## Reviews/Evaluations

# Antihistamines, H1 Receptor Antagonist Class Review

## Background

Histamine was first identified in 1910 and recognized in the 1920s as a major pathogenic mediator of allergic disorders. Histamine receptor antagonist was introduced in 1937, and from 1942 to 1981, more than 40 compounds have reached the market.(1) Antihistamines have been categorized over the years as first, second or third-generation classes. Although very effective, the first-generation antihistamines such as diphenhydramine, chlorpheniramine, clemastine, hydroxyzine or triprolidine do cause marked sedation, central nervous system (CNS) dysfunction and anticholinergic adverse effects, resulting in performance or cognitive function impairment and therapy non-adherence. The second-generation antihistamines, included astemizole, terfenadine, loratadine, cetirizine, and fexofenadine, have been known as the "nonsedating antihistamines," were developed in the 1980s to minimize these side effects. Terfenadine and astemizole were removed from the market due to serious cardiovascular events related to torsade de pointes. The newest antihistamine agent, desloratadine, an active metabolite of loratadine has been categorized under the third-generation antihistamines and is currently the only agent in this class.(2)

These agents have been used clinically to treat various allergic disorders such as seasonal or perennial allergic rhinitis and chronic urticaria. The annual sales of prescription antihistamines for treatment of allergic rhinitis, a high-prevalence disease in the United States have exceeded $3 billion reported in 1997.(3) The "nonsedating antihistamines," specifically loratadine and fexofenadine have been identified as the most commonly prescribed drugs in the treatment of allergic rhinitis in a managed care population.(4)

During the last 2 years, the direct-to-consumer advertising from pharmaceutical industry, have had significant impact on utilization of this drug class. Last year, a FDA advisory panel made the recommendation that fexofenadine, loratadine and cetirizine be made available over-the-counter.(5)

## Pharmacology

Antihistamines are reversible competitive antagonists of histamine at $H_1$ receptor sites. They do not prevent histamine release or bind to the histamine that has already been released. The $H_1$ receptor blockade results in decreased vascular permeability, reduction of pruritus and relaxation of smooth muscle in the respiratory and gastrointestinal tracts.(1) They are clinically efficacious for alleviating symptoms of allergic rhinitis that are attributed to the early-phase reaction, such as rhinorrhea, pruritus, and sneezing. However, they are less efficacious in controlling nasal congestion, which is related to the late-phase reaction.

Second or third generation antihistamines have entered the market that demonstrated improved peripheral $H_1$ receptor selectivity, decreased lipophilicity in order to minimize CNS side effects and additional antiallergic properties apart from histamine antagonism. They interfere with mediator release from mast cells either by inhibiting calcium ion influx across mast cell/basophil plasma membrane or by inhibiting intracellular calcium ion release within the cells. They may also inhibit the late-phase allergic reaction by acting on leukotrienes or prostaglandins, or by producing an anti-platelet activating factor effect.(1) Desloratadine has shown in vitro studies to have direct effects on inflammatory mediators such as inhibition of the intracellular adhesion molecule-1 (ICAM-1) expression by nasal epithelial cells, thus demonstrating anti-inflammatory and immunomodulatory activities distinct from the second-generation antihistamines. This additional property may explain why desloratadine can

significantly improve nasal congestion in several double-blind, placebo-controlled studies.(6)

## Indications

First-generation antihistamines are approved for hypersensitivity reactions, type 1 that includes perennial or seasonal allergic rhinitis, vasomotor rhinitis, allergic conjunctivitis, urticaria. These agents can also be used as adjunctive anaphylactic therapy. Diphenhydramine, hydroxyzine, and promethazine, have other indications in addition to the use in allergic reactions. Diphenhydramine is used as anti-tussive, sleep aid, anti-parkinsonism or for motion sickness. Hydroxyzine can be used as pre-medication or following general anesthesia sedative, adjunctive analgesic in preoperative or prepartum, and anti-emetic agent. Promethazine is used for motion sickness, pre- and postoperative or obstetric sedation, or adjunctive analgesia for postoperative pain.(7) (See Table 1.)

**Table 1. FDA Approved Indications for First-Generation Antihistamines (7,8,9)**

| Drug Name | FDA Approved Age for Use | Indications* | Pregnancy Category |
|---|---|---|---|
| Azatadine (Optimine) | ≥ 12 years old | PAR, SAR, CU | B |
| Azelastine | ≥ 3 years old | PAR, SAR, VR, AC | C |
| Brompheniramine (Dimetane) | > 6 years old | AR, HR Type 1 | C |
| Chlorpheniramine (Chlor-Trimeton) | > 2 years old | AR | B |
| Clemastine (Tavist) | > 6 years old | PAR, SAR, CU | B |
| Cyproheptadine (Periactin) | ≥ 2 years old | PAR, SAR, CU | B |
| Dexchlorpheniramine (Polaramine) | ≥ 2 years old | PAR, SAR, CU | B |
| Hydroxyzine (Atarax, Vistaril) | Can be given < 6 years old | Pruritus, Sedation, Analgesia, Anti-emetic | C |
| Promethazine (Phenergan) | > 2 years old | HR Type 1, Sedation, Motion sickness, Analgesia | C |
| Tripelennamine (PBZ) | > 1 month old | PAR, SAR, CU | B |

*PAR = perennial allergic rhinitis, SAR = seasonal allergic rhinitis, CU = chronic urticaria, HR Type 1 = hypersensitivity reaction type 1, AR = allergic rhinitis, VMR = vasomotor rhinitis, AC = allergic conjunctivitis

Second- and third-generation antihistamines are only indicated in certain allergic disorders. (See Table 2.)

**Table 2. FDA Approved Indications for Second- and Third-Generation Antihistamines (7,8)**

| Drug Name | Age Restriction | Indications* | Pregnancy Category |
|---|---|---|---|
| Cetirizine (Zyrtec) | ≥ 2 years old | PAR, SAR, CIU | B |

| | | | |
|---|---|---|---|
| Fexofenadine (Allegra) | ≥ 6 years old | SAR, CIU | C |
| Loratadine (Claritin) | ≥ 2 years old | SAR, CIU | B |
| Desloratadine (Clarinex) | ≥ 12 years old | PAR, SAR, CIU | C |
| *PAR = perennial allergic rhinitis, SAR = seasonal allergic rhinitis, CIU = chronic idiopathic urticaria | | | |

## Contraindications / Precautions

*First-generation antihistamines*(7,8,9): Hypersensitivity to specific or structurally related antihistamines; newborn or premature infants; nursing mothers; narrow-angle glaucoma; stenosing peptic ulcer; symptomatic prostatic hypertrophy; bladder neck obstruction; pyloroduodenal obstruction; lower respiratory tract symptoms (including asthma); monoamine oxidase inhibitor (MAOI) use; elderly, debilitated patients (cyproheptadine).

*Second- and third-generation antihistamines*(7,8): Hypersensitivity to specific or structurally related antihistamines. Desloratadine is contraindicated in those with loratadine hypersensitivity, and cetirizine is contraindicated in those with a known hypersensitivity to hydroxyzine.

## Adverse effects

*First-generation antihistamines*(7,8):
1. Allergic - photosensitivity, anaphylactic shock, drug rash, dermatitis
2. Cardiovascular - postural hypotension, palpitations, reflex tachycardia, venous thrombosis at injection site (IV promethazine)
3. Central nervous system (CNS) - drowsiness, sedation, dizziness, disturbed coordination, fatigue, confusion, extrapyramidal reactions may occur with high doses
4. Gastrointestinal - epigastric distress, anorexia, bitter taste (nasal spray)
5. Genitourinary - urinary frequency, dysuria, urinary retention
6. Respiratory - chest tightness, wheezing, dry mouth, nose and throat, thickening of bronchial secretions, epistaxis and nasal burning (nasal spray)

*Second- and third-generation antihistamines*(7,8):
1. Allergic - photosensitivity, anaphylactic shock, drug rash, dermatitis
2. Central nervous system* - somnolence/ drowsiness, headache, fatigue, sedation
3. Respiratory** - dry mouth, nose and throat (cetirizine, loratadine)
4. Gastrointestinal** - nausea, vomiting, abdominal distress (cetirizine, fexofenadine)

*CNS side effects are comparable to placebo in clinical studies with the exception of cetirizine that has shown significantly more sedation, somnolence and drowsiness than placebo, and may be similar to the first-generation antihistamines.
**Respiratory and gastrointestinal side effects are less frequent than the first-generation antihistamines.

## Drug Interactions

| **Table 3. Antihistamines Drug Interactions (7,8,9)** | | |
|---|---|---|
| **Precipitant Drug** | **Object Drug** | **Effect** |

| | | |
|---|---|---|
| Antihistamines | alcohol, CNS depressants | Additive CNS depressant effects; may be less likely with second- or third-generation agents |
| **Azole Antifungals**: fluconazole, itraconazole, keoconazole, miconazole | loratadine, desloratadine | Increase object drug plasma level |
| Cimetadine | loratadine | Increase object drug plasma level |
| Levodopa | promethazine | Decrease effect of levodopa |
| **Macrolide Antibiotics**: azithromycin, clarithromycin, erythromycin | loratadine, desloratadine | Increase object drug plasma level |
| **MAOIs**: phenelzine, isocarboxazid, tranylcypromine | first-generation antihistamines | May prolong and intensify anticholingergic and sedative effects of antihistamines; may result in hypotension and extrapyramidal side effects |
| **Protease Inhibitors**: ritonavir, indinavir, saquinavir, nelfinavir | first-generation antihistamines, loratadine | Increase object drug plasma level |
| **Serotonin Reuptatke Inhibitors (SSRIs):** fluoxetine, fluvoxamine, nefazodone, paroxetine, sertraline | first-generation antihistamines | Increase object drug plasma level |

## Dosing and Administration

**Table 4. Antihistamines Dosing and Administration (7,8,9)**

| Drug name | Usual dose (Adult) (a) | Renal dysfunction(a) | Hepatic dysfunction | Route of administration(b) |
|---|---|---|---|---|
| Azelastine | PO: 1-2 mg q12h<br>IN: 2 sprays bid<br>OP: 1 gtt bid | Not required | Not required | PO, IN, OP |
| Brompheniramine | 4 mg q4-6h | No information | No information | PO, IV, IM, SC |
| Chlorpheniramine | 4 mg q4-6h | Not required | No information | PO, IV, IM, SC |
| Clemastine | 1 mg q12h | No information | No information | PO |
| Cyproheptadine | 4 mg q8h | No information | Dose reduction may be | PO |

| | | | | |
|---|---|---|---|---|
| | | | needed | |
| Dexchlorpheniramine | 2 mg q4-6h | Not required | No information | PO |
| Hydroxyzine | 25-100 mg q4-8h | No information | Increase dosing interval to q12-24h | PO, IM |
| Promethazine | 12.5-25 mg q6-24h | Not required | No information | PO, IM, IV |
| Tripelennamine | 25-50 mg q4-6h | No information | No information | PO |
| Cetirizine | 5 or 10 mg qd | CrCl < 11-31 ml/min: 5 mg qd | 5 mg qd | PO |
| Desloratadine | 5 mg qd | 5 mg qod | 5 mg qod | PO |
| Fexofenadine | 60 mg bid | CrCl < 80 ml/min: 60 mg qd | Not required | PO |
| Loratadine | 10 mg qd | CrCl < 30 ml/min: 10 mg qod | 10 mg qod | PO |

(a) qd = daily, qod = every other day, gtt = drop
(b) PO = oral, IM = intramuscularly, IV = intravenous, SC = subcutaneous, IN = intranasal, OP = ophthalmic

## Clinical Efficacy

Efficacy of antihistamines in the treatment of allergic conditions such allergic rhinitis or urticaria has mostly been based on subjective evaluation of clinical symptom relief by investigators and patients in clinical trials. Objective measures such as measuring the time to onset and duration of suppression of the wheal and flare skin reaction after an epicutaneous histamine injection or allergen skin testing have been questioned in its clinical value. The allergic response in these tests mimics the early phase of the allergic response without the mast cell degranulation and the subsequent release of mediators from mast cells, neurons, and other cells along with the influx of granulocytes; thus no full allergic response in these tests.(10)

**Table 5. Efficacy of Antihistamines**

| Study/ Indication (a) | Study Design | Sample Size | Treatment Groups(b) | Duration (days) | Efficacy assessment | Results (b) |
|---|---|---|---|---|---|---|
| Meltzer, et al.(11) SAR | Double blind, randomized, spring allergy season, outdoor parks | 279 | Cet 10 mg qd<br>Lor 10 mg qd<br>Pla qd | 2 | Major & total symptom complex scores, patient assessment | Cet > Lor = Pla |

| | | | | | | |
|---|---|---|---|---|---|---|
| Prenner, et al.(12) SAR | Double blind, randomized, 2-phase, crossover treatment of non-responders | 659 | Fex 60 mg bid Lor 10 mg qd | Phase 1: 14 Phase 2: 16 | Physician and patient rated total symptom severity | Phase 1 - Lor > Fex (pts); Lor = Fex (MD)Phase 2 - Lor = Fex (pts & MD) |
| Howarth, et al.(13) SAR | Double blind, randomized | 722 | Fex 120 mg qd Fex 180 mg qd Cet 10 mg qd Pla qd | 14 | Total symptom score | Fex 120 = Fex 180 = Cet > Pla |
| Day, et al.(14) SAR | Double blind, randomized, allergen exposure unit | 202 | Cet 10 mg Lor 10 mg qd Placebo qd | 2 | Total & major symptom complex scores, | Cet > Lor = Pla |
| Druce, et al. (15) AR | Double blind, randomized | 338 | Bro 12 mg bid Lor 10 mg qd Pla bid | 7 | Investigator and subject global symptom | Bro > Lor > Pla |
| Berger et al. (16) SAR | Double blind, randomized | 1070 | Lor 10 mg qd plus Bec 2 sprays per nostril bid Aze 2 sprays per nostril bid | 7 | Physician assessment of need for additional anti-rhinitis meds, patient global symptom | Aze = Lor + Bec |
| Sienra-Monge, et al. (17) PAR | Double blind, randomized, longitudinal | 80 (children 2-6 years old) | Cet 0.2 mg/kg qd Lor 0.2 mg/kg qd | 28 | Histamine skin tests, eosinophil counts, investigator and subject global symptom | Cet > Lor (wheal response) Cet = Lor (eosinophil count) Cet = Lor (symptom) |
| Breneman (18) CIU | Double blind, randomized, allergy practice settings | 188 | Cet 10 mg qd Hyd 25 mg tid Pla | 28 | Investigator and patient rated symptoms | Cet = Hyd > Pla |
| Monroe, et al.(19) CIU | Double blind, randomized | 203 | Lor 10 mg qd Hyd 25 tid | 12 | Physician and patient rated symptoms | Lor = Hyd > Pla |

(a) PAR = perennial allergic rhinitis, SAR = seasonal allergic rhinitis, AR = allergic rhinitis, CIU = chronic idiosyncratic urticaria
(b) Cet = cetirizine, Lor = loratadine, Pla = placebo, Fex = fexofenadine, Bro = brompheniramine, Bec = beclomethasone, Aze = Azelastine, Hyd = hydroxyzine, MD = physicians, pts = patients

There are limited clinical trials that compare the efficacy and safety of first-generation antihistamines with second- or third-generation antihistamines. For the treatment of chronic idiosyncratic urticaria, two clinical studies included above have shown that cetirizine or loratadine is comparable to hydroxyzine in controlling symptoms based on patients and investigators evaluations. The frequency of somnolence and dry mouth was lower with cetirizine and loratadine than hydroxyzine in these two studies.(18,19)

In the management of allergic rhinitis, various clinical trials included here have shown comparable efficacy in controlling symptoms among the second-generation antihistamines based on patients and investigators assessment. Currently, there are no studies available that compare the clinical efficacy of desloratadine to other antihistamines. Given the variable treatment period of these studies, it is difficult to compare the overall efficacy between these agents. All oral antihistamines are effective for the sneezing, rhinorrhea, nasal or ocular pruritus, postnasal discharge or conjunctivitis of allergic rhinitis, but are minimally effective on nasal congestions.(20,21,22) Azelastine, the only topical antihistamine approved in the United States has shown to provide additional potential benefits include the abilities to affect nasal congestion in some patients and to attenuate both the late- and the early-phase reactions.(16,20)

Desloratadine have shown mixed results in providing nasal decongestant effect in patients with seasonal allergic rhinitis in randomized, double blind, placebo-controlled studies. Four studies reported no statistically significant difference between desloratadine and placebo in nasal congestion reduction while two studies reported significant nasal congestion reduction with desloratadine over placebo in patients with seasonal allergic rhinitis. These six studies had variable treatment period (7 days to 4 weeks) and sample size (47 to 1532 patients). All evaluated clinical efficacy based on patients' assessment of symptom. One of these studies also reported patients taking pseudoephedrine 240 mg qd showed a significant reduction in nasal stuffiness when compared with desloratadine 5 mg qd.(23)

The current practice has been adding a decongestant to an antihistamine in treating allergic rhinitis, if nasal obstruction is present.(1) All the second-generation antihistamines are available as a combination product with an oral decongestant to reduce nasal congestion in allergic rhinitis. Desloratadine currently is not available as a combination with an oral decongestant. It will be interesting to see if its manufacturer will introduce the combination product line with an oral decongestant in the future, if it truly has its claim in reducing nasal congestion.

## Cost Comparison

**Table 6. Cost of Monthly Supply of Second-Generation Antihistamines (24)**

| Drug | Dose | Monthly Cost ($) |
|---|---|---|
| Cetirizine | 10 mg qd | 60-75 |
| Fexofenadine | 60 mg bid | 70-100 |
| Loratadine | 10 mg qd | 75-100 |
| Desloratadine | 5 mg qd | 60-75 |

## Summary

The decision to choose one antihistamine agent over another for the treatment of allergic rhinitis or chronic idiosyncratic urticaria should be based on cost, dosing frequency, availability, contraindications and adverse effects. All of the first-generation antihistamines are available in generic with reduced costs and many are available over-the-counter in comparison to the second- and third-generation antihistamines. However, with a FDA advisory panel recommending second-generation antihistamines switching to over-the-counter status and with the coming of these products going off patent and having generic availability, the costs difference between first-generation and second-generation antihistamines may be less of an issue in the near future.

The second- and third-generation antihistamines have demonstrated clinical efficacy without the sedating effects characteristic of first-generation antihistamines. The feeling of sedation and drowsiness is very subjective, perceived by the affected individual only and may not be evident to clinical examiners. A person may not feel sleepy or drowsy, but can still be found significantly impaired on cognitive function actions. Such a person is at risk for occurrences of motor vehicle accidents or traumatic work-related injuries.(25) A study evaluated the effects of fexofenadine, diphenhydramine, alcohol, and placebo on driving performance found drowsiness was a poor predictor of impairment and subjects performed similarly when taking fexofenadine or placebo. Subjects that took diphenhydramine had the poorest driving performance, followed by alcohol.(26)

The Joint Task Force on Practice Parameters in Allergy, Asthma, and Immunology in its updated executive summary on diagnosis and management of rhinitis noted that given the sedation and performance impairment from first-generation antihistamines: risks to individuals and society, second-generation antihistamines that are associated with less risk or no risk for these side effects should usually be considered before sedating antihistamines for treatment of allergic rhinitis. This is even mandated in some segments of the transportation industry. In addition, the advocate for "AM/PM" antihistamine therapy, dosing daytime non-sedating second generation antihistamine, followed by a first-generation (and cheaper) antihistamine in the evening to reduce cost and avoid daytime sedation and performance impairment is ineffective strategy because considerable daytime sedation still occurs.(27)

The $H_1$ receptor antagonist class review is provided here. This class of drugs will likely continue to significantly impact the prescribing practices and account for large amount of prescription costs in our health care system as the prevalence of allergic disorders such as allergic rhinitis remains high.

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