

HISTAMINE ANTAGONIST

A histamine antagonist is an agent that inhibits action of histamine via histamine receptors.

Clinical effects

Histamines will produce increased vascular permeability causing fluid to escape from capillaries into the tissues, which leads to the classic symptoms of an allergic reaction – a runny nose and watery eyes.

Antihistamines suppress the histamine-induced wheal (swelling) and flare (vasodilation) response by blocking the binding of histamine to its receptors on nerves, vascular smooth muscle, glandular cells, endothelium, and mast cells. They effectively exert competitive antagonism of histamine for H₁-receptors. Itching and sneezing are suppressed by antihistamine blockade of H₁-receptors on nasal sensory nerves. Antihistamines are commonly used for relief of allergies caused by intolerances of proteins.

- **H₁ receptor antagonist**

H₁ antihistamines are used as treatment for symptoms of allergies such as runny nose. Allergies are caused by an excessive type 1 hypersensitivity response of the body to allergens, such as pollen released by plants. An allergic reaction, which if severe enough can lead to anaphylaxis, results in excessive release of histamines and other mediators by the body. Other uses of H₁ antihistamines help with symptoms of local inflammation that results from various conditions, such as insect stings, even if there is no allergic reaction.

Examples:

Clemastine	Chlorpheniramine
Diphenhydramine (Benadryl)	Levocetirizine
Doxylamine (most commonly used as an OTC sedative)	Olopatadine (used locally)
Loratadine	Quetiapine (antipsychotic)
Desloratadine	Meclizine (most commonly used as an antiemetic)
Fexofenadine	Dimenhydrinate (most commonly used as an antiemetic)
Pheniramine	embramine
Cetirizine	dimethindene
Ebastine	dexchlorpheniramine
Promethazine	

Indications

H₁-antihistamines are clinically used in the treatment of histamine-mediated allergic conditions. include:

Allergic rhinitis	Diarrhea
Allergic conjunctivitis	Pruritus (atopic dermatitis, insect bites)
Allergic dermatological conditions (contact dermatitis)	Anaphylactic or anaphylactoid reactions—adjunct only
Urticaria	Nausea and vomiting (first-generation H ₁ -antihistamines)
Angioedema	Sedation (first-generation H ₁ -antihistamines)
Promethazine	

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Adverse drug reactions

Adverse drug reactions are most commonly associated with the first-generation H₁-antihistamines. This is due to their relative lack of selectivity for the H₁-receptor.

The most common adverse effect is sedation; this "side-effect" is utilized in many OTC sleeping-aid preparations. Other common adverse effects in first-generation H₁-antihistamines include dizziness, tinnitus, blurred vision, euphoria, uncoordination, anxiety, insomnia, tremor, nausea and vomiting, constipation, diarrhea, dry mouth, and dry cough. Infrequent adverse effects include urinary retention, palpitations, hypotension, headache, hallucination, and psychosis.

The newer second-generation H₁-antihistamines are far more selective for peripheral histamine H₁-receptors and have a far better tolerability profile compared to the first-generation agents. The most common adverse effects noted for second-generation agents include drowsiness, fatigue, headache, nausea and dry mouth.

First-generation (non-selective, classical)

These are the oldest H₁-antihistaminergic drugs and are relatively inexpensive and widely available. They are effective in the relief of allergic symptoms, but are typically moderately to highly potent muscarinic acetylcholine receptor (anticholinergic) antagonists as well. These agents also commonly have action at α -adrenergic receptors and/or 5-HT receptors. This lack of receptor selectivity is the basis of the poor tolerability profile of some of these agents, especially compared with the second-generation H₁-antihistamines. Patient response and occurrence of adverse drug reactions vary greatly between classes and between agents within classes.

Class	Description	Examples
Ethylenediamines	Ethylenediamines were the first group of clinically effective H ₁ -antihistamines developed.	<ul style="list-style-type: none">• Mepyramine (pyrilamine)• Antazoline
Ethanolamines	Diphenhydramine was the prototypical agent in this group. Significant anticholinergic adverse effects, as well as sedation, are observed in this group but the incidence of gastrointestinal adverse effects is relatively low.	<ul style="list-style-type: none">• Diphenhydramine• Carbinoxamine• Doxylamine• Clemastine• Dimenhydrinate
Alkylamines	Alkylamines are considered to have relatively fewer sedative and gastrointestinal adverse effects, but relatively greater incidence of paradoxical central nervous system (CNS) stimulation.	<ul style="list-style-type: none">• Pheniramine• Chlorphenamine (chlorpheniramine)• Dexchlorpheniramine• Brompheniramine• Triprolidine• Dimetindene
Piperazines	These compounds are structurally-related to the ethylenediamines and the ethanolamines, and produce significant anticholinergic adverse effects. Compounds from this group are often used for motion sickness, vertigo, nausea, and vomiting. The second-generation H ₁ -antihistamine cetirizine also belongs to this chemical group.	<ul style="list-style-type: none">• Cyclizine• Chlorcyclizine• Hydroxyzine• Meclizine

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Tricyclics and Tetracyclics	These compounds differ from the phenothiazine antipsychotics in the ring-substitution and chain characteristics. They are also structurally-related to the tricyclic antidepressants (and tetracyclics), explaining the H1-antihistaminergic adverse effects of those three drug classes and also the poor tolerability profile of tricyclic H1-antihistamines. The second-generation H1-antihistamine loratadine was derived from compounds in this group.	<ul style="list-style-type: none">• Promethazine• Alimemazine (trimeprazine)• Cyproheptadine• Azatadine• Ketotifen
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Second-generation and third-generation (selective, non-sedating)

Second-generation

Second generation H1-antihistamines are newer drugs that are much more selective for peripheral H1 receptors in preference to the central nervous system histaminergic and cholinergic receptors. This selectivity significantly reduces the occurrence of adverse drug reactions compared with first-generation agents, while still providing effective relief of allergic conditions. The reason for their reduction in sedative effects is due to the fact that most of these compounds are zwitterionic at physiological pH (around pH 7.4). Being zwitterionic in nature means that the compounds are very polar and therefore will not cross the blood brain barrier and so will act mainly outside the central nervous system leaving these antihistamines with little or no sedative qualities.

Systemic:

- ✓ Acrivastine
- ✓ Astemizole
- ✓ Cetirizine
- ✓ Ebastine
- ✓ Bilastine
- ✓ Bepotastine
- ✓ Ketotifen
- ✓ Loratadine
- ✓ Mizolastine
- ✓ Terfenadine

Topical:

- ✓ Azelastine
- ✓ Levocabastine
- ✓ Olopatadine

Third-generation

Systemic:

- ✓ Levocetirizine
- ✓ Desloratadine
- ✓ Fexofenadine

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- **H₂ receptor antagonist**

The H₂ receptor antagonists are a class of drugs used to block the action of histamine on parietal cells in the stomach, decreasing the production of acid by these cells. H₂ antagonists are used in the treatment of dyspepsia, Examples: **cimetidine, ranitidine, famotidine, nizatidine, Roxatidine** and **Lafutidine**.

Clinical use

H₂-antagonists are used by clinicians in the treatment of acid-related Gastrointestinal conditions. To be specific, these indications may include:

- ✓ Peptic ulcer disease (PUD)
- ✓ Gastroesophageal reflux disease (GERD/GORD)
- ✓ Dyspepsia
- ✓ Prevention of stress ulcer (a specific indication of ranitidine)

People that suffer from infrequent heartburn may take either antacids or H₂-receptor antagonists for treatment. The H₂-antagonists offer several advantages over antacids, including longer duration of action (6–10 hours vs 1–2 hours for antacids), greater efficacy, and ability to be used prophylactically before meals to reduce the chance of heartburn occurring. Proton pump inhibitors, however, are the preferred treatment for erosive esophagitis since they have been shown to promote healing better than H₂-antagonists.

Adverse effects

H₂ antagonists are, in general, well-tolerated, except for **cimetidine**, wherein all of the following adverse drug reactions (ADRs) are common. Infrequent ADRs include hypotension. Rare ADRs include: headache, tiredness, dizziness, confusion, diarrhea, constipation, and rash. In addition, cimetidine may also cause gynecomastia in males, loss of libido, and impotence, which are reversible upon discontinuation.

Drug interactions

With regard to pharmacokinetics, **cimetidine** in particular interferes with some of the body's mechanisms of drug metabolism and elimination through the liver cytochrome P450 pathway. To be specific, cimetidine is an inhibitor of the P450 enzymes CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4. By reducing the metabolism of drugs through these enzymes, cimetidine may increase their serum concentrations to toxic levels. Many drugs are affected, including warfarin, theophylline, phenytoin, lidocaine, quinidine, propranolol, labetalol, methadone, metoprolol, tricyclic antidepressants, some benzodiazepines, dihydropyridine calcium channel blockers, sulfonyleureas, metronidazole, and some recreational drugs such as ethanol and methylenedioxymethamphetamine.

Ranitidine is not as potent a CYP metabolism inhibitor as cimetidine, although it still shares several of the latter's interactions (such as with warfarin, theophylline, phenytoin, metoprolol, and midazolam). **Famotidine** has negligible effect on the CYP system, and appears to have no significant interactions.