



Department of Vermont Health Access

Therapeutic Class Review

Second-Generation Histamine H₁-receptor Antagonists (Antihistamines)

Overview/Summary

Oral antihistamines have been a mainstay in the treatment of allergic rhinitis and chronic idiopathic urticaria since their development in the first half of the 20th century.¹ Antihistamines block and act as inverse agonists at histamine-1 (H1) receptors, reducing histamine binding and stabilizing the inactive form of the H1 receptor.² Histamine is the most studied mediator of early allergic response. It is responsible for mucous secretion, vascular permeability, and sensory nerve stimulation leading to the symptoms associated with allergic rhinitis.³ Although first-generation antihistamines are effective at ameliorating symptoms associated with allergic rhinitis and chronic idiopathic urticaria, use in practice is limited by their lack of selectivity for the H1-receptor, and their ability to cross the blood-brain barrier both resulting in adverse effects. Second-generation antihistamines were developed to maintain the efficacy of the first-generation agents, while reducing associated side effects. Due to a more complex chemical structure, the movement of second generation antihistamines across the blood brain barrier is reduced. The second-generation agents also have a higher selectivity for peripheral H1 receptors with little or no affinity for muscarinic receptors.² In addition to a safer adverse event profile, second-generation agents have a longer duration of action, which allows for once or twice-daily dosing.

There are currently five single entity second-generation antihistamines available on the market in various formulations. They include cetirizine (Zyrtec[®]), desloratadine (Clarinet[®]), fexofenadine (Allegra[®]), levocetirizine (Xyzal[®]) and loratadine (Claritin[®]). All are available generically with the exception of desloratadine. A patent litigation settlement will allow generic desloratadine to be marketed beginning the first quarter of 2012.⁴ Cetirizine, fexofenadine and loratadine are available over-the-counter without a prescription in various formulations with or without pseudoephedrine. All of the single entity agents are Food and Drug Administration (FDA)-approved for the treatment of seasonal allergic rhinitis and chronic idiopathic urticaria.⁵⁻¹⁰ Potential off-label uses of antihistamines include adjunct therapy for asthma, and various idiopathic allergic conditions.¹¹⁻¹² The safety of antihistamines has theoretically improved with the isolation of active metabolites of previously available agents. Desloratadine is the major active metabolite of loratadine and has a prolonged half-life compared to loratadine.⁷ Levocetirizine, the active R enantiomer of cetirizine, has shown an approximately two-fold higher affinity for the H1 receptor than cetirizine.⁹ All of the single entity agents are approved for use in patients ≥6 months of age, except loratadine, which is approved for patients ≥2 years of age.¹¹⁻¹²

In a systematic review, the second generation antihistamines were shown to be effective at reducing total nasal symptom scores for seasonal allergic rhinitis by an average of 23.5%, which was less effective than intranasal corticosteroids (40.7%).¹³ For perennial allergic rhinitis, second-generation antihistamines improved symptoms (51.4%) compared to intranasal corticosteroids (37.3%). Additionally, all second-generation antihistamines have been shown to have extensive wheal and flare inhibition in patients with chronic idiopathic urticaria.¹⁴ In general, second generation antihistamines exhibit favorable pharmacokinetics. They have a rapid onset of action, near complete absorption, widespread tissue penetration, all while having minimal central nervous system penetration.² Despite the amount of evidence supporting second-generation antihistamines for the treatment of allergic rhinitis, they are not effective in the treatment of nasal congestion.

Because of the limited efficacy of antihistamines for the treatment of nasal congestion, they are often combined with a decongestant. Second-generation antihistamines combined with pseudoephedrine have been shown to improve symptoms and quality of life in patients with allergic rhinitis and nasal congestion compared to antihistamines alone.¹⁵ Pseudoephedrine is an alpha-1 receptor agonist that causes

vasoconstriction in the nasal mucosa, decreasing inflammation of the airways.¹¹ All second-generation antihistamines with the exception of levocetirizine, are available in combination with pseudoephedrine. Although acrivastine is available in combination with pseudoephedrine it is not currently available in the United States as a single entity agent.¹² The combination products are only indicated for the treatment of seasonal allergic rhinitis, with the exception of cetirizine/pseudoephedrine which is additionally approved for the treatment of perennial allergic rhinitis.^{12,16-18} Second-generation antihistamine/pseudoephedrine combinations are approved for use in patients ≥12 years of age.

Allergic rhinitis has been estimated to affect between 10 and 30% of all adults and up to 40% of children.¹⁴ Alternatively, up to 20% of individuals experience idiopathic urticaria at sometime in their life, with 25% of these cases becoming a chronic.¹⁹ According to the current clinical guidelines for the management of allergic rhinitis, treatment should consist of patient education, allergen avoidance activities and pharmacological therapies. Intranasal corticosteroids should be considered first-line therapy in the majority of patients with moderate to severe allergic rhinitis and may also be effective in some forms of nonallergic rhinitis.¹⁹ Although, intranasal corticosteroids are the most effective drugs for treating allergic rhinitis, in patients with a strong preference for the oral route, second-generation antihistamines are a reasonable alternative. Considering their safety profile, second generation antihistamines should be considered as first-line symptomatic treatment for urticaria.²⁰

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Single Entity Agents		
Cetirizine* (All Day Allergy [®] , All Day Allergy Children's [®] , Zyrtec [®] , Zyrtec Children's Allergy [®] , Zyrtec Children's Hives Relief [®] , Zyrtec Hives Relief [®])	Second-generation antihistamine	✓ †
Desloratadine (Clarinet [®] , Clarinet Reditabs [®])	Second-generation antihistamine	-
Fexofenadine* (Allegra [®] , Allegra ODT [®])	Second-generation antihistamine	✓ †
Levocetirizine* (Xyzal [®])	Second-generation antihistamine	✓
Loratadine* (Alavert [®] , Claritin [®] , Claritin Children's Allergy [®] , Claritin Reditabs [®] , Clear-atine Children's [®] , Dimetapp ND [®] , Equate Allergy Relief 24-Hour [®] , Triaminic Allerchews [®])	Second-generation antihistamine	✓ †
Combination Products		
Acrivastine/pseudoephedrine (Semprex-D [®])	Second-generation antihistamine/nasal decongestant	-
Cetirizine/pseudoephedrine* (Zyrtec-D [®] , All Day Allergy-D 12-Hour [®])	Second-generation antihistamine/nasal decongestant	✓ †
Desloratadine/pseudoephedrine (Clarinet-D 12-hour [®] , Clarinet-D 24-hour [®])	Second-generation antihistamine/nasal decongestant	-
Fexofenadine/pseudoephedrine* (Allegra-D 12-hour [®] , Allegra-D 24-hour [®])	Second-generation antihistamine/nasal decongestant	✓ †
Loratadine/pseudoephedrine* (Alavert Allergy & Sinus D 12-hour [®] , Claritin-D 12-hour [®] , Claritin-D [®] 24-hour [®] , Clear-Atadine-D [®] Equaline 24-Hour Allergy and Congestion Relief [®])	Second-generation antihistamine/nasal decongestant	✓ †

ODT=orally disintegrating tablet

* Product is available over-the-counter in at least one dosage form or strength.

† Generic is available in at least one dosage form or strength.

Indications

Table 2. Food and Drug Administration Approved Indications¹¹⁻¹²

Generic Name	Seasonal Allergic Rhinitis	Perennial Allergic Rhinitis	Chronic Idiopathic Urticaria
Single Entity Agents			
Cetirizine	✓	✓	✓
Desloratadine	✓	✓	✓
Fexofenadine	✓		✓
Levocetirizine	✓	✓	✓
Loratadine	✓		✓
Combination Products			
Acrivastine/pseudoephedrine	✓		
Cetirizine/pseudoephedrine	✓	✓	
Desloratadine/pseudoephedrine	✓		
Fexofenadine/pseudoephedrine	✓		
Loratadine/pseudoephedrine	✓		

Pharmacokinetics**Table 3. Pharmacokinetics^{5-12,16-18}**

Generic Name	Bioavailability (%)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Single Entity Agents				
Cetirizine	≥70*	60	None	7.4 to 9.0
Desloratadine	Not reported	40.6	3-OH-desloratadine	27
Fexofenadine	Not reported	11	None	14 to 18
Levocetirizine	≥85	85.4	None	7 to 9
Loratadine	Not reported	40	Descarboethoxyloratadine	12 to 15
Combination Products				
Acrivastine/pseudoephedrine	Not reported	84/65	Propionic acid derivative/norpseudoephedrine	1.9/6.2 [†]
Cetirizine/pseudoephedrine	Not reported	70/65	Norpseudoephedrine	7.9/6.0 [†]
Desloratadine/pseudoephedrine	Not reported	40/80	3-OH-desloratadine/norpseudoephedrine	27/6 [†]
Fexofenadine/pseudoephedrine	Not reported	11/65	Norpseudoephedrine	14.4/6.0 [†]
Loratadine/pseudoephedrine	Not reported	80/65	Descarboethoxyloratadine/norpseudoephedrine	8.4/6.0 [†]

* Reported for the oral solution, which is considered bioequivalent to other available formulations.

† The mean elimination half-life of pseudoephedrine is dependent on urinary pH. The elimination half-life is approximately three to six or nine to 16 hours when the urinary pH is five or eight, respectively.

Clinical Trials

Clinical trials have demonstrated that second-generation antihistamines are effective in treating and providing symptomatic relief of seasonal and perennial allergic rhinitis (SAR and PAR), as well as chronic idiopathic urticaria (CIU).¹³⁻¹⁵ In a systematic review conducted by Benninger and colleagues, oral antihistamines were determined to be less effective than intranasal corticosteroids at reducing symptoms of SAR (40.7 vs 23.5%; *P* value not reported), but more effective than intranasal corticosteroids for improving symptoms of PAR (51.4 vs 37.3%; *P* value not reported).¹³ Second-generation antihistamines in combination with pseudoephedrine can further improve symptoms of allergic rhinitis and provide an additional benefit of treating allergy-associated nasal congestion.¹⁵

In clinical trials, desloratadine, fexofenadine and levocetirizine have been shown to significantly improve symptoms of CIU compared to placebo.¹⁴ In a study by Monroe et al, treatment with desloratadine was

associated with a reduction in reflective pruritus scores after the first week of treatment (47.9 vs 21.9%; $P<0.001$), and throughout the trial compared to placebo (58.4 vs 40.4%; $P=0.04$). Patients receiving desloratadine showed a significant reduction in scores for both the number of hives (40.8 vs 19.9%; $P<0.001$) and the size of the largest hive (39.0 vs 19.3%; $P<0.001$) compared to patients receiving placebo.²¹ Similar results were reported by Ring et al in patients diagnosed with CIU.²² After six weeks, desloratadine was associated with significant improvements in reflective pruritus scores compared with patients who were treated with placebo (74.0 vs 48.7%; $P<0.001$). Instantaneous morning pruritus scores (24 hours post-dose) remained significantly reduced for patients in the desloratadine group compared to placebo (45.1 vs 3.5%; $P<0.033$), verifying the 24-hour activity of desloratadine for reducing symptoms of pruritus.

Kaplan and colleagues studied fexofenadine against placebo in 255 patients with a history of CIU. Fexofenadine treatment reduced diary scores for the mean number of wheals compared to placebo over four weeks (0.78 vs 0.40; $P<0.001$). Furthermore, improvements in pruritus severity scores were higher in the fexofenadine-treatment group compared to placebo (1.04 vs 0.57; $P<0.001$).²³ In a small trial against loratadine (N=18), Boyle et al determined that fexofenadine had a significantly greater percentage inhibition of wheal compared to placebo and loratadine (43.1 vs 10.0 and 15.2%, respectively; $P<0.001$).²⁶ For the mean time to onset of wheal inhibition, fexofenadine was significantly faster than placebo (2.26 vs 5.27 hours; $P<0.001$) and loratadine (2.26 vs 5.44 hours; $P<0.01$). A study by Purohit et al found no difference between cetirizine and fexofenadine for the time required to reach 95% wheal inhibition ($P=0.34$).²⁹

In another study comparing cetirizine to fexofenadine for the treatment of CIU, 51.9% of cetirizine-treated patients were symptom-free after four weeks compared to treatment with fexofenadine (4.4%; $P=0.00001$).²⁶ Additionally, fewer patients receiving cetirizine were considered to be non-responders compared to treatment with fexofenadine (11.5 vs 53.3%; P value not reported). Garg et al found no difference in wheal and flare response in 50 patients with CIU after six weeks of treatment with cetirizine or levocetirizine.²⁷ Cetirizine was associated with a greater relief of itching 24 hours post-dose in 70% of patients ($P<0.005$). Potter and colleagues concluded that levocetirizine decreased pruritus severity scores significantly more than desloratadine (1.17 vs 1.04; $P<0.001$) after four weeks of treatment in 886 patients.³⁰ Symptomatic improvement following treatment was reported by 95.9% of patients in the levocetirizine group, and 93.9% of patients in the desloratadine treatment group (P value not reported).

Desloratadine has been shown to be more effective than placebo at reducing symptoms of PAR. Kim et al reported a significant reduction in total symptom scores (TSS) for patients who were treated with desloratadine compared to those treated with placebo (26.6 vs 22.3%; $P=0.001$).³² In a four week placebo-controlled study (N=676), desloratadine improved TSS scores by 35.0% compared to placebo (27.4%; $P=0.005$). Patients treated with desloratadine had statistically significant improvements from baseline in individual symptom scores compared to placebo for rhinorrhea and sneezing, ($P\leq 0.005$ for both comparisons), and for postnasal drip/drainage and nasal itching ($P\leq 0.013$ for both comparison).³³

Patients with PAR who were treated with levocetirizine had significantly improved total four symptom scores (T4SS) after four weeks of treatment (56.0 vs 29.2%; $P<0.001$) compared to patients who received placebo.³⁵ Levocetirizine continued to provide greater relief of T4SS over the six week treatment period ($P<0.001$). In a study by Lee et al, patients randomized to receive cetirizine had greater reductions in TSS scores after 12 weeks of treatment compared to levocetirizine and placebo treatment groups (5.54 vs 3.30 and 0.18, respectively; $P<0.05$).³⁶ There was no difference in quality of life between patients receiving cetirizine or levocetirizine. In a study by Lai et al, patients with PAR who were given cetirizine for three months had greater improvements in TSS at all evaluated time periods compared to patients who received ketotifen or oxatomide (not currently available in the United States) ($P<0.05$).³⁸ At week 12, cetirizine was significantly more effective at reducing rhinorrhea compared to the other two active treatment groups and placebo ($P<0.01$).

All agents listed in Table 2 have been shown to be effective at ameliorating the symptoms associated with SAR. Treatment with fexofenadine was associated with a greater improvement in scores for allergy associated "impairment at work" vs placebo (-5.6 vs 3.4%; $P=0.016$), and "impairment while working" due

to allergy symptoms compared to placebo (-5.6 vs 3.2%; $P=0.019$).³⁴ Fexofenadine also significantly improved quality of life scores when compared to placebo over two weeks of treatment (values not reported; $P=0.005$). Van Cauwenberge et al studied fexofenadine, loratadine and placebo in 688 patients with SAR and found that fexofenadine and loratadine treatment significantly reduced TSS scores from baseline compared with placebo ($P\leq 0.0001$ and $P\leq 0.001$ for fexofenadine and loratadine, respectively).³⁵ Fexofenadine and loratadine treatments groups were not directly compared for improvement in SAR symptoms.

Treatment with cetirizine has been shown to reduce total symptom complex scores more than loratadine or placebo. In a two day environmental exposure unit study for symptoms of SAR, 202 patients received cetirizine, loratadine or placebo once daily.⁴² Cetirizine was associated with a 36.7% reduction in total symptom complex scores compared to patients treated with loratadine or placebo (15.4 and 12.0%, respectively; $P\leq 0.01$). In another study, Day et al found that cetirizine produced significantly greater reductions than loratadine for the individual symptoms of runny nose ($P<0.001$), itchy nose ($P=0.013$), sniffles ($P=0.008$), postnasal drip ($P=0.003$), itchy ears and eyes ($P=0.038$), itchy throat ($P=0.019$), nose blows ($P=0.001$) and nasal congestion ($P<0.001$).⁴³ In two studies, desloratadine was shown to have a smaller effect on total nasal symptom scores (TNSS) compared to diphenhydramine over one week of treatment ($P<0.001$) and was not significantly different from placebo ($P=0.12$) for symptom improvements.⁴⁵ In another two day environmental exposure unit study, major symptom complex scores were significantly reduced with levocetirizine treatment compared to desloratadine (6.510 ± 0.406 vs 4.650 ± 0.407 ; $P=0.001$) and placebo (2.830 ± 0.501 ; $P<0.001$).⁴⁷ There were no differences between levocetirizine or desloratadine treatment groups in regards to patient satisfaction at the completion of the study.

All second-generation antihistamine/pseudoephedrine combination products are considered to be equally effective at reducing symptoms of allergic rhinitis and nasal congestion. In a study by Dockhorn et al, 702 patients received acrivastine/pseudoephedrine, the individual components, or placebo over 14 days.⁴⁸ Patients who received the combination treatment had significant reductions in mean diary symptom scores compared to acrivastine alone (7.6 vs 5.0; $P<0.001$), pseudoephedrine alone (5.8; $P=0.002$) and placebo (3.9; $P<0.001$). These results were confirmed by Williams and colleagues in a study of 676 patients with SAR who were randomized to receive acrivastine/pseudoephedrine, each individual agent alone or placebo over 14 days.⁴⁹

Desloratadine in combination with pseudoephedrine has been found to effectively reduce TSS by 39% compared with pseudoephedrine alone (32%; $P=0.001$) and desloratadine alone (34%; $P\leq 0.02$).⁵⁰ In a study by Grubbe et al (N=598) patients who received desloratadine/pseudoephedrine reported greater reductions in TSS plus nasal congestion scores compared to patients who were randomized to receive desloratadine (37.4 vs 26.7%; $P<0.001$) or pseudoephedrine (31.2%; $P=0.006$).⁵³ Despite reductions in symptoms after 14 days of treatment, there was no difference in patient reported improvements in SAR between the treatment groups. Both fexofenadine and loratadine combinations were shown to be effective at reducing both TSS and TNSS compared to their individual ingredients, but have not been compared against other antihistamine/pseudoephedrine combination products.^{52,54}

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Chronic Idiopathic Urticaria				
Monroe et al ²¹ Desloratadine 5 mg QD vs placebo	DB, MC, PC, PG, RCT Patients ≥12 years of age with a ≥6 week history of CIU and experiencing an active flare with visible wheals for ≥3 days/week, and a total reflective pruritus score at baseline of ≥14	N=226 6 weeks	Primary: Change from baseline in average reflective AM/PM pruritus scores during the first week of treatment Secondary: Change from baseline in reflective AM/PM scores for the number of hives, size of the largest hive, TSS, instantaneous AM, instantaneous PM, and reflective AM/PM scores for pruritus	Primary: The reduction from baseline in patient-evaluated mean AM/PM reflective pruritus scores over the first week of treatment was significantly greater in the desloratadine treatment group than in the placebo group (1.05 [47.9%] vs 0.52 [21.9%]; <i>P</i> <0.001). The improvement with desloratadine was maintained throughout the trial. After six weeks, desloratadine-treated patients continued to have significantly improved symptom scores compared to patients treated with placebo (58.4 vs 40.4%; <i>P</i> =0.04) Secondary: Compared to placebo, treatment with desloratadine significantly reduced scores for the number of hives (40.8 vs 19.9%) and the size of the largest hive (39.0 vs 19.3%) (<i>P</i> <0.001 for both comparisons). Compared to placebo, desloratadine treatment provided a significantly greater improvement in AM/PM reflective total TSS over the first week of treatment (43.3 vs 21.4%; <i>P</i> <0.001). Patient-evaluated symptom control 24 hours post-dose (AM instantaneous pruritus score) improved 36.6% with desloratadine compared to placebo (14.8%; <i>P</i> =0.005). After the first week of treatment, desloratadine improved AM reflective, PM reflective, AM/PM instantaneous, and PM instantaneous assessments of pruritus and TSS compared to placebo (<i>P</i> values not reported). Patients treated with desloratadine had significantly greater improvements in reflective TSS over the first week of treatment compared to placebo (43.3 vs 21.4%; <i>P</i> <0.001). An improvement in TSS of 37.6% was realized as early as 24 hours after the first dose (day two of analysis) in desloratadine-treated patients compared with 14.1% for patients given placebo (<i>P</i> <0.001).
Ring et al ²² Desloratadine 5 mg QD vs	DB, MC, PC, PG, RCT Patients ≥12 years of age with a ≥6 week history of CIU	N=190 6 weeks	Primary: Change from baseline in average reflective AM/PM pruritus scores during first week of	Primary: Patients treated with desloratadine had significantly greater reductions from baseline in average AM/PM reflective pruritus scores over the first week of treatment compared to placebo (1.22 [56.0%] vs 0.49 [21.5%]; <i>P</i> <0.001). After six weeks of treatment, pruritus scores remained significantly improved for patients receiving desloratadine compared to patients treated with placebo (74.0 vs 48.7%;

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo	experiencing an active flare that must have been active for ≥3 weeks before screening, visible wheals for ≥3 days/week and a total reflective pruritus score at baselines of ≥14		<p>treatment</p> <p>Secondary: Changes in reflective AM/PM TSS, scores for the number of hives, and size of largest hive, individual AM and PM instantaneous scores for pruritus and, interference with sleep and daily activities</p>	<p>$P<0.001$).</p> <p>Secondary: Patients in the desloratadine group reported significantly greater reductions in AM/PM reflective TSS after one week compared to patients in the placebo group (51.6 vs 19.3%; $P<0.001$). Furthermore, desloratadine-treated patients maintained significant reductions in AM/PM reflective TSS compared to placebo for the duration of the trial ($P<0.001$).</p> <p>Over the first week of treatment, desloratadine significantly reduced scores for the number of hives and the size of the largest hive compared to placebo (values not provided; $P<0.001$ for both comparisons). Patients treated with desloratadine continued to have a reduced number of hives at all analyses of the study compared to placebo-treated patients ($P=0.011$ to $P<0.001$).</p> <p>Significant reductions in instantaneous AM pruritus scores (24 hours post-dose) were seen after the first week in patients who were receiving desloratadine compared to placebo (45.1 vs 3.5%; $P<0.001$). At week six, instantaneous AM pruritus remained significantly improved for patients treated with desloratadine compared to placebo (68.9 vs 46.0%; $P<0.033$).</p> <p>Treatment with desloratadine was associated with improved sleep (AM reflective score; $P\leq 0.03$), and increases in daily activities (PM reflective score) compared to placebo ($P<0.001$).</p>
Kaplan et al ²³ Fexofenadine 180 mg QD vs placebo	DB, MC, PC, PG, RCT Patients ≥12 years of age with a diagnosis of CIU and a history of wheals ≥3 days/week for the previous 6 weeks; to qualify, patients must have reflectively rated	N=255 4 weeks	<p>Primary: Change from baseline in mean number of wheals score and mean daily severity pruritus scores (0=none and 4=very severe)</p> <p>Secondary: Improvements in wheals and pruritus,</p>	<p>Primary: Patients treated with fexofenadine experienced a significant reduction in the mean number of daily wheals (mean number of wheals score) in comparison to patients in the placebo group (0.78 vs 0.40; $P<0.001$). Similarly, significantly greater reductions in pruritus severity scores were observed in patients treated with fexofenadine vs placebo (1.04 vs 0.57; $P<0.001$).</p> <p>Secondary: Fexofenadine was associated with significant improvements in mean number of wheals scores compared to placebo at each week throughout the treatment period ($P=0.003$ to $P<0.001$). By the fourth week of treatment, fexofenadine continued to improve mean number of wheals scores compared to placebo (1.20 vs 0.76; $P<0.02$).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	pruritus in the past 12 hours as ≥ 2 on a scale of 4		wheals and pruritus at trough drug levels, MoTSS, and global assessment of CIU	<p>Mean reductions in instantaneous mean number of wheals and pruritus severity scores (evaluated immediately before the next dose) were significantly greater for patients treated with fexofenadine vs placebo ($P < 0.02$ and $P < 0.001$, respectively).</p> <p>Significantly greater improvements in morning and evening MoTSS (a sum of scores for the frequency, size, and duration of lesions in addition to pruritus severity scores), were observed for patients treated with fexofenadine vs placebo at each weekly evaluation, and at the completion of the study ($P < 0.001$ for all weekly and overall comparisons).</p> <p>Global assessment evaluations for improvement completed by both patients and providers resulted in higher improvement scores for patients in the fexofenadine treatment group vs placebo (values not reported; $P < 0.001$ for both comparisons).</p>
<p>Nettis et al²⁴</p> <p>Levocetirizine 5 mg QD</p> <p>vs</p> <p>placebo</p>	<p>DB, PC, RCT</p> <p>A diagnosis of CIU was required for inclusion into the study</p>	<p>N=106</p> <p>8 weeks</p>	<p>Primary: Change from baseline in TSS, number of wheals, number of daily episodes, size of wheals, pruritus severity and quality of life</p> <p>Secondary: Not reported</p>	<p>Primary: After six weeks of treatment, levocetirizine significantly reduced TSS compared to placebo (81 vs 1%; $P < 0.05$). Moreover, 27 patients treated with levocetirizine (53%) had complete resolution of symptoms, compared to zero patients in the placebo group at the end of treatment ($P < 0.05$). Complete resolution of symptoms was still apparent in 24% of levocetirizine-treated patients one week after discontinuing therapy.</p> <p>Patients treated with levocetirizine had significant reductions in the number of urticaria episodes compared to placebo throughout the trial ($P < 0.05$). Levocetirizine treatment was associated with an 84% reduction in the number of separate episodes during the first three weeks of treatment. After the treatment phase was completed, there was a 33% increase in the number of urticaria episodes in patients treated with levocetirizine.</p> <p>During the six week treatment period, levocetirizine therapy significantly reduced the number of wheals by 79% from baseline ($P < 0.05$). At the one-week follow-up visit, 58% of levocetirizine-treated patients continued having a reduced number of wheals compared to placebo ($P < 0.05$). Furthermore, levocetirizine treatment reduced scores for size of wheals by 75% compared with baseline ($P < 0.05$).</p> <p>Levocetirizine was more effective than placebo at reducing patient scores for pruritus throughout the trial. At the end of the treatment period, patients receiving</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>levocetirizine reported an 85% reduction in pruritus severity ($P<0.05$). There were small, not significant changes in pruritus scores for placebo-treated patients throughout the trial.</p> <p>Levocetirizine treatment significantly increased quality of life compared to patients treated with placebo (P values not reported).</p> <p>Secondary: Not reported</p>
<p>Kapp et al²⁵</p> <p>Levocetirizine 5 mg QD</p> <p>vs</p> <p>placebo</p>	<p>DB, MC, PC, PG, RCT</p> <p>Patients with CIU and a history of wheals ≥ 3 days/week for the previous 6 weeks and ≥ 3 days of moderate or severe pruritus and wheals over the one week enrollment period</p>	<p>N=166</p> <p>4 weeks</p>	<p>Primary: Change in pruritus severity scores after one and four weeks of treatment</p> <p>Secondary: Changes in the number and size of wheals, the presence/absence of dermatographism, angioedema, and pressure-induced urticaria, HRQL and the impact of the disease on lost workdays reported by DLQI</p>	<p>Primary: After the first week of treatment, patients in the levocetirizine group had significant reductions in mean pruritus severity scores compared to patients treated with placebo (1.04 vs 0.26; $P<0.001$). After four weeks, the mean pruritus severity score remained significantly improved for levocetirizine-treated patients compared to patients receiving placebo (1.12 vs 0.50; $P<0.001$). Levocetirizine-treated patients reported a shorter duration of pruritus after the first week, and throughout the entire study period, compared to placebo ($P<0.001$ for all comparisons).</p> <p>At week four, investigator assessment indicated that 85.3% of the patients treated with levocetirizine had mild or no pruritus compared to 66.7% of those receiving placebo (P values not reported).</p> <p>Secondary: Objective data relative to the number and size of wheals favored the levocetirizine group, with the number of wheal score decreasing from two (seven to 12 wheals) to one (one to six wheals; $P<0.001$) and the size of the wheals decreasing from 1.75 to 0.96 ($P=0.001$). There were no differences between the two groups with regard to the presence of angioedema, dermatographism, and pressure induced urticaria.</p> <p>The overall DLQI score decreased by 7.3 units in the levocetirizine group vs 2.4 units with placebo, correlating to a 24% improvement and 8% improvement, respectively; P values not reported. Patients treated with levocetirizine had lower work absenteeism compared to placebo (0.8 vs 1.8 days/month, respectively; P value not reported). Presenteeism (decrease in productivity while at work) was five times higher in placebo treated patients compared to levocetirizine-treated patients (P values not reported).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Boyle et al ²⁶ Fexofenadine 60 mg BID vs loratadine 10 mg QD vs placebo	DB, PC, RCT, XO Healthy patients 18 to 85 years of age with no history of SAR or PAR	N=18 1 day	Primary: Mean percentage reduction in histamine-induced wheal and flare areas, time to onset of action, duration of action, mean maximum inhibition and the time to maximum inhibition Secondary: Not reported	Primary: Fexofenadine had a significantly greater overall inhibition of wheal compared to placebo and loratadine (43.1 vs 10.0 and 15.2%, respectively; $P<0.001$ for both comparisons). Fexofenadine also produced a significantly greater overall percentage of flare inhibition compared to placebo (43.0 vs 3.5%; $P<0.01$) and loratadine (8.9%; $P<0.001$). There was no difference in the percentage of wheal or flare inhibition between loratadine and placebo. For the mean time to onset of wheal inhibition, fexofenadine was significantly faster than placebo (2.26 vs 5.27 hours; $P<0.001$) and loratadine (2.26 vs 5.44 hours; $P<0.01$). The onset of wheal inhibition with loratadine was not significantly different from placebo. For wheal inhibition, fexofenadine had a significantly longer mean duration of action compared to loratadine (11.47 vs 6.28 hours; $P<0.05$) and placebo (11.47 vs 2.83 hours; $P<0.001$). Fexofenadine provided a significantly greater mean maximum inhibition of wheal and flare compared to loratadine and placebo ($P<0.01$). There was no difference in mean maximum inhibition of wheal and flare between loratadine and placebo. Maximum wheal inhibition was achieved significantly faster with fexofenadine compared to loratadine ($P<0.01$). Secondary: Not reported
Garg et al ²⁷ Cetirizine 10 QD vs levocetirizine 5 mg QD	OL, XO Patients with CIU who were attending an allergy clinic; patients received cetirizine for six weeks, and those showing complete symptomatic control were given levocetirizine for six additional weeks	N=50 12 weeks	Primary: Weekly assessment of wheal flare and itch response using a visual analog scale and adverse events Secondary: Not reported	Primary: There was no significant difference between cetirizine and levocetirizine in wheal and flare response over six weeks of treatment. Cetirizine was more efficacious than levocetirizine in itch response (24 hours vs 14 to 16 hours; $P<0.005$) in 70% of the patients. Occasional headache and fatigue were noted in 10% of the patients in the levocetirizine group. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Handa et al ²⁸ Cetirizine 10 mg QD vs fexofenadine 180 mg QD	DB, RCT Patients 17 to 65 years of age with CIU for ≥2 days/week for six consecutive weeks	N=116 4 weeks	Primary: Response to treatment defined by patients attaining symptom free response, partial improvement, or no improvement Secondary: Not reported	Primary: After four weeks of treatment, more patients in the cetirizine group became symptom-free compared to the fexofenadine group (51.9 vs 4.4%; <i>P</i> =0.00001). Moreover, fewer cetirizine-treated patients were reported as non-responders compared to fexofenadine (11.5 vs 53.3%; <i>P</i> value not reported). More patients treated with fexofenadine had a partial response to therapy compared to cetirizine (42.2 vs 36.5%; <i>P</i> value not reported). Secondary: Not reported
Purohit et al ²⁹ Fexofenadine 180 mg QD vs cetirizine 10 mg QD	DB, RCT, XO Healthy patients 18 to 60 years of age with no personal history of allergies or positive IgE test result	N=42 1 day	Primary: Time to reach 95% inhibition of histamine induced wheal response Secondary: Percentage of patients exhibiting 95% inhibition of wheal and flare before or at the median time to 95% inhibition	Primary: There were no differences between the treatment groups for the time required to reach 95% inhibition of histamine induced wheals (2.46±0.71 vs 2.55±0.57 hours for fexofenadine and cetirizine, respectively; <i>P</i> =0.34). Secondary: The percentage of patients who experienced 95% wheal inhibition at or before the mean time of 2.5 hours did not differ between treatment groups (29 vs 24% for fexofenadine and cetirizine, respectively; <i>P</i> =0.37). Furthermore, there was no difference observed between the fexofenadine and cetirizine groups for the percentage of patients who experienced a 95% reduction in flares at, or before the median time of three hours (<i>P</i> =0.12).
Potter et al ³⁰ Levocetirizine 5 mg QD vs desloratadine 5 mg QD	DB, MC, PG, RCT Patients ≥18 years of age with a history of CIU for ≥6 weeks in the past 3 months; all patients had a pruritus severity score ≥2 and the number of wheal	N=886 4 weeks	Primary: Change in mean pruritus severity scores after the first week of treatment Secondary: Changes in mean pruritus severity scores after the fourth week of	Primary: Both treatments decreased pruritus severity scores after the first week of treatment, but levocetirizine was more effective than desloratadine (1.17 vs 1.04; <i>P</i> <0.001). Secondary: The difference between treatment groups was apparent from the first day of treatment (<i>P</i> =0.013). Levocetirizine continued to significantly reduce pruritus scores over the entire study period (1.33 vs 1.23; <i>P</i> =0.004). Patients treated with levocetirizine had significant reductions in pruritus duration

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	score ≥1 for at least 3 days in the week prior to randomization		treatment, mean changes in pruritus duration, number and size of wheals, mean CIU composite score, quality of life and investigator/patient global satisfaction with treatment	<p>scores compared to those receiving desloratadine after both the first week of treatment (1.03 vs 0.89; $P<0.002$) and for the entire duration of the study (1.18 vs 1.08; $P=0.009$). Scores for wheal size were reduced in levocetirizine-treated patients after the initial week of treatment compared to desloratadine ($P=0.025$), but after four weeks, there were no differences in scores between the patients receiving levocetirizine or desloratadine ($P=0.085$). Moreover, after four weeks of treatment, there were no differences in the number of wheals for patients who received levocetirizine or desloratadine ($P=0.353$).</p> <p>Composite scores for CIU were consistent with those reported for pruritus severity scores in both treatment groups. Quality of life was significantly improved for patients in both treatment groups. After the first week of treatment, 48.8% of levocetirizine and 41.1% of patients treated with desloratadine considered their sleep unaffected by the symptoms of CIU. This percentage increased to 66.8% and 63.2% for levocetirizine and desloratadine, respectively, at the end of the four week treatment period.</p> <p>Symptomatic improvement following treatment was reported by 95.9% of patients in the levocetirizine group, and 93.9% of patients in the desloratadine group.</p>
Anuradha et al ³¹ Loratadine 10 mg QD vs levocetirizine 5 mg QD	OL, RCT Patients 12 to 60 years of age with a history of CIU	N=60 4 weeks	Primary: Change from baseline in TSS Secondary: Not reported	<p>Primary: After four weeks of treatment, patients receiving levocetirizine experienced greater improvements in TSS compared to patients receiving loratadine (13.32 vs 4.85%; $P<0.001$). Moreover, at last follow up visit, a greater number of patients in the levocetirizine treatment group maintained TSS improvements compared to loratadine-treated patients (72.0 vs 34.5%; $P=0.025$).</p> <p>Secondary: Not reported</p>
Perennial Allergic Rhinitis				
Kim et al ³² Desloratadine 5 mg QD vs	DB, MC, PC, RCT Patients ≥12 years of age with a history of PAR for ≥2 years, a positive skin allergen test, a	N=1,179 4 weeks	Primary: Change from baseline in AM/PM reflective TSS after four weeks Secondary:	<p>Primary: Patients treated with desloratadine had significantly greater improvements in AM/PM reflective TSS after four weeks compared to patients in the placebo group (3.9 [26.6%] vs 3.2 [22.3%]; $P=0.001$). The difference in symptom reduction between groups began as early as day two of treatment ($P<0.02$).</p> <p>Secondary:</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo	TSS score ≥ 9 , a TNSS score ≥ 5 , and a TNNSS ≥ 4 at baseline		Changes from baseline in TNSS, TNNSS, and PNIF	<p>Reductions from baseline in TNSS were greater with desloratadine compared to placebo (2.1 [23.7%] vs 1.8 [19.8%]; $P=0.004$). Improvements were significant at all time points ($P \leq 0.04$) except on day two. Similarly, desloratadine treatment was significantly more effective than placebo at reducing TNNSS (1.8 [30.6%] vs 1.5 [25.9%]; $P < 0.001$) beginning on day two of treatment and continuing for the duration of the study.</p> <p>Both the desloratadine and placebo groups increased PNIF throughout the study. Desloratadine significantly improved morning PNIF compared to placebo (10.2 vs 7.6 L/minute; $P=0.03$), but there was no difference in evening values between the groups.</p>
<p>Simons et al³³</p> <p>Desloratadine 5 mg QD</p> <p>vs</p> <p>placebo</p>	<p>DB, MC, PC, PG, RCT</p> <p>Patients ≥ 12 years of age with a history of PAR for ≥ 2 years with a positive skin test within the previous 12 months, and a TSS ≥ 10 at screening</p>	<p>N=676</p> <p>4 weeks</p>	<p>Primary: Change from baseline in AM/PM instantaneous TSS scores</p> <p>Secondary: AM/PM reflective TSS, TNSS, TNNSS, and each of several individual symptom scores</p>	<p>Primary: After four weeks of treatment, patients treated with desloratadine had greater improvements in AM/PM instantaneous TSS scores compared to placebo (35.0 vs 27.4%; $P=0.005$).</p> <p>Secondary: Patients who received desloratadine had greater reductions from baseline in AM/PM reflective TSS scores compared to patients in the placebo group (37.9 vs 32.3%; $P=0.007$).</p> <p>Patients treated with desloratadine had significantly greater improvements in instantaneous and reflective TNSS throughout the study than patients who received placebo ($P \leq 0.005$). Moreover, desloratadine treatment was associated with a greater mean percentage improvement in TNSS after four weeks of treatment when compared to placebo (values not reported; $P=0.023$).</p> <p>Patients randomized to the desloratadine treatment group had a statistically significant decrease from baseline in individual symptom scores compared to placebo for rhinorrhea and sneezing, ($P \leq 0.005$ for both comparisons), as well as for postnasal drip/drainage and nasal itching ($P \leq 0.013$ for both comparisons). There was no difference between treatment groups for improvements in nasal congestion.</p>
<p>Potter et al³⁴</p> <p>Levocetirizine 5 mg</p>	DB, MC, PC, PG, RCT	<p>N=306</p> <p>4 weeks</p>	<p>Primary: Change from baseline in T4SS</p>	<p>Primary: During the first two weeks of treatment, patients receiving levocetirizine had significant improvements from baseline in T4SS scores compared to placebo (1.46</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo	Children 6 to 12 years of age with ≥1 year history of PAR and a positive skin test to house dust mites in the previous 12 months; children must have had a T4SS score ≥5 at any point of the selection period		during the first two weeks of treatment Secondary: Change from baseline in T4SS during the four-week treatment period, changes in PRQLQ scores from baseline, and investigators global evaluation of disease	[19.4%] vs 0.76 [10.1%]; <i>P</i> =0.001). Secondary: Reductions in T4SS scores associated with levocetirizine treatment continued throughout the treatment period. At the end of week four, T4SS scores remained significantly improved for patients treated with desloratadine compared to placebo (1.94 [25.7%] vs 1.32 [17.5%]; <i>P</i> =0.008). Levocetirizine improved the five PRQLQ domains: nose symptoms, eye symptoms, practical problems, other symptoms and activity limitations more than treatment with placebo during the first week of treatment (0.4 vs 0.2; <i>P</i> =0.015), and at week two (0.6 vs 0.4; <i>P</i> =0.014). There was no difference in PRQLQ domains between patients receiving levocetirizine or placebo at week four. For global evaluation of improvement, investigators rated 57.1% of patients treated with levocetirizine as “markedly or moderately improved”, compared to 44.7% of patients treated with placebo. This outcome was determined not to be statistically significant (<i>P</i> value not reported).
Potter et al ³⁵ Levocetirizine 5 mg QD vs placebo	DB, MC, PC, RCT Patients ≥12 years of age with a positive skin test to house dust mites within the previous 12 months and a T4SS ≥5 during the run-in period	N=294 8 weeks	Primary: Change from baseline in T4SS after weeks one and four (for the results to be significant, the difference in scores had to be 50% or higher for treatment compared to placebo) Secondary: Mean T4SS over the six week treatment period, mean individual symptom scores after week one, four and over	Primary: Patients treated with levocetirizine experienced greater reductions in mean T4SS compared to placebo after the first and fourth week of treatment (2.63 vs 1.41 and 3.40 vs 2.18 for the first and fourth week, respectively; <i>P</i> <0.001 for both comparisons). The relative improvement in T4SS over the first four weeks was significantly greater for patients receiving levocetirizine than the reductions for patients treated with placebo (3.40 [56.0%] vs 2.18 [29.2%]; <i>P</i> <0.001). Secondary: Levocetirizine treatment continued to improve T4SS over the total six week treatment period compared to placebo (3.64 [47.0%] vs 2.47 [33.1%]; <i>P</i> <0.001). Levocetirizine treatment significantly improved all individual symptoms to a greater extent than placebo across all treatment weeks (<i>P</i> <0.001 for all symptoms except ocular pruritus [<i>P</i> =0.008], and nasal congestion [<i>P</i> =0.002]). Furthermore, patients in the levocetirizine treatment group had significantly reduced nasal congestion symptom scores over six weeks of treatment in comparison to placebo-treated patients (<i>P</i> <0.001). Relative improvement of nasal congestion was seen in 83% of patients receiving levocetirizine.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			the total treatment period	
Lee et al ³⁶ Cetirizine 10 mg QD vs levocetirizine 5 mg QD vs placebo	DB, PC, RCT Children 6 to 12 years of age with moderate-to-severe PAR ≥1 year confirmed by a positive skin test to house dust mites	N=74 12 weeks	Primary: Change from baseline in TSS, PRQLQ, nPEFR, serum IgE levels, and blood eosinophil counts Secondary: Not reported	Primary: Patients treated with cetirizine had significant reductions in TSS at both four and eight weeks compared to levocetirizine (3.34 vs 2.33 and 4.40 vs 2.59 at weeks four and eight, respectively; <i>P</i> <0.05 for both comparisons). After 12 weeks of treatment, cetirizine was associated with significant improvements in TSS compared to both levocetirizine and placebo (5.54 vs 3.30 and 0.18, respectively; <i>P</i> <0.05). After 12 weeks, patients in both treatment groups had significant reductions in PRQLQ scores compared to placebo (19.73 and 24.09 vs 1.63 for cetirizine and levocetirizine vs placebo, respectively; <i>P</i> <0.05 for both comparisons vs placebo). There was no difference between cetirizine and levocetirizine in regards to PRQLQ scores (<i>P</i> =0.095). Treatment with cetirizine significantly improved nPEFR values after 12 weeks compared to levocetirizine (59.35 vs 21.67; <i>P</i> <0.05) and placebo (2.50; <i>P</i> <0.05). Cetirizine significantly improved nPEFR scores compared to levocetirizine at both weeks four and eight (<i>P</i> <0.05 for both comparisons). There were no changes in IgE levels between the treatment groups after 12 weeks of treatment. Cetirizine reduced total blood eosinophil counts compared to both levocetirizine and placebo (<i>P</i> <0.05). Secondary: Not reported
Ciprandi et al ³⁷ Desloratadine 5 mg QD vs levocetirizine 5 mg QD	DB, PC, PG, RCT Patients ≥18 years of age with a history of PAR for ≥2 years, a positive skin test to perennial allergens, experiencing	N=30 4 weeks	Primary: Change from baseline in TSS over four weeks, changes in nasal airflow and decongestion evaluated by rhinomanometry,	Primary: After four weeks of treatment, TSS was significantly improved for patients in both the desloratadine and levocetirizine groups compared to placebo (no values reported; <i>P</i> <0.05 and <i>P</i> <0.01 for desloratadine and levocetirizine, respectively). Furthermore, both treatments were more effective than placebo at relieving symptoms of nasal obstruction, sneezing, rhinorrhea and itchy nose (<i>P</i> <0.001 and <i>P</i> <0.05 for desloratadine and levocetirizine, respectively, compared to placebo). Patients treated with levocetirizine had significant increases in nasal airflow

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo	rhinitis symptoms during the previous 2 weeks, and a TSS score ≥ 6 at baseline		eosinophil counts, and cytokine counts Secondary: Not reported	<p>compared to placebo (29 vs -13%; $P < 0.001$). There was also a greater increase in nasal airflow for patients in the desloratadine group compared to placebo (7 vs -13%; $P < 0.05$).</p> <p>Levocetirizine induced a significant increase in total nasal airflow volume after decongestion challenge (before therapy, 705.3\pm35.1 mL/second; after therapy, 790.9\pm42.5 mL/second; $P < 0.05$). Desloratadine did not significantly modify the total nasal airflow before or after treatment (P value not reported). Patients who were treated with placebo experienced reductions in total nasal airflow ($P < 0.05$).</p> <p>Significant reductions in eosinophil counts ($P < 0.03$) were seen in patients who received levocetirizine, whereas desloratadine and placebo did not affect eosinophil counts. Furthermore, both levocetirizine and desloratadine treatment groups had reductions in interleukin-4, while placebo did not affect interleukin-4 counts ($P < 0.05$ for both comparisons vs placebo).</p> <p>Secondary: Not reported</p>
Lai et al ³⁸ Cetirizine 10 mg QD vs ketotifen 1 mg BID vs oxatomide* 1 mg/kg BID vs placebo	DB, PC, RCT Patients 6 to 12 years of age with a ≥ 1 year history of moderate- to-severe PAR; patients had to have a positive skin test to house dust mites, and a positive response to mite-specific IgE	N=80 3 months	Primary: Changes in TSS, PRQLQ, nPEFR scores from baseline and change in eosinophil counts Secondary: Not reported	<p>Primary: Cetirizine, oxatomide and ketotifen significantly reduced TSS from baseline compared to placebo after four, eight, and twelve weeks ($P < 0.01$ for all comparisons vs placebo). After twelve weeks, cetirizine-treated patients had lower TSS compared to both oxatomide and ketotifen ($P < 0.05$).</p> <p>Treatment with cetirizine significantly improved mean rhinorrhea scores compared to placebo at weeks four, eight and twelve, ($P < 0.01$) and appeared to be significantly more efficacious than oxatomide at reducing rhinorrhea scores for both weeks eight and twelve ($P < 0.01$). At week twelve, cetirizine was significantly more effective at reducing rhinorrhea compared to the other two active treatment groups and placebo (values not reported; $P < 0.01$ for all comparisons).</p> <p>Cetirizine significantly reduced nasal obstruction more than placebo or ketotifen at week four ($P < 0.01$). At week eight and twelve, cetirizine continued to improve mean nasal congestion scores compared to placebo ($P < 0.01$), ketotifen ($P < 0.01$), and oxatomide ($P < 0.05$ for week eight and $P < 0.01$ for week twelve, respectively).</p> <p>Both cetirizine and oxatomide groups had reductions in PRQLQ scores compared</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>to the placebo group ($P<0.05$) at week twelve of treatment. Notably, there was no difference in PRQLQ scores between patients treated with cetirizine or oxatomide.</p> <p>Treatment with cetirizine significantly improved nPEFR after twelve weeks compared to oxatomide ($P<0.05$), ketotifen, and placebo ($P<0.01$ for both comparisons).</p> <p>There was no difference in total eosinophil counts between treatment groups.</p> <p>Secondary: Not reported</p>
Seasonal Allergic Rhinitis				
<p>Okubo et al³⁹</p> <p>Fexofenadine 60 mg BID</p> <p>vs</p> <p>placebo</p>	<p>DB, PC, RCT</p> <p>Japanese patients 20 to 55 years of age with cedar pollinosis symptoms for ≥ 2 years and a positive IgE test specific for Japanese cedar pollen; patients had to have a TSS score ≥ 4 with at least 2 symptoms rated higher than moderate on the first day of treatment</p>	<p>N=206</p> <p>2 weeks</p>	<p>Primary: Change from baseline in quality of life scores</p> <p>Secondary: Change from baseline in each of seven RQLQ domains, WPAI-AS questionnaire scores</p>	<p>Primary: Fexofenadine treatment significantly improved quality of life scores when compared to placebo over two weeks of treatment (values not reported; $P=0.005$).</p> <p>Secondary: Patients in the fexofenadine treatment group reported significantly greater improvements in four of seven RQLQ domains: activities ($P=0.047$), practical problems ($P=0.003$), nasal symptoms ($P=0.003$) and ophthalmic symptoms ($P\leq 0.001$).</p> <p>Treatment with fexofenadine was associated with greater reductions WPAI-AS scores for “impairment at work” due to allergy symptoms (5.6 vs +3.4%; $P=0.016$), and “impairment while working” due to allergy symptoms compared to placebo (5.6 vs +3.2%; $P=0.019$). There was no difference between treatment groups for percentage of work time missed.</p>
<p>Nathan et al⁴⁰</p> <p>Cetirizine/pseudoephedrine 5/120 mg BID</p>	<p>DB, MC, PC, PG, RCT</p> <p>Men and women with SAR</p>	<p>N=274</p> <p>5 weeks</p>	<p>Primary: Change from baseline in TSSC symptom scores</p>	<p>Primary: Cetirizine/pseudoephedrine was associated with a significant improvement in SAR symptoms throughout the study. The primary outcome, TSSC score, was reduced by 3.9 points (42.3%) overall in the cetirizine/pseudoephedrine group compared to a decrease of 2.3 points (23.6%) in the placebo group ($P<0.001$).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo	documented by a positive skin test in the previous 15 months, a symptom score of moderate or greater for ≥4 days before randomization; patients had to have mild-to-moderate asthma for ≥6 months preceding the study		Secondary: Mean change in individual SAR symptom scores and patient global assessment	Cetirizine/pseudoephedrine remained significantly more effective at reducing TSSC scores at both week two (3.7 vs 2.0; $P<0.001$), and week four compared to placebo (4.2 vs 2.7; $P<0.001$). Secondary: Cetirizine/pseudoephedrine was significantly more effective than placebo at reducing each individual SAR symptom at weeks two and four compared to placebo ($P=0.003$ to $P<0.001$). A significantly greater percentage of patients in the cetirizine/pseudoephedrine group reported improvements in SAR after five weeks compared to patients receiving placebo (50.4 vs 22.5%; $P<0.001$). Moreover, investigators determined that more patients in the cetirizine/pseudoephedrine group responded to therapy than patients treated with placebo (49.8 vs 22.7%; $P<0.001$).
Alejandro-Serra et al ⁴¹ Loratadine/ pseudoephedrine 0.2/2.4 mg/kg vs placebo	DB, PC, RCT, XO Patients 3 to 15 years of age with a diagnosis of SAR; confirmation of diagnosis was based on rhinoscopy and a positive skin allergen test	N=40 5 weeks	Primary: Change from baseline in mean TSS Secondary: Not reported	Primary: Patients treated with loratadine/pseudoephedrine had significantly greater reductions in mean TSS compared to placebo, (4.29 [27.8%] vs 2.31 [10.7%]; $P<0.001$). Moreover, combination therapy reduced the symptoms of sneezing/itching ($P<0.001$), nasal congestion ($P<0.01$) and nasal dripping ($P<0.05$) to a greater extent than placebo. Secondary: Not reported
Day et al ⁴² Cetirizine 10 mg QD vs loratadine 10 mg QD vs placebo	DB, PG, RCT Patients ≥16 years of age with a diagnosis of SAR that required pharmacologic treatment for ≥2 years preceding the study; diagnosis of SAR	N=202 2 days	Primary: Change from baseline in TSC and MSC scores Secondary: Change from baseline in TSC plus nasal congestion scores, changes in individual rhinitis	Primary: Overall, cetirizine reduced TSC scores by 36.7% compared to both loratadine and placebo (15.4 and 12.0% respectively; $P\leq 0.01$ for both comparisons). Cetirizine maintained improvements in TSC scores over all three evaluation periods compared to loratadine and placebo ($P\leq 0.01$). Cetirizine had a faster onset of action, determined by reductions in TSC scores one hour post-dose, compared to placebo ($P\leq 0.02$). The onset of loratadine was evident within three hours of dosing ($P\leq 0.02$). Cetirizine also reduced MSC scores by 37.4% compared to both loratadine and placebo (14.7 and 6.7% respectively; $P\leq 0.01$ for both comparisons). Cetirizine-

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	by skin test must have been completed in the last year		symptoms, and subject global and satisfaction evaluations	<p>treated patients reported significant reductions in MSC scores at all evaluation points of the study compared to patients receiving placebo ($P \leq 0.01$). The onset of action as assessed by reductions in MSC scores vs placebo was evident within one hour with cetirizine ($P \leq 0.01$) and three hours with loratadine ($P \leq 0.02$), patterns were consistent with reductions for TSC scores.</p> <p>Secondary: Overall, cetirizine reduced TSC plus nasal congestion scores by 33.7% compared to both loratadine and placebo (13.7 and 11.1% respectively; $P \leq 0.01$ for both comparisons).</p> <p>At both endpoints and all three assessment periods, cetirizine had significantly greater reductions in nose blows, runny nose/sniffles, itchy nose, watery eyes and postnasal drip compared to loratadine ($P \leq 0.05$ for all comparisons). Compared to placebo, treatment with cetirizine significantly reduced the number of nose blows, sneezes, runny nose/sniffles and postnasal drip ($P \leq 0.05$ for all comparisons).</p> <p>Treatment with cetirizine resulted in a larger percentage of improved patients compared to loratadine, but the differences between groups were not statistically significant. Patients treated with cetirizine reported increased satisfaction with therapy compared to both loratadine and placebo (64.1 vs 45.5 and 41.5%, respectively; $P = 0.04$).</p>
<p>Day et al⁴³</p> <p>Cetirizine 10 mg QD vs loratadine 10 mg QD vs placebo</p> <p>On day one, eligible patients evaluated baseline symptoms</p>	<p>DB, PG, RCT</p> <p>Patients ≥ 16 years of age with a history of SAR that required pharmacologic treatment for ≥ 2 years preceding the study and a positive skin test completed in the last year</p>	<p>N=360</p> <p>2 days</p>	<p>Primary: Change from baseline in TSC and MSC scores</p> <p>Secondary: Changes from baseline in TSC plus nasal congestion scores, individual rhinitis symptoms and subject global and satisfaction evaluations</p>	<p>Primary: Overall, patients treated with cetirizine had a 25.4% reduction in TSC scores compared to loratadine (11.2%; $P = 0.006$) and placebo (4.8%; $P < 0.001$). Improvements in TSC between loratadine and placebo was significant ($P = 0.002$). Cetirizine-treated patients had significant improvements in TSC scores compared to placebo at all evaluated periods ($P < 0.001$), and compared to loratadine at period I; ($P < 0.003$), but not periods II or III. Patients in the loratadine group experienced reductions in TSC scores in periods I and III compared with placebo ($P < 0.001$ for both), but not during period II.</p> <p>Cetirizine was associated with greater improvements in MSC scores (23.2%) compared to both loratadine (8.1%; $P \leq 0.01$) and placebo (12.0%; $P < 0.001$). The reductions in MSC scores between loratadine and placebo were also significant ($P < 0.001$). At each period, the reductions in MSC scores were significantly greater for cetirizine compared to placebo ($P < 0.001$), and the mean percentage reductions</p>

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<p>every 30 minutes from 8:30AM to 10:30AM (first dose of medication given at 10:00AM).</p> <p>Evaluations of patient-reported symptoms were completed every 30 minutes on day one from 10:00AM to 3:00PM (period I), on day 2 from 8:30AM to 10:00AM (period II) and on day 2 from 10:00AM to 2:30PM (period III).</p>				<p>in MSC scores with loratadine were greater than placebo at each period as well ($P=0.019$ to $P<0.001$). Cetirizine produced significantly greater percentage MSC score reductions than loratadine at periods I ($P=0.005$), and period II ($P=0.026$).</p> <p>Secondary: Overall, cetirizine reduced TSC plus nasal congestion scores by 23.9% compared to both loratadine (10.0%; $P=0.005$) and placebo (+4.8%; $P<0.001$).</p> <p>Cetirizine was more effective than loratadine for improving the individual symptoms of runny nose ($P<0.001$), itchy nose ($P=0.013$), sniffles ($P=0.008$), postnasal drip ($P=0.003$), itchy ears and eyes ($P=0.038$), itchy throat ($P=0.019$), nose blows ($P=0.001$) and nasal congestion ($P<0.001$). Additionally, cetirizine was significantly more effective at reducing all symptoms except cough compared to placebo ($P<0.001$).</p> <p>More patients treated with cetirizine reported experiencing major or moderate improvement in allergy symptoms when compared with placebo (55.0 vs 30.3%; $P=0.0001$). Patients who received loratadine also had improvements in allergy symptoms when compared to placebo (53.5 vs 30.3%; $P=0.003$).</p> <p>Cetirizine was associated with greater patient satisfaction compared to placebo (70.9 vs 45.4%; $P=0.0012$). Similar results were seen for the loratadine group compared to placebo (66.4%; $P=0.0012$).</p>
<p>Meltzer et al⁴⁴</p> <p>Cetirizine 10 mg QD</p> <p>vs</p> <p>loratadine 10 mg QD</p> <p>vs</p> <p>placebo</p> <p>Eligible patients evaluated baseline</p>	<p>DB, DD, PG, RCT</p> <p>Patient ≥ 12 years of age with a ≥ 2 year history of SAR with a positive skin allergen test within the previous year</p>	<p>N=279</p> <p>2 days</p>	<p>Primary: Changes from baseline in MSC and TSC scores</p> <p>Secondary: Change from baseline in TSC plus nasal congestion scores, change in individual rhinitis symptoms and subject global satisfaction</p>	<p>Primary: Cetirizine significantly reduced overall MSC scores when compared to both loratadine and placebo (5.9 vs 4.4 and 4.4; $P\leq 0.01$ for both comparisons). Moreover, cetirizine was more effective at reducing MSC scores over the first 24 hours of treatment compared to loratadine and placebo (4.1 vs 2.3 and 2.6, respectively; $P<0.01$),</p> <p>Patients receiving cetirizine significantly reduced TSC scores more than both loratadine and placebo after the two day treatment period (9.4 vs 7.3 and 7.5 for loratadine and placebo, respectively; $P\leq 0.01$ for both comparisons). Improvements in TSC scores were seen with cetirizine treatment in the first 24 hours compared to loratadine (6.3 vs 3.8; $P\leq 0.01$), but not compared to placebo ($P\leq 0.10$).</p> <p>Secondary:</p>

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<p>symptoms hourly from 7:30AM to 10:30AM (first dose of medication given at 10:00AM).</p> <p>Evaluations of patient-reported symptoms were completed hourly from 11:00AM to 4:00PM (period I); at 6:00, 8:00, and 10:00PM at home (period II), hourly the following morning from 8:00AM to 10:00AM (period III) and from 11:00AM to 4:00PM (period IV).</p>			<p>evaluations</p>	<p>Treatment with cetirizine was associated with a significant reduction in TSC plus nasal congestion scores when compared to both loratadine and placebo (values not reported; $P \leq 0.01$ for both comparisons). Cetirizine-treated patients reported improvements in TSC plus nasal congestion scores at four time points compared to loratadine throughout the trial ($P \leq 0.04$).</p> <p>Compared to loratadine, cetirizine treatment significantly ($P \leq 0.05$ for all comparisons) reduced nose blows in periods I and III, runny nose or sniffles in period IV, itchy eyes or ears in period I, and itchy nose in periods I, II and IV. Sneezing was reduced more with cetirizine treatment across all periods compared to loratadine. Compared to placebo, cetirizine significantly reduced ($P \leq 0.05$ for all comparisons) nose blows during all periods, sneezes in periods II, III and IV, runny nose or sniffles in periods II and IV, itchy nose in periods II and III and itchy eyes or ears in period II.</p> <p>More patients treated with cetirizine showed improved global efficacy (74%) compared to loratadine and placebo (57 and 59% respectively; P value not reported). Patient satisfaction was also higher in the cetirizine group, but none of the treatment differences were significant.</p>
<p>Raphael et al⁴⁵</p> <p>Desloratadine 5 mg QD</p> <p>vs</p> <p>diphenhydramine 50 mg TID</p> <p>vs</p> <p>placebo</p>	<p>DB, DD, MC, PC, RCT</p> <p>Patients 12 to 65 years of age with a history of at least moderate SAR, a positive skin test within the past year and a minimum of at least moderate-to-severe symptoms at baseline</p>	<p>N=610</p> <p>1 week</p>	<p>Primary: Change from baseline in TNSS as evaluated by patients</p> <p>Secondary: Changes from baseline in TSS, individual symptom scores and the global evaluation of response to treatment</p>	<p>Primary: Treatment with diphenhydramine reduced TNSS scores significantly more than patients treated with desloratadine (5.69 vs 3.88; $P < 0.001$) and placebo (3.20; $P < 0.001$). Diphenhydramine treatment was associated with a 46.7% greater reduction in TNSS scores than desloratadine ($P < 0.001$). There was no difference in the reduction in TNSS scores between desloratadine and placebo ($P = 0.12$).</p> <p>Secondary: Overall, TSS was significantly reduced from baseline with diphenhydramine compared with both desloratadine and placebo (10.71 vs 7.36 and 6.61, respectively; $P < 0.001$ for both comparisons). Diphenhydramine was associated with a 45.5% greater reduction in TSS compared to desloratadine ($P < 0.001$). There was no difference in TSS reduction between desloratadine and placebo groups ($P = 0.35$).</p> <p>Treatment with diphenhydramine was associated with statistically and clinically significant improvements vs desloratadine and placebo for all eight SAR symptoms except nasal congestion. Desloratadine was associated with significant</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				improvements in symptoms for sneezing only compared to placebo ($P=0.04$). Diphenhydramine had an 81.2% ($P<0.001$) greater improvement in the patient mean global response to treatment score compared to patients who received desloratadine.
Van Cauwenberge et al ⁴⁶ Fexofenadine 120 mg QD vs loratadine 10 mg QD vs placebo	DB, MC, PC, PG, RCT Patients 12 to 75 years of age with a history of SAR for ≥ 2 years, a positive skin test within the previous 12 months and a history of responding to treatment with antihistamines	N=688 2 weeks	Primary: Change from baseline in reflective TSS scores Secondary: Changes from baseline in mean instantaneous TSS, mean severity scores of the individual reflective symptoms including nasal congestion, and patient and physicians' evaluation of overall effectiveness of the medications	Primary: Fexofenadine and loratadine significantly reduced TSS from baseline compared to placebo (values not reported; $P\leq 0.0001$ and $P\leq 0.001$ for fexofenadine and loratadine, respectively). Secondary: Fexofenadine and loratadine significantly reduced instantaneous TSS from baseline compared to placebo (values not reported; $P\leq 0.0001$ and $P\leq 0.005$ for fexofenadine and loratadine, respectively). Both fexofenadine and loratadine significantly reduced 24-hour symptom scores from baseline compared to placebo for sneezing, rhinorrhea, itchy nose and itchy and watery or red eyes (values not reported; $P\leq 0.005$ and $P\leq 0.05$ for fexofenadine and loratadine, respectively). Fexofenadine was significantly better than loratadine for reducing symptom scores for itchy, watery or red eyes in addition to nasal congestion ($P\leq 0.05$ for both comparisons). Physician assessment of overall treatment success was 44, 40 and 36% for patients receiving fexofenadine, loratadine and placebo, respectively (P value not reported).
Day et al ⁴⁷ Levocetirizine 5 mg QD vs desloratadine 5 mg QD vs	DB, PC, PG, RCT Patients ≥ 16 years of age with a ≥ 2 year history of SAR, a positive skin test to ragweed within the past year and a TSS score of ≥ 18 for three	N=373 2 days	Primary: Change from baseline in MSC score over period I Secondary: Reduction in MSC scores over periods II and III, change in TSC scores, nasal obstruction scores	Primary: Over the first period of treatment, MSC scores were significantly reduced with levocetirizine compared to desloratadine (6.51 ± 0.406 vs 4.65 ± 0.407 ; $P=0.001$) and placebo (2.83 ± 0.501 ; $P<0.001$). Moreover, greater improvements in MSC scores were seen in desloratadine-treated patients compared to placebo ($P<0.001$). Secondary: Levocetirizine continued to significantly improve MSC scores during period II compared to desloratadine (4.740 ± 0.392 vs 3.370 ± 0.397 ; $P=0.015$) and placebo (0.000 ± 0.486 ; $P<0.001$). The treatment difference between patients treated with desloratadine and placebo remained significant for this period ($P<0.001$). In period

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<p>placebo</p> <p>On day one, eligible patients evaluated baseline symptoms every 30 minutes from 8:30AM to 10:30AM (first dose of medication given at 10:00AM).</p> <p>Evaluations of patient-reported symptoms were completed every 30 minutes on day 1 from 10:00AM to 3:00PM (period I), on day 2 from 8:30AM to 10:00AM (period II) and on day 2 from 10:00AM to 2:30PM (period III).</p>	<p>consecutive visits</p>		<p>over periods I, II and III and subject global satisfaction and evaluation</p>	<p>III, treatment with levocetirizine remained more effective at improving MSC scores compared to desloratadine (7.910±0.452 vs 6.220±0.460; <i>P</i>=0.010), and placebo (3.330±0.564; <i>P</i><0.001).</p> <p>Levocetirizine was associated with significant reductions in TSC scores compared to desloratadine over periods I (treatment difference, -2.70; <i>P</i>=0.003) and III (treatment difference, -2.37; <i>P</i>=0.017), but there was no difference between treatments at period II (<i>P</i>=0.084). Both levocetirizine and desloratadine improved TSC from baseline throughout all three evaluation periods compared to placebo (<i>P</i><0.01 for all comparisons).</p> <p>In period I, there was a significant difference in favor of levocetirizine in the reduction of all symptoms except for cough and itchy throat (<i>P</i> values not reported). In period II, levocetirizine continued to be more effective than desloratadine for improving nasal symptoms, including runny nose, nose blows, and sneezes (<i>P</i> values not reported). In the final period, levocetirizine improved symptoms of runny nose, itchy nose, sniffles, and sneezes more than desloratadine (<i>P</i> values not reported). Levocetirizine reduced all symptoms more than placebo through all periods, except for cough (<i>P</i> values not reported).</p> <p>During period I, levocetirizine reduced nasal obstruction to a greater extent than both desloratadine and placebo (<i>P</i>=0.007 and <i>P</i><0.001; respectively). Levocetirizine and desloratadine had similar effects on nasal congestion at periods II and III, but only levocetirizine was better than placebo at reducing nasal obstruction in period III (<i>P</i>=0.014).</p> <p>There was no difference between levocetirizine and desloratadine in patient satisfaction at the completion of the study. Both active treatments were significantly better than placebo (<i>P</i><0.001).</p>
<p>Dockhorn et al⁴⁸</p> <p>Acrivastine/pseudoephedrine 8/60 mg QID</p> <p>vs</p>	<p>DB, MC, PC, PG, RCT</p> <p>Patients ≥12 years of age with a ≥2 year history of SAR and a positive skin test to ragweed</p>	<p>N=702</p> <p>2 weeks</p>	<p>Primary:</p> <p>Changes from baseline in mean diary symptom scores, allergy symptom scores and nasal congestion scores</p>	<p>Primary:</p> <p>Treatment with acrivastine/pseudoephedrine significantly reduced mean diary symptom scores from baseline more than acrivastine alone (7.6 vs 5.0; <i>P</i><0.001), pseudoephedrine alone (5.8; <i>P</i>=0.002) and placebo (3.9; <i>P</i><0.001). Furthermore, acrivastine/pseudoephedrine-treated patients had a significantly greater reduction in diary symptom scores for 13 days of the trial compared to acrivastine alone, nine days relative to pseudoephedrine alone and for all days compared to placebo (<i>P</i> values not reported).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
acrivastine* 8 mg QID vs pseudoephedrine 60 mg QID vs placebo			Secondary: Not reported	<p>Patients treated with acrivastine/pseudoephedrine significantly reduced mean allergy symptom scores compared to pseudoephedrine alone (11.4 vs 10.0; $P < 0.001$). Moreover, combination therapy reduced allergy symptom scores more so than both acrivastine and placebo alone (11.4 vs 10.6 and 8.7, respectively; P values not reported).</p> <p>Mean nasal congestion scores were significantly improved after two weeks of treatment with acrivastine/pseudoephedrine compared to acrivastine alone (14.1 vs 13.5; $P < 0.001$), pseudoephedrine alone (13.5; P value not reported), and placebo (12.4; P values not reported).</p> <p>Secondary: Not reported</p>
Williams et al ⁴⁹ Acrivastine/ pseudoephedrine 8/60 mg QID vs acrivastine* 8 mg QID vs pseudoephedrine 60 mg QID vs placebo	DB, MC, PC, PG, RCT Patients ≥ 18 years of age with a ≥ 2 year history of SAR and a positive skin test to mountain cedar antigen	N=676 2 weeks	<p>Primary: Changes from baseline in mean diary symptom scores, nasal congestion scores and allergy symptom scores</p> <p>Secondary: Not reported</p>	<p>Primary: Treatment with acrivastine/pseudoephedrine significantly reduced mean diary symptom scores from baseline compared to acrivastine alone (7.2 vs 6.3; $P < 0.001$), pseudoephedrine alone (5.1; $P < 0.001$) and placebo (5.0; $P < 0.001$). Furthermore, acrivastine/pseudoephedrine-treated patients had significantly greater reductions in mean symptom scores for 13 days of the trial compared to acrivastine alone, and for all days of the trial relative to pseudoephedrine alone and placebo (P values not reported).</p> <p>Therapy with acrivastine/pseudoephedrine significantly reduced mean allergy symptom scores compared to pseudoephedrine alone (no values provided; $P < 0.001$). Moreover, combination therapy improved allergy symptom scores more than both acrivastine alone and placebo (no values or P value reported). Acrivastine/pseudoephedrine had greater reductions in allergy symptom scores on all 14 evaluation days throughout the study compared to pseudoephedrine ($P < 0.001$).</p> <p>Mean nasal congestion scores were significantly reduced after two weeks of treatment with acrivastine/pseudoephedrine compared to acrivastine alone (no values reported; $P < 0.001$), pseudoephedrine alone and placebo (no values or P value reported).</p> <p>Secondary:</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Not reported
<p>Pleskow et al⁵⁰</p> <p>Desloratadine/pseudoephedrine 5/240 mg QD</p> <p>vs</p> <p>desloratadine 5 mg QD</p> <p>vs</p> <p>pseudoephedrine 240 mg QD</p>	<p>DB, DD, MC, PG, RCT</p> <p>Patients ≥12 years of age and a ≥2 year history of SAR with a positive skin test in the previous 12 months; patients must have had a total nasal rhinorrhea score ≥14, total nasal congestion score ≥14, TNSS ≥42 and TNNSS ≥35</p>	<p>N=1,121</p> <p>2 weeks</p>	<p>Primary: Changes from baseline in mean AM/PM reflective TSS (excluding nasal congestion) and mean AM/PM reflective nasal congestion scores</p> <p>Secondary: Not reported</p>	<p>Primary: Throughout the treatment period, desloratadine/pseudoephedrine was significantly more effective in reducing AM/PM reflective TSS (excluding nasal congestion) compared to pseudoephedrine alone (6.09 [39%] vs 5.08 [32%]; $P=0.001$). Moreover, combination treatment was significantly more effective at reducing TSS (excluding nasal congestion) over two weeks compared with desloratadine alone (6.09 [39%] vs 5.10 [34%]; $P\leq 0.02$).</p> <p>Patients treated with desloratadine/pseudoephedrine had greater improvements in AM/PM nasal congestion scores compared to both desloratadine alone (0.90 [33%] vs 0.74 [28%]; $P<0.001$) and pseudoephedrine alone (0.90 [33%] vs 0.78 [29%]; $P\leq 0.02$). There was no difference between monotherapy treatment groups in regards to nasal congestion scores ($P=0.35$).</p> <p>Secondary: Not reported</p>
<p>Bronsky et al⁵¹</p> <p>Loratadine/pseudoephedrine 10/240 mg QD</p> <p>vs</p> <p>loratadine 10 mg QD</p> <p>vs</p> <p>pseudoephedrine 120 mg BID</p> <p>vs</p> <p>placebo</p>	<p>DB, DD, MC, PG, RCT</p> <p>Patients 12 to 60 years of age with a ≥1 year history of moderate-to-severe SAR, a positive allergen skin test and a TSS ≥11 at baseline for at least 50% of the days of the run-in period</p>	<p>N=879</p> <p>2 weeks</p>	<p>Primary: Changes from baseline in TSS, TNSS, TNNSS, nasal stuffiness score and global response to treatment</p> <p>Secondary: Not reported</p>	<p>Primary: After two weeks of treatment, reductions in TSS were significantly greater for patients treated with loratadine/pseudoephedrine than for the other three treatment groups (values not reported; $P\leq 0.05$ for all comparisons).</p> <p>Patients receiving loratadine/pseudoephedrine had significant improvements in TNSS relative to patients treated with loratadine or placebo (values not reported; $P<0.01$). After two weeks of treatment, patients treated with pseudoephedrine also had significantly greater reductions in TNSS compared to placebo (values not reported; $P<0.01$).</p> <p>Mean reductions in TNNSS from baseline were significantly greater with loratadine/pseudoephedrine or loratadine alone compared to pseudoephedrine alone or placebo (values not reported; $P<0.01$).</p> <p>Loratadine/pseudoephedrine was associated with significant improvements in nasal stuffiness score compared to loratadine alone ($P\leq 0.02$), pseudoephedrine alone ($P\leq 0.04$) and placebo ($P\leq 0.02$).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>A larger number of patients treated with loratadine/pseudoephedrine had a physician-determined therapeutic response to treatment compared to loratadine alone, pseudoephedrine alone, and placebo (58 vs 49, 49 and 39%, respectively; <i>P</i> values not reported).</p> <p>Secondary: Not reported</p>
<p>Prenner et al⁵²</p> <p>Loratadine 10 mg QD</p> <p>vs</p> <p>fexofenadine 60 mg BID</p> <p>Phase I consisted of a 14-day treatment period with loratadine or fexofenadine.</p> <p>After 14 days, patients who experienced a <25% reduction in TSS were considered to be non-responders and subsequently enrolled into phase II.</p> <p>In phase II, non-responders to loratadine received fexofenadine, whereas non-responders to fexofenadine received loratadine for 14 more days of treatment.</p>	<p>DB, DD, MC, RCT, XO (non-responders)</p> <p>Patients 12 to 60 years of age with a ≥2 year history of SAR; patients were required to have a positive skin test to seasonal allergens</p>	<p>N=659</p> <p>4 weeks</p>	<p>Primary: Change in TSS scores from baseline to phase I, rate of symptomatic relief in phase II for non-responders to phase I as defined by a <25% improvement in investigator assessed TSS symptoms</p> <p>Secondary: Not reported</p>	<p>Primary: At the end of phase I, patients treated with loratadine had significantly greater improvements in TSS compared to fexofenadine-treated patients (39.8 vs 30.6%; <i>P</i>=0.019), however, no difference was seen between treatment groups for investigator assessment of symptom severity (<i>P</i>=0.063).</p> <p>Of the 389 total patients who were considered responders in phase I, treatment with loratadine was associated with greater improvements in investigator-assessed TSS compared to fexofenadine (67.8 vs 57.0%; <i>P</i>=0.037).</p> <p>More non-responders from phase I reported symptomatic relief when switched from fexofenadine to loratadine in phase II than patients who were switched from loratadine to fexofenadine (62.4 vs 51.2%; <i>P</i>=0.005). Patients taking fexofenadine were twice as likely to be non-responders in phase II compared to loratadine (21.7 vs 10.6%, <i>P</i>=0.011).</p> <p>Secondary: Not reported</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Grubbe et al⁵³</p> <p>Desloratadine/ pseudoephedrine 2.5/120 mg BID</p> <p>vs</p> <p>desloratadine 5 mg QD plus placebo</p> <p>vs</p> <p>pseudoephedrine 120 mg BID</p>	<p>DB, DD, MC, PC, PG, RCT</p> <p>Patients ≥12 years of age and a ≥2 year history of SAR and sensitivity to a seasonal allergen confirmed via skin testing</p>	<p>N=598</p> <p>2 weeks</p>	<p>Primary: Changes from baseline in AM/PM reflective TSS excluding congestion, and TSS including nasal congestion</p> <p>Secondary: Patient reported improvements in SAR</p>	<p>Primary: During the 14 day treatment period, desloratadine/pseudoephedrine significantly reduced AM/PM reflective TSS excluding nasal congestion compared to both desloratadine alone (6.54 [46.0%] vs 5.09 [33.5%]; <i>P</i><0.001) and pseudoephedrine alone (5.07 [35.9%]; <i>P</i><0.001).</p> <p>Similarly, desloratadine/pseudoephedrine was more efficacious at reducing TSS with nasal congestion when compared to both desloratadine alone (0.93 [37.4%] vs 0.66 [26.7%]; <i>P</i><0.001) and pseudoephedrine alone (0.75 [31.2%]; <i>P</i>=0.006). Significant improvements with combination treatment were seen as early as day two of treatment and remained significant at all time points compared to desloratadine monotherapy (<i>P</i><0.005).</p> <p>Secondary: At study completion, patient reported mean reductions in the overall condition of SAR were 40.0, 33.8 and 33.6% in the desloratadine/pseudoephedrine, desloratadine alone and pseudoephedrine alone groups, respectively, but the differences were not statistically significant (<i>P</i>=0.062).</p>
<p>Sussman et al⁵⁴</p> <p>Fexofenadine/ pseudoephedrine 60/120 mg BID</p> <p>vs</p> <p>fexofenadine 60 mg BID</p> <p>vs</p> <p>pseudoephedrine 120 mg BID</p>	<p>DB, MC, PC, PG, RCT</p> <p>Patients 12 to 65 years of age with a history of ragweed allergy confirmed by skin test; patients must have had evidence of a positive response to antihistamines for SAR and TSS ≥6 at baseline</p>	<p>N=651</p> <p>2 weeks</p>	<p>Primary: Change from baseline in average 7PM reflective TSS minus the 7PM reflective nasal congestion score, and change from baseline in average 7PM reflective nasal congestion score</p> <p>Secondary: Changes from baseline in 7PM instantaneous TSS minus nasal congestion score, 7PM instantaneous</p>	<p>Primary: Reductions in the 7PM reflective TSS minus nasal congestion score from baseline were significantly greater with fexofenadine/pseudoephedrine than pseudoephedrine alone (2.32 vs 1.42; <i>P</i><0.0001), but not significantly different from patients who received fexofenadine alone (2.32 vs 2.05; <i>P</i>=0.1579).</p> <p>The reduction in 7PM reflective nasal congestion score was significantly greater for patients receiving combination therapy compared to fexofenadine alone (0.56 vs 0.36; <i>P</i><0.0005). There was no difference between nasal congestion score reductions for patients treated with combination therapy compared to pseudoephedrine alone (0.36 vs 0.45; <i>P</i>=0.0590).</p> <p>Secondary: Changes in 7PM instantaneous TSS minus nasal congestion score were consistent with reflective scores described above. Patients receiving combination therapy has significantly greater reductions in TSS minus nasal congestion score scores at 7PM and bedtime compared to placebo (<i>P</i>=0.0001 and <i>P</i>=0.0341 for 7PM and bedtime comparisons, respectively).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			nasal congestion score, 7PM 12-hour reflective individual symptom scores, bedtime instantaneous TSS minus nasal congestion score and bedtime instantaneous nasal congestion score	<p>Compared to fexofenadine alone, patients receiving combination treatment had significantly improved nasal congestion score at 7PM ($P=0.0007$) but there were no significant differences in regards to bedtime scores ($P=0.1939$).</p> <p>Treatment with fexofenadine/pseudoephedrine was associated with significant improvements compared to pseudoephedrine alone for symptoms of sneezing ($P<0.0001$), rhinorrhea ($P=0.0002$), itchy nose ($P=0.0002$) and itchy, watery, red eyes ($P=0.0006$). Combination therapy significantly improved symptoms of nasal congestion compared to fexofenadine alone ($P=0.0005$).</p>
Perennial Allergic Rhinitis and Seasonal Allergic Rhinitis				
<p>Benninger et al¹³</p> <p>Nasal antihistamine-based therapies</p> <p>vs</p> <p>oral antihistamine-based therapies</p> <p>vs</p> <p>leukotriene receptor antagonist-based therapies</p> <p>vs</p> <p>intranasal corticosteroid-based therapies</p> <p>vs</p>	<p>SR</p> <p>RCTs of ≥ 20 patients with a physician documented history of SAR or PAR, treatment with a Food and Drug Administration-approved agent for allergic rhinitis and a primary outcome of TNSS (≥ 2 weeks for SAR and 4 to 6 weeks for PAR)</p>	<p>N=15,780 (50 trials)</p> <p>Treatment duration for each trial was ≥ 14 days</p>	<p>Primary: Change from baseline in TNSS for patients with SAR and PAR and change in nasal congestion, nasal itching, sneezing and rhinorrhea nasal symptom scores</p> <p>Secondary: Not reported</p>	<p>Primary: The median percent reduction from baseline in TNSS for patients with SAR was 40.7, 23.5, 22.2, 17.0 and 15.0% for patients receiving intranasal corticosteroids, oral antihistamines, intranasal antihistamines, leukotriene receptor antagonists and placebo, respectively; $P<0.001$ for intranasal corticosteroids vs all other treatments. Notably, only three studies of leukotriene receptor antagonists met criteria for inclusion in the analysis.</p> <p>For symptoms of PAR, clinical trials with four to six weeks of data were only available for oral antihistamines, intranasal corticosteroids and placebo. Patients with PAR experienced improvements of 51.4, 37.3 and 24.8% with oral antihistamines, intranasal corticosteroids and placebo, respectively; $P=0.03$ for oral antihistamines vs placebo.</p> <p>In studies of allergic rhinitis lasting ≥ 2 weeks, intranasal corticosteroids reduced symptoms of nasal congestion more than treatment with oral antihistamines, intranasal antihistamines and placebo (39.9 vs 22.7, 18.6 and 13.4%, respectively; $P=0.007$ for intranasal corticosteroids vs the other treatment arms.</p> <p>Oral antihistamines were considered to be more effective than intranasal corticosteroids, intranasal antihistamines and placebo (38.9 vs 34.7, 23.4 and 13.8%; $P=0.04$ for intranasal corticosteroids vs placebo. For oral antihistamines, only three studies met criteria for inclusion for this comparison.</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo-based therapies				<p>For sneezing, the intranasal corticosteroids had greater improvements in nasal symptom scores than intranasal antihistamines and placebo (46.6 vs 27.7 and 14.1%, respectively; <i>P</i>=0.02 for intranasal corticosteroids vs intranasal antihistamines and placebo). There was inadequate data for the comparison of oral antihistamines.</p> <p>For rhinorrhea, the overall trend was that oral antihistamines were comparable to intranasal corticosteroids (46.0 vs 43.9%; <i>P</i> value not reported) and had greater efficacy compared to intranasal antihistamines and placebo (20.6 and 14.8%, respectively; <i>P</i> values not reported).</p> <p>Secondary: Not reported</p>

*Agent not available in the United States.

Drug regimen abbreviations: BID=twice daily, QD=once daily, QID= four times daily, TID=three times daily

Study abbreviations: DB=double-blind, DD=double-dummy, MC=multicenter, OL=open-label, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial, SR=systematic review, XO=crossover

Miscellaneous abbreviations: CIU=chronic idiopathic urticaria, DLQI=dermatology life quality index, HRQL=health-related quality of life, IgE=immunoglobulin, MoTSS=modified total symptom score, MSC=major symptom complex, MTSS=mean total symptom score, nPEFR=nasal peak expiratory flow rate, PAR=perennial allergic rhinitis, PNIF=peak nasal inspiratory flow, PRQLQ=pediatric rhinoconjunctivitis quality of life questionnaire, RQLQ=Rhinoconjunctivitis Quality of Life Questionnaire, SAR=seasonal allergic rhinitis, T4SS=total 4 symptom score, TNSS=Total Nasal Symptom Score, TNNSS=total non-nasal symptom score, TSC=total symptom complex score, TSS=total symptom score, TSSC=total symptom severity complex, WPAI-AS=Work Productivity and Activity Impairment Questionnaire-Allergy Specific

Table 5. Special Populations^{5-12,16-18}

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Single Entity Agents					
Cetirizine	A dose of 5 mg once daily in patients ≥ 77 years of age is recommended. Approved for use in children ≥ 6 months of age.	Renal dose adjustment is required; for creatinine clearances of 11 to 31 mL/minute, a dose of 5 mg once daily is recommended.	Hepatic dose adjustment is required; a dose of 5 mg once-daily is recommended.	B	Yes (3%).
Desloratadine	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Approved for use in children ≥ 6 months of age.	Renal dose adjustment is required; for adult patients with renal impairment a dose of 5 mg every other day is recommended.	Hepatic dose adjustment is required; for adult patients with hepatic impairment a dose of 5 mg every other day is recommended.	C	Yes (0.1%)*.
Fexofenadine	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Approved for use in children ≥ 6 months of age.	Renal dose adjustment is required; for patients six months to two years of age with renal impairment, the dosing is 15 mg once-daily; for patients two to 11 years of age, the dosing is 30 mg once-daily; for patients ≥ 12 years of age the dosing is 60 mg once-daily.	No dosage adjustment required.	C	Unknown
Levocetirizine	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Approved for use in children ≥ 6	Renal dose adjustment is required; for creatinine clearances of ≥ 50 to ≤ 80 mL/minute, a dose of 2.5 mg once-daily is recommended; for creatinine	No dosage adjustment required.	B	Yes (3%).

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	months of age.	clearances of ≥ 30 to ≤ 50 mL/minute, a dose of 2.5 mg every other day is recommended; for creatinine clearances of ≥ 10 to ≤ 30 mL/minute, a dose of 2.5 mg twice-weekly is recommended.			
Loratadine	No dosage adjustment required in elderly patients. Approved for use in children ≥ 2 years of age.	Renal dose adjustment is required; for patients ≥ 6 years of age with a creatinine clearance of ≤ 30 mL/minute, a dose of 10 mg every other day is recommended; for patients two to five years of age with a creatinine clearance of ≤ 30 mL/minute, a dose of 5 mg every other day is recommended.	Hepatic dose adjustment is required; for patients ≥ 6 years of age; a dose of 10 mg every other day is recommended; for patients two to five years of age, a dose of 5 mg every other day is recommended.	B	Yes (0.1%)*.
Combination Products					
Acrivastine/ pseudoephedrine	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Approved for use in children ≥ 12 years of age.	Not recommended for use in patients with a creatinine clearance of ≤ 48 mL/minute.	Not studied in hepatic dysfunction.	B	Unknown
Cetirizine/ pseudoephedrine	Safety and efficacy in elderly patients have not been established. Approved for use	Renal dose adjustment is required; for creatinine clearances of ≤ 31 mL/minute, a	Hepatic dose adjustment is required; a maximum dose of 5/120 mg once-daily is	C	Unknown

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	in children ≥12 years of age.	dose of 5/120 mg once-daily is recommended.	recommended.		
Desloratadine/ pseudoephedrine	Safety and efficacy in elderly patients have not been established. Approved for use in children ≥12 years of age.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	C	Unknown
Fexofenadine/ pseudoephedrine	Safety and efficacy in elderly patients have not been established. Approved for use in children ≥12 years of age.	Not studied in renal dysfunction.	No dosage adjustment required (should generally be avoided).	C	Unknown
Loratadine/ pseudoephedrine	No dosage adjustment required in elderly patients. Approved for use in children ≥12 years of age.	Renal dose adjustment is required; for creatinine clearances of ≤30 mL/minute, a dose of 5/120 mg once-daily is recommended.	No dosage adjustment required (should generally be avoided).	B	Unknown

* Following oral doses of loratadine, only minimal amounts of loratadine or desloratadine were excreted in breast milk (<0.1% of loratadine dose).

Adverse Drug Events

Table 6 summarizes the most common adverse events associated with the single and combination second-generation antihistamines. Second-generation antihistamines are generally well tolerated, and are not associated with the significant sedative and anticholinergic adverse events that are characteristic of the first-generation antihistamines. The most common adverse events with these agents are headache, fatigue and nausea. The second-generation antihistamines have been extensively studied in the pediatric population with the most commonly reported adverse events in this population non-specific, including diarrhea, cough and fever.

Table 6. Adverse Drug Events (%) ^{5-12,16-18}

Adverse Event(s)	Single Entity Agents					Combination Products				
	Cetirizine	Desloratadine	Fexofenadine	Levocetirizine	Loratadine	Acrivastine/Pseudoephedrine	Cetirizine/Pseudoephedrine	Desloratadine/Pseudoephedrine	Fexofenadine/Pseudoephedrine	Loratadine/Pseudoephedrine
Cardiac Disorders										
Arrhythmias	-	-	-	-	-	-	-	-	✓	✓
Cardiac failure	-	-	-	-	-	✓	-	-	-	-
Edema	-	-	-	-	-	-	-	-	-	✓
Hypertension	-	-	-	-	✓	-	-	-	-	✓
Hypotension	-	-	-	-	✓	-	-	-	-	✓
Syncope	-	-	-	-	✓	-	-	-	-	✓
Palpitation	-	✓	-	-	✓	✓	-	✓	✓	✓
Tachycardia	-	✓	-	-	✓	✓	-	✓	✓	✓
Central Nervous System										
Asthenia	-	-	-	-	✓	-	-	-	-	-
Blepharospasm	-	-	-	-	✓	-	-	-	-	✓
Confusion	-	-	-	-	-	-	-	-	-	✓
Convulsions	-	-	-	-	-	-	-	-	-	✓
Dizziness	2	4	2	-	✓	✓	1	1.1 to 2.0	✓	4
Dysphonia	-	-	-	-	2	-	-	-	-	✓
Fatigue	6	5	0.9 to 1.3	1 to 4	3 to 4	-	2.4	-	-	4
Flushing	-	-	-	-	✓	-	-	-	-	-
Hyperkinesia	-	-	-	-	3*	-	-	-	-	✓
Hypertonia	-	-	-	-	✓	-	-	-	-	✓
Hypoesthesia	-	-	-	-	✓	-	-	-	-	-
Impotence	-	-	-	-	✓	-	-	-	-	✓
Sedation	14	2	1 to 3	5 to 6	8	✓	1.9	4	✓	7
Thirst	-	-	-	-	✓	-	-	-	-	-
Tremor	-	-	-	-	✓	-	-	-	✓	✓
Vertigo	-	-	-	-	✓	-	-	-	-	✓
Xerostomia	5	3	-	2 to 3	3	-	3.6	8	✓	8 to 14
Dermatological										
Acne	-	-	-	-	-	-	-	-	-	✓
Dermatitis	-	-	-	-	✓	-	-	-	-	-
Dry skin/hair	-	-	-	-	✓	-	-	-	-	✓
Eczema	-	-	-	-	✓	-	-	-	-	✓

Adverse Event(s)	Single Entity Agents					Combination Products				
	Cetirizine	Desloratadine	Fexofenadine	Levocetirizine	Loratadine	Acrivastine/Pseudoephedrine	Cetirizine/Pseudoephedrine	Desloratadine/Pseudoephedrine	Fexofenadine/Pseudoephedrine	Loratadine/Pseudoephedrine
Erythematous rash	-	-	-	-	-	-	-	-	-	✓
Increased sweating	-	-	-	-	✓	-	-	-	-	✓
Photosensitivity	-	-	-	-	✓	-	-	-	-	-
Pruritus	-	-	-	-	✓	-	-	✓	-	✓
Purpura	-	-	-	-	✓	-	-	-	-	-
Rash	-	3 [†]	-	-	2*	-	-	4	-	✓
Urticaria	-	-	-	-	-	-	-	-	-	✓
Endocrine and Metabolic										
Dysmenorrhea	-	-	2	-	-	-	-	-	-	-
Gastrointestinal										
Abdominal pain	4.4 to 5.6 [†]	-	-	2	2*	-	-	-	✓	✓
Constipation	-	-	-	-	✓	-	-	-	-	✓
Diarrhea	1.9 to 3.1 [†]	15 [†]	3 to 4 [†]	4 [†]	3	-	-	-	-	✓
Dyspepsia	-	3	4.4 to 4.7	-	✓	✓	-	-	✓	3
Flatulence	-	-	-	-	✓	-	-	-	-	✓
Gastritis	-	-	-	-	✓	-	-	-	-	✓
Increased appetite	-	-	-	-	✓	-	-	-	-	✓
Nausea	3 [†]	5	2 to 12	1.5	✓	✓	-	2	✓	3
Stomatitis	-	-	-	-	2*	-	-	-	-	✓
Vomiting	-	-	4 to 12 [†]	4 [†]	-	-	-	-	-	-
Genitourinary										
Breast pain	-	-	-	-	✓	-	-	-	-	-
Dysmenorrhea	-	2	1.5	1.5	✓	✓	-	-	-	2
Dysuria	-	-	-	-	-	-	-	-	✓	✓
Micturition frequency	-	-	-	-	✓	-	-	-	-	✓
Urinary incontinence	-	-	-	-	✓	-	-	-	-	-
Urinary retention	-	-	-	-	✓	-	-	-	-	✓
Urinary tract infection	-	4 [†]	-	-	-	-	-	-	-	✓
Metabolism and Nutrition Disorders										
Dehydration	-	-	-	-	-	-	-	-	-	✓
Increased thirst	-	-	-	-	-	-	-	-	-	✓
Musculoskeletal										
Arthralgia	-	-	2	-	✓	-	-	-	-	-

Adverse Event(s)	Single Entity Agents					Combination Products				
	Cetirizine	Desloratadine	Fexofenadine	Levocetirizine	Loratadine	Acrivastine/Pseudoephedrine	Cetirizine/Pseudoephedrine	Desloratadine/Pseudoephedrine	Fexofenadine/Pseudoephedrine	Loratadine/Pseudoephedrine
Back pain	-	-	2.5 to 2.5	-	✓	-	-	-	3	-
Headache	11 to 14 [†]	14	4.8 to 10.3	-	12	✓	-	8	11	19
Myalgia	-	2 to 3	2.6	-	✓	-	-	-	-	-
Pyrexia	-	-	2 [†]	4 [†]	-	-	-	-	-	-
Ophthalmic										
Blurred vision	-	-	-	-	✓	-	-	-	-	-
Conjunctivitis	-	-	-	2	2*	-	-	-	-	-
Eye pain	-	-	-	-	✓	-	-	-	-	-
Loss of accommodation	✓	-	-	-	-	-	-	-	-	-
Psychiatric										
Aggressive reactions	-	-	-	-	-	-	-	-	-	✓
Agitation	-	-	-	-	✓	-	-	-	✓	✓
Amnesia	-	-	-	-	✓	-	-	-	-	-
Anorexia	-	-	-	-	-	-	-	2	-	2
Anxiety	-	-	-	-	✓	-	-	-	✓	4
Decreased libido	-	-	-	-	✓	-	-	-	-	✓
Depression	-	-	-	-	✓	-	-	-	-	✓
Fever	-	6 to 17 [†]	2.4 [†]	4 [†]	-	-	-	-	-	-
Emotional lability	-	3 [†]	-	-	-	-	-	-	-	✓
Euphoria	-	-	-	-	-	-	-	-	-	✓
Impaired concentration	-	-	-	-	✓	-	-	-	-	✓
Insomnia	-	-	✓	-	✓	✓	4	10	-	5 to 16
Nervousness	-	-	✓	-	4*	✓	-	-	-	-
Paranoia	-	-	✓	-	-	-	-	-	-	✓
Sleep disorder	-	-	✓	-	-	-	-	-	-	-
Respiratory										
Bronchitis	-	-	-	-	✓	-	-	-	-	✓
Bronchospasm	1.9 to 3.1 [†]	-	-	-	-	-	-	-	-	-
Cough	2.8 to 4.4 [†]	11 [†]	4 [†]	3 [†]	-	✓	-	-	-	3
Dyspnea	-	-	-	-	-	-	-	-	-	✓
Increased sputum	-	-	-	-	-	-	-	-	-	✓
Nasopharyngitis	-	-	-	4 to 6	-	-	-	-	-	-
Pharyngitis	2 to 6 [†]	3 to 4	-	1 to 2	3*	✓	1.7 to 2.0	3	-	-

Adverse Event(s)	Single Entity Agents					Combination Products				
	Cetirizine	Des-loratadine	Fexo-fenadine	Levo-cetirizine	Loratadine	Acrivastine/Pseudo-ephedrine	Cetirizine/Pseudo-ephedrine	Des-loratadine/Pseudo-ephedrine	Fexo-fenadine/Pseudo-ephedrine	Loratadine/Pseudo-ephedrine
Pneumonia	-	-	-	-	-	-	-	-	-	✓
Rhinitis	-	-	1 to 3	-	-	-	-	-	-	-
Sinusitis	-	-	-	-	-	-	1.1 to 2.0	-	-	✓
Upper respiratory infection	-	11 [†]	3.1 to 4.3 [‡]	-	2*	-	-	-	3	✓
Wheezing	-	-	-	-	4*	-	-	-	-	✓

✓ Percent not specified.

- Event not reported or incidence <2%.

* Adverse event reported with oral solution.

† Adverse event reported in children ≤5 years of age.

‡ Adverse event reported in children six to 12 years of age.

Contraindications/Precautions^{5-12,16-18}

The second-generation antihistamines are contraindicated in patients with a known hypersensitivity to piperazine (cetirizine, levocetirizine) or piperidine (desloratadine, fexofenadine, and loratadine) ring structures. Specifically, levocetirizine is contraindicated in patients with end-stage renal disease (creatinine clearance ≤ 10 mL/minute), patients undergoing hemodialysis and children six months to 11 years of age with renal impairment. No such recommendation is included for cetirizine. Both desloratadine and levocetirizine should be considered contraindicated in any patient with a known hypersensitivity to loratadine and cetirizine, respectively. Moreover, all pseudoephedrine-containing combination products are contraindicated in patients with narrow-angle glaucoma, urinary retention, severe hypertension, severe coronary artery disease, or anyone who has experience idiosyncratic reactions to adrenergic agents. The pseudoephedrine containing combination products are also contraindicated in any patient who has been treated with a monoamine oxidase inhibitor in the previous 14 days.

Loratadine should be used with caution in patients with renal or hepatic insufficiency. Sympathomimetic amines including pseudoephedrine should be used with caution in patients with hypertension, diabetes mellitus, ischemic heart disease, increased intraocular pressure, hyperthyroidism and renal impairment or prostatic hypertrophy.

Drug Interactions**Table 7. Drug Interactions**^{11,12}

Generic Name	Interacting Medication or Disease	Potential Result
Single Entity Agents		
Cetirizine, levocetirizine	Ritonavir	Ritonavir may increase the exposure and reduce the clearance of cetirizine.
Fexofenadine	Droperidol	Concurrent use of droperidol and fexofenadine may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).
Loratadine	Amiodarone	Concurrent use of amiodarone and loratadine may result in increased risk of QT interval prolongation and torsades de pointes.
Combination Products		
Second generation antihistamine/pseudoephedrine combination products (all)	Dihydroergotamine	Concurrent use of dihydroergotamine and pseudoephedrine may result in extreme elevation of blood pressure and headache.
Second generation antihistamine/pseudoephedrine combination products (all)	Guanethidine	Concurrent use of pseudoephedrine and guanethidine may result in a loss of blood pressure control and increase the risk of developing cardiac arrhythmias.
Second generation antihistamine/pseudoephedrine combination products (all)	Linezolid	Concurrent use of pseudoephedrine and linezolid may result in an increase in blood pressure.
Second generation antihistamine/pseudoephedrine combination products (all)	Midodrine	Concurrent use of pseudoephedrine and midodrine may result in an enhanced pressor effect of midodrine.
Second generation antihistamine/pseudoephedrine combination products (all)	Methyldopa	Concurrent use of methyldopa and pseudoephedrine may result in loss of blood pressure control and possibly hypertensive urgency.

Generic Name	Interacting Medication or Disease	Potential Result
Second generation antihistamine/pseudoephedrine combination products (all)	Monoamine oxidase inhibitors (MAOIs)	Concurrent use of pseudoephedrine and MAOIs may result in severe hypertension, hyperpyrexia, and headache.
Second generation antihistamine/pseudoephedrine combination products (all)	Sodium bicarbonate	Concurrent use of sodium bicarbonate and pseudoephedrine may result in pseudoephedrine toxicity (agitation, hypertension, and tachycardia).
Cetirizine/pseudoephedrine	Ritonavir	Ritonavir may increase the exposure and reduce the clearance of cetirizine.
Fexofenadine/pseudoephedrine	Droperidol	Concurrent use of droperidol and fexofenadine may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).
Loratadine/pseudoephedrine	Amiodarone	Concurrent use of amiodarone and loratadine may result in increased risk of QT interval prolongation and torsades de pointes.

Dosage and Administration

Table 8. Dosing and Administration ^{5-12,16-18}

Generic Name	Adult Dose	Pediatric Dose	Availability
Single Entity Agents			
Cetirizine	<p><u>Seasonal allergic rhinitis, perennial allergic rhinitis, and chronic idiopathic urticaria:</u> Capsule, chewable tablet, oral solution, tablet: initial, 5 to 10 mg PO daily; maintenance, 5 to 10 mg PO daily; maximum, 10 mg PO daily</p>	<p><u>Seasonal allergic rhinitis, perennial allergic rhinitis, and chronic idiopathic urticaria in children and adolescents aged 6 to 11 years:</u> Capsule, chewable tablet, oral solution, tablet: initial, 5 to 10 mg PO daily; maintenance, 5 to 10 mg PO daily; maximum, 10 mg PO daily</p> <p><u>Seasonal allergic rhinitis, perennial allergic rhinitis, and chronic idiopathic urticaria in children and adolescents aged 2 to 5 years:</u> Oral solution: initial, 2.5 mg PO daily; maintenance, 5 mg PO daily; maximum, 5 mg PO daily</p> <p><u>Seasonal allergic rhinitis, perennial allergic rhinitis, and chronic idiopathic urticaria in children and adolescents aged 6 months to 2 years:</u> Oral solution: initial, 2.5 mg PO daily; maintenance, 2.5 mg PO daily; maximum, 5 mg PO</p>	<p>Capsule: 5 mg</p> <p>Chewable tablet: 5 mg 10 mg</p> <p>Oral solution: 1 mg/mL</p> <p>Tablet: 5 mg 10 mg</p>

Generic Name	Adult Dose	Pediatric Dose	Availability
Desloratadine	<p><u>Seasonal allergic rhinitis, perennial allergic rhinitis, and chronic idiopathic urticaria:</u> Orally disintegrating tablet, oral solution, tablet: initial, 5 mg PO daily; maintenance, 5 mg PO daily</p>	<p>daily in children aged 1 year and older</p> <p><u>Seasonal allergic rhinitis, perennial allergic rhinitis, and chronic idiopathic urticaria in children and adolescents aged 6 to 11 years:</u> Orally disintegrating tablet, oral solution, : initial, 2.5 mg PO daily; maintenance, 2.5 mg PO daily</p> <p><u>Seasonal allergic rhinitis, perennial allergic rhinitis, and chronic idiopathic urticaria in children and adolescents aged 12 months to 5 years:</u> Oral solution: initial, 1.25 mg PO daily; maintenance, 1.25 mg PO daily</p> <p><u>Seasonal allergic rhinitis, perennial allergic rhinitis, and chronic idiopathic urticaria in children and adolescents aged 6 months to 11 months:</u> Oral solution: initial, 1 mg PO daily; maintenance, 1 mg PO daily</p>	<p>Orally disintegrating tablet: 2.5 mg 5 mg</p> <p>Oral solution: 0.5 mg/mL</p> <p>Tablet: 5 mg</p>
Fexofenadine	<p><u>Seasonal allergic rhinitis and chronic idiopathic urticaria:</u> Tablet: initial, 60 mg PO BID; maintenance, 60 mg PO BID to 180 mg PO daily</p>	<p><u>Seasonal allergic rhinitis, and chronic idiopathic urticaria in children and adolescents aged 6 to 11 years:</u> Orally disintegrating tablet, oral suspension, tablet: initial, 30 mg PO BID; maintenance, 30 mg PO BID</p> <p><u>Seasonal allergic rhinitis, and chronic idiopathic urticaria in children and adolescents aged 2 to 6 years:</u> Oral suspension: initial, 30 mg PO BID; maintenance, 30 mg PO BID</p> <p><u>Chronic idiopathic urticaria in children and adolescents aged 6 months to 2 years:</u> Oral suspension: initial, 15 mg PO BID; maintenance, 15 mg PO BID</p>	<p>Orally disintegrating tablet: 30 mg</p> <p>Oral suspension: 6 mg/mL</p> <p>Tablet: 30 mg 60 mg 180 mg</p>

Generic Name	Adult Dose	Pediatric Dose	Availability
Levocetirizine	<u>Seasonal allergic rhinitis, perennial allergic rhinitis, and chronic idiopathic urticaria:</u> Oral solution, tablet: initial, 5 mg PO daily; maintenance, 5 mg PO daily	<u>Seasonal allergic rhinitis, perennial allergic rhinitis, and chronic idiopathic urticaria in children and adolescents aged 6 to 11 years:</u> Oral solution, tablet: initial, 2.5 mg PO daily; maintenance, 2.5 mg PO daily; maximum, 2.5 mg <u>Seasonal allergic rhinitis, perennial allergic rhinitis, and chronic idiopathic urticaria in children and adolescents aged 6 months to 5 years:</u> Oral solution: initial, 1.25 mg PO daily; maintenance, 1.25 mg PO daily; maximum, 1.25 mg	Oral solution: 0.5 mg/mL Tablet: 5 mg
Loratadine	<u>Seasonal allergic rhinitis and chronic idiopathic urticaria:</u> Capsule, chewable tablet, orally disintegrating tablet, oral solution, tablet: initial, 10 mg PO daily; maintenance, 10 mg PO daily; maximum, 10 mg PO daily	<u>Seasonal allergic rhinitis, and chronic idiopathic urticaria in children and adolescents aged 2 to 5 years:</u> Chewable tablet, oral solution: initial, 5 mg PO daily; maintenance, 5 mg PO daily; maximum, 5 mg PO daily	Capsule: 10 mg Chewable tablet: 5 mg Orally disintegrating tablet: 5 mg 10 mg Oral solution: 1 mg/mL Tablet 5 mg 10 mg
Combination Products			
Acrivastine/ pseudoephedrine	<u>Seasonal allergic rhinitis:</u> Capsule: initial, 8/60 mg PO every 4 to 6 hours; maintenance, 8/60 mg PO every 4 to 6 hours; maximum, 32/240 mg PO daily	Safety and efficacy in children have not been established.	Capsule: 8/60 mg
Cetirizine/ pseudoephedrine	<u>Seasonal allergic rhinitis and perennial allergic rhinitis:</u> Extended-release tablet: initial, 5/120 mg PO BID; maintenance, 5/120 mg PO BID	Safety and efficacy in children have not been established.	Extended-release tablet: 5/120 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
Desloratadine/ pseudoephedrine	<u>Seasonal allergic rhinitis:</u> Extended-release tablet: initial, 2 (2.5/120 mg) PO BID or 1 (5/240 mg) PO daily; maintenance, 2 (2.5/120 mg) PO BID or 1 (5/240 mg) PO daily; maximum, 5/240 mg PO daily	Safety and efficacy in children have not been established.	Extended-release tablet: 2.5/120 mg (12 hour) 5/240 mg (24 hour)
Fexofenadine/ pseudoephedrine	<u>Seasonal allergic rhinitis:</u> Extended-release tablet: initial, 2 (60/120 mg) PO BID or 1 (180/240 mg) PO daily; maintenance, 2 (60/120 mg) PO BID or 1 (180/240 mg) PO daily; maximum, 180/240 mg PO daily	Safety and efficacy in children have not been established.	Extended-release tablet: 60/120 mg (12 hour) 180/240 mg (24 hour)
Loratadine/ pseudoephedrine	<u>Seasonal allergic rhinitis:</u> Extended-release tablet: initial, 2 (5/120 mg) PO BID or 1 (10/240 mg) PO daily; maintenance, 2 (5/120 mg) PO BID or 1 (10/240 mg) PO daily; maximum, 10/240 mg PO daily	Safety and efficacy in children have not been established.	Extended-release tablet: 5/120 mg (12 hour) 10/240 mg (24 hour)

Clinical Guidelines

Table 9. Clinical Guidelines

Clinical Guideline	Recommendations
Allergic Rhinitis and its Impact on Asthma and the Global Allergy and Asthma European Network: Guideline Revisions (2010) ⁵⁵	<p><u>Diagnosis</u></p> <ul style="list-style-type: none"> The diagnosis of allergic rhinitis is based upon the concordance between typical history of allergic symptoms and diagnostic response. Typical symptoms of allergic rhinitis include rhinorrhea, sneezing, nasal obstruction and pruritus. Diagnostic tests are based on the demonstration of allergen-specific immunoglobulin E (IgE) in the skin or blood. Many asymptomatic patients can have positive skin tests or detectable serum levels of IgE. <p><u>Treatment</u></p> <ul style="list-style-type: none"> The treatment of allergic rhinitis should consider the severity and duration of the disease, the patient's preference, as well as the efficacy, availability and cost of the medication. A stepwise approach depending on the severity and duration of rhinitis is proposed. Not all patients with moderate/severe allergic rhinitis are controlled despite optimal pharmacotherapy. Intranasal glucocorticoids are recommended over oral H₁-antihistamines for the treatment of allergic rhinitis in adults and children. They are the most effective drugs for treating allergic rhinitis. In many patients with strong preferences for the oral route, an alternative choice

Clinical Guideline	Recommendations
	<p>may be reasonable.</p> <ul style="list-style-type: none"> • Second-generation oral or intranasal H₁-antihistamines are recommended for the treatment of allergic rhinitis and conjunctivitis in adults and children. • First generation oral H₁-antihistamines are not recommended when second-generation ones are available, due to safety concerns. • Intranasal H₁-antihistamines are recommended for the treatment of adults and children with seasonal allergic rhinitis, but data regarding their relative safety and efficacy is limited. Therefore, their use in persistent allergic rhinitis is not recommended. • Intramuscular glucocorticoids and long-term use of oral glucocorticoids are not recommended due to safety concerns. • Topical cromones are recommended in the treatment of allergic rhinitis but they are only modestly effective. • Montelukast is recommended for adults and children with seasonal allergic rhinitis, and in pre-school children with persistent allergic rhinitis. Montelukast has limited efficacy in adults with persistent allergic rhinitis. • Intranasal ipratropium is recommended for the treatment of rhinorrhea associated with allergic rhinitis. • Intranasal decongestants may be used for a short period (<5 days) for patients with severe nasal obstruction. Nasal decongestants should not be used in pre-school aged children. • Combination oral decongestants and oral H₁-antihistamines may be used for the treatment of allergic rhinitis in adults, but should not be administered regularly due to adverse effects. • For patients experiencing ocular symptoms associated with allergic rhinitis intraocular antihistamines or chromones may be considered.
<p>Joint Task Force on Practice Parameters for Allergy and Immunology: The Diagnosis and Management of Rhinitis: An Updated Practice Parameter (2008)¹⁹</p>	<p><u>Diagnosis</u></p> <ul style="list-style-type: none"> • An effective evaluation of a patient with rhinitis includes a determination of the pattern, chronicity, and seasonality of nasal and related symptoms; response to medications; presence of coexisting conditions; occupational exposure; and a detailed environmental history and identification of precipitating factors. • A physical examination with emphasis on the upper respiratory tract should be performed in patients with a history of rhinitis. • Skin testing is the preferred test for the diagnosis of IgE-mediated sensitivity and is indicated to provide evidence of allergic basis for the causes of the patient's symptoms. • Nasal smears for eosinophils are not necessary for routine use in diagnosing allergic rhinitis but may be useful when the diagnosis of allergic rhinitis is in question. • The measurement of total IgE should not be routinely performed. • Cytotoxic tests, provocation-neutralization, electrodermal testing, applied kinesiology, iridology, and hair analysis are not recommended diagnostic procedures. <p><u>Treatment</u></p> <ul style="list-style-type: none"> • The management and monitoring of rhinitis should be individualized and based on symptoms, physical examination findings, comorbidities, patient age and patient preferences. • Environmental control measures include avoidance of known allergic triggers when possible.

Clinical Guideline	Recommendations
	<ul style="list-style-type: none"> • The available second-generation oral antihistamines, which are generally preferred over first-generation antihistamines, appear to be equally effective in the treatment of allergic rhinitis. • Concerning the second generation antihistamines, fexofenadine, loratadine, and desloratadine do not cause sedation at recommended doses; loratadine and desloratadine may cause sedation at doses exceeding the recommended dose; cetirizine and intranasal azelastine may cause sedation at recommended doses. • Intranasal antihistamines are efficacious and equal to or “superior” to oral second-generation antihistamines for treatment of seasonal allergic rhinitis. • Intranasal antihistamines may be considered for use as first-line treatment for allergic and nonallergic rhinitis. • Leukotriene receptor antagonists alone or in combination with antihistamines are effective in the treatment of allergic rhinitis. • Topical decongestants are not recommended for regular daily use but can be considered for short-term management of nasal congestion. • Intranasal corticosteroids are the most effective medication class for controlling symptoms of allergic rhinitis and all are considered equally efficacious. • Intranasal corticosteroids can provide significant relief of symptoms when used on a regular basis as well as an as-needed basis. • Intranasal corticosteroids may be useful in the treatment of some forms of nonallergic rhinitis. • A short course of oral corticosteroids may be appropriate for very severe or intractable nasal symptoms or significant nasal polyposis. • Intranasal cromolyn sodium may be effective for the prevention and treatment of allergic rhinitis. • Intranasal anticholinergics may be effective in reducing rhinorrhea and are more effective when used in combination with intranasal corticosteroids. • Allergen immunotherapy is effective and should be considered for patients with allergic rhinitis who have demonstrable evidence of specific IgE antibodies to clinically relevant allergens. • Surgery may be indicated in the management rhinitis.
<p>Institute for Clinical Systems Improvement: Diagnosis and Treatment of Respiratory Illness in Children and Adults (2011)⁵⁶</p>	<p><u>Diagnosis</u></p> <ul style="list-style-type: none"> • Patients can present with any of the following symptoms: congestion, rhinorrhea, pruritus, sneezing, posterior nasal discharge, and sinus pressure/pain. • A past medical history of facial trauma or surgery, asthma, rhinitis, atopic dermatitis, or thyroid disease may be suggestive of a rhinitis. In addition, a family history of atopy or other allergy associated conditions make allergic rhinitis more likely. • The most common physical findings suggestive of rhinitis tend to be swollen nasal turbinates, rhinorrhea and pruritus however allergic conjunctivitis may also be present. • Symptoms suggestive of allergic etiology include sneezing, itching of the nose, palate or eyes, and clear rhinorrhea. Nasal congestion is the most significant complaint in patients with perennial rhinitis. • Diagnostic testing should be considered if the results would change management. • Skin tests and radioallergosorbent tests identify the presence of IgE antibody to a specific allergen and are used to differentiate allergic from

Clinical Guideline	Recommendations
	<p>nonallergic rhinitis and to identify specific allergens causing allergic rhinitis.</p> <ul style="list-style-type: none"> • A nasal smear for eosinophils is a good predictor of a patient's response to treatment topical nasal corticosteroids. • Peripheral blood eosinophil count, total serum IgE level, Rinkel method of skin titration and sublingual provocation testing are not recommended. <p><u>Treatment</u></p> <ul style="list-style-type: none"> • If a clinical diagnosis is obvious, symptomatic treatment, which consists of education on avoidance and medication therapy, should be initiated. • Avoidance of triggers is recommended. • Intranasal corticosteroids are the most effective single agents for controlling the spectrum of allergic rhinitis symptoms and should be considered first-line therapy in patients with moderate to severe symptoms. • Regular daily use of intranasal corticosteroids is required to achieve optimal results. • It may be best to start treatment one week prior to the start of the allergy season for prophylaxis. • Clinical response does not seem to vary significantly between the available intranasal corticosteroids. • Systemic corticosteroids should be reserved for refractory or severe cases of rhinitis. Injectable steroids are not generally recommended. • Antihistamines are effective at controlling all symptoms associated with allergic rhinitis except nasal congestion. • Antihistamines are somewhat less effective than intranasal corticosteroids but they can be used on a daily or as needed basis. • Second-generation antihistamines are recommended because they are less sedating and cause less central nervous system impairment. • Leukotriene inhibitors may be as effective as second-generation antihistamines for the treatment of allergic rhinitis and less effective than intranasal corticosteroids. • Oral decongestants are effective in reducing nasal congestion. Oral decongestants can be a useful addition to antihistamines. • Topical decongestants, which have the potential to induce rebound congestion after three days, are effective for the short-term relief of nasal congestion. • Cromolyn is less effective than intranasal corticosteroids and is most effective when used prior to the onset of allergic symptoms. • Cromolyn is a good alternative for patients who are not candidates for corticosteroids. • Intranasal anticholinergics are effective in relieving anterior rhinorrhea in allergic and nonallergic rhinitis. • Reserve immunotherapy for patients with significant allergic rhinitis in which avoidance activities and pharmacotherapy are insufficient to control symptoms. • If adequate relief is achieved appropriate follow-up should include further education on avoidance activities and medications. • If patients anticipate unavoidable exposure to known allergens they should begin the use of medications prior to exposure. • If adequate relief is not achieved within two to four weeks consider a trial of another medication, allergen skin testing by a qualified physician,

Clinical Guideline	Recommendations
	<p>a complete nasal examination, or a diagnosis of nonallergic rhinitis.</p> <ul style="list-style-type: none"> • Treatment options for nonallergic rhinitis include intranasal corticosteroids, oral decongestants and antihistamines, topical antihistamines, and nasal strips.
<p>American Academy of Family Physician: Treatment of Allergic Rhinitis (2010)³</p>	<ul style="list-style-type: none"> • Treatment should be based on the patient's age and severity of symptoms. • Intranasal corticosteroids are the most effective treatment and should be first-line therapy for mild to moderate disease. • Moderate to severe disease not responsive to intranasal corticosteroids should be treated with second-line therapies, including antihistamines, decongestants, cromolyn, leukotriene receptor antagonists, and nonpharmacologic therapies (e.g., nasal irrigation). • Immunotherapy should be considered in patients with inadequate response to usual treatments. • Omalizumab has been shown to be effective in reducing nasal symptoms and improving quality of life scores in patients with allergic rhinitis. However, its high cost (average wholesale price of \$679 to \$3,395/month) and lack of Food and Drug Administration approval for home administration are the main limitations to its use.
<p>A Joint initiative of the European Academy of Allergology and Clinical Immunology, the Global Allergy and Asthma European Network and the European Dermatology Forum and the World Allergy Organization: Management of Urticaria (2009)²⁰</p>	<p><u>Treatment</u></p> <ul style="list-style-type: none"> • Sedating antihistamines should not be used for the routine management of chronic urticaria as first line agents, except in situations where proven to be more effective or tolerated than nonsedating H₁-antihistamines. This recommendation is based on strong evidence regarding potentially serious side-effects of old sedating antihistamines and the availability of the second generation nonsedating antihistamines which not only lack these side-effects but also have a higher efficacy and duration of action. • Considering their safety profile, second generation antihistamines should be considered as first line symptomatic treatment for urticaria. • For acute urticaria and acute exacerbations of chronic spontaneous urticaria, a short course of corticosteroids may, however, be helpful to reduce disease duration. • Cyclosporine is recommended only for patients with severe disease refractory to any dose of antihistamine. Cyclosporine has a far better risk/benefit ratio compared with corticosteroids. • For the treatment of chronic spontaneous urticaria and symptomatic dermographism, ultraviolet-A and ultraviolet-B treatment for one to three months can be added to antihistamine treatment. • While antihistamines at up to quadruple the recommended dosages will control symptoms in the majority of patients with urticaria in general practice, alternative treatments are needed for the remaining unresponsive patients. Before initiating an alternative therapy, it is recommended to wait for one to four weeks to allow full effectiveness of the antihistamines before considering referral to a specialist. • Since the severity of urticaria may fluctuate, and since spontaneous remission may occur at any time, it is also recommended to re-evaluate the necessity for continued or alternative drug treatment every three to six months.
<p>British Association of Dermatologists: Guidelines for Evaluation and</p>	<p><u>Treatment</u></p> <ul style="list-style-type: none"> • Nonspecific aggravating factors such as overheating, stress, alcohol, and drugs with the potential to worsen urticaria (aspirin and codeine) should be minimized.

Clinical Guideline	Recommendations
<p>Management of Urticaria in Adults and Children (2007)⁵⁸</p>	<ul style="list-style-type: none"> • Nonsteroidal anti-inflammatory drugs should be avoided in aspirin-sensitive patients with urticaria. • All patients should be offered the choice of at least two nonsedating H₁ antihistamines because response varies between individuals. • It has become common practice to increase the dose above the recommended doses for patients who do not respond when the potential benefits are considered to outweigh any risks. • The use of sedating antihistamines as monotherapy is now less common due to concerns about reduced concentration and performance but they can be effective and well tolerated by some individuals. Doxepin has useful antihistaminic properties but has sedating and anticholinergic side-effects. <ul style="list-style-type: none"> ○ Addition of a sedating antihistamine at night to a nonsedating antihistamine by day may help patients sleep better although it probably has little additional clinical effect on urticaria. • The addition of a H₂-antihistamine, may give better control of urticaria than an H₁ antihistamine taken alone although, in practice, it may be more helpful for dyspepsia that may accompany severe urticaria. • Leukotriene receptor antagonists may be taken in addition to an H₁ antihistamine for poorly controlled urticaria but there is little evidence that they are useful as monotherapy. • Oral corticosteroids may shorten the duration of acute urticaria although lower doses are often effective. Long-term oral corticosteroids should not be used in chronic urticaria except in very selected cases under regular specialist supervision. • Intramuscular epinephrine can be life saving in anaphylaxis and in severe laryngeal angioedema but should be used with caution in hypertension and ischemic heart disease. • Immunomodulating therapies for chronic autoimmune urticaria should be restricted to patients with disabling disease who have not responded to optimal conventional treatments.

Conclusions

Second-generation antihistamines have been shown to significantly improve the symptoms of allergic rhinitis and chronic idiopathic urticaria, without the unwanted adverse effects associated with the first-generation agents.³ All of the second-generation antihistamines are Food and Drug Administration-approved for the treatment of seasonal allergic rhinitis and all of the single entity agents are additionally indicated for chronic idiopathic urticaria.^{5-12,16-18} Currently, all the single entity second-generation antihistamines are available generically with the exception of desloratadine. Cetirizine, fexofenadine and loratadine can be purchased over-the-counter without a prescription.^{4-6,8} Currently acrivastine/pseudoephedrine and desloratadine/pseudoephedrine are the only combination second generation antihistamine agents not available generically. Although the combination acrivastine/pseudoephedrine is available in the United States, acrivastine alone is not.

Current evidence supports the use of second-generation antihistamines in the treatment of seasonal and perennial allergic rhinitis as well as chronic idiopathic urticaria. In a systematic review by Benninger et al, second-generation antihistamines were associated with a 23.5% reduction from baseline in total nasal symptom scores for seasonal allergic rhinitis, and a 51.4% reduction in symptoms for perennial allergic rhinitis.¹³ Although intranasal corticosteroids were found to be more effective for seasonal allergic rhinitis (40.7%), they were not found to be as effective as long term oral antihistamines in patients with perennial allergic rhinitis (37.3%). Overall, clinical trials have not consistently demonstrated one single entity second generation antihistamine agent as more efficacious, or safe, than the others. Furthermore, there

is a lack of head to head trials comparing the combination second generation antihistamine products, rendering a comparison of the agents difficult.

Current consensus guidelines are consistent amongst organizations that antihistamines are somewhat less effective than intranasal corticosteroids but may be used on a daily or as needed basis. Second-generation antihistamines are recommended as they are less sedating and cause less central nervous system impairment compared to first generation agents.^{55,56} Oral decongestants can be a useful addition to antihistamines in the treatment of nasal congestion. Considering their efficacy and safety profile, second generation antihistamines should be considered as first-line symptomatic treatment of urticaria. Additionally, all patients should be offered the choice of at least two nonsedating antihistamines as response varies between individuals.^{20,57}

Appendix I: Utilization Within This Drug Class for DVHA: July 1, 2010 to December 31, 2010

Medication	Unique utilizers	# of Rx's	Market Share (%)	Plan Cost \$	Avg \$/Rx
<i>Single Agents</i>					
Loratadine tabs/syrup/RDT	3,482	7,889	51.30%	\$92,059.90	\$11.67
Cetirizine tabs/ syrup	2,685	6,183	40.21%	\$90,571.25	\$14.65
Fexofenadine	360	1,078	7.01%	\$47,756.12	\$44.30
Allegra	26	74	0.48%	\$4,871.82	\$65.83
Clarinex	20	64	0.42%	\$7,706.67	\$120.42
Xyzal	19	42	0.27%	\$3,693.12	\$87.93
Clarinex Reditabs	7	17	0.11%	\$1,882.83	\$110.75
Claritin	6	15	0.10%	\$424.52	\$28.30
Claritin Reditabs	3	9	0.06%	\$180.69	\$20.08
Allegra ODT	3	6	0.04%	\$343.03	\$57.17
Total	6,613	15,381	100%	\$249,652.82	\$16.23
<i>Combination Products</i>					
Loratadine/pseudoephedrine	264	445	71.09%	\$11,165.27	\$25.09
Allegra-D 24	19	45	7.19%	\$5,663.89	\$125.86
Fexofenadine/pseudoephedrine	23	41	6.55%	\$4,243.02	\$103.49
Cetirizine/pseudoephedrine	13	36	5.75%	\$1,610.46	\$44.73
Allegra-D 12	12	28	4.47%	\$3,686.36	\$131.55
Clarinex-D 24	4	12	1.92%	\$1,522.16	\$126.85
Claritin-D 12	3	10	1.60%	\$510.77	\$51.08
Claritin-D 24	3	9	1.43%	\$289.87	\$32.21
Total:	NA	626	100%	\$28,691.80	\$45.83

Recommendations

In recognition of the following factors:

- The well-established role of the single entity and combination second-generation antihistamine products for the treatment of allergic rhinitis (perennial and seasonal) and chronic idiopathic urticaria.
- The record of efficacy and safety of the single entity and combination second generation antihistamine products over first generation antihistamine products.
- Comparable safety and efficacy profiles between all agents in the class.
- The availability of generic formulations for cetirizine, fexofenadine, levocetirizine and loratadine.

...it is recommended that no changes be made to the current Department of Vermont Health Access (DVHA) second-generation antihistamines approval criteria (see below).

fexofenadine

- The diagnosis or indication for the requested medication is allergic rhinitis or chronic idiopathic urticaria.

AND

- The patient has had a documented side effect, allergy, or treatment failure to loratadine (OTC) AND cetirizine (OTC).

Allegra tablets, Clarinex tablets, Claritin capsules/tablets, levocetirizine tablets, Xyzal tablets

- The diagnosis or indication for the requested medication is allergic rhinitis or chronic idiopathic urticaria.

AND

- The patient has had a documented side effect, allergy, or treatment failure to loratadine (OTC) AND cetirizine (OTC).

AND

- The patient has had a documented side effect, allergy, or treatment failure to fexofenadine.

AND

- If the request is for Xyzal, the patient must also have a documented intolerance to levocetirizine tablets.

Allegra ODT, cetirizine chewable tablets, Clarinex reditabs, Claritin chewable tablets, Claritin Reditabs

- The diagnosis or indication for the requested medication is allergic rhinitis or chronic idiopathic urticaria.

AND

- The patient has had a documented side effect, allergy, or treatment failure to loratadine (OTC) rapidly disintegrating tablets.

Allegra suspension, Clarinex syrup, Claritin Syrup, Xyzal syrup

- The diagnosis or indication for the requested medication is allergic rhinitis or chronic idiopathic urticaria.

AND

- The patient has had a documented side effect, allergy, or treatment failure to loratadine syrup AND cetirizine syrup.

Allegra-D, cetirizine-D, Clarinex-D, Claritin-D, fexofenadine-PSE

- The diagnosis or indication for the requested medication is allergic rhinitis.

AND

- The patient has had a documented side effect, allergy, or treatment failure to loratadine-D (OTC).

AND

- If the request is for Fexofenadine-PSE, the patient must also have a documented intolerance to Allegra-D 12 hr.

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