Antihistamines, Minimally Sedating Review

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Antihistamines, Minimally Sedating Review

FDA-Approved Indications

Drug	Manufacturer	Indication(s)
acrivastine/pseudoephedrine (Semprex D®)[1]	UCB	- Relief of symptoms associated with seasonal allergic rhinitis (AR) in adults and children 12 years of age and older
cetirizine (Zyrtec® OTC)[23]	generic McNeil Consumer	- Temporary relief of symptoms due to hay fever or other respiratory allergies (sneezing; runny nose; itchy, watery eyes; itchy throat or nose) in adults and children two years of age and older - Relief of symptoms associated with seasonal AR due to allergens such as ragweed, grass and tree pollens in adults and children two years of age and older - Relief of symptoms associated with perennial AR due to allergens such as dust mites, animal dander and molds in adults and children six months of age and older - Treatment of uncomplicated skin manifestations of chronic idiopathic urticaria (CIU) in adults and children six months of age and older
cetirizine/pseudoephedrine (Zyrtec-D® OTC 12 Hour)[4]	generic McNeil Consumer	- Relief of nasal and non-nasal symptoms associated with seasonal or perennial AR in adults and children 12 years of age and older
desloratadine (Clarinex®, Clarinex Redi-Tabs®)[5]	Schering	- Relief of nasal and non-nasal symptoms of seasonal AR in patients two years of age and older - Relief of nasal and non-nasal symptoms of perennial AR in patients six months of age and older - Symptomatic relief of pruritus, reduction in the number of hives, and size of hives, in patients with CIU six months of age and older
desloratatine/pseudoephedrine (Clarinex-D® 12-Hour)[6]	Schering	- Relief of nasal and non-nasal symptoms of seasonal AR including nasal congestion in adults and children 12 years of age and older
desloratadine/ pseudoephedrine (Clarinex-D® 24-Hour)[7]	Schering	- Relief of nasal and non-nasal symptoms of seasonal AR including nasal congestion in patients 12 years of age and older
fexofenadine (Allegra®)[8]	generic	- Relief of symptoms of seasonal AR in patients six years of age and older - Treatment of uncomplicated skin manifestations of CIU in patients six years of age and older
fexofenadine (Allegra® Oral Suspension)	Sanofi-Aventis	- Relief of symptoms of seasonal AR in children ages two to 11 years - Treatment of uncomplicated skin manifestations of CIU in children six months to 11 years of age

FDA-Approved Indications (continued)

Drug	Manufacturer	Indication(s)
fexofenadine orally disintegrating tablet (Allegra ODT®)[9]	Sanofi-Aventis	- Treatment of symptoms related to seasonal AR and CIU in children ages six to 11 years of age
fexofenadine/pseudoephedrine (Allegra-D® 12 Hour)[10]	generic	- Relief of symptoms associated with seasonal AR in adults and children 12 years of age and older
fexofenadine/pseudoephedrine (Allegra-D® 24 Hour)[11]	Sanofi-Aventis	- Relief of symptoms associated with seasonal AR in adults and children 12 years of age and older
levocetirizine (Xyzal®)[12]	Sanofi-Aventis	- Relief of symptoms associated with seasonal AR in adults and children two years of age and older - Relief of symptoms associated with perennial AR in adults and children six months of age and older - Treatment of uncomplicated skin manifestations of CIU in adults and children six months of age and older
loratadine OTC (Alavert®, Claritin®, generic)[13]	generic	- Temporary relief of symptoms due to hay fever or other respiratory allergies in adults and children six years and older (syrup for ages two years and older)
loratadine ODT OTC (Alavert Quick Dissolving, Claritin Redi-Tabs, generic)[14]	generic	- Temporary relief of symptoms due to hay fever or other respiratory allergies in adults and children six years and older
loratadine OTC (Children's Claritin® Chewable)	Schering-Plough Healthcare Products	- Temporary relief of symptoms due to hay fever or other respiratory allergies in patients two years and older
loratadine/pseudoephedrine OTC (Alavert Allergy & Sinus, Claritin-D® 12 Hour, generic)[15]	generic	- Temporary relief of symptoms due to hay fever or other respiratory allergies in adults and children 12 years and older
loratadine/pseudoephedrine OTC (Claritin-D 24 Hour, generic)[16]	generic	- Temporary relief of symptoms due to hay fever or other respiratory allergies in adults and children 12 years and older

The combination antihistamine/pseudoephedrine products have an additional indication of temporary reduction in swelling of nasal passages and temporary restoration of freer breathing through the nose.[17]

Overview

Allergic Rhinitis (AR)

Rhinitis is defined as inflammation of the membranes lining the nose and is characterized by nasal congestion, rhinorrhea, sneezing, itching of the nose, and/or postnasal drainage. Although rhinitis may be caused by non-allergic (infectious, hormonal, occupational) factors, allergic rhinitis (AR) is the most common form.[18]

There are two common forms of AR: seasonal allergic rhinitis and perennial allergic rhinitis. Seasonal allergic rhinitis (SAR) occurs when plant pollens are at their highest levels in spring, summer, and early fall. Perennial allergic rhinitis (PAR) occurs year-round and is usually caused by home or workplace pollutants. Individuals may have one or both forms of allergic rhinitis. As

a matter of fact, the 2008 updated guidelines from the American Academy of Allergy, Asthma and Immunology (AAAAI) on the diagnosis and management of rhinitis introduces for the first time the classification of episodic allergic rhinitis.[19] Episodic allergic rhinitis is neither seasonal nor perennial but is triggered by sporadic exposure to inhalant aeroallergens.

Estimates from 2003 suggest 10 to 30 percent of adults and up to 40 percent of children experience allergic rhinitis.[20] Direct costs, including physician visits and medications, associated with allergic rhinitis are $1.16 to $4.5 billion per year.[21] Indirect costs, which include lost productivity, approach $3.8 billion per year. AR is the number one cause for work absenteeism. In children, approximately two million school days per year are lost due to allergic rhinitis.[22]

Allergic rhinitis is characterized by inflammation of the nasal mucous membranes due to an allergic response. As a result, most patients with AR experience nasal congestion. However, nasal congestion is also present in common chronic rhinosinusitis. An important distinguishing feature of AR is concomitant clear rhinorrhea and frequent sneezing. Ocular irritation or burning is nearly exclusive to AR. Mucoid postnasal discharge in the posterior pharynx is also indicative of AR.

Avoidance of allergens is fundamental to the management of AR. An effort to alter the home and work environments is crucial, and in perennial allergies (dust and mold), allergen avoidance is the cornerstone of treatment. Patients with seasonal allergies (trees, weeds, etc.) experience difficulty avoiding common allergens during certain times each year. Initiation of treatment one to two weeks preceding onset of a budding season will often result in more effective reduction of symptoms.

Intranasal corticosteroids and oral antihistamines are the primary treatment options for AR.[23] Alternative agents, such as leukotriene modifiers, cromolyn sodium, and antihistamine nasal sprays may be appropriate in some patients.

Intranasal corticosteroids are most effective in controlling symptoms of AR. The agents are highly effective in relieving nasal allergy symptoms (congestion, sneezing, runny nose).

Oral antihistamines are particularly effective in severe rhinorrhea, sneezing, pruritus, and conjunctivitis associated with AR, although less effective for nasal congestion. The usefulness of first-generation (sedating) antihistamines is reduced because the agents may produce significant sedation, performance impairment, and/or anticholinergic effects. Consequently, the second-generation (minimally sedating) antihistamines, associated with a lower incidence of side effects, are generally considered before sedating antihistamines, especially in adults and school-age children. For patients with more significant nasal congestion, several of the minimally sedating antihistamines are available as combination dosage forms with pseudoephedrine, a decongestant.

The 2008 updated guidelines from the American Academy of Allergy, Asthma and Immunology (AAAAI) discuss several recent developments in the management of AR.[24] The guidelines recognize the importance of pulmonary function testing, particularly in patients with co-morbidities including asthma, sinusitis, and sleep apnea. Advantages and disadvantages of single and combination therapies of medications released in the last ten years are discussed. Consideration of using a rhinitis action plan is advocated. Charts are included to assist physicians in assessing symptoms severity and establishing a treatment plan. The role of each therapeutic class is summarized and oral antihistamines are considered most effective for treatment for seasonal and perennial AR when used continuously. Due to rapid onset of action,

antihistamines, dosed when needed, can be an appropriate treatment option for episodic AR. Oral antihistamines are as effective as intranasal corticosteroids for the treatment of ocular symptoms, but are less effective than intranasal corticosteroids for nasal congestion and allergic rhinitis symptoms. Second generation antihistamines are preferred over the first generation agents due to more favorable side effect profile (less sedation and fewer anticholinergic side effects) as well as a safer option for use in pregnancy. Oral decongestants are not recommended in children younger than six years of age.

Chronic Idiopathic Urticaria (CIU)

Urticaria is defined as the transient appearance of elevated, erythematous pruritic wheals (hives). The condition commonly affects the trunk and extremities, sparing the palms and soles, but may affect any epidermal or mucosal surface. Urticaria is predominantly due to release of mast cell mediators, mainly histamine, as a result of an ongoing immediate hypersensitivity reaction. Chronic idiopathic urticaria (CIU), where disease activity continues for more than six weeks, is common, comprising 70 percent of all cases.[25] Chronic idiopathic urticaria can occur at any age; however, CIU is most common in young adults. In most patients, the lesions clear spontaneously or respond rapidly to treatment with antihistamines; however some patients continue to have lesions for prolonged periods. Of patients with CIU and angioedema, 75 percent have symptoms for longer than one year, 50 percent have symptoms for longer than five years, and 20 percent have symptoms for decades.

When attempts at identifying the cause of urticaria have failed (thus eliminating the possibility of reducing exposure), the patient requires treatment. Minimally-sedating H_1-receptor antagonists represent the basic therapy for all CIU patients. Older sedating antihistamines, such as hydroxyzine and diphenhydramine, may be indicated if symptoms are severe, are associated with angioedema, and if the patient is anxious and/or disturbed at night.[26] If clinical response is not adequate, H_2-inhibitory drugs may be added to the antihistamine.[27] Other agents reported to be beneficial in some cases include doxepin, a tricyclic antidepressant with anti-H_1 and anti-H_2 properties, and the leukotriene receptor antagonists. If all agents fail, a course of glucocorticoids may be required. Third-line therapies involving immunosuppressive agents are only appropriate for patients with CIU refractory to other measures.[28]

All of the minimally sedating antihistamines are effective treatments for CIU.[29,30,31,32] Little comparative data regarding the use of these agents in CIU is available, and therefore the focus of the review is AR.

Pharmacology

Minimally sedating antihistamines are selective, competitive, peripherally-acting histamine H_1-receptor antagonists with little or no central or autonomic nervous system activity.[33,34]

Pharmacokinetics[35]

Drug (Metabolite)	t_{max} (hr)	$t_{1/2}$ (hr)	Protein Binding (%)	Excretion (%)	Onset of Action (hr)	Duration of Action (hr)
acrivastine (Semprex-D)[36] (1 metabolite)	1.14 ± 0.23	1.9 ± 0.3 (3.8 ± 1.4 0)	50 ± 2.0	Urine: 84 Feces: 13	1	12
cetirizine (Zyrtec)[37,38] (1 metabolite)	1	8.3	93	Urine: 50	0.3-1	≥ 24
desloratadine (Clarinex)[39,40] (6 metabolites)	3	27	82-87	--	1	24
fexofenadine (Allegra)[41,42] (no metabolites)	2.6	14.4	60–70	Urine: 11 Feces: 80	1	>12
fexofenadine ODT (Allegra ODT)[43] (no metabolites)	2	14.4	60–70	Urine: 11 Feces: 80	1	>12
levocetirizine (Xyzal)[44] (4 metabolites)	0.9	8	91-92	Urine: 85 Feces: 13	1	24
loratadine[45] (12 metabolites, including desloratadine)	1.2 ± 0.3 (1.5 ± 0.7)	7.8 ± 4.2 (24 ± 9.8)	98 (73–76)	Trace	3-4	24

Results are mean ± standard deviation.

t_{max} = time from oral intake to peak plasma drug concentration; $t_{1/2}$ = elimination half-life

Contraindications/Warnings[46,47,48,49,50]

Pseudoephedrine, the decongestant component of Allegra-D, Claritin-D, Clarinex-D, Zyrtec-D, and Semprex D, is contraindicated in patients with narrow-angle glaucoma, urinary retention, severe hypertension, severe coronary artery disease, and in patients who take monoamine oxidase (MAO) inhibitors or have recently (prior two weeks) discontinued an MAO inhibitor. The antihypertensive effects of some medications (including beta-adrenergic blockers) may be reduced by pseudoephedrine. Increased ectopic pacemaker activity can occur when pseudoephedrine is used concomitantly with digoxin.

Levocetirizine (Xyzal) is contraindicated in children ages six to eleven years of age with renal impairment and in patients with end stage renal disease with a creatinine clearance (CrCl) less than 10 mL/min or undergoing hemodialysis.

Fexofenadine orally-disintegrating tablets (Allegra ODT) contain phenylalanine, a component of aspartame. This formulation is not recommended for use in patients with phenylketonuria.

The other agents do not have specific contraindications. However, cautious use in patients with renal impairment as well as geriatric patients is recommended. Cetirizine is contraindicated in those patients with a known hypersensitivity to it or any of its ingredients or hydroxyzine.

Drug Interactions

Drug	azithromycin	erythromycin	grapefruit juice	ketoconazole	theophylline	Al and Mg containing antacids
acrivastine (Semprex D)[51]	--	--	--	--	--	--
cetirizine (Zyrtec)[52]	--	--	--	--	16 percent decrease in cetirizine clearance	--
desloratadine (Clarinex)[53,54,55]	15 percent increase in desloratadine C_{max} 15 percent increase in major metabolite C_{max}	24 percent increase in desloratadine C_{max} 43 percent increase in major metabolite C_{max}	--	45 percent increase in desloratadine C_{max} 43 percent increase in major metabolite C_{max}	--	--
fexofenadine (Allegra)[56,57,58]	69 percent increase in fexofenadine C_{max}	82 percent increase in fexofenadine C_{max}	30 percent decrease in fexofenadine bioavailability	135 percent increase in fexofenadine C_{max}	--	43 percent decrease in fexofenadine C_{max} when given within 15 minutes
levocetirizine (Xyzal)[59]	--	--	--	--	--	--
loratadine (Claritin)[60]	--	increase in loratadine levels	--	increase in loratadine levels	--	--

Adverse Effects

Adults

Drug	Dry mouth	Dyspepsia	Fatigue	Headache	Insomnia	Nausea	Somnolence
acrivastine/ pseudoephedrine (Semprex D)[61]	7	2	nr	19	4	2	12
cetirizine (Zyrtec)[62]	5	<2	5.9-9	>2	<2	>2	11-14
desloratadine (Clarinex)[63]	3	3	2.1-5	14	nr	5	2.1
desloratadine/ pseudoephedrine (Clarinex-D 12-Hour)[64]	8	nr	4	8	10	2	3
desloratadine/ pseudoephedrine (Clarinex-D 24-Hour)[65]	8	nr	3	6	5	2	3
fexofenadine (Allegra)[66]	nr	1.3	1.3	10.6	<1	1.6	1.3-2.2
fexofenadine/ pseudoephedrine (Allegra-D 12-hour)[67]	2.8	2.8	nr	13	12.6	7.4	nr
levocetirizine (Xyzal)[68]	2-3	nr	1-4	nr	nr	nr	5-6
loratadine (Claritin)[69]	2-4	2-3	4-6	12-18	1-4	2	4-8
loratadine/ pseudoephedrine 12 hr (Claritin D-12 hr)[70]	14	3	4	19	16	3	7
loratadine/ pseudoephedrine 24 hr (Claritin D-24 hr)[71]	8	nr	3	nr	5	3	6

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative. nr = not reported.

The package insert for Zyrtec-D reports only the adverse effects attributed to Zyrtec alone (refer to Zyrtec information for Zyrtec-D adverse reaction data).[72]

Adverse Effects

Children

Drug	Abdominal Pain	Cough	Fatigue	Nausea	Pharyngitis	Somnolence	Headache
cetirizine (Zyrtec)[73]	4.4-5.6	2.8-4.4	nr	1.9-2.8	2.8-6.2	1.9-4.2	11-14
desloratadine (Clarinex)[74]	nr	10.8	5	3-5	3-4.5	9.1	14
fexofenadine (Allegra)[75]	nr	3.8	nr	nr	nr	nr	7.2
levocetirizine (Xyzal)[76]	nr	3	nr	nr	nr	3	nr
loratadine (Claritin)[77]	2	4	3	nr	nr	nr	nr

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative. nr = not reported.

Specific adverse effects data for fexofenadine ODT (Allegra) are not available.

Somnolence

A literature search (MEDLINE and cross-references) was performed using the keywords driving and antihistamine.[78] Sixteen studies using the on-the-road driving test during normal traffic were included in the review. Studies were double-blinded and placebo-controlled and included a positive control. First-generation antihistamines (diphenhydramine, triprolidine, terfenadine, d-chlorpheniramine, clemastine) significantly impair driving performance after both one-time and repeated (daily) administration. Second-generation antihistamines (cetirizine, loratadine and acrivastine) may also impair driving performance, but the magnitude and extent of impairment depend on the administered dose, sex, and time between testing and treatment administration. Tolerance develops after four to five days of administration, but impairment is not absent. The third-generation antihistamine (fexofenadine) produced no driving impairment after both one-time and repeated administration.

loratadine (Claritin) versus fexofenadine (Allegra) versus certirizine (Zyrtec)

Post-marketing reports of sedation or drowsiness were obtained for a total of 43,363 patients receiving loratadine, fexofenadine, or cetirizine.[79] Compared with loratadine, the odds ratios (adjusted for age and sex) for the incidence of sedation were 0.63 ($p=0.1$) for fexofenadine and 3.53 ($p<0.0001$) for cetirizine. No increased risk of accident or injury was evident with any of the drugs. These data indicate that fexofenadine and loratadine may be more appropriate than cetirizine for people working in safety-critical jobs.

loratadine (Claritin) versus cetirizine (Zyrtec)

A double-blind study compared the somnolence and motivation profiles of loratadine and cetirizine in 60 patients.[80] In the study, patients aged 12 years and older and actively exhibiting symptoms of AR were randomized to receive loratadine 10 mg or cetirizine 10 mg daily at

8 a.m. for one week. After patients took the medication, somnolence and degree of motivation to perform activities were recorded in an electronic diary using a visual analog scale at four times during the workday (8 a.m., 10 a.m., 12 p.m., and 3 p.m.). A statistically significant difference in somnolence scores between the loratadine and cetirizine groups at 10 a.m. ($p=0.008$), 12 p.m. ($p=0.001$), and 3 p.m. ($p<0.001$), with the cetirizine group showing a greater degree of somnolence was reported. Likewise, statistically significant differences in motivation scores between the loratadine and cetirizine groups at 10 a.m. ($p=0.014$), 12 p.m. ($p=0.001$), and 3 p.m. ($p<0.001$) were reported, indicating patients taking loratadine were comparatively more motivated during the workday. The results of the study demonstrate, in patients who have AR, cetirizine use promotes somnolence and decreases motivation to perform activities during the workday compared with loratadine.

desloratadine (Clarinex) versus diphenhydramine (Benadryl)

One randomized, double-blind, three-way, crossover study conducted in Europe evaluated the effect of a single dose of desloratadine 5 mg, diphenhydramine 50 mg, or placebo on standard over-the-road driving tests (n=18).[81] No significant differences were noted between desloratadine and placebo in standard deviation of lateral position (SDLP), whereas diphenhydramine treatment significantly increased SDLP ($p<0.001$ for both comparisons). Brake reaction time was significantly faster following treatment with desloratadine than diphenhydramine (473.72 ms versus 541.22 ms; $p<0.001$) or placebo (512.06 ms; $p=0.033$). The majority of performance tests showed no significant differences among groups.

Special Populations

Pediatrics[82,83,84,85,86]

Safety and effectiveness of acrivastine/pseudoephedrine (Semprex-D) in pediatric patients under the age of 12 years have not been established.

Safety and effectiveness of levocetirizine (Xyzal) in pediatric patients under six months of age have not been established. The recommended doses for children ages six months to 11 years should not be exceeded.

Recommended doses of fexofenadine (Allegra) in pediatric patients ages six months to 11 years are based on cross-study comparison of the pharmacokinetics of fexofenadine in adults and pediatric patients.

A multicenter, double-blind, randomized, placebo-controlled, parallel-group, two-week trial was conducted in 453 preschool children ages two to five years old with allergic rhinitis to compare the safety and tolerability of twice daily fexofenadine (Allegra) 30 mg versus placebo.[87] To facilitate dosing, capsule contents were mixed with applesauce. Safety assessments included physical examination, laboratory testing, twelve-lead electrocardiography, vital signs and adverse event reporting. Treatment emergent adverse effects were observed in 116 of the 231 participants who received placebo. Of patients receiving fexofenadine, 111 of the 222 participants had treatment emergent adverse effects. Nineteen of the 116 participants (8.2 percent) and 21 of the 111 participants (9.5 percent) were determined to have a potential link to the study medication, placebo or fexofenadine, respectively. No clinically relevant differences were noted in any of the other safety parameters under study. The findings suggest fexofenadine is well tolerated in children ages two to five years of age with allergic rhinitis.

Safety and effectiveness of desloratadine (Clarinex) and cetirizine (Zyrtec) in pediatric patients

under six months of age have not been established.

Safety and effectiveness of loratadine (Claritin) in pediatric patients under two years of age have not been established.

Combination products containing pseudoephedrine in excess of 60 mg daily should not be used in children under 12 years of age.

Pregnancy[88,89,90,91,92]

No adequate, well-controlled studies have been conducted in pregnant women. All agents should be used only if clearly needed during pregnancy. Cetirizine (Zyrtec), acrivastine (Semprex D), levocetirizine (Xyzal), and loratadine (Claritin) are Pregnancy Category B. Desloratadine (Clarinex) and fexofenadine/fexofenadine ODT (Allegra, Allegra ODT) are Pregnancy Category C.

Hepatic impairment[93,94,95,96]

A 50 percent reduction in dosage or dosage frequency is recommended for cetirizine (Zyrtec), desloratadine (Clarinex), and loratadine (Claritin). Patients with hepatic impairment did not demonstrate any differences from healthy patients when using fexofenadine, fexofenadine ODT (Allegra, Allegra ODT). Consult product labeling.

Renal impairment[97,98,99,100,101]

A 50 percent reduction in dosage or dosage frequency is recommended for cetirizine (Zyrtec), desloratadine (Clarinex), fexofenadine/fexofenadine ODT (Allegra, Allegra ODT), and loratadine (Claritin) with renal impairment. Acrivastine/pseudoephedrine (Semprex-D) is not recommended for use in patients with creatinine clearance (CrCl) ≤ 48 mL/min. Patients with renal impairment demonstrated higher plasma levels of fexofenadine (Allegra) as well as longer elimination half lives than observed in healthy volunteers. Levocetirizine (Xyzal) requires a dosage adjustment in the renally impaired. Consult product labeling.

Race and Gender[102]

No studies have been done to determine the effect of race on the pharmacokinetics of desloratadine (Clarinex). In addition, there have been no clinically significant gender-related differences noted with the use of desloratadine (Clarinex).

Age[103]

A dosing adjustment of cetirizine (Zyrtec) may be necessary in patients 77 years of age and older.

Dosages

Drug	Adult Dose (including children 12 years and older)	Pediatric Dose	Availability
acrivastine/pseudoephedrine (Semprex D)[104]	1 capsule four times daily	--	8 mg acrivastine/60 mg pseudoephedrine capsules
cetirizine (Zyrtec)[105]	5 or 10 mg daily 65 yrs and older: 5 mg daily	**6 – 11 yrs**: 5 or 10 mg daily **2 – 5 yrs**: 2.5 – 5 mg (½ – 1 tsp or 5 mg chewable tab) daily **6 – 23 mo**: 2.5 mg (½ tsp) daily **12 – 23 mo**: may increase to 2.5 mg (½ tsp) every 12 hours	5 mg and 10 mg tablets 5 mg and 10 mg chewable tablets 1 mg/mL syrup
cetirizine/pseudoephedrine (Zyrtec-D 12 Hour)[106]	1 tablet twice daily	--	5 mg cetirizine/120 mg pseudoephedrine extended-release (12 hour) tablets
desloratadine (Clarinex, Clarinex Redi-Tabs)[107]	5 mg daily	**6 – 11 yrs**: 2.5 mg (1 tsp) daily **12 mo – 5 yrs**: 1.25 mg (½ tsp) daily **6 – 11 mo**: 1 mg (2 mL) daily	5 mg tablets 0.5 mg/mL syrup 2.5 mg and 5 mg orally disintegrating tablets
desloratadine/ pseudoephedrine (Clarinex-D 12-Hour)[108]	1 tablet every 12 hours	--	2.5 mg desloratadine/120 mg pseudoephedrine extended-release (12 hour) tablets
desloratadine/ pseudoephedrine (Clarinex-D 24-Hour)[109]	1 tablet daily	--	5 mg desloratadine/240 mg pseudoephedrine extended-release (24 hour) tablets
fexofenadine(Allegra)[110]	60 mg twice daily or 180 mg daily	**6 – 11 yrs**: 30 mg twice daily	30 mg, 60 mg and 180 mg tablets
fexofenadine (Allegra Oral Suspension)[111]	--	**2 yrs – 11 yrs**: 30 mg (1 tsp) twice daily. Decrease dose to 30 mg (1 tsp) once daily in cases of poor renal function. **6 mo – 23 mo**: 15 mg (½ tsp) twice daily Decrease dose to 15 mg (½ tsp) once daily in cases of poor renal function.	6 mg/mL oral suspension
fexofenadine ODT (Allegra ODT)[112]	--	**6 – 11 yrs**: 30 mg twice daily on an empty stomach	30 mg orally disintegrating tablet

Dosages (continued)

Drug	Adult Dose (including children 12 years and older)	Pediatric Dose	Availability
fexofenadine/ pseudoephedrine (Allegra-D 12 hour)[113]	1 tablet twice daily	--	60 mg fexofenadine/120 mg pseudoephedrine extended-release (12 hour) tablets
fexofenadine/ pseudoephedrine (Allegra-D 24 hour)[114]	1 tablet once a day on an empty stomach (ages 12 years and older)	--	180 mg fexofenadine/240 mg pseudoephedrine extended-release (24 hour) tablets
levocetirizine (Xyzal)[115]	5 mg (2 tsp) once daily in the evening	**6 – 11 yrs**: 2.5 mg (1 tsp) once daily in the evening **6 months – 5 yrs:** 1.25 mg (½ tsp) once daily in the evening	5 mg tablets 2.5 mg/5 mL oral solution
loratadine (Claritin)[116,117]	10 mg daily	**6 – 11 yrs**: 10 mg (2 tsp) daily **2 – 5 yrs**: 5 mg (1 tsp) daily	10 mg tablets 10 mg orally disintegrating tablets 1 mg/mL syrup 10 mg orally disintegrating tablets for children
loratadine chewable (Children's Claritin)[118]	10 mg (2 chew tablets) daily	**6 – 11 yrs**: 10 mg (2 chew tablets) daily **2 – 5 yrs**: 5 mg (1 chew tablet) daily	5 mg chewable tablets
loratadine/ pseudoephedrine 12 hr[119]	1 tablet twice daily	--	5 mg loratadine/120 mg pseudoephedrine extended-release (12 hour) tablets
loratadine/ pseudoephedrine 24 hr[120]	1 tablet daily	--	10 mg loratadine/240 mg pseudoephedrine extended-release (24 hour) tablets

Clinical Trials

Search Strategy

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the use of all drugs in this class. Randomized, controlled, comparative trials are considered the most relevant in the category. Studies included for analysis in the review were published in English, performed with human participants and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

Allergic rhinitis

cetirizine (Zyrtec) versus fexofenadine (Allegra)

A study compared the duration of effect and efficacy of cetirizine 10 mg, fexofenadine 180 mg, and placebo in allergic subjects (n=575) exposed to pollen in the environmental exposure unit.[121] Patients were exposed to ragweed pollen for two days and randomized in a double-blind fashion to once-daily cetirizine 10 mg, fexofenadine 180 mg or placebo. The total symptom severity complex score (TSSC) is the sum of the severity ratings (0=absent to 3=severe) of several self-rated symptoms including runny nose, sneezing, itchy nose/palate/throat, and itchy/watery eyes. Treatment evaluation was divided into three periods: period one (TSSC zero to five hours after the first dose), period two (TSSC 21-24 hours after the first dose) and period three (TSSC zero to two hours after the second dose). The onset of action was comparable, and similar efficacy was observed in period one for both active treatments. For period two, the reduction in baseline was greater for cetirizine (-3.6) compared with fexofenadine (-2.7; $p<0.001$) and placebo (-2; $p<0.001$), representing a 33 percent greater reduction for cetirizine versus fexofenadine. For period three, cetirizine also reduced TSSC to a greater extent, as compared to fexofenadine (-5.2 versus -4.6; $p=0.017$) and placebo (-3.9; $p<0.001$). Treatment-related adverse events were similar in all groups with an incidence of somnolence of 1.3 percent for both active medications.

Another randomized, double-blind study of 599 patients compared the response to treatment between single doses of cetirizine 10 mg, fexofenadine 180 mg, and placebo at five to 12 hours after pollen exposure in an environmental exposure unit.[122] The primary efficacy endpoint was the change in TSSC score at 12 hours post dose. Cetirizine produced a 26 percent greater reduction in TSSC at 12 hours (-4.3 versus -3.4; $p=0.001$) and a 14 percent greater reduction overall (-5 versus -4.4; $p<0.001$) than fexofenadine. The incidence of treatment-emergent adverse events and somnolence was similar among all three groups.

In a multicenter, double-blind study, 821 patients were enrolled to receive fexofenadine 120 mg or 180 mg once daily, cetirizine 10 mg once daily, or placebo for two weeks for the treatment of seasonal allergic rhinitis (SAR).[123] The total symptom score (TSS) was calculated for four individual symptoms: sneezing, rhinorrhea, itchy nose, palate or throat, and itchy, watery, or red eyes. There were no differences in efficacy between the two doses of fexofenadine or between either dose of fexofenadine and cetirizine. The combined incidence of drowsiness or fatigue was greater with cetirizine (nine percent) than with placebo (four percent) or fexofenadine (four percent).

In a two-week, double-blind, randomized study, 495 subjects with moderate to severe SAR received fexofenadine 180 mg or cetirizine 10 mg once daily without regard to food intake to compare effects on symptoms, drowsiness, and motivation.[124] Improvement in daily 12-hour reflective and instantaneous individual symptoms and total symptom score (TSS) were statistically equivalent between the two treatment groups. As measured by visual analog scores, patients receiving fexofenadine experienced significantly less overall drowsiness compared to baseline than those receiving cetirizine ($p=0.011$). Although there was a trend toward greater improvements in overall motivation with fexofenadine compared with cetirizine ($p=0.0504$), improvements in overall motivation were statistically equivalent.

cetirizine (Zyrtec) versus loratadine (Claritin)

In a randomized, double-blind trial using an environmental exposure unit, cetirizine and loratadine were compared to placebo in 360 patients.[125] Subjects were randomized to two days at the environmental exposure unit (six to seven hours daily) along with administration of one of the two active treatments or placebo. Evaluation of symptom scores indicated onset of action was earlier with cetirizine 10 mg (one hour, $p \leq 0.001$) than with loratadine 10 mg (three hours, $p \leq 0.01$). Cetirizine produced a 25.4 percent reduction in symptom scores overall versus an 11.2 percent decrease with loratadine ($p=0.006$) and a 4.8 percent increase with placebo ($p<0.001$). Loratadine was also significantly more effective than placebo ($p=0.002$). Cetirizine reduced symptom scores after the first dose versus placebo ($p \leq 0.001$) and at most time points versus loratadine ($p \leq 0.05$). Adverse events were reported in 1.7 percent of patients in each active-treatment group and in 2.5 percent in the placebo group.

A double-blind study was performed to evaluate the effectiveness of cetirizine and loratadine versus placebo in patients with AR.[126] Ninety patients with moderate to severe AR were given either cetirizine 10 mg, loratadine 10 mg, or placebo daily for four weeks. The investigators demonstrated antihistamines showed good effectiveness in patients with AR as determined by rhinomanometry and by symptom score versus placebo. In addition, cetirizine performed better in comparison to loratadine (Claritin) versus placebo.

In a double-blind study, 80 children (two to six years of age) with PAR were randomized to receive cetirizine or loratadine 0.2 mg/kg once daily for twenty-eight days.[127] According to patients' daily diary assessments, cetirizine was more effective than loratadine in relieving the symptoms of rhinorrhea, sneezing, nasal obstruction, and nasal pruritus. Both treatments were well tolerated.

desloratadine (Clarinex) versus fexofenadine (Allegra)

Forty-nine patients with SAR were randomized into a double-blind, placebo-controlled cross-over study during the grass pollen season, comparing two weeks of treatment with fexofenadine 180 mg or desloratadine 5 mg taken once daily in the morning.[128] Measurements were made for peak nasal inspiratory flow (PNIF), the primary outcome variable, as well as nasal and eye symptoms. There were significant ($p<0.05$) improvements, compared to placebo, with fexofenadine and desloratadine for PNIF, nasal blockage, nasal irritation, and total nasal symptoms but not nasal discharge or eye symptoms. There were no significant differences between active treatments.

fexofenadine (Allegra) versus loratadine (Claritin)

A double-blind, two-phase, multicenter study was conducted to compare therapeutic responses to loratadine and fexofenadine in patients who failed initial therapy with the other drug.[129] In the study, 661 patients were randomized to receive loratadine 10 mg once daily or fexofenadine 60 mg twice daily for 14 days (phase one); non-responders subsequently received the alternate medication for 14 days (phase two). Mean decreases in TSS were significantly greater with loratadine than with fexofenadine for the patients who completed phase one (-12.7 versus -10.2, respectively; $p=0.019$) and for the patients who responded to initial therapy (-6.6 versus. -6.1, respectively; $p=0.037$). Of the 389 patients who responded to initial therapy, 61 percent had received loratadine and 57 percent had received fexofenadine. More non-responders to initial therapy had moderate, marked, or complete relief of symptoms after switching to loratadine than

after switching to fexofenadine (62.4 versus 51.2 percent, respectively; p=0.005). Overall, loratadine provided significantly better therapeutic response than fexofenadine in patients who failed to respond to initial therapy with the other drug.

A double-blind study compared the efficacy, safety and impact on quality of life (QoL) of fexofenadine, loratadine, and placebo in patients with SAR.[130] In the study, 688 patients were randomized to receive fexofenadine 120 mg, loratadine 10 mg, or placebo daily for two weeks. Although both agents were more effective than placebo in reducing individual symptom scores, fexofenadine was significantly better than loratadine in improving itchy, watery, red eyes, as well as in relieving nasal congestion ($p \leq 0.05$ for both symptoms). Fexofenadine was also significantly better than loratadine ($p \leq 0.03$) and placebo ($p \leq 0.005$) in improving QoL; the differences were of a magnitude considered to be clinically relevant. Loratadine had no statistically significant effect on QoL compared with placebo. The incidence of adverse events was low and similar across all treatment groups.

To compare loratadine with fexofenadine and placebo in relieving symptoms of spring/summer SAR, investigators performed a double-blind study in patients aged 12 to 60 years.[131] Patients were randomized to loratadine 10 mg once daily, fexofenadine 60 mg twice daily, or matching placebo for seven days. Overall, administration of either loratadine or fexofenadine provided similar reductions from baseline TSS compared to placebo. Median time to 25 percent reduction and maximum reduction in morning TSS occurred significantly earlier in patients receiving loratadine. At the initial assessment following the first dose, loratadine demonstrated a significant reduction from baseline in symptoms compared with fexofenadine. Time-to-event analysis indicated that a more significant reduction in symptoms occurs earlier with loratadine than with fexofenadine.

levocetirizine (Xyzal) versus placebo

Six placebo-controlled, randomized, double-blind controlled trials with 2,412 patients (265 patients between the ages of 12 to 17) were conducted to determine the efficacy of levocetirizine in management of symptoms associated with seasonal and perennial allergic rhinitis.[132] Efficacy was assessed using a TSS from patient recording of four or five symptoms (sneezing, rhinorrhea, nasal pruritis, nasal congestion, and/or ocular pruritis). Patients recorded daily symptoms using a 0-3 categorical severity scale (0=absent, 1=mild, 2=moderate, and 3=severe). One of the studies allowed recording of symptoms in an instantaneous manner one hour prior to the next dose. The primary endpoint was the mean TSS averaged over the first week then over the first two weeks for seasonal AR trials, and four weeks for perennial AR trials. Total symptom scores were significantly reduced in the active treatment groups in both seasonal and perennial AR trials ($p<0.001$).

Chronic Idiopathic Urticaria

cetirizine (Zyrtec) versus fexofenadine (Allegra)

An Indian study compared the efficacy and safety of cetirizine 10 mg and fexofenadine 180 mg in the treatment of CIU.[133] A total of 116 patients, aged 17 to 65 years, with CIU (urticarial wheals for at least two days per week for six consecutive weeks before entry) were enrolled in the randomized, double-blind, four-week long study. Ninety-seven patients (52 assigned to cetirizine, 45 assigned to fexofenadine) completed the study. The response in both the groups at the end of the treatment period was as follows: symptom free (cetirizine 51.9 percent, fexofenadine 4.4 percent); partial improvement (cetirizine 36.5 percent, fexofenadine 42.2

percent); no improvement (cetirizine 11.5 percent, fexofenadine 53.3 percent). Adverse effects noted were mild with no significant difference between the two.

desloratadine (Clarinex) versus levocetirizine (Xyzal)

In a multi-center, double-blind study, 886 patients with CIU were randomized to receive either levocetirizine 5 mg or desloratadine 5 mg, once daily in the morning for four weeks.[134] Levocetirizine led to a significantly greater decrease in pruritus severity than desloratadine over the first treatment week ($p<0.001$) and the entire four-week treatment period ($p=0.004$). In addition, levocetirizine decreased pruritus duration and the mean CIU composite scores to a significantly greater extent than desloratadine during the first week ($p=0.002$ and $p=0.005$, respectively) and over the entire study ($p=0.009$ and $p<0.05$, respectively).

Summary

Comparative data are available for cetirizine (Zyrtec), fexofenadine (Allegra), and loratadine (Claritin) with limited or no comparative data available for desloratadine (Clarinex) or levocetirizine (Xyzal). All agents in the category are similar in efficacy. Although some studies do indicate cetirizine may be more effective than loratadine at providing symptomatic relief, cetirizine causes significantly more sedation in many patients. Levocetirizine (Xyzal) is the active isomer of cetirizine. An increased risk of somnolence exists at higher doses of levocetirizine (Xyzal).

The rationale for using minimally sedating antihistamines over clinically effective, first generation antihistamines (like diphenhydramine) is symptoms of AR can be controlled without inducing a level of sedation interfering with daily activities. Cetirizine causes sedation in up to 14 percent of patients. Current data suggest the least likelihood of sedation with fexofenadine (Allegra) or desloratadine (Clarinex). Fexofenadine (Allegra) tends to cause the fewest CNS effects because its absorption into the brain is minimal. An orally disintegrating form of fexofenadine ODT (Allegra ODT) is now available for pediatric use. It is designed to dissolve on the tongue and be swallowed with or without water. An OTC chewable form of Claritin is also now available as an alternative dosage form for children and others who may have difficulty swallowing tablets. Cetirizine and loratadine (Claritin) are now available over-the-counter (OTC) in various dosage forms.

Antihistamine/decongestant combination products should be administered when both the antihistaminic and nasal decongestant activity is desired.

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