Antihistamines

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Continuing Education Activity

Antihistamines remain a cornerstone of therapy for allergic and acid-related disorders, yet evolving evidence continues to reshape their clinical use. This activity provides an in-depth review of the pharmacology, therapeutic applications, and safety considerations of H1 and H2 receptor antagonists—agents widely used across multiple care settings. Participants explore current understanding of histamine receptor physiology, mechanisms of action, and distinctions between first- and second-generation antihistamines, with emphasis on clinical decision-making for allergic rhinitis, chronic urticaria, and gastroesophageal reflux disease.

Learners examine updated evidence-based prescribing practices, emerging safety data, including withdrawal symptoms and cardiotoxicity, and the management of special populations such as pediatric, geriatric, and pregnant patients. The course also highlights advances in pharmacogenomics that enable personalized selection of antihistamines and reviews novel treatment options, including biologics and small molecules for refractory urticaria.

Through interactive case studies, expert commentary, and interprofessional discussion, participants strengthen their competence in optimizing therapy, mitigating adverse effects, and enhancing patient education. This activity addresses key knowledge and performance gaps identified in recent clinical reviews, supporting the development of coordinated, patient-centered strategies. By completing this program, healthcare professionals are better equipped to integrate new evidence into practice, improve patient safety, and promote collaborative management of allergy and gastrointestinal disorders.

Objectives:

- Differentiate between first-generation and second-generation H1 antihistamines, including their pharmacokinetic properties, adverse effect profiles, and appropriate clinical uses.
- Apply updated evidence-based guidelines for antihistamine use in allergic rhinitis, urticaria, gastroesophageal reflux disease, and peptic ulcer disease, including appropriate dosing and up-dosing strategies.
- Identify key safety considerations, contraindications, and monitoring requirements for antihistamine therapy, particularly in vulnerable populations such as those with hypertension or chronic diseases, pediatrics, geriatrics, and pregnant patients.

- Implement evidence-based antihistamine therapy by applying pharmacology, clinical use, and safety principles, while examining emerging biologics, small-molecule therapies, pharmacogenomics, and interprofessional collaboration to optimize patient outcomes.

Access free multiple choice questions on this topic.

Indications

Antihistamines are a class of pharmacologic agents that mitigate pathophysiologic manifestations mediated by histamine. Therapeutic targeting is primarily directed toward the histamine H1 and H2 receptor subtypes, which mediate distinct physiologic and pathophysiologic processes. H1 receptor antagonists are indicated for the management of IgE- and non–IgE-mediated allergic disorders, including allergic rhinitis and chronic urticaria, whereas H2 receptor antagonists are used in the suppression of gastric acid secretion in conditions such as gastroesophageal reflux disease and greater suppression of gastric acid control in combination with proton pump inhibitors. H2 receptor antagonists are also helpful in functional dyspepsia.

H1 receptor antagonists are further subclassified into first-generation and second-generation agents. First-generation H1 antagonists are highly lipophilic and readily cross the blood-brain barrier, engaging both central and peripheral H1 receptors and eliciting central nervous system (CNS) effects including sedation, psychomotor impairment, and anticholinergic adverse events. In contrast, second-generation H1 antihistamines exhibit peripheral receptor selectivity and minimal central penetration, resulting in an improved safety profile with reduced sedative potential. Contemporary evidence-based guidelines endorse second-generation H1 antihistamines as first-line therapy for allergic rhinitis and urticaria due to their superior efficacy, favorable tolerability, and lower incidence of central adverse effects.

Food and Drug Administration–Approved Indications

H1 antihistaminesare indicated for allergic rhinitis, conjunctivitis, dermatologic reactions, sinusitis, acute and chronic urticaria, angioedema, atopic dermatitis, adjunct therapy, bronchitis (symptomatic), and motion sickness.

H2 antihistamines (H2 receptor antagonists) are indicated for peptic ulcer disease, gastroesophageal reflux disease, gastritis, and Zollinger-Ellison syndrome.

Recent approvals include dupilumab (an anti-IL-4Rα biologic) and remibrutinib (a Bruton's tyrosine kinase inhibitor) for antihistamine-refractory chronic spontaneous urticaria. Ranitidine was withdrawn due to risks of NDMA contamination. Famotidine and nizatidine remain principal H-2 antagonists. Non–FDA-approved uses include diphenhydramine for insomnia; however, caution is advised, especially in older patients.

H1 antihistamines

- First-generation (sedating): Diphenhydramine, chlorpheniramine, dimenhydrinate, doxylamine, hydroxyzine, and meclizine.
- Second-generation (non-sedating, preferred): Cetirizine, levocetirizine, loratadine, desloratadine, fexofenadine, and azelastine (nasal formulation).[9][10]

H2 antihistamines (H2 receptor antagonists): Cimetidine, famotidine, and nizatidine (FDA-approved and available in the United States); roxatidine (not FDA-approved in the United States, available in some other countries).

A concise summary of FDA-approved antihistamines and their indications is provided below.

First-Generation Systemic Antihistamines

- Diphenhydramine: Adjunct to epinephrine for anaphylaxis; allergic reactions to blood or plasma; other uncomplicated allergic conditions when oral therapy is not feasible; relief of hay fever or upper respiratory allergy symptoms, including runny nose, sneezing, and itchy eyes, nose, or throat; prevention and treatment of motion sickness.
- Chlorpheniramine maleate: Temporary relief of hay fever or other upper respiratory allergy symptoms, such as a runny nose, sneezing, itchy or watery eyes, and an itchy nose or throat.
- Hydroxyzine: Relief of anxiety and tension; management of pruritus associated with chronic urticaria, atopic, or contact dermatoses; and pre- and postoperative sedation.
- Promethazine: Perennial and seasonal allergic rhinitis; prevention and control of motion sickness, nausea, and vomiting; and pre- and postoperative sedation.[11]
- Meclizine: Vertigo associated with vestibular system diseases (eg, Meniere disease) and prevention and treatment of motion sickness.
- Dimenhydrinate: Prevention and treatment of nausea, vomiting, and vertigo associated with motion sickness.
- Doxylamine succinate:Doxylamine succinate, used in combination with pyridoxine to manage nausea and vomiting during pregnancy, is also available over the counter (OTC) as a nighttime sleep aid.[12]

Second-Generation Systemic Antihistamines

- Cetirizine: Relief of perennial and seasonal allergic rhinitis; chronic idiopathic urticaria; and intravenous form for acute urticaria.

- Levocetirizine: Relief of seasonal and perennial allergic rhinitis; uncomplicated skin manifestations of chronic idiopathic urticaria.
- Loratadine: Relief of hay fever or upper respiratory allergy symptoms, including runny nose, sneezing, itchy or watery eyes; chronic idiopathic urticaria.
- Desloratadine: Relief of nasal and non-nasal symptoms of seasonal and perennial allergic rhinitis; chronic idiopathic urticaria.
- Fexofenadine:Relief of seasonal allergic rhinitis symptoms; uncomplicated skin manifestations of chronic idiopathic urticaria.[13]

Intranasal Antihistamines

- Azelastine: Seasonal allergic rhinitis in adults and pediatric patients aged 6 or older.[14]
- Olopatadine: Seasonal allergic rhinitis in adults and pediatric patients aged 6 or older.[15]

Ophthalmic Antihistamines

- Alcaftadine: Prevention of itching associated with allergic conjunctivitis.[16]
- Bepotastine: Itching associated with allergic conjunctivitis.[17]
- Ketotifen: Temporary relief of itchy eyes due to pollen, dander, and grass.[18]
- Olopatadine: Ocular itching associated with allergic conjunctivitis.[19]

Mechanism of Action

Four histamine receptor subtypes (H1, H2, H3, and H4) belong to the superfamily of G protein–coupled receptors. H1 mediates allergic reactions, vasodilation, bronchoconstriction, and pruritus and contributes to central nervous system (CNS) wakefulness. H2 stimulates gastric acid secretion and regulates gastric mucosal blood flow, with additional effects on cardiac and vascular function. H3 acts as an inhibitory autoreceptor and heteroreceptor in the CNS, regulating the release of histamine and other neurotransmitters. H4 modulates the chemotaxis of immune cells and inflammatory responses, particularly in mast cells, eosinophils, and T cells. Histamine released during allergic and inflammatory responses increases vascular permeability and promotes vasodilation, leading to edema. H1 antihistamines act as antagonists at H1 receptors to mitigate these effects, relieving allergy symptoms. First-generation agents penetrate the CNS, antagonizing central H1 receptors and causing sedation and anticholinergic effects. Second-generation antihistamines act peripherally with longer half-lives (12-24 hours versus 4-6 hours) and improved tolerability. Both classes undergo hepatic metabolism through cytochrome P450 pathways. H2 antihistamines block histamine binding on parietal cells, inhibiting the cAMP-PKA pathway that stimulates acid secretion, thus reducing stomach acid.

Pharmacokinetics

Absorption: First-generation systemic antihistamines are rapidly absorbed orally, reaching peak plasma concentrations in 1 to 3 hours, with variable bioavailability due to first-pass metabolism. Second-generation systemic agents are also well absorbed orally and minimally affected by food except for a slight reduction with fexofenadine. Intranasal azelastine is absorbed locally across the nasal mucosa, with low systemic bioavailability (approximately 40%). At the same time, ophthalmic antihistamines such as olopatadine, ketotifen, alcaftadine, and bepotastine exhibit minimal systemic absorption and primarily act locally, with very low plasma concentrations.

Distribution: First-generation systemic antihistamines are highly lipophilic, widely distributed, and cross the blood-brain barrier, resulting in CNS effects and sedation, with moderate-to-high protein binding. Second-generation agents have low CNS penetration, minimal sedation, moderate protein binding, and predominantly peripheral distribution. Intranasal azelastine exhibits limited systemic distribution with negligible CNS penetration, and ophthalmic agents remain confined mainly to ocular tissues with minimal systemic exposure.

Metabolism: First-generation systemic antihistamines undergo hepatic metabolism via CYP2D6, CYP2C9, or CYP1A2, depending on the specific drug (eg, diphenhydramine via CYP2D6 and promethazine via CYP2D6 or CYP1A2). Second-generation agents vary, with loratadine and desloratadine extensively metabolized hepatically via CYP3A4 and CYP2D6, whereas cetirizine, levocetirizine, and fexofenadine undergo minimal hepatic metabolism. Intranasal azelastine is primarily metabolized in the liver via CYP3A4, whereas ophthalmic antihistamines undergo minimal systemic metabolism, with some hepatic metabolism possible if absorbed systemically.

Excretion: First-generation systemic antihistamines are primarily renally excreted, with half-lives ranging from 3 to 12 hours that may be prolonged in older patients or those with hepatic or renal impairment. Second-generation agents exhibit variable excretion pathways. Cetirizine and levocetirizine are mostly renally excreted. In contrast, fexofenadine is predominantly eliminated unchanged via the feces (approximately 80% through biliary excretion), with only minimal renal excretion. Loratadine and desloratadine have half-lives ranging from 8 to 24 hours, which allows for once-daily dosing.

Administration

Available Dosage Forms and Strengths

Oral administration is the standard method, with tablets and liquids being the most common forms of administration. Intranasal sprays are also available for the management of allergic rhinitis. Intravenous and intramuscular formulations are used in hospital settings for acute allergic reactions or dystonic responses to antipsychotics. Emerging nasal sprays, sublingual formulations, and rapid-acting medications address allergic rhinitis and provide rapid symptom relief.

- Diphenhydramine
  - Oral tablets: 25 and 50 mg
  - Fast-melt tablets: 12.5 mg
  - Capsules: 25 and 50 mg
  - Syrup: 12.5 mg/5 mL
  - Injectable solution: 50 mg/mL
- Chlorpheniramine
  - Oral tablets: 4 mg
  - Extended-release tablets: 8 and 12 mg
  - Syrup: 2 mg/5 mL
- Hydroxyzine
  - Tablets: 10, 25, and 50 mg
  - Capsules: 25, 50, and 100 mg
  - Syrup: 10 mg/5 mL
  - Injectable solutions: 25 and 50 mg/mL
- Promethazine
  - Tablets: 12.5, 25, and 50 mg
  - Syrup: 6.25 mg/5 mL
  - Suppositories: 12.5, 25, and 50 mg
  - Injectable solutions: 25 and 50 mg/mL for IV/IM use
- Meclizine
  - Tablets: 12.5, 25, and 32 mg
  - Chewable tablets: 25 mg
- Doxylamine succinate
  - Tablets: 25 mg (for sleep)
  - Combination with pyridoxine: 10 mg/10 mg delayed-release tablet (for nausea/vomiting of pregnancy)

- Cetirizine
    - Tablets: 5 and 10 mg
    - Syrup: 5 mg/5 mL
    - Injectable solution: 10 mg/mL
- Levocetirizine
    - Tablets: 5 mg
    - Oral solution: 5 mg/5 mL
- Loratadine
    - Tablets: 10 mg
    - Syrup: 10 mg/5 mL
    - Oral solution: 10 mg/5 mL
- Desloratadine
    - Tablets: 5 mg
    - Syrup: 5 mg/5 mL
- Fexofenadine
    - Tablets (60 and 180 mg)
    - Oral suspension (30 mg/5 mL)
- Azelastine
    Nasal spray: 0.1% (137 mcg/actuation) and 0.15% (205.5 mcg/actuation).
- Olopatadine
    - Nasal spray: 0.6% (665 mcg/actuation)
    - Ophthalmic solution: Various strengths
- Alcaftadine
    Ophthalmic solution: 0.25%
- Bepotastine
    Ophthalmic solution: 1.5%
- Ketotifen
    Ophthalmic solution: 0.025%

Adult Dosage

- Diphenhydramine
    - Oral administration: 25 to 50 mg every 4 to 6 hours as needed, with a maximum dose of 300 mg/d.
    - Intravenous or intramuscular administration: 25 to 50 mg per dose.
- Chlorpheniramine: 4 mg orally every 4 to 6 hours, not exceeding 24 mg/d.
- Hydroxyzine
    - For anxiety and insomnia, 50 to 100 mg orally 4 times daily
    - For allergic reactions, 25 mg orally 3 to 4 times daily
- Promethazine
    - Oral administration: 12.5 mg before meals and bedtime, or 25 mg at bedtime as required for allergy symptoms.
    - Intravenous or intramuscular administration: 12.5 to 25 mg per dose.
- Meclizine
    - For motion sickness, 25 to 50 mg orally 1 hour before travel
    - For vertigo, 25 to 100 mg/d in divided doses
- Dimenhydrinate: 50 to 100 mg orally every 4 to 6 hours as needed for motion sickness, with a maximum dose of 400 mg/d.
- Doxylamine succinate: 25 mg orally once daily, 30 minutes before bedtime, for insomnia.
- Cetirizine
    - Oral administration: 5 to 10 mg once daily for allergic rhinitis and urticaria
    - Intravenous administration: 10 mg once daily for acute urticaria
- Levocetirizine: 5 mg orally once daily
- Loratadine: 10 mg orally once daily
- Desloratadine: 5 mg orally once daily
- Fexofenadine: 60 mg orally twice daily or 180 mg once daily
- Azelastine nasal spray (0.1%/0.15%)
    - 0.1%: 1 or 2 sprays per nostril twice daily
    - 0.15%: 2 sprays per nostril once daily

- Olopatadine nasal spray (0.6%): 2 sprays per nostril twice daily
- Alcaftadine ophthalmic solution: 1 drop in each eye once daily
- Bepotastine ophthalmic solution: 1 drop in each eye twice daily
- Ketotifen ophthalmic solution: 1 drop in each eye twice daily [23]

Specific Patient Populations

Hepatic impairment: No antihistamine is universally safe in patients with liver disease, as the risks vary by antihistamine type and the severity of the liver condition. Fexofenadine, loratadine, and desloratadine are often considered safer options for long-term use. However, in severe liver conditions, particularly with advanced liver failure, antihistamines can worsen hepatic encephalopathy and should be avoided.[24]

Renal impairment: Among the FDA-approved second-generation antihistamines, desloratadine, fexofenadine, and levocetirizine exhibit varying renal elimination and dosing considerations in patients with kidney impairment. Desloratadine, which is about 47% metabolized and 45% renally excreted, should be used with caution in severe renal impairment. Fexofenadine, with approximately 80% fecal and 11% renal elimination, does not require dose adjustment in renal dysfunction. Levocetirizine undergoes about 13% hepatic and 85% renal elimination, necessitating dose adjustments based on creatinine clearance. Levocetirizine is contraindicated in patients with a creatinine clearance of less than 10 mL/min.[25] The official product labeling should always be checked before dose adjustments are made in pediatrics, geriatrics, or in patients with hepatic or renal impairment.

Pregnancy considerations: As mentioned above, doxylamine is preferred for nausea and vomiting during pregnancy in combination with pyridoxine. Doxylamine should be used only if the benefits outweigh the risks, with loratadine and cetirizine generally preferred alternatives.

Breastfeeding considerations: Most modern antihistamines are likely compatible with breastfeeding, though product labels often caution due to limited safety data. The FDA recommends prioritizing drugs commonly used by women of reproductive age or with established safety information. Exclusive breastfeeding is advised for 6 months, but unfounded safety concerns contribute to early cessation. Studies of 9 antihistamines—cetirizine, chlorpheniramine, clemastine, ebastine, epinastine, loratadine, promethazine, terfenadine, and triprolidine—show relative infant doses below 5%, indicating minimal risk. Assessment should consider drug potency, half-life, maternal dosing, breastfeeding patterns, and infant age or organ immaturity. First-generation sedating antihistamines may cause drowsiness or irritability and are generally second-line. Second-generation non-sedating antihistamines, such as loratadine and cetirizine, have low milk transfer rates and favorable adverse effect profiles, making them a preferred choice for breastfeeding women. However, the use should only be considered after meticulous risk-benefit evaluation.[26]

Pediatric patients: Second-generation antihistamines are generally preferred due to their safety and efficacy. First-generation antihistamines should be avoided in children younger than 6 due to risks of respiratory depression and arrhythmias. [27]

Geriatric patients: Older adults are at increased risk of adverse effects from anticholinergic and sedating first-generation antihistamines. The 2024 American Geriatric Society Beers Criteria classifies these agents as potentially inappropriate, recommending the use of second-generation antihistamines with dose adjustments based on renal function.

Adverse Effects

- H1 first-generation antihistamines: Common adverse effects include sedation, cognitive impairment, and anticholinergic adverse effects such as dry mouth, urinary retention, constipation, and blurred vision. Dizziness, tinnitus, and delirium may occur at high doses. The increased risk of falls and cognitive decline in older adults has led to restrictions on the use of first-generation antihistamines, particularly diphenhydramine. QT prolongation and cardiotoxicity are concerns in at-risk populations.

- H1 second-generation antihistamines: These agents generally cause minimal sedation. However, 2025 FDA warnings cite severe pruritus upon abrupt cetirizine or levocetirizine cessation after long-term use; a gradual taper is recommended.[U.S. Food & Drug. FDA requires warning about rare but severe itching after stopping long-term use of oral allergy medicines cetirizine or levocetirizine (Zyrtec, Xyzal, and other trade names)]
- H2 antihistamines: Generally well tolerated, but cimetidine can cause gynecomastia, galactorrhea, and clinically significant CYP450-mediated drug interactions. Rare adverse effects include gastrointestinal disturbances and dizziness; ranitidine was withdrawn due to carcinogen risk.

Cardiotoxicity, particularly QT prolongation, requires electrocardiogram (ECG) monitoring in patients receiving high-risk drugs or those with predisposing conditions.

Drug-Drug Interactions

- Benzodiazepines, opioids, or alcohol: These drugs produce additive CNS and respiratory depression when used with antihistamines, increasing sedation, hypoventilation, and fall risk. Combination should generally be avoided; if necessary, the lowest doses should be used to closely monitor respiration and consciousness.

- Tricyclic antidepressants, antipsychotics, or antimuscarinics: Concomitant use can enhance anticholinergic and sedative effects, leading to dry mouth, constipation, urinary retention, delirium, and possible angle-closure glaucoma. Polypharmacy should be avoided, particularly in older adults, and monitoring for cognitive impairment or urinary retention is recommended.

- Monoamine oxidase inhibitors: Co-administration can intensify anticholinergic and CNS depressant effects, resulting in excessive sedation, confusion, or cardiovascular instability. Concomitant use should be avoided or reserved for situations with close monitoring.

- CYP3A4 inhibitors (eg, ketoconazole, itraconazole, clarithromycin, or ritonavir): These drugs reduce the metabolism of loratadine, desloratadine, and azelastine, increasing systemic exposure and the risk of sedation or cardiac effects. Potent inhibitors should be avoided, or lower doses of antihistamines should be used with careful monitoring.

- CYP2D6 inhibitors (eg, fluoxetine, paroxetine, and quinidine): These medications can reduce the clearance of diphenhydramine and promethazine, leading to enhanced sedation and anticholinergic toxicity. Dose adjustment or selection of non-CYP2D6 substrates is recommended.

- QT-prolonging drugs (eg, class I/III antiarrhythmics, macrolides, fluoroquinolones, certain antipsychotics, or methadone): Co-administration may lead to additive QT prolongation and torsades de pointes, particularly with promethazine. ECG monitoring and electrolyte correction are advisable if used together.

- Fruit juices (eg, apple, orange, or grapefruit) and polyvalent cation antacids (eg, aluminum or magnesium): These can reduce the intestinal absorption of fexofenadine by inhibiting the organic anion transporter or chelation, thereby decreasing its efficacy. Doses should be separated by at least 2 hours, or juice should be avoided around the time of administration.

- P-glycoprotein inhibitors (eg, erythromycin, ketoconazole, or verapamil): These drugs can increase fexofenadine concentrations by reducing its efflux, thereby increasing systemic exposure and risk of adverse effects.

- Cholinesterase inhibitors (eg, donepezil, rivastigmine, or galantamine): First-generation antihistamines may counteract cognitive benefits and worsen confusion due to their central antimuscarinic actions. Second-generation, non-sedating drugs should be preferred in such patients.

- Sedating psychotropics (eg, mirtazapine, trazodone, or some antipsychotics): Concomitant use enhances sedation and orthostatic hypotension, predisposing to falls and impaired concentration. The combination should be limited, and non-sedating antihistamines should be considered for effective allergy control.

Contraindications

QT prolongation or concurrent use of other QT-prolonging drugs requires caution. During pregnancy and lactation, use should be limited to situations where the benefits outweigh the risks; loratadine and cetirizine are preferred. Renal and hepatic impairment necessitate careful use and dose adjustment.

Comorbidities such as hypertension, cardiovascular disease, urinary retention, and glaucoma also warrant caution, as first-generation antihistamines with anticholinergic properties may exacerbate these conditions.

Box Warning (Promethazine)

Promethazine injection should not be used in pediatric patients younger than 2 because of the risk of fatal respiratory depression. Cases of respiratory depression, including deaths, have been reported in children younger than 2. Caution should be exercised when administering promethazine hydrochloride injection to pediatric patients aged 2 or older. Severe tissue injury can result from intravenous administration, leading to significant chemical irritation and tissue damage. Irritation and damage can result from perivascular extravasation, unintended intra-arterial injection, and intraneuronal or perineuronal infiltration. Adverse reactions include burning, pain, thrombophlebitis, tissue necrosis, and gangrene. In some cases, surgical intervention, including fasciotomy, skin graft, and amputation, has been required. Because of the risks associated with intravenous injection, the preferred method of administering promethazine injection is deep intramuscular injection. Subcutaneous injection is contraindicated.

Monitoring

Monitoring and Safety Considerations

Older patients should be carefully monitored for signs of anticholinergic toxicity, including confusion, urinary retention, dry mouth, and constipation, as well as increased fall risk due to sedation or orthostatic hypotension. Regular cognitive and functional assessments can help detect

early adverse effects. ECG monitoring is recommended for patients at risk for QTc prolongation, particularly those with pre-existing cardiac disease, electrolyte imbalances, or concurrent use of other QTc-prolonging medications.

Pharmacogenomics

Genetic variations have a significant impact on the metabolism of antihistamines and the clinical response. Polymorphisms in *CYP2D6* and *CYP3A4* may alter plasma concentrations and efficacy, whereas *ABCB1* variants influence CNS penetration and sedation risk of second-generation antihistamines. Pharmacogenomic-guided dosing could enhance safety and therapeutic outcomes by personalizing drug selection and strategies.

Drug Interactions

Clinicians should remain alert to clinically significant interactions. Cimetidine, a known inhibitor of multiple CYP enzymes, can increase systemic levels and toxicity of medications such as benzodiazepines and warfarin. Co-administration with other QTc-prolonging agents raises the risk of arrhythmias. Additionally, antihistamines may counteract the effects of cholinesterase inhibitors in patients with dementia and can potentiate CNS depression when combined with alcohol, opioids, or sedatives.

Patient Counseling

Comprehensive patient education is essential. Patients should receive guidance on appropriate treatment duration, be aware of withdrawal-related itching that may occur with long-term antihistamine discontinuation, and avoid overlapping sedating agents and alcohol. Patients should also be encouraged to report new or worsening symptoms, review all OTC products for hidden antihistamine content, and maintain adherence to prescribed regimens for safe and effective symptom control.

Toxicity

Signs and Symptoms of Overdose

First-generation antihistamine overdose can cause CNS depression, paradoxical excitation, respiratory failure, anticholinergic toxicity, and arrhythmias. The Centers for Disease Control and Prevention analyzed data from the State Unintentional Drug Overdose Reporting System across 43 US states and the District of Columbia to evaluate the role of antihistamines, particularly first-generation H1 antihistamines, in fatal overdoses between 2019 and 2020. Deaths involving antihistamines alone were rare (<0.1%), highlighting that synergistic toxicity with other sedatives, particularly opioids, was the major contributor to fatality. The findings showed that approximately 15% of all overdose deaths during the study period were antihistamine-positive, and about 4% were antihistamine-involved (listed as a cause of death). Diphenhydramine accounted for most cases, representing the predominant agent among first-generation H1 antihistamines detected.

The co-involvement of opioids, especially illicitly manufactured fentanyls, was strikingly high, with over 80% of antihistamine-involved deaths also involving opioids. The sedative and anticholinergic properties of first-generation H1 antagonists, such as diphenhydramine, can potentiate opioid-induced respiratory depression and increase fatal overdose risk. The severity of poisoning from second-generation antihistamines appears to be low among children and considerably lower than poisoning caused by first-generation antihistamines.

Management of Overdose

Treatment of an antihistamine overdose is supportive with activated charcoal and monitoring. Consult a medical toxicologist in case of a complex overdose and contact the poison control center for the latest recommendations.

Enhancing Healthcare Team Outcomes

Second-generation antihistamines provide superior symptom control and improved safety compared to first-generation agents. Fexofenadine exhibits minimal sedation, whereas cetirizine and levocetirizine may cause mild drowsiness in some patients. Rupatadine, which combines histamine and platelet-activating factor antagonist properties, is currently under review for approval in the United States. The 2024 consensus guidelines support updosing of second-generation antihistamines for refractory urticaria.

Public Health and Over-the-Counter Misuse

Increased misuse of diphenhydramine among youth, linked to social media *Benadryl challenges*, precipitated FDA warnings and pharmacist-led awareness campaigns.[Social Media Challenge: Encouraging Adolescents to Engage in Dangerous Over-the-Counter Drug Use] OTC availability does not equate to safety, especially for children, older, and cardiac-compromised individuals.

Controversies and Emerging Areas

Combination H1/H2 blockade offers limited additional benefits in refractory urticaria, except in select cases of severe disease. No proven antiviral benefit of antihistamines against COVID-19, despite early in vitro results. Biologic agents and oral small molecules are transforming the management of chronic urticaria.

Research Advances

H4 receptor antagonists show promising anti-inflammatory activity against pruritus and atopic dermatitis but have yet to secure regulatory approval. The clinical efficacy of diamine oxidase supplementation for histamine intolerance remains inconclusive.

Emerging Histamine Receptors and Future Therapeutics

Beyond the classical H1 and H2 receptors, research on H3 and H4 antagonists is advancing rapidly. H4 receptors, expressed on mast cells, dendritic cells, and T cells, modulate inflammatory cell chemotaxis and vascular permeability. Selective H4 antagonists reduce inflammation and vascular leakage in preclinical models of asthma and dermatitis; however, as of 2025, no H3 or H4 receptor antagonists have received clinical approval.

Antihistamines Beyond Allergy: Repurposing and Novel Indications

Recent studies demonstrate that some second-generation H1 antihistamines may modulate the tumor microenvironment, inhibit histamine-mediated immunosuppression, and reduce cancer cell proliferation.. These insights open possibilities for repurposing antihistamines as adjunctive oncology therapeutics, and ongoing clinical trials are exploring these applications.

Pharmacogenomics and Personalized Medicine

Genetic variation in CYP450 enzymes, notably CYP2D6 and CYP3A4, as well as transporters such as ABCB1, influences the metabolism, tissue distribution, efficacy, and adverse effect profiles of antihistamines. Although pharmacogenomic testing is not yet routine, emerging evidence supports its future role in guiding personalized dosing, particularly for patients with chronic urticaria who are resistant to high-dose antihistamines. Polymorphisms in the histamine H1 receptor gene also correlate with response variability.

Antihistamines and COVID-19

In vitro studies indicate that certain H1 antihistamines, such as acrivastine, interfere with SARS-CoV-2 spike protein binding and viral entry by targeting H1 receptors, thereby reducing pseudoviral infection in cell and mouse models. However, current clinical trial data do not support the use of antihistamines for the treatment or prevention of COVID-19 in humans.

Novel Biologic and Small-Molecule Agents for Refractory Urticaria

Management of chronic spontaneous urticaria has advanced with the FDA approvals of biologics, such as dupilumab, which targets the IL-4/IL-13 pathways, and remibrutinib, an oral Bruton's tyrosine kinase inhibitor that modulates mast cell function. In early clinical trials, monoclonal antibodies targeting the mast cell growth factor receptor cKIT (e.g., barzolvolimab, briquilimab) have shown promising disease-modifying activity. These developments broaden the options for patients who are antihistamine-refractory.

Clinical Trials and Future Directions

Phase III trials are ongoing for novel biologics, histamine receptor antagonists, and therapy adjuncts targeting allergic and inflammatory conditions. Innovations in drug delivery, including nanocarriers, transdermal patches, and microneedles, aim to enhance bioavailability and

adherence. The rise of biomarker-driven personalized medicine informs trial design and patient selection, optimizing outcomes.

Effective allergy and antihistamine management relies on interprofessional collaboration. The clinician evaluates the patient, establishes the diagnosis, and selects appropriate antihistamine therapy. Advanced Practice Providers, including nurse practitioners and physician associates, conduct patient assessments, initiate or adjust therapy within protocol, and reinforce adherence. Nurses administer medications, monitor for immediate adverse reactions, provide patient counseling, and document responses in the medical record. Pharmacists ensure correct drug selection, verify dosing, identify potential drug interactions, counsel on adverse effects, and provide guidance on safe use during special conditions such as pregnancy or breastfeeding. Immunologists contribute expertise in complex or refractory allergic cases, advising on immunotherapy or advanced diagnostic testing. Patient education underpins all roles, ensuring patients understand the purpose of their medication, dosing schedules, potential adverse effects, and when to seek medical attention, thereby improving adherence and clinical outcomes. Collaborative review and decision-making ensure clinicians, pharmacists, nurses, and other professionals contribute their expertise to optimize antihistamine therapy. This approach reduces adverse effects, ensures appropriate dosing, and improves patient adherence and clinical outcomes. An interprofessional team approach and effective communication with patients and other healthcare professionals, including clinicians, advanced practice providers, pharmacists, and nurses, are crucial to minimizing potential adverse effects and enhancing patient outcomes related to antihistamine therapy.

Review Questions

- Access free multiple choice questions on this topic.
- Comment on this article.

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