histamine release. Although in 50% or more of cases the cause is unknown, it can be caused by a hypersensitivity reaction to food, insect stings, infection or febrile illness, or an allergic reaction to chemicals or drugs.[3] Three antihistamines, cetirizine, fexofenadine, and an oral version of olopatadine (currently available in the US only as a nasal spray and eye drop and not indicated for urticaria), were shown to have similar efficacy in reducing histamine-induced flare compared with placebo.[26,27]

Second-generation H1 antihistamines are considered first-line treatment for urticaria in both US and international practice guidelines.[28] Avoid first-generation products in this condition, but if used they should be dosed at bedtime due to sedation.[29] Instead of adding another agent as second-line therapy, both the US and international guidelines recommend high-dose second-generation antihistamines, up to fourfold greater than standard doses. Consider high-dose therapy in patients with unresolved urticaria after 1 to 4 weeks of standard therapy. It is also recommended to dose the medications on a scheduled basis as opposed to an as-needed regimen. The US guidelines consider adding a first-generation agent as viable second-line option, whereas international guidelines state this offers no clinical advantage in the treatment of urticaria. US guidelines also differ by advocating the addition of an H2 antagonist to a second-generation H1 antihistamine because of potential synergistic effects and a favorable safety profile. H2 antagonists are also considered an alternative therapy in the international guidelines.[30]

Key points

- Second-generation H1 antihistamines are first-line therapy for urticaria.
- Second-line therapy for urticaria may include escalating the dose of the initial antihistamine up to fourfold, adding another second-generation antihistamine, or adding an H2 antihistamine.
- Adding a first-generation agent as second-line therapy is a debatable alternative for urticaria.

Anaphylaxis. Anaphylaxis is defined as a severe hypersensitivity reaction characterized by rapidly developing upper or lower airway obstruction, and usually associated with skin and mucosal changes.[31] In an anaphylactic reaction, mast cells and basophils release inflammatory mediators, including histamine, prostaglandins, and leukotrienes, into the surrounding tissue. Histamine release causes pruritus and urticaria, whereas prostaglandins and leukotrienes contribute to bronchoconstriction.[32] Despite theoretical roles of histamine in anaphylaxis, H1 and H2 antihistamines do not contribute to the relief of airway obstruction and should not be substituted for epinephrine as the initial or sole treatment.[33] First-line therapy for anaphylaxis is epinephrine injected I.M. at 0.2 to 0.5 mg every 5 to 15 minutes as needed until improvement occurs in adults. The dose for anaphylaxis in children is 0.01 mg/kg body weight not to exceed 0.3 mg every 5 to 15 minutes. H1 and H2 antihistamines may be used as adjunctive treatment options to relieve the histamine-associated symptoms of anaphylaxis, such as hives, pruritus, flushing, and urticaria not relieved after epinephrine injection.[34] When an oral agent is desired, the low-sedating but fast-acting cetirizine is preferred to diphenhydramine or chlorpheniramine to minimize cognitive impairment.[33]



Consider minimizing use of antihistamines in older adults because of increased incidence of sedation and anticholinergic adverse reactions.

Key point

- Epinephrine is the mainstay for anaphylaxis, and H1 and H2 antihistamines should not be used as the sole first-line therapy for anaphylaxis.

Antihistamine premedication and drug-induced pseudoallergy. Although supporting evidence is limited and empirically derived, antihistamines are commonly used as "premedication" in a variety of clinical situations with the intent to limit adverse reactions. For instance, diphenhydramine is given prior to many anticancer monoclonal antibodies, such as rituximab, trastuzumab, and cetuximab, to prevent or reduce the severity of I.V. infusion reactions.[35] H1 and H2 antihistamines, as monotherapy or dual therapy and usually combined with glucocorticoids, are used to diminish drug-related reactions with oncologic platinum agents, taxanes, anthracyclines, and bleomycin.[35] Diphenhydramine is often given with acetaminophen to prevent blood product–related transfusion reactions, especially if the patient had a previous transfusion reaction.[36] The same can be said for those receiving iodinated contrast media. Mast cells found near neurons are involved in the modulation of pain signals offering a therapeutic opportunity using antihistamines.[37] Premedicating with loratadine is used to decrease the severity of bone pain related to granulocyte colony-stimulating factor use following chemotherapy.[38]

Opiates can induce histamine release from mast cells and pruritus is a common nonallergic adverse reaction of opioid medications, especially when injected.[39] Stimulation of C-fiber neuronal pathways between the skin and the CNS involving H1-mediated histamine receptors and nonhistamine modulators such as serotonin, kinases, cytokines, and others contributes to the problem. Opiates and endogenous endorphins themselves are thought to contribute to pruritus in a more direct fashion because some of the effect can be controlled by opioid antagonists such as naloxone and naltrexone.[40]

Considering mast cell histamine release in response to opiates, it makes sense from a mechanism standpoint to use antihistamines for prevention. Limited data exist to guide choice of which H1 antihistamine to use in prevention or treatment of these conditions. Factors such as effectiveness, dosing frequency, and adverse reactions must be considered. Because better adherence to nonsedating second-generation H1 antihistamines is likely, these drugs may offer better efficacy overall.[40] In a review of controlled studies comparing sedating and nonsedating OAHs in treatment of urticarial conditions, it was found that the newer nonsedating antihistamines such as cetirizine, loratadine, and fexofenadine were either as effective or

Dose comparison of H2 antihistamines in the treatment of GERD[49,82,83*]

H2 antihistamine	Rx dosage for GERD (normal renal function)	Rx dosage for GERD (impaired renal function, CrCl < 50 mL/min)	OTC dosing for heartburn	Approximate equivalent dose
cimetidine (Tagamet)	800 mg BID or 400 mg QID for 12 weeks	300 mg every BID	200 mg once daily	400 mg
famotidine (Pepcid)	20 mg BID for 6 weeks	10 mg BID or 20 mg every 48 hours	10 to 20 mg every 12 hours	20 mg
nizatidine (Axid) (not available in US)	150 mg BID for up to 12 weeks	150 mg once daily or every other day if CrCl is less than 20 mL/min	Not available OTC	150 mg
ranitidine (Zantac)	150 mg BID	150 mg once daily	75 to150 mg up to twice daily	150 mg

*Common dosages from manufacturers' package inserts—not an exhaustive list

more effective than older sedating antihistamines such as chlorpheniramine or hydroxyzine.[41] Because these newer agents do not cross the blood-brain barrier, there is a higher margin of safety when using them at the high end of the dosing range.

Key point

- Second-generation H1 antihistamines as premedication/combined medications may be useful in preventing or minimizing drug-related adverse reactions involving histamine-mediated conditions including pruritus, urticaria, and pain.

Gastroesophageal reflux disease. Gastroesophageal reflux disease (GERD) is a condition where gastric contents are regurgitated into the esophagus, oral cavity, and lungs for a prolonged period of time.[42] Patients with GERD most commonly present with symptoms of heartburn, belching, dysphagia, and chest pain due to reflux. GERD is also an independent risk factor for asthma exacerbations due to aspiration of stomach microparticulate matter and/or esophageal irritation causing vagally mediated bronchoconstriction.[43] Another lung condition associated with GERD is idiopathic pulmonary fibrosis (IPF). Studies of this serious and sometimes fatal disease have shown that GERD is among several possible sources of lung injury in IPF. Smoking, inflammation, and autoimmunity are also linked to IPF. The cause-and-effect nature of IPF and GERD is not fully understood.[44] Chronic GERD may also lead to narrowing of the esophagus and cellular changes of the esophageal lining that could lead to a precancerous condition (Barrett esophagus) or even cancer if left untreated.[45]

Treatment approaches to GERD consist of lifestyle modifications, antacids, H2-receptor antagonists, and proton pump inhibitors (PPI). PPIs have been demonstrated superior to H2-receptor antagonists due to faster healing times for erosive esophagitis and reduced GERD symptoms.[46] Although PPIs have been the mainstay of empiric GERD treatment, there has been an increased awareness of a variety of potential adverse reactions related to chronic PPI dosing, including nutritional deficiencies (magnesium, iron, and B12), increased risk of *Clostridium difficile* colitis, osteoporosis and bone fractures, community-acquired pneumonia, enteric infections, ischemic heart disease, chronic kidney injury, and dementia.[47] Patients on chronic PPIs should be assessed, and dose reduction or discontinuation should be considered when possible.[48] H2-receptor antagonists offer an alternative to PPIs and have been demonstrated an effective treatment for mild-intermittent reflux, which is defined as fewer than two episodes per week.[42] The common OTC and prescription H2-receptor antagonists with efficacy include cimetidine, famotidine, nizatidine, and ranitidine. (See *Dose comparison of H2 antihistamines in the treatment of GERD*.) All have comparative efficacy.

Patients taking H2-receptor antagonists for GERD prevention should take the dose 30 to 60 minutes prior to the largest meal of the day but may also be used at the onset of symptoms. Maintenance therapy may be taken regardless of meals and is recommended as twice-daily therapy for GERD-associated esophagitis for up to 12 weeks.[49] Patients using once-daily dosing or combination H2-antagonist/PPI therapy should take a single H2 antagonist dose in the evening.

The most common adverse reactions of H2-receptor antagonists experienced by patients range anywhere from 1% to 10% and include headaches, dizziness, and diarrhea. Dosing adjustments should be considered in older adults and patients with renal impairment. Drug-drug interactions should be evaluated in patients taking H2-receptor antagonists, especially cimetidine. Cimetidine is the shortest acting in the class (4 to 8 hours). Cimetidine inhibits the cytochrome P450 enzymes 3A4, 2D6, 1A2, and 2C9 and therefore can lead to higher levels of many drugs metabolized by these liver enzymes, including drugs such as warfarin, phenytoin, tricyclic antidepressants, and many others.[50,51]

When treating children for GERD, expert opinion states to try nonpharmacologic approaches for a minimum 2-week trial, such as smaller more frequent meals and elimination of cow's milk from the diet. Based on guideline review of PPIs and H2-receptor antagonists (H2RAs) trials, there is uncertainty whether either class reduces crying/distress, visible regurgitation/vomiting or heartburn in children compared with placebo, if one class is better than the other for reducing the same symptoms, or if the either class leads to significant adverse reactions compared with placebo or each other. Despite inclusive evidence from trials, the guidelines do provide a strong expert opinion that either class can be used for decreasing heartburn type symptoms for a short 4- to 8-week course but not for visible regurgitation or crying/distress. There is also strong expert opinion that for children with efflux-related erosive esophagitis PPIs are preferred but H2RAs can be used if PPIs are either not available or contraindicated.[52] This recommendation is consistent with adult data showing better efficacy with PPIs for this condition. Although randomized control studies reviewed by the working group failed to demonstrate serious adverse events with PPIs or H2RAs, case control studies in children do show an increase in infections, as seen in adult patients. Expert opinion, therefore, does recommend regular assessment of the ongoing need of long-term acid suppression therapy in infants and children with GERD.

Key points

- H2 antihistamines are effective in treating and preventing GERD symptoms and may be a safer choice to consider over long-term PPI therapy.
- Proper counseling on product choice, dosing, adverse reactions, and interactions is important in this commonly relied-upon antihistamine class.
- Although all available H2 antihistamines share only minor differences in onset of action, potency, symptom relief, and adverse reactions, cimetidine should be avoided because of significant drug interactions.

Motion sickness/vertigo. Antihistamines and other medications that exhibit anticholinergic effects are very useful in the treatment and prevention of motion sickness.[53] Motion sickness is a syndrome that may include nausea, vomiting, sweating, dizziness, belching, hyperventilation, and stomach awareness. Hyperventilation may also be present and can contribute to dyspnea, paresthesia, and anxiety.[54] This syndrome can be elicited in individuals experiencing passive motion such as traveling in a boat, vehicle, train, or airplane. Motion sickness can also be caused by the illusion of passive motion such as watching large movie screens or playing video or virtual reality games. It can also be elicited or exacerbated by active head motions during passive movement.[55] Motion sickness is a physiologic response that can occur in healthy people but also may be influenced by various pathologies and involves the visual, proprioceptive, and vestibular systems.[56]

Therapeutic targets for motion sickness consist of the neurotransmitters histamine, acetylcholine, and norepinephrine generally and may also involve gamma aminobutyric acid and serotonin. Medications that suppress conflicting sensory afferent signals in the area of the brain that processes both vestibular and visual signals include antihistamines, anticholinergics, benzodiazepines, and sympathomimetics.[54]

Antihistamines are useful for prevention and treatment of motion sickness and vertigo. They should generally be taken before motion begins as they are less effective in suppressing symptoms when they have begun. Antihistamines useful for motion sickness and vertigo include dimenhydrinate, diphenhydramine, meclizine, chlorpheniramine, and promethazine.[53] First-generation H1 antihistamines tend to be more effective for motion sickness and vertigo because of high lipophilicity and ability to cross the blood-brain barrier. (See *First-generation oral H1 antihistamines useful in prevention and treatment of motion sickness.*) These antihistamines exhibit anticholinergic properties. In vertigo, this effect is key in decreasing stimulation of vestibular muscarinic receptors. Thus, these medications act as vestibular suppressants. In addition to the effects on vertigo, sedating antihistamines inhibit centers in the brain that control vomiting and

First-generation oral H1 antihistamines useful in prevention and treatment of motion sickness

Medication	Oral dosage	Frequency	Available dosage forms†
dimenhydrinate	50 mg	Every 4 hours	Dramamine (OTC), Driminate (OTC), Motion Sickness (OTC)
diphenhydramine	25 to 50 mg	Every 6 hours	Benadryl Allergy (OTC), Banophen (OTC)
meclizine	25 to 50 mg	Every 24 hours	Bonine (OTC), Dramamine Less Drowsy (OTC), Travel Sickness (OTC)
chlorpheniramine*[84]	4 to 12 mg	3 hours prior to motion stimulus	Chlor-Trimeton Allergy (OTC), Allergy Time (OTC), Aller-Chlor (OTC)
promethazine	12.5 to 25 mg	Every 4 hours	Phenadoz (Rx), Phenergan (Rx), Promethagan (Rx)

*off-label use
†not an exhaustive list, OTC and Rx only

help to alleviate nausea related to motion sickness via histamine antagonism and other mechanisms.[57] Educate patients about sedation while taking these medications. Older patients are at high risk for anticholinergic adverse reactions and sedation, so extreme caution should be exercised if they are used. Nonsedating second-generation H1 antihistamines are less likely to cross the blood-brain barrier, and are not effective for vertigo and motion sickness.[1]

Key points

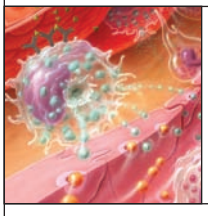
- Nonsedating antihistamines are not useful in the prevention or treatment of motion sickness.
- Antihistamines are more effective in preventing motion sickness when taken 30 to 60 minutes prior to exposure to motion rather than treating it after exposure and symptoms have started.

Insomnia. It is estimated that symptoms of insomnia are experienced by 30% to 50% of the population.[58,59] Patients seeking prescription therapy for sleep disturbances increased threefold between the years of 1999 and 2010.[60] Insomnia can be considered difficulty falling asleep, staying asleep, or getting poor-quality sleep. Common causes include medications, depression, anxiety, stressful events, changes in environment, and poor sleep habits or sleep hygiene. Insomnia can be transient, short-term, or chronic. Because histamine is a neurotransmitter that promotes wakefulness in the CNS and is produced in the hypothalamus, H1 antihistamines have the opposite effect. First-generation antihistamines, such as diphenhydramine and doxylamine, are marketed in many OTC sleep aids. It is important to note that while antihistamines are marketed and often used as sleep aids, current medical guidelines do not recommend their use nor are they generally recommended by sleep specialists. Medications more appropriate for insomnia include benzodiazepines, nonbenzodiazepine agonists such as zolpidem and zaleplon, melatonin agonists, and antidepressants such as doxepin and trazodone.[61,62] Aspects of antihistamines that influence their use in insomnia include they are quickly absorbed, have a sedating effect aiding in sleep onset, have a long half-life that may benefit sleep maintenance, and are readily available.[59] Diphenhydramine is typically dosed at 50 mg at bedtime for insomnia. Doxylamine is taken as 25 mg at bedtime. The relevant adverse reaction profile of these treatments is due to antagonism at the muscarinic acetylcholine receptor; anticholinergic effects include blurred vision, dry mouth, constipation, urinary retention, and mental confusion, especially in older adults.[59] Antihistamines used for insomnia can cause the so-called hangover effect or residual sedation the next day following nighttime administration.[63,64] Antihistamines as a sleep aid should never be used on a long-term basis. Antihistaminic activity occurs in other drug classes as well including the antidepressants doxepin, amitriptyline, and the antipsychotics chlorpromazine, risperidone, and olanzapine. These drugs are occasionally used to treat insomnia.[65]

Key points

- Common antihistamines used for sleep can cause sedation as well as anticholinergic adverse reactions such as dry mouth, constipation, urinary retention, and blurred vision.
- Residual sedation and impairment of cognitive and motor skills can occur the next day following an evening dose of antihistamine for insomnia potentially putting a patient at risk.

Anxiety. Another use of antihistamines is the treatment of anxiety or generalized anxiety disorder (GAD), as limited evidence indicates it may impact anxiety symptoms. Hydroxyzine, available in the hydrochloride (Atarax) and pamoate (Vistaril) salt forms, is a unique H1 antagonist, indicated for relief of anxiety symptoms and tension associated with psychoneurosis and as adjunctive treatment in disease states in which anxiety is manifested.[66,67] Recent guidelines suggest hydroxyzine may reduce symptoms more effectively than placebo, but does not appear to be more effective than other classes of medications listed as first- and second-line GAD treatment (benzodiazepines).[68,69] Hydroxyzine hydrochloride (Atarax) is available as a tablet, whereas hydroxyzine pamoate (Vistaril) is in capsule form. Although the hydrochloride salt form is commonly used to treat urticaria and the pamoate salt is preferred for anxiety due to its lipophilicity, there is no conclusive evidence to indicate one salt form has advantages over the other.[70] Both are considered equivalent in terms of efficacy and adverse reactions according to the manufacturers.[66,67] Due to the paucity of data available, sedative effect, and lack of controlled studies the provider should engage in shared decision-making regarding the choice of this medication for the management of anxiety symptoms.[69]



Residual sedation and impairment of cognitive and motor skills can occur the next day following an evening dose of antihistamine for insomnia.

Key point

- Hydroxyzine in either salt form is not recommended as first- or second-line management in treating the symptoms of anxiety but may have a role in select patients.

Pregnancy-related uses. Antihistamines may be considered when caring for pregnant women in that pregnancy may be complicated by a new or worsening onset of symptoms related to pruritus, allergic rhinitis, and nausea and vomiting. When considering the use of any medication in pregnancy, the practitioner and pharmacist should weigh the risk to benefit of medication use for both the mother and the fetus. Additionally, it is prudent to always check guidelines for medication dosing in pregnancy because guidelines in this population change frequently. Drugs taken during the first trimester may impact structural fetal development and when taken in later trimesters may impact functional defects or growth disorders. Studies have evaluated the use of antihistamines in pregnancy and conclude that H1 antihistamines are considered safe and fail to demonstrate significant risk of fetal malformations.[71-74] First-generation antihistamines that are considered safe include chlorpheniramine, diphenhydramine, and hydroxyzine. Brompheniramine is not recommended during the third trimester related to possible effects on neonates and premature infants.[75] Second-generation antihistamines such as loratadine, cetirizine, and fexofenadine may be considered and in general do not seem to be associated with an increased risk for fetal malformations.[72,74] Study outcomes do not specifically demonstrate an increase in teratogenic effects in humans. Some medications cross the placenta so it is incumbent on the provider to identify those that do and select the preferred medications for that condition.[75]

Key point

- Conservative measures are preferred as first-line approach to pregnancy-induced pruritus, allergic rhinitis, and nausea and vomiting. If conservative measures fail, first-generation antihistamines are preferred over second-generation.

Cautions and contraindications

CNS depression is a hallmark adverse reaction of first-generation antihistamines, which may impair physical and mental abilities. Combining with other CNS depressants, such as alcohol, will enhance adverse reactions. Older adults will be more prone to the anticholinergic and sedative properties. Children are more prone to the CNS excitation effects. This is commonly known as the "paradoxical reaction," whereas adults are more likely to experience CNS depression. Overdose of sedating H1 antihistamines can lead to blockade of multiple receptors including histamine, acetylcholine, serotonin, and norepinephrine receptors as well as sodium and potassium channels. Signs and symptoms that result may include psychosis, hallucinations, seizures, tremor, lethargy, and insomnia.[25]

Contraindications for sedating H1 antihistamines include use in newborn and premature infants,

lactating women, narrow-angle glaucoma, acute asthma exacerbations, concomitant use of monoamine oxidase inhibitors, benign prostatic hypertrophy (BPH), hypersensitivity to the antihistamine, and GI obstruction.[67,76] As BPH is quite common in aging men, it is important to counsel that use of antihistamines, especially sedating H1 antihistamines, can cause urinary retention due to anticholinergic effects in this population.[77] Warnings for cautious use also exist for patients who have respiratory tract diseases such as emphysema and chronic bronchitis. Sedating antihistamines may cause photosensitization, so patients should be encouraged to use sunscreen and protective clothing.

Second-generation nonsedating antihistamines are much less likely to cause severe adverse reactions but in high-dose situations, drowsiness and cardiac arrhythmias can occur.[1] Common adverse reactions patients may experience with normal use include urinary retention, vasodilation, constipation, blurred vision, dry eyes, reduced motor skills, and impaired performance of routine tasks. These effects become more pronounced if alcohol is consumed.

Compared with some other CNS stimulants, the H3 inverse agonist/antagonist antihistamines do not appear to have drug abuse potential.[78] Pitolisant does appear to have dose-dependent CNS-related adverse reactions in clinical trials, worsening insomnia, headache, anxiety, and irritability.[79]

Due to limited published clinical studies with H4 antagonists, it is too early to describe the adverse reaction profile.

Pharmacist and NP role

Antihistamines are easily accessible and commonly used by the public for a variety of conditions. Direct-to-consumer marketing and the vast number of available antihistamine products may confuse patients. Pharmacists, as drug experts, are routinely called on to recommend best treatment advice. NPs, especially those in primary care, assess, diagnose, and recommend treatment plans for patients throughout the lifespan in which antihistamines may be indicated. Gaining extensive knowledge of available antihistamines allows both providers to provide personalized counseling. Expert counseling includes proper drug-drug and drug-disease interaction screening, age-based dosing or avoidance, as well as what to expect in terms of both benefits and adverse reaction profiles.

In terms of antihistamine choice and the pharmacist/NP role in recommending antihistamines for specific conditions, limited clinical guidance exists that provides specific reasons to choose one antihistamine over another beyond those that distinguish between the first-generation sedating antihistamines and the newer second-generation nonsedating antihistamines. Efficacy in some instances appears to be related to the degree of lipophilicity and crossover into the CNS. Because efficacy and adverse reaction profiles appear to be similar within the generations of antihistamines, product choice may be driven by price, availability, and previous experience with a product.

Conclusion

Antihistamines are a large, versatile, and effective class of medications that provide patients with many treatment options for disease states and conditions including but not limited to allergic rhinitis, urticaria, GERD, motion sickness, and anxiety. These common and often self-treatable conditions afford providers myriad opportunities to make a positive impact on patient care. It is likely that continued research will expand the utility of antihistamines as efforts to further understand histamine pharmacology continue to define its role in disease. Keeping up-to-date and informed on this class of medication will continue to be important to practicing pharmacists and NPs and their patients.

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