Antihistamines, Minimally Sedating Review

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FDA-Approved Indications

Drug	Manufacturer	Indication(s)
acrivastine/pseudoephedrine (Semprex D®)[1]	UCB	- Relief of symptoms associated with seasonal AR in adults and children 12 years of age and older
cetirizine OTC (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 2 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 infections of CIU in adults and children six months of age and older
cetirizine/pseudoephedrine OTC (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

* Zyrtec/Zyrtec-D are only available over-the-counter effective February 2008.

Drug	Manufacturer	Indication(s)
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 eleven - Treatment of uncomplicated skin manifestations of CIU in children six months to eleven years of age
fexofenadine orally disintegrating tablet (Allegra ODT®)[9]	Sanofi-Aventis	- Treatment of symptoms related to seasonal AR and CIU in children ages 6 to 11 years of age
fexofenadine/pseudoephedrine (Allegra-D® 12 Hour)[10]	Sanofi-Aventis	- 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 or perennial AR in adults and children six years 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
loratadine OTC (Claritin)[14]	generic	- Temporary relief of symptoms due to hay fever or other respiratory allergies in adults and children six years and older
loratadine ODT OTC (Alavert Quick Dissolving, Claritin Redi-Tabs, generic)[15]	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)[16]	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)[17]	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.[18]

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.[19] Estimates from 2002 have shown that 10 to 30 percent of adults and up to 40 percent of children have allergic rhinitis.[20] Some figures estimate that approximately $1.8 billion per year are spent in direct costs, which include physician visits and medications.[21] Approximately $3.8 billion per year are spent in indirect costs, which include the result of lost productivity. For children, there are approximately two million lost school days per year 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 complain of nasal congestion. However, this is also true in common chronic rhinosinusitis. An important distinguishing characteristic of AR is an associated clear rhinorrhea and frequent sneezing. The presence of ocular irritation or burning is also found almost exclusively in AR. The presence of mucoid postnasal discharge in the posterior pharynx is also indicative of AR.

Avoidance of allergens is fundamental to the management of AR. There must be an effort made to alter the home and work environments. In perennial allergies (dust and mold), this is the cornerstone of treatment. Patients with seasonal allergies (trees, weeds, etc.) have a difficult time avoiding these common allergens during certain times each year. Beginning the treatment regimen one to two weeks before the onset of a budding season will often result in more effective reduction of symptoms.

The major classes of agents used to treat symptoms of AR are intranasal corticosteroids and oral antihistamines. Alternative agents, such as leukotriene modifiers, cromolyn sodium and antihistamine nasal spray may be appropriate in some patients.

Nasally inhaled corticosteroids are the most effective medication in controlling symptoms of AR. These agents are highly effective in relieving nasal allergy symptoms (congestion, sneezing, runny nose) but usually not the ocular symptoms.

Oral antihistamines are particularly effective against severe rhinorrhea, sneezing, pruritus, and conjunctivitis associated with AR, although they have less effect on nasal congestion. The usefulness of the first-generation (sedating) antihistamines is reduced because they may produce significant sedation, performance impairment and/or anticholinergic effects. Consequently, the second-generation (minimally sedating) antihistamines that are associated with a lower incidence of these side effects should usually be 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 American Academy of Allergy, Asthma and Immunology (AAAAI) recommends a stepwise approach for managing AR. For patients with persistent, mild to moderate AR, an oral, minimally sedating antihistamine (with or without a decongestant) and/or an inhaled nasal corticosteroid are recommended.[23] For severe AR, combination therapy with a nasal

corticosteroid and a minimally sedating antihistamine (with or without a decongestant) is recommended. For children or those with perennial AR (PAR), azelastine (Astelin®) inhaled nasal antihistamine and nasal cromolyn sodium may be considered as alternative therapies. Because montelukast (Singulair®), a leukotriene antagonist, was not approved for seasonal AR (SAR) at the time of publication, the AAAAI guidelines do not specifically address this agent. It is anticipated that montelukast (Singulair) will find its predominant use in patients with concurrent SAR and asthma.

Chronic Idiopathic Urticaria (CIU)

Urticaria is defined as the transient appearance of elevated, erythematous pruritic wheals (hives). It commonly involves the trunk and extremities, sparing the palms and soles, but it may involve 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), in which disease activity continues for more than six weeks, is common comprising 70 percent of all cases.[24] Chronic idiopathic urticaria can occur at any age; however it is most common in young adults. Although in the majority of patients the lesions clear spontaneously or respond rapidly to treatment with antihistamines, a minority of patients continue to have lesions that may last for years. 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 the urticaria have failed (thus eliminating the possibility of reducing exposure), the patient requires treatment. The 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 disturbed at night.[25] If the clinical response is not adequate, H_2-inhibitory drugs may be added to the antihistamine.[26] Other agents that have been 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 these 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.[27]

All of the minimally sedating antihistamines appear to be effective treatments for CIU.[28,29,30,31] There are only a small amount of comparative data regarding the use of these agents in CIU, therefore the focus of this review remains on AR.

Pharmacology

The minimally sedating antihistamines are selective, competitive, peripheral-acting histamine H_1-receptor antagonists that have little or no central or autonomic nervous system activity.[32,33]

Pharmacokinetics[34]

Drug (Metabolite)	t_{max} (hr)	$t_{1/2}$ (hr)	Protein Binding (%)	Excretion (%)	Onset of Action (hr)	Duration of Action (hr)
acrivastine (Semprex-D)[35] (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)[36,37] (1 metabolite)	1	8.3	93	Urine: 50	0.3-1	≥ 24
desloratadine (Clarinex)[38, 39] (6 metabolites)	3	27	82-87	--	1	24
fexofenadine (Allegra)[40,41] (no metabolites)	2.6	14.4	60–70	Urine: 11 Feces: 80	1	>12
fexofenadine ODT (Allegra ODT)[42] (no metabolites)	2	14.4	60–70	Urine: 11 Feces: 80	1	>12
levocetirizine (Xyzal)[43] (4 metabolites)	0.9	8	91-92	Urine: 85 Feces: 13	1	24
loratadine[44] (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[45,46,47,48,49]

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 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.

Drug Interactions

Drug	azithromycin	erythromycin	grapefruit juice	ketoconazole	theophylline	Al and Mg containing antacids
acrivastine (Semprex D)[50]	--	--	--	--	--	--
cetirizine (Zyrtec)[51]	--	--	--	--	16 percent decrease in cetirizine clearance	--
desloratadine (Clarinex)[52,53,54]	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)[55,56,57]	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)[58]	--	--	--	--	--	--
loratadine (Claritin)[59]	--	increase in loratadine levels**	--	increase in loratadine levels**	--	--

Adverse Effects

Adults

Drug	Dry mouth	Dyspepsia	Fatigue	Headache	Insomnia	Nausea	Somnolence
acrivastine/pseudoephedrine (Semprex D)[60]	7	2	nr	19	4	2	12
cetirizine (Zyrtec)[61]	5	<2	5.9-9	>2	<2	>2	11-14
desloratadine (Clarinex)[62]	3	3	2.1-5	14	nr	5	2.1
desloratadine/ pseudoephedrine (Clarinex-D 12-Hour)[63]	8	nr	4	8	10	2	3
desloratadine/ pseudoephedrine (Clarinex-D 24-Hour)[64]	8	nr	3	6	5	2	3
fexofenadine (Allegra)[65]	nr	1.3	1.3	10.6	<1	1.6	1.3-2.2
fexofenadine/ pseudoephedrine (Allegra-D 12-hour)[66]	2.8	2.8	nr	13	12.6	7.4	nr
levocetirizine (Xyzal)[67]	2-3	nr	1-4	nr	nr	nr	5-6
loratadine (Claritin)[68,69,70]	2-4	2-3	4-6	12-18	1-4	2	4-8
loratadine/ pseudoephedrine 12 hr (Claritin D-12 hr)[71]	14	3	4	19	16	3	7
loratadine/ pseudoephedrine 24 hr (Claritin D-24 hr)[72]	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 indicates only the adverse reactions attributed to Zyrtec alone (refer to Zyrtec information for Zyrtec-D adverse reaction data).[73]

Adverse Effects

Children

Drug	Abdominal Pain	Cough	Fatigue	Nausea	Pharyngitis	Somnolence	Headache
cetirizine (Zyrtec)[74]	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)[75]	nr	10.8	5	3-5	3-4.5	9.1	14
fexofenadine (Allegra)[76]	nr	3.8	nr	nr	nr	nr	7.2
levocetirizine (Xyzal)[77]	nr	3	nr	nr	nr	3	nr
loratadine (Claritin)[78]	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.[79] Sixteen studies using the on-the-road driving test during normal traffic were included in the review. Studies were double-blind 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) was shown to produce 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.[80] 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.[81] In this 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, their somnolence and degree of motivation to perform activities were recorded in an electronic diary using a visual analog scale four times during the workday (8 a.m., 10 a.m., 12 p.m., and 3 p.m.). There was 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. In parallel with the somnolence scores, there were 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), indicating that patients taking loratadine were relatively more motivated during the workday. The results of this study demonstrate that, 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 European study evaluated a single dose of desloratadine 5 mg, diphenhydramine 50 mg, or placebo on standard over-the-road driving tests (n=18).[82] 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[83,84,85,86,87]

The safety and effectiveness of levocetirizine (Xyzal) in pediatric patients under six years of age have not been established. The use of levocetirizine (Xyzal) in patients ages 12 to 17 is based on the extrapolation of adult efficacy studies.

The recommended doses of fexofenadine (Allegra) in pediatric patients ages 6 months to 11 years are based on cross-study comparison of the pharmacokinetics of fexofenadine (Allegra) 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) 30mg versus placebo.[88] To facilitate dosing, capsule content was mixed with applesauce. Safety assessments included physical examination, laboratory testing, twelve lead electrocardiography, vital signs and adverse event reporting. Treatment emergent adverse events were observed in 116 of the 231 participants who received placebo. Of those receiving fexofenadine (Allegra), 111 of the 222 participants had treatment emergent adverse effects. A small number of both 19 of the 116 (8.2 percent) and 21 of the 111 (9.5 percent) were determined to have a potential link to the study medication, placebo or fexofenadine (Allegra), respectively. No clinically relevant differences were noted in any of the other safety parameters under study. These findings suggest that fexofenadine (Allegra) is well tolerated in children ages two to five years of age with allergic rhinitis.

The safety and effectiveness of desloratadine (Clarinex) in pediatric patients under six months of age have not been established.

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

The safety and effectiveness of cetirizine (Zyrtec) in pediatric patients under six months of age have not been established.

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

Pregnancy[89,90,91,92,93]

No adequate, well-controlled studies have been conducted in pregnant women. All of these 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[94,95,96,97]

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[98,99,100,101,102]

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). Acrivastine/pseudoephedrine (Semprex-D) is not recommended for use in pts 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[103]

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[104]

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

Dosages

Drug	Adult Dose	Pediatric Dose	Availability
acrivastine/pseudoephedrine (Semprex D)[105]	1 capsule four times daily	--	8 mg acrivastine/60 mg pseudoephedrine capsules
cetirizine (Zyrtec)[106]	5 or 10 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)[107]	1 tablet twice daily	--	5 mg cetirizine/120 mg pseudoephedrine extended-release (12 hour) tablets
desloratadine (Clarinex, Clarinex Redi-Tabs)[108]	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)[109]	1 tablet every 12 hours	--	2.5 mg desloratadine/120 mg pseudoephedrine extended-release (12 hour) tablets
desloratadine/ pseudoephedrine (Clarinex-D 24-Hour)[110]	1 tablet daily	--	5 mg desloratadine/240 mg pseudoephedrine extended-release (24 hour) tablets
fexofenadine(Allegra)[111]	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)[112]	--	**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)[113]	--	**6 – 11 yrs**: 30 mg twice daily on an empty stomach	30 mg orally disintegrating tablet

Drug	Adult Dose	Pediatric Dose	Availability
fexofenadine/ pseudoephedrine (Allegra-D 12 hour)[114]	1 tablet twice daily	--	60 mg fexofenadine/120 mg pseudoephedrine extended-release (12 hour) tablets
fexofenadine/ pseudoephedrine (Allegra-D 24 hour)[115]	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)[116]	5 mg once daily in the evening	**6 – 11 yrs**: 2.5 mg once daily in the evening	5 mg tablets 2.5 mg/5 mL oral solution
loratadine (Claritin)[117,118]	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)[119]	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[120]	1 tablet twice daily	--	5 mg loratadine/120 mg pseudoephedrine extended-release (12 hour) tablets
loratadine/ pseudoephedrine 24 hr[121]	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, www.ifpma.org/clinicaltrials, 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 this 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 exposed to pollen in the environmental exposure unit (n=575).[122] 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 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.[123] 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 were 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).[124] 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.[125] 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 ($p=0.011$) while 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.[126] Subjects were randomized to two days

of 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 that the 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.[127] Ninety patients with moderate to severe AR were given either cetirizine 10 mg, loratadine 10 mg, or placebo daily for four weeks. The investigators found that the 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.[128] 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.[129] 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 the therapeutic responses to loratadine and fexofenadine in patients who failed initial therapy with the other drug.[130] 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 SAR patients.[131] 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.[132] 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 the management of symptoms associated with seasonal and perennial allergic rhinitis.[133] 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 these 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 compares the efficacy and safety of cetirizine 10mg and fexofenadine 180 mg in the treatment of CIU.[134] 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). Side effects noted were mild with no significant difference between the two.

Summary

There is little significant difference among the currently available minimally sedating antihistamines. 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 appear to be similar in efficacy. Although some studies do indicate that cetirizine (Zyrtec) may be more effective than loratadine at providing symptomatic relief, it does so at the cost of causing significantly more sedation. The newest product, levocetirizine (Xyzal), is the active isomer of cetirizine (Zyrtec). Despite the less sedating properties of levocetirizine (Xyzal), there is an increased risk of somnolence at higher doses of levocetirizine (Xyzal).

The rationale for using the minimally sedating antihistamines over the clinically effective, first generation antihistamines (like diphenhydramine) is that symptoms of AR can be controlled without inducing a level of sedation that can interfere with daily activities. Cetirizine (Zyrtec) has been shown to cause sedation in up to 14 percent of patients. It is best reserved for those with more severe allergic disease or patients that do not optimally respond to one of the other agents. 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. A new orally disintegrating form of fexofenadine ODT (Allegra ODT) has become available for pediatric use. It is designed to dissolve on the tongue, followed by swallowing with or without water. An OTC chewable form of Claritin is now available as an alternative dosage form for children and others who may have difficulty swallowing tablets. Cetirizine (Zyrtec) and loratadine (Claritin) are now available over-the-counter (OTC) in various dosage forms.

Acrivastine/pseudoephedrine (Semprex-D) capsules should be administered when both the antihistamine activity of acrivastine and the nasal decongestant activity of pseudoephedrine are desired.

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