Therapeutic Class Overview
Intranasal Histamine H_1-receptor Antagonists (Antihistamines)

Therapeutic Class

- **Overview/Summary:** The four intranasal histamine-1 receptor antagonist (H_1-antihistamines) products that are approved for the management of rhinitis include azelastine (Astelin®, Astepro®), olopatadine (Patanase®) and azelastine hydrochloride/fluticasone propionate (Dymista®).[1-4] Allergic rhinitis, often referred to as rhinosinusitis, is a condition characterized by episodes of sneezing, rhinorrhea, nasal congestion, itchy and watery eyes, nose and palate. Other common symptoms may include cough, postnasal drip, and fatigue.[5] Allergic rhinitis is also referred to in terms of the cyclical or persistent nature of symptoms. Seasonal allergic rhinitis is that which occurs at a particular time of the year; whereas, perennial allergic rhinitis describes symptoms that are present year round. Mast cell activation, histamine release, prostaglandin and leukotrienes propagation, along with other cytokine mediators (e.g., platelet activating factor, tumor necrosis factor, transforming growth factor beta, eosinophils, etc.) are known to play a direct role in the disease pathology and symptomatology.[6] Allergic rhinitis may be classified by its intermittent or persistent pattern and by severity (mild or moderate to severe). Intermittent patterns involve the presence of symptoms for less than four days per week or for less than four weeks; whereas persistent patterns entail the presence of symptoms more than four days per week and for more than four weeks. Conditions associated with allergic rhinitis include: allergic conjunctivitis, sinusitis, asthma, atopic dermatitis, oral allergy syndrome, eustachian tube dysfunction, sleep disturbances, nasal obstruction leading to anosmia, and migraine headaches.[5,7]

  Astelin® nasal spray is the only agent within the class that is available generically. This product contains 0.1% azelastine hydrochloride in an aqueous solution with benzalkonium chloride and edetate disodium. Astepro® nasal spray contains 0.15% azelastine hydrochloride in an isotonic aqueous solution with sorbitol and sucralose. The difference in formulation was made to minimize the potential for the adverse event of bitter taste that is associated with Astelin®. Azelastine hydrochloride/fluticasone propionate is the only product available that combines an H_1-antihistamine and a steroid. This product is indicated for patients who require treatment with both azelastine and fluticasone propionate for symptomatic relief.[1-4]

Table 1. Current Medications Available in the Therapeutic Class[1-4]

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Single-Entity Agents			
Azelastine hydrochloride (Astelin®*, Astepro®)	Relief of the symptoms of seasonal allergic rhinitis, relief of the symptoms of perennial allergic rhinitis (Astepro®) and relief of the symptoms of vasomotor rhinitis (Astelin®)	Nasal spray: 137 µg/spray (Astelin®) 205.5 µg/spray (Astepro®)	✔
Olopatadine hydrochloride (Patanase®)	Relief of the symptoms of seasonal allergic rhinitis	Nasal spray: 665 µg/spray	-
Combination Products			
Azelastine hydrochloride/ fluticasone propionate (Dymista®)	Relief of the symptoms of seasonal allergic rhinitis†	Nasal spray: 137 µg /50 µg/ spray	-

*Generic is available in at least one dosage form or strength.
†In patients 12 years of age and older when treatment with both azelastine hydrochloride and fluticasone propionate is required.

Evidence-based Medicine

- Azelastine hydrochloride nasal spray has been found to be safe and effective over 14 days of treatment in placebo-controlled trials.[8-10] In a study by Shah et al comparing azelastine hydrochloride 0.1% and 0.15% formulations, there was a significantly greater improvement in total nasal symptom score (TNSS) for patients treated with azelastine 0.15% compared to patients receiving azelastine 0.1% (*P*=0.047).[11]
- Olopatadine hydrochloride has been proven safe and effective in placebo-controlled trials using various doses of olopatadine hydrochloride.[12-17] Head-to-head studies have not demonstrated any statistically significant differences in efficacy between olopatadine hydrochloride and azelastine hydrochloride.[18-20] In a study by Shah et al, there was no statistically significant difference between the treatments with regard to TNSS score or quality of life over 16 days of treatment.
- The results of a study by Ratner and colleagues demonstrated that the combination of azelastine hydrochloride nasal spray and fluticasone propionate nasal spray was significantly more effective compared to the individual agents alone in improving various symptom scores. The TNSS score improved by 27.1% with fluticasone, 24.8% with azelastine and 37.9% with the combination (*P*<0.05 for the combination vs either agent alone).[21] Other randomized trials comparing the combination of azelastine hydrochloride nasal spray and fluticasone propionate nasal spray have also demonstrated significant improvements in TNSS, individual symptom scores and quality of life compared to each agent administered as monotherapy.[22-24]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
    - Intranasal corticosteroids should be considered first-line therapy in patients with moderate to severe allergic rhinitis and may also be effective in some forms of nonallergic rhinitis.[25-27]
    - Oral or intranasal antihistamines and cromolyn can be considered alternatives in patients who prefer not to use intranasal corticosteroids.[25-27]
- Other Key Facts:
    - The role of the intranasal antihistamines in the treatment of rhinitis has been well established.
    - In general, intranasal corticosteroids are considered first-line agents for the treatment of rhinitis. Intranasal antihistamines may be considered as alternative agents.[25-27]
    - Generic azelastine hydrochloride 0.1% (Astelin®) is available.[28]
    - The individual components of the azelastine hydrochloride/fluticasone propionate (Dymista®) combination product are available generically.[28]

References

1. Astelin® [package insert]. Somerset (NJ): Meda Pharmaceuticals, Inc.; 2012 Jan.
2. Astepro® [package insert]. Somerset (NJ): Meda Pharmaceuticals, Inc.; 2010 Nov.
3. Dymista® [package insert]. Somerset (NJ): Meda Pharmaceuticals, Inc.; 2012 Sep.
4. Patanase® [package insert]. Fort Worth (TX): Alcon Laboratories, Inc.; 2012 Feb.
5. deShazo RD, Kemp SF. Pathogenesis of allergic rhinitis (rhinosinusitis). In: Basow DS (Ed). UpToDate [database on the internet]. Waltham (MA): UpToDate; 2013 [cited 2013 Jul 8]. Available at: http://www.utdol.com/utd/index.do.
6. deShazo RD, Kemp SF. Pharmacotherapy of allergic rhinitis. In: Basow DS (Ed). UpToDate [database on the internet]. Waltham (MA): UpToDate; 2013 [cited 2013 Jul 8]. Available at: http://www.utdol.com/utd/index.do.
7. Brozek J, Bousquet J, Baena-Cagnani C, Bonini S, Canonica GW, Casale TB, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision. J Allergy Clin Immunol. 2010;126:466-76.
8. Lumry W, Prenner B, Corren J, Wheeler W. Efficacy and safety of azelastine nasal spray at a dose of 1 spray per nostril trice daily. Ann Allergy Asthma Immunol. 2007;99:267-72.
9. van Bavel J, Howland W, Amar NJ, Wheeler W, Sacks H. Efficacy and safety of azelastine 0.15% nasal spray administered once daily in subjects with seasonal allergic rhinitis. Allergy and Asthma Proceedings. 2009;30(5):512-18.
10. Howland WC, Amar NJ, Wheeler W, Sacks H. Efficacy and safety of azelastine 0.15% nasal spray administered once daily in patients with allergy to Texas mountain cedar pollen. Int Forum Allergy Rhinol. 2011 Jul-Aug;1(4):275-9.
11. Shah S, Berger W, Lumry W, La Force C, Wheeler, Sacks H. Efficacy and safety of azelastine 0.15% nasal spray and azelastine 0.10% nasal spray in patients with seasonal allergic rhinitis. Allergy and Asthma Proceedings. 2009;30(6):628-33.
12. Patel P, Roland PS, Marple BF, et al. An assessment of the onset and duration of action of olopatadine nasal spray. Otolaryngology-Head and Neck Surgery. 2007;137:918-24.
13. Shah S, Nayak A, Ratner P, Roland P, Wall GM. Effects of olopatadine hydrochloride nasal spray 0.6% in the treatment of seasonal allergic rhinitis: a phase III, multicenter, randomized, double-blind, active- and placebo-controlled study in adolescents and adults. Clin Therap. 2009;31(1):99-107.

14. Meltzer EO, Garadi R, LaForce C, Chadwick SJ, Berger WE, Gross G, et al. Comparative study of sensory attributes of two antihistamine nasal sprays: olopatadine 0.6% and azelastine 0.1%. Allergy Asthma Proc. 2008;29:659-68.
15. Lieberman P, Meltzer EO, LaForce CF, Darter AL, Tort MJ. Two-week comparison study of olopatadine hydrochloride nasal spray 0.6% vs azelastine hydrochloride nasal spray 0.1% in patients with vasomotor rhinitis. Allergy Asthma Proc. 2011 Mar-Apr;32(2):151-8.
16. Ratner PH, Hampel FC, Amar NJ, Van Bavel JH, Mohar D, Marple BF, et al. Safety and efficacy of olopatadine hydrochloride nasal spray for the treatment of seasonal allergic rhinitis to mountain cedar. Annals of Allergy, Asthma, & Immunology. 2005;95(5):474-9.
17. Carr W, Bernstein J, Lieberman P, Meltzer E, Bachert C, et al. A novel intranasal therapy of azelastine with fluticasone for the treatment of allergic rhinitis. J Allergy Clin Immunol. 2012 May;129(5):1282-1289.e10.
18. Shah S, Nayak A, Ratner P, Roland P, Wall GM. Effects of olopatadine hydrochloride nasal spray 0.6% in the treatment of seasonal allergic rhinitis: a phase III, multicenter, randomized, double-blind, active- and placebo-controlled study in adolescents and adults. Clin Therap. 2009;31(1):99-107.
19. Meltzer EO, Garadi R, LaForce C, Chadwick SJ, Berger WE, Gross G, et al. Comparative study of sensory attributes of two antihistamine nasal sprays: olopatadine 0.6% and azelastine 0.1%. Allergy Asthma Proc. 2008;29:659-68.
20. Lieberman P, Meltzer EO, LaForce CF, Darter AL, Tort MJ. Two-week comparison study of olopatadine hydrochloride nasal spray 0.6% vs azelastine hydrochloride nasal spray 0.1% in patients with vasomotor rhinitis. Allergy Asthma Proc. 2011 Mar-Apr;32(2):151-8.
21. Ratner PH, Hampel FC, Amar NJ, Van Bavel JH, Mohar D, Marple BF, et al. Safety and efficacy of olopatadine hydrochloride nasal spray for the treatment of seasonal allergic rhinitis to mountain cedar. Annals of Allergy, Asthma, & Immunology. 2005;95(5):474-9.
22. Carr W, Bernstein J, Lieberman P, Meltzer E, Bachert C, et al. A novel intranasal therapy of azelastine with fluticasone for the treatment of allergic rhinitis. J Allergy Clin Immunol. 2012 May;129(5):1282-1289.e10.
23. Meltzer EO, Laforce C, Ratner P, Price D, Ginsberg D, Carr W. MP29-02 (a novel intranasal formulation of azelastine hydrochloride and fluticasone propionate) in the treatment of seasonal allergic rhinitis: A randomized, double-blind, placebo-controlled trial of efficacy and safety. Allergy Asthma Proc. 2012 Jul;33(4):324-32.
24. Hampel FC, Ratner PH, Van Bavel J, Amar NJ, Daftary P, Wheeler W, et al. Double-blind, placebo-controlled study of azelastine and fluticasone in a single nasal spray delivery device. Ann Allergy Asthma Immunol. 2010 Aug;105(2):168-73.
25. Wallace DV, Dykewicz MS, Bernstein DI, Blessing-Moore J, Cox L, Khan DA, et al. The diagnosis and management of rhinitis: An updated practice parameter of the joint task force on practice parameters for allergy and immunology. J Allergy Clin Immunol. 2008;122:S1-S84.
26. Snellman L, Adams W, Anderson G, Godfrey A, Gravley A, Johnson K, et al. Diagnosis and Treatment of Respiratory Illness in Children and Adults (Fourth edition; 2013 January). Institute for Clinical Systems Improvement. Available at: https://www.icsi.org/guidelines__more/.
27. Brozek J, Bousquet J, Baena-Cagnani C, Bonini S, Canonica GW, Casale TB, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision. J Allergy Clin Immunol. 2010;126:466-76.
28. Drugs@FDA [database on the Internet]. Rockville (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2013 [cited 2013 Jul 8]. Available from: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm.

Therapeutic Class Review
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Overview/Summary

The four intranasal histamine-1 receptor antagonist (H_1-antihistamines) products that are approved for the management of rhinitis include azelastine (Astelin®, Astepro®), olopatadine (Patanase®) and azelastine hydrochloride/fluticasone propionate (Dymista®).[1-4] Allergic rhinitis, often referred to as rhinosinusitis, is a condition characterized by episodes of sneezing, rhinorrhea, nasal congestion, itchy and watery eyes, nose and palate. Other common symptoms may include cough, postnasal drip, and fatigue.[5] Allergic rhinitis is also referred to in terms of the cyclical or persistent nature of symptoms. Seasonal allergic rhinitis is that which occurs at a particular time of the year; whereas, perennial allergic rhinitis describes symptoms that are present year round. Mast cell activation, histamine release, prostaglandin and leukotrienes propagation, along with other cytokine mediators (e.g., platelet activating factor, tumor necrosis factor, transforming growth factor beta, eosinophils, etc.) are known to play a direct role in the disease pathology and symptomatology.[6] Allergic rhinitis may be classified by its intermittent or persistent pattern and by severity (mild or moderate to severe). Intermittent patterns involve the presence of symptoms for less than four days per week or for less than four weeks; whereas persistent patterns entail the presence of symptoms more than four days per week and for more than four weeks. Mild disease is classified as the presence of symptoms without the presence of sleep disturbances, impairment in school or work performance, impairment in daily activities, leisure and/or sport activities, or troublesome symptoms. If one or more of these complications are present the condition is considered moderate-severe in nature. Conditions associated with allergic rhinitis include: allergic conjunctivitis, sinusitis, asthma, atopic dermatitis, oral allergy syndrome, eustachian tube dysfunction, sleep disturbances, nasal obstruction leading to anosmia, and migraine headaches.[5,7]

Treatment goals involve the resolution of symptoms, minimization of morbidity, preventing the development of disease progression, improving the individual's quality of life, minimizing adverse drug events, reducing direct and indirect economic costs associated with disease progression and loss of productivity (e.g., miss work or school days), and ensuring the appropriate step-wise approach of drug therapy to utilize targeted therapies specific to symptomatology and reduce unnecessary healthcare spending.[5-7] Non-pharmacologic approaches to preventing and managing the symptoms of allergic include: allergen avoidance (dust mites, animal dander, mold, and smoke exposure, etc.), nasal saline irrigation, exclusive breastfeeding for at least the first three months for all infants irrespective of the family history of atopy, as well as multifaceted interventions to reduce early life exposure to house dust mite (e.g., bed encasings, hard wood flooring vs carpeting, washing bedding in temperatures exceeding 55 C [131 F]).[7] Pharmacological approaches to managing allergic rhinitis include single-entity and combination approaches with agents from the following classes of medications: intranasal H_1-antihistamines, intranasal corticosteroids, intranasal cromolyn, intranasal ipratropium, oral non-sedating H_1-antihistamines, decongestants, leukotriene receptor antagonists, oral glucocorticoids, immunotherapy, and ocular administration of medications for ocular symptoms, when present. Intranasal glucocorticoids are the most effective drugs for treating allergic rhinitis and are recommended over oral H_1-antihistamines for the treatment of allergic rhinitis in adults and children. Intranasal H_1-antihistamines are recommended for the treatment of adults and children with seasonal allergic rhinitis; however, data regarding their relative safety and efficacy is limited.[5-7]

Astelin® nasal spray is the only agent within the class that is available generically. This product contains 0.1% azelastine hydrochloride in an aqueous solution with benzalkonium chloride and edetate disodium. Astepro® nasal spray contains 0.15% azelastine hydrochloride in an isotonic aqueous solution with sorbitol and sucralose. The difference in formulation was made to minimize the potential for the adverse event of bitter taste that is associated with Astelin®. Azelastine hydrochloride/fluticasone propionate is the only product available that combines an H_1-antihistamine and a steroid and is indicated when patients require treatment with both azelastine and fluticasone propionate for symptomatic relief.[1-4]

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Single-Entity Agents		
Azelastine hydrochloride (Astelin®*, Astepro®)	Intranasal H_1-antihistamines	✔
Olopatadine hydrochloride (Patanase®)	Intranasal H_1-antihistamines	-
Combination Products		
Azelastine hydrochloride/fluticasone propionate (Dymista®)	Intranasal H_1-antihistamines/intranasal corticosteroid	-

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

Indications

Table 2. Food and Drug Administration-Approved Indications[2,3,5,6,10]

Indication	Single Entity Agents		Combination Products
	Azelastine Hydrochloride	Olopatadine Hydrochloride	Azelastine Hydrochloride/ Fluticasone Propionate
Relief of the symptoms of seasonal allergic rhinitis	✔ *†	✔ ‡	✔ §
Relief of the symptoms of vasomotor rhinitis	✔ (Astelin®)		
Relief of the symptoms of perennial allergic rhinitis	✔ (Astepro®)		

*Astelin is approved for use in patients ≥5 years of age.
†Astepro is approved for use in patients ≥12 year of age.
‡ Patanase is approved for use in patients ≥6 years of age.
§ Dymista is approved for use in patients ≥12 years of age who require treatment with both azelastine hydrochloride and fluticasone propionate for symptomatic relief.

Pharmacokinetics

Table 3. Pharmacokinetics[1-4,9]

Generic Name	Bioavailability (%)	Absorption (%)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Single-Entity Agents					
Azelastine hydrochloride	40	Not reported	Not reported	Desmethyl-azelastine	22
Olopatadine hydrochloride	57	Not reported	70	6 minor metabolites	8 to 12
Combination Products					
Azelastine hydrochloride/ fluticasone propionate	40/2.9 to 3.2*	Not reported	Not reported/<5	Desmethyl-azelastine	25/7.8

*When administered in combination with azelastine hydrochloride, fluticasone propionate bioavailability is 44 to 61% greater than what is observed with monotherapy (2%).

Clinical Trials

Clinical trials demonstrating the safety and efficacy of the intranasal histamine-1 receptor antagonist (H_1-antihistamines) for their respective FDA-approved indications are outlined in Table 4.[10-32]

Azelastine hydrochloride formulations (Astelin® and Astepro®) have been shown to be safe and effective over 14 days of treatment in placebo-controlled trials.[10-12] When Astelin® was compared to Astepro® in a two week trial, there was a significantly greater improvement in total nasal symptom score (TNSS) for patients treated with Astepro® compared to patients treated with Astelin® (P=0.047).[13]

A meta-analysis comparing azelastine hydrochloride nasal spray to other agents used in the management of seasonal allergic rhinitis and perennial allergic rhinitis, including beclomethasone nasal spray and loratadine combination, terfenadine (not available in the U.S.), oral cetirizine, budesonide nasal spray, ebastine (not available in the U.S.), levocabastine (not available in the U.S) and oral loratadine did not identify a statistically significant difference in treatment response, despite multiple analyses. For TNSS, azelastine was more efficacious compared to placebo (effect size, 0.36; 95% confidence interval, 0.26 to 0.46).[22]

The combination of azelastine hydrochloride with fluticasone propionate nasal spray was significantly more effective compared to the individual agents in various symptom scores. The improvement in TNSS score from baseline was 37.9% for the combination therapy compared to 27.1 and 24.8%, respectively with single-entity fluticasone and azelastine (P<0.05 for the combination vs either agent alone).[29] Other randomized trials comparing the combination of azelastine hydrochloride nasal spray and fluticasone propionate nasal spray have also demonstrated significant improvements in TNSS, individual symptom scores, and quality of life ratings compared to each agent administered as monotherapy.[30-32]

Olopatadine hydrochloride (Patanase®) has been proven safe and effective in placebo-controlled trials across a wide range of doses.[16-21] Head-to-head studies have not demonstrated any statistically significant differences in efficacy between olopatadine hydrochloride and azelastine hydrochloride formulations.[13,26,27] In a single-dose crossover study comparing Astelin® with olopatadine hydrochloride, 60.6% of patients favored olopatadine hydrochloride, 30.3% favored Astelin®, and 9.2% had no preference. Mean patient preference was significantly greater with olopatadine hydrochloride compared to Astelin® for overall aftertaste, overall preference and likelihood of use.[26] Both Astelin® and olopatadine hydrochloride significantly reduced vasomotor rhinitis symptom scores from baseline in a two week clinical trial; however, the difference between treatments was not statistically significant.[27]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Lumry et al[10] Azelastine nasal spray, 1 spray in each nostril BID (Astelin®) vs placebo	2 DB, PC, RCT Patients 12 to 75 years of age with moderate-to-severe SAR who remained symptomatic after 1 week placebo lead in period	N=554 2 weeks	Primary: Change from baseline in TNSS Secondary: Change from baseline to day 14 in individual symptoms, patient global evaluation and RQLQ and adverse events	Primary: In both studies the mean difference in TNSS was significantly different in favor of azelastine compared to placebo (2.69 vs 1.31; *P*=0.01 for study one and 3.68 vs 2.50; *P*=0.02 for study two). Secondary: The mean percent improvement with azelastine was significantly better for itchy nose (*P*=0.02), runny nose (*P*=0.03) and sneezing (*P*<0.001), but not for nasal congestion (*P* value not reported) compared to placebo in study one. The mean percent improvement with azelastine was significantly better for itchy nose (*P*=0.04), sneezing (*P*<0.02) and congestion (*P*=0.01), but not for runny nose (*P* value not reported) compared to placebo in study two. A significantly greater number of patients rated their symptom improvement as "better" with azelastine compared to placebo in study one (67 vs 52%; *P*<0.001). A significantly greater number of patients rated their symptom improvement as "better" with azelastine compared to placebo in study two (74 vs 58%; *P*<0.01). The daily activity and nasal symptom domains of the RQLQ were significantly improved with azelastine compared to placebo in both studies (*P*<0.05 for all). The overall RQLQ was not significantly different between the two groups in study one, but was in favor of azelastine in study two (*P*=0.02). In patients treated with azelastine, 8.3% reported a bitter taste and 0.4% reported somnolence. No other significant differences in adverse events were reported.
van Bavel et al[11] Azelastine 0.15%, 2 sprays in each nostril QD	DB, PC, PG, RCT Patients 12 years of age and older with moderate to	N=536 14 days	Primary: 12-hour rTNSS Secondary: 24-hour iTNSS,	Primary: The LS mean improvement from baseline in the 12-hour rTNSS was significantly greater in the azelastine group compared to placebo (*P*<0.001). The LS mean percentage change in the 12-hour rTNSS was significantly

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo	severe SAR		daily change from baseline in 12-hour rTNSS, 12-hour reflective SSCS, adult RQLQ	greater in the azelastine group compared to placebo (*P*<0.001). Secondary: The LS mean change from baseline in the 24-hour iTNSS was significantly greater in the azelastine group compared to placebo (*P*<0.001). The LS mean percent change from baseline in the 24-hour iTNSS was significantly greater in the azelastine group compared to placebo (*P*<0.001). The mean daily change from baseline in 12-hour rTNSS was significantly greater for the azelastine group compared to placebo (*P*<0.05) on all study days except day 10. The mean daily change from baseline in 24-hour iTNSS was significantly greater for the azelastine group compared to placebo (*P*<0.05). The LS mean change from baseline in the 12-hour reflective SSCS was significantly greater for the azelastine group compared to placebo (*P*<0.001). The LS mean percent change from baseline in the 12-hour reflective SSCS was significantly greater for the azelastine group compared to placebo (*P*<0.002). The overall score for the RQLQ was significantly improved from baseline in the azelastine group compared to placebo (*P*=0.023).
Howland et al[12] Azelastine 0.15%, 2 sprays in each nostril QD vs placebo	DB, MC, PC, PG, RCT Patient 12 years of age and older with a ≥2-year history of allergy to Texas mountain cedar (*Juniperus ashei*) pollen (confirmed by a positive skin	N=506 14 days	Primary: Change from baseline in the 12-hour rTNSS Secondary: Change from baseline in the 24-hour iTNSS, rTOSS, daily change in rTNSS	Primary: The mean improvement from baseline in the 12-hour rTNSS was significantly greater for patients receiving azelastine compared to placebo (3.57 vs 2.14; *P*<0.001). The mean percentage improvement in 12-hour rTNSS was significantly greater in the azelastine group compared to the placebo group (19.3 vs 11.4%, respectively; *P*<0.001). Secondary: The mean improvement from baseline in 24-hour iTNSS (administered in the morning prior to dosing) was significantly greater in the azelastine group compared to the placebo group (1.43 vs 0.83; *P*<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	test), a 12-hour rTNSS of ≥8/12 and a congestion score of ≥2/3		and iTNSS, RQLQ and safety	There was a statistically significant improvement in the 12-hour rTOSS for patients randomized to receive azelastine compared to placebo (*P*<0.001). Patients receiving azelastine experienced a statistically significant improvement in daily rTNSS on all days of the evaluation period compared to placebo (*P*<0.05). Moreover, azelastine treatment was associated with statistically significant improvements in 24-hour iTNSS compared to placebo on all days except day six and nine (*P*<0.05). The overall RQLQ score was significantly higher following treatment with azelastine compared to placebo (1.12 vs 0.74; *P*<0.001). The most commonly reported adverse event in the azelastine group was nasal discomfort (3.6%) while epistaxis was reported most frequently in the placebo group (1.6%). There were no changes in vital signs or reports of moderate or severe epistaxis, nasal irritation or mucosal bleeding during the study.
Shah et al[13] Azelastine 0.1%, 2 sprays in each nostril BID vs azelastine 0.15% in each nostril BID vs placebo	AC, DB, PC, PG, RCT Patients 12 years of age and older with SAR	N=526 14 days	Primary: 12-hour rTNSS Secondary: iTNSS, 12-hour reflective rTNSS individual symptom scores, onset of action, 12-hour reflective SSCS, 12-hour reflective SSCS individual symptom scores and RQLQ	Primary: TNSS scores improved from baseline in both groups by day 14 (*P*<0.001). The LS mean improvement in the 12-hour rTNSS was significant for both azelastine groups compared to placebo (*P*<0.001). The LS mean percent improvement was significant for both azelastine groups compared to placebo (*P*<0.001). The rTNSS improvement in the azelastine 0.15% group was significantly greater compared to the azelastine 0.1% group (*P*=0.047). Secondary: Both azelastine groups showed significant improvements in the LS mean and LS mean percent changes in iTNSS compared to placebo. The LS mean and LS mean percent change from baseline in the 12-hour rTNSS for nasal congestion, rhinorrhea, itchy nose and sneezing showed significant differences from placebo in both azelastine groups (*P*<0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				The azelastine 0.15% group showed a significant difference from placebo by 30 minutes ($P<0.01$). The LS mean and LS mean percent improvements in the 12-hour reflective SSCS were significant for both azelastine groups compared to placebo ($P\leq0.002$). The LS mean change from baseline in 12-hour reflective SSCS for the symptoms of postnasal drip, itchy eyes, cough and headache showed significant improvements in both azelastine groups compared to placebo ($P<0.05$). The overall score for the RQLQ was significantly improved from baseline in the azelastine 0.15% group compared to placebo ($P<0.001$) The azelastine 0.15% group showed significant improvements in all domains of the RQLQ compared to placebo ($P<0.001$).
Bernstein et al[14] (abstract) Azelastine 0.15%, 1 or 2 spray(s) in each nostril BID vs azelastine 0.1%, 1 or 2 sprays in each nostril BID vs placebo	DB, PC, RCT Patients with SAR	N=835 14 days	Primary: TNSS Secondary: Not reported	Primary: All azelastine groups produced comparable improvements in TNSS compared to placebo. The percent changes from baseline in TNSS were significantly greater in the two sprays/nostril dosing groups compared to the one spray/nostril dosing groups ($P<0.01$). The incidence of bitter taste was 7% in patients treated with azelastine 0.15% and 8% for patients treated with azelastine 0.1% when administered as two sprays/nostril. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Shah et al[15] Olopatadine 0.6%, 2 sprays in each nostril BID vs azelastine 0.1%, 2 sprays in each nostril BID vs placebo	AC, DB, MC, PC, PG, RCT Patients 12 years of age and older with SAR	N=544 16 days	Primary: Overall rTNSS Secondary: RQLQ	Primary: The mean change from baseline in overall rTNSS was significantly greater in the olopatadine group compared to placebo (*P*=0.003). The difference between the olopatadine and azelastine groups was not significant. Secondary: The mean change in overall RQLQ score was significantly greater in the olopatadine group compared to placebo (*P*=0.005). The difference between the olopatadine and azelastine groups was not significant.
Meltzer et al[16] (abstract) Olopatadine 0.6%, 1 spray in each nostril BID vs placebo	2 DB, MC, RCT Pooled analysis of children 6 to 11 years of age with SAR	N=not reported 14 days	Primary: Change from baseline in rTNSS rTOSS, PRQLQ and CGTSQ-AR Secondary: Not reported	Primary: Children randomized to receive treatment with olopatadine experienced significantly greater improvements in rTNSS compared to placebo (*P*=0.0012). Similarly rTOSS scores for ocular symptoms were significantly improved following treatment with olopatadine compared to placebo (*P*=0.0094). There was a statistically significant reduction in overall PRQLQ score for patients receiving olopatadine compared to those randomized to placebo (*P*=0.0003). The mean summary CGTSQ-AR score was significantly improved over the course of the study with olopatadine compared to placebo (*P*=0.0013). The most commonly reported treatment-related adverse events in the olopatadine group were epistaxis and dysgeusia. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Meltzer et al[17] Olopatadine 0.4%, 2 sprays in each nostril BID vs olopatadine 0.6%, 2 sprays in each nostril BID vs placebo	DB, MC, PC, PG, RCT Patients 12 to 80 years of age with SAR and positive allergic sensitivity test	N=565 2 weeks	Primary: Percent change from baseline in rTNSS Secondary: Percent change from baseline in iTNSS, individual symptoms (runny nose, itching nose, sneezing, stuffy nose, watery eyes and itchy eyes) and RQLQ	Primary: Treatment with 0.4 or 0.6% olopatadine resulted in a significant improvement in rTNSS as compared to placebo (*P*=0.004 and *P*<0.001 respectively). The average percent reductions were 35.8 and 39.2% respectively, compared to 27.0% for placebo. Secondary: Treatment with 0.4 or 0.6% olopatadine resulted in a significant improvement in iTNSS compared to placebo (*P*=0.02 and *P*=0.003 respectively). The average reductions were 31.6 and 33.3% respectively, compared to 23.6% for placebo. Treatment with 0.4 or 0.6% olopatadine significantly improved rTNSS and iTNSS evaluation of most symptoms compared to placebo (reflective values: runny nose; *P*=0.046 and *P*=0.001 respectively, itchy nose; *P*=0.005 and *P*<0.001 respectively, sneezing; *P*<0.001 for both strengths). rTNSS and iTNSS scores for severity of stuffy nose were not significantly improved (reflective values for both strengths; *P*=0.70 and *P*=0.85). The quality of life scores for both treatment strengths were significantly improved from baseline compared to placebo (*P*=0.02 and *P*<0.001 for respective strengths compared to placebo). The 0.6% strength improved in all seven domains, while the 0.4% improved in four of the seven domains.
Ratner et al[18] Olopatadine 0.4%, 2 sprays in each nostril BID vs olopatadine 0.6%, 2 sprays in each nostril BID	DB, MC, PC, PG, RCT Patients 12 to 80 years of age with SAR and positive allergic sensitivity test	N=675 2 weeks	Primary: Percent change from baseline in rTNSS Secondary: Percent change from baseline in iTNSS, individual symptoms (runny nose, itching nose, sneezing,	Primary: Treatment with 0.4 or 0.6% olopatadine resulted in a significant improvement in rTNSS compared to placebo (*P*<0.001 for both). The average percent reductions were 27.6 and 30.1% respectively, compared to 18.7% for placebo. Secondary: Treatment with 0.4 or 0.6% olopatadine resulted in a significant improvement in iTNSS compared to placebo (*P*<0.001 and *P*=0.002 respectively). The average percent reductions were 24.3 and 26.2% respectively, compared to 15.8% for placebo. Treatment with 0.4 or 0.6% olopatadine resulted in a significant improvement

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo			stuffy nose, watery eyes and itchy eyes) and safety	in rTNSS and iTNSS for most symptoms compared to placebo (reflective values: runny nose; *P*<0.001 for 0.6% only, itchy nose and sneezing; *P*<0.001 for both strengths and symptoms, itchy eyes; *P*<0.001 and *P*=0.008, and watery eyes; *P*=0.002 and *P*=0.009). Adverse events were not considered serious. Bitter taste was the most common adverse event and somnolence occurred in 0.4 and 1.3% of the 0.6 and 0.4% olopatadine treatment groups respectively. No changes in laboratory results were seen.
Fairchild et al[19] Olopatadine 0.4%, 2 sprays in each nostril BID vs olopatadine 0.6%, 2 sprays in each nostril BID vs placebo	DB, MC, PC, RCT Patients 12 years of age and older with a 2 year history of SAR and positive skin test to relevant pollen	N=1,233 2 weeks	Primary: rTNSS change from baseline Secondary: Safety, RQLQ, and WPAI-AS	Primary: The absolute and percent change from baseline in rTNSS was significantly greater for both treatment groups compared to placebo (*P*<0.0001 for both, with decrease of 3.1 [-34.0%] for 0.6% and of 2.9 [-31.3%] for 0.4%, compared to placebo 2.1 [-22.5%]). Secondary: The most commonly reported adverse events were unpleasant taste and headache. Dysgeusia was reported more frequently in the 0.6 and 0.4% strengths than placebo (13.0 and 7.4% compared to 0.5% respectively). RQLQ score improved significantly in both treatment groups compared to placebo (*P*<0.0001 and *P*=0.0002). Changes in RQLQ scores correlated with changes in rTNSS (*P*<0.001). WPAI-AS scores on work impairment (*P*=0.0009 and *P*=0.0198) and activity impairment (*P*=0.0027 and *P*=0.0400) improved significantly in both treatment groups compared to placebo, but not in classroom impairment. Changes in WPAI-AS scores for work impairment improvement and activity impairment improvement correlate with changes in rTNSS (*P*<0.001 for both).
Hampel et al[20] Olopatadine 0.4%, 2 sprays in each nostril BID vs	DB, MC, RCT Patients 12 years of age and older with 2 year history of SAR and positive skin allergy	N=675 2 weeks	Primary: RQLQ Secondary: TNSS	Primary: Both treatments resulted in significant improvement in RQLQ (score change from baseline, 1.1 for both treatments) compared to placebo (score change from baseline, 0.8; *P*<0.01). The treatment strengths were not different from each other in RQLQ. The improvement in RQLQ is considered clinically significant as it correlates

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
olopatadine 0.6%, 2 sprays in each nostril BID vs placebo	test			with TNSS scores. Secondary: TNSS scores improved for both treatment strengths compared to placebo. The treatment strengths were not different from each other in RQLQ scores (*P* values not reported).
Patel et al[21] Olopatadine 0.2%, 2 sprays in each nostril vs olopatadine 0.4%, 2 sprays in each nostril vs olopatadine 0.6%, 2 sprays in each nostril vs placebo	DB, PC, PG, RCT, single dose Patients 17 to 65 years of age with a history of SAR during the fall season and allergic to short ragweed pollen	N=320 12 hours	Primary: TNSS change from baseline Secondary: Patient global rating, individual symptoms, and safety	Primary: Treatment resulted in significant change in TNSS score from baseline at the first time point of 30 minutes until the last at 11.5 hours (*P*<0.05 for all strengths compared to placebo). The 0.4 and 0.6% strengths achieved significant improvement compared to placebo at 14 of 16 time points; the 0.2% strengths achieved significance at 12 of the 16 time points. The 0.6% strengths achieved maximum decrease in TNSS sooner than other strengths (*P* value not given). Secondary: The 0.4 and 0.6% strengths were significantly better than placebo in the number of patients rating symptoms as very much and moderately better. Patients reported significant improvement in runny nose and itchy nose with the 0.2% strength at four and five time points respectively, the 0.4% strength at eight and two time points respectively, and the 0.6% strength at 12 and eight time points respectively. All treatments resulted in significant improvement over placebo in sneezing at all time points. All treatments achieved significant improvement over placebo at 90 minutes (*P* value not reported). Adverse events occurring during treatment were determined to be non-serious.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Lee et al[22] Azelastine nasal spray vs placebo or active comparators (budesonide nasal spray, cetirizine, ebastine*, levocabastine*, loratadine, terfenadine*, and the combination of beclomethasone nasal spray and loratadine)	MA Patients 12 years of age and older diagnosed with allergic rhinitis or nonallergic VMR	N=2,906 34 trials/data points ranging in duration from 2 days to 8 weeks	Primary: NNT, TNSS Secondary: Not reported	Primary: For azelastine compared to placebo the point estimates for the risk difference were positive ranging from 0.05 (95% CI, -0.08 to 0.17) to 0.33 (95% CI, 0.16 to 0.50). This resulted in NNT's ranging from 3 to 20 and a summary NNT of 5 (95% CI, 3.3 to 10.0). Results for heterogeneity of the azelastine vs placebo trials was significant (*P*=0.054). For azelastine compared to active comparators the point estimate for the risk difference was 0.015 (95% CI, -0.044 to 0.073). This resulted in a point estimate for the NNT of 66.7, which was not significantly different between azelastine and the comparators. Results for heterogeneity of the azelastine vs comparator trials was significant (*P*=0.006). For TNSS azelastine was more efficacious compared to placebo (effect size, 0.36; 95% CI, 0.26 to 0.46). Secondary: Not reported
Ghimire[23] Azelastine nasal spray (Group A) vs beclomethasone nasal spray (Group B) vs placebo nasal spray (Group C)	CC, PRO, R Patients with a history allergic rhinitis who were symptomatic	N=75 4 weeks	Primary: TSC, individual symptom score Secondary: Adverse events	Primary: In group A and B the TSC was reduced by 84% compared to 38% in group C. In group A and B the mean score for sneezing was reduced by 95.0% compared to 28.3% in group C. In group A and B the mean score for rhinorrhea was reduced by 94.4 and 95.3% compared to 25.0% in group C. Group B was the only one to reduce stuffiness significantly (95.0%). Secondary: No significant adverse events were observed in the treatment groups.
Patel et al[24] Olopatadine 0.6%, 2 sprays in each nostril	DB, PC, PG, RCT Patients 18 years of age and older	N=425 12 hours	Primary: TNSS change from baseline	Primary: Olopatadine treatment resulted in a significant change in TNSS from baseline, at all 16 time points, between zero and 720 minutes, compared to placebo (*P*<0.05) and at all time points between 60 and 600 minutes after dose when

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs mometasone 50 µg nasal spray vs placebo	with moderate to severe SAR and sensitivity to ragweed		Secondary: Patient global rating and individual symptoms	compared to mometasone (*P*<0.05). Significant differences in TNSS compared to placebo were first seen at 30 minutes after olopatadine dose, compared to 150 minutes after mometasone dose. Secondary: Patients reported improvement in allergy symptoms significantly more often in the olopatadine group than the placebo and the mometasone group at four hours: olopatadine, 88.0%; compared to placebo, 59.3%; and mometasone, 73.9%; and at 12 hours: olopatadine, 62.7%; compared to placebo, 29.8%; and mometasone, 50.7% (*P*<0.05 for all). Olopatadine treatment resulted in significant improvement in symptom scores compared to placebo for the following: sneezing, runny, itchy and stuffy nose and compared to mometasone: runny nose, itchy nose and stuffy nose at >60% of the time points.
Pipkorn et al[25] Study 1, phase 1: Olopatadine 0.1% nasal spray vs placebo Study 1, phase 2: olopatadine 0.2% nasal spray vs placebo Study 2:	2 DB, R, XO Patients 20 to 64 years of age free of symptoms at time of study enrollment, in good physical condition, taking no medications, and documented symptoms of SAR confirmed by skin test to ragweed or Timothy grass	Study 1, phase 1: N=16 Study 1, phase 2: N=19 Study 2: N=18 Duration not specified	Primary: Number of sneezes after each dose and levels of mediators (albumin, and lysozyme) Secondary: VAS scores for rhinorrhea, nasal pruritus, nasal congestion, and posterior nasal drainage, histamine levels	Primary: Study 1, phase 1: Compared to placebo, pretreatment with olopatadine significantly reduced sneezing (*P*=0.008). There was a significant difference in favor of the treatment group in lysozyme but not in albumin level. Study 1, phase 2: Compared to placebo, pretreatment with olopatadine significantly reduced sneezing (*P*=0.002). There was a significant difference in favor of the treatment group in lysozyme and albumin level. Study 2: There was no significant difference between the two groups in reduced sneezing (*P*=0.33). There was no significant difference in between the two groups in lysozyme (*P*=0.12) and albumin level (*P*=0.88). Secondary: Study 1, phase 1: Compared to placebo, pretreatment with olopatadine significantly reduced

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Azelastine nasal spray (Astelin®) vs olopatadine 0.1% nasal spray				rhinorrhea (*P*<0.001), pruritus (*P*<0.001), congestion (*P*=0.002) and posterior nasal drip (*P*=0.03). There was no significant difference in histamine level. Study 1, phase 2: Compared to placebo, pretreatment with olopatadine significantly reduced rhinorrhea (*P*=0.048), pruritus (*P*=0.01), congestion (*P*=0.01) and posterior nasal drip (*P*=0.005). There was a significant difference in histamine level in the treatment group. Study 2: There was no significant difference between the two groups in the reduction of rhinorrhea (*P*=0.12), pruritus (*P*=0.37), congestion (*P*=0.98), posterior nasal drip (*P*=0.98) and histamine level (*P*=0.83).
Meltzer et al[26] Azelastine nasal spray (Astelin®) vs olopatadine nasal spray Patients received one administration of each treatment consisting of two sprays in each nostril. Each medication was separated by a 24 hour washout period.	DB, MC, R, XO Patients 18 years of age and older with at least a 2 years history of SAR or PAR symptomatic at the time of enrollment	N=110 4 to 17 days (depending on patient specific washout period)	Primary: Mean patient preference and overall aftertaste Secondary: Sensory attribute of taste perception, overall product preference, likelihood of use over extended time, perceptions of smell and nasal irritation, sensation of medication dripping out of nose/down throat, moistness of nose and throat, overall satisfaction	Primary: Overall 60.6% of patients favored olopatadine, 30.3% favored azelastine and 9.2% had no preference (*P*=0.0005). Mean patient preference was significantly greater with olopatadine compared to azelastine for overall aftertaste (*P*=0.0005), overall preference (*P*=0.0001), and likelihood of use (*P*=0.0004). Secondary: Mean patient satisfaction scores for immediate taste were significantly better with olopatadine compared to azelastine (*P*=0.0001), but there was no significant difference in 45 minute after taste (*P* not reported). Immediately post dose, mean satisfaction was significantly greater for olopatadine compared to azelastine in smell, nasal congestion, urge to sneeze, dripping down nose, dripping down throat, and overall satisfaction ($P \leq 0.0146$). There was no significant difference in moistness of nose or throat. Forty-five minutes post dose mean satisfaction was significantly greater for olopatadine compared to azelastine in nasal irritation, urge to sneeze and overall satisfaction ($P \leq 0.0487$). There was no significant difference in smell, dripping down nose, dripping down throat, and moistness of nose or throat. No significant differences in adverse events were reported in the two groups.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Lieberman et al[27] Azelastine 0.1%, 2 sprays in each nostril BID vs olopatadine 0.6%, 2 sprays in each nostril BID	DB, MC, PG, RCT Patients 12 years of age and older with VMR and a ≥2-year history of chronic rhinitis symptoms related to defined triggers (*e.g.*, changes in climate, strong smells, and tobacco smoke) with a positive histamine skin-prick test and a TVSS score ≥6	N=129 14 days	Primary: Change from baseline in rTVSS Secondary: Change from baseline in individual VMR symptom scores, TSQM and PGA responders	Primary: Both azelastine and olopatadine significantly reduced rTVSS scores from baseline (-6.5 and -5.9, respectively; *P*<0.001 for both compared to baseline); however, the difference between treatments was not statistically significant (*P*=0.354). Secondary: Both azelastine and olopatadine significantly reduced reflective and instantaneous symptom scores compared to baseline (*P*<0.05 for all). There was no statistically significant difference between the treatments with regard to any of the individual reflective symptom scores (*P*>0.05 for all) or instantaneous scores for the individual symptoms (*P*>0.05 for all). Patients treated with azelastine or olopatadine reported similar satisfaction scores in the individual TSQM domains of effectiveness (61.7 vs 60.7; *P*=0.749), convenience (81.5 vs 78.1, respectively; *P*=0.312), adverse events (90.9 vs 89.9, respectively; *P*=0.747) and PGA (58.9 vs 56.9; *P*=0.687). A similar proportion of patients receiving azelastine or olopatadine reported an overall improvement in their condition following treatment (75.9 vs 82.5%, respectively; *P*=0.384).
Berger et al[28] Azelastine nasal spray, 2 sprays in each nostril BID (Astelin®) vs cetirizine 10 mg QD	DB, MC, R Patients 12 years of age and older with moderate-to-sever SAR	N=360 2 weeks	Primary: rTNSS Secondary: RQLQ, individual symptoms, safety	Primary: Compared to baseline, the combined morning and evening 12-hour rTNSS was significantly improved in both treatment groups (*P*<0.001). The mean improvement from baseline rTNSS in the ITT population was 4.6±4.2 in the azelastine group compared to 3.9±4.3 in the cetirizine group (*P*=0.14), correlating to a percent change of 23.9 and 19.6% in the azelastine and cetirizine groups, respectively (*P*=0.08). The mean improvement from baseline in rTNSS for the evaluable population was 4.6±4.2 in the azelastine group compared to 3.8±4.3 in the cetirizine group (*P*=0.09), correlating to a percent change of 24.2 and 19.2% in the azelastine and cetirizine groups, respectively (*P*=0.046).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Compared to baseline, each individual RQLQ domain score and the overall RQLQ score was significantly improved in both treatment groups (*P*<0.001). Compared to cetirizine, azelastine significantly improved each domain of the RQLQ (*P*≤0.05) and the overall RQLQ score (*P*=0.002). Compared to cetirizine, azelastine significantly improved nasal congestion (*P*=0.49) and sneezing (*P*=0.01) to a greater extent; however, there was no significant difference in improvement in itchy nose and runny nose. Bitter taste was the common adverse event with azelastine. No other significant difference was noted in adverse events.
Ratner et al[29] Azelastine nasal spray, 2 sprays in each nostril BID (Astelin®) and placebo nasal spray once in the morning vs fluticasone nasal spray, 2 sprays in each nostril QD in the morning and placebo nasal spray BID vs azelastine nasal spray, 2 sprays in each nostril BID (Astelin®) and fluticasone nasal spray, 2 sprays in each nostril	DB, DD, MC, PG, R Patients 12 years and older with a minimum 2-year history of allergy to Texas mountain cedar confirmed in the past year by positive skin test	N=151 2 weeks	Primary: Change from baseline in TNSS Secondary: Change from baseline for each individual treatment day, change from baseline for each individual symptom score, change from baseline in the RQLQ, safety	Primary: Compared to baseline all three treatment groups significantly improved TNSS (*P*<0.001). In the azelastine, fluticasone and combination groups the mean improvement from baseline TNSS was 4.8±4.3, 5.2±4.6 and 7.4±5.6, respectively. The improvement from baseline TNSS was 27.1% with fluticasone, 24.8% with azelastine and 37.9% with the combination (*P*<0.05 for the combination vs either agent alone). Compared to azelastine and fluticasone administered alone, there were absolute improvements of 11.0 (*P*=0.007) and 13.0% (*P*=0.02) with the combination treatment. Secondary: Compared to either single treatment, combination treatment was significantly more efficacious in treating the symptoms of congestion and itchy nose (*P*<0.05). Compared to fluticasone alone, combination treatment was significantly more efficacious in treating the symptom of runny nose (*P*<0.05). Compared to azelastine alone, combination treatment was significantly more efficacious in treating the symptom of sneezing (*P*<0.05). On study days three to 14, combination treatment was significantly more efficacious compared to azelastine alone (*P*<0.05). On study days four and six

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
QD in the morning				to 11, combination treatment was significantly more efficacious than fluticasone alone (*P*<0.05). Compared to baseline, all three treatments significantly improved overall RQLQ as well as the individual domains of RQLQ (*P*<0.01). In the overall RQLQ score the mean change from baseline was greater for the combination (1.92) compared to azelastine (1.21) and fluticasone alone (1.40). The difference was significant compared to azelastine but not fluticasone. Bitter taste was the most common adverse event with azelastine (8.2 vs 2.0% in the fluticasone group and 13.5% in the combination group). Headache was reported in 4.1% of the azelastine group, 4.0% of the fluticasone group and 5.8% of the combination treatment group.
Carr et al[30] Azelastine/fluticasone propionate 137 µg/50 µg 1 spray in each nostril BID vs azelastine 137 µg 1 spray in each nostril BID (Astelin®) vs fluticasone propionate 50 µg 1 spray in each nostril BID vs placebo	MA (3 RCT) Patients 12 years of age and older with a ≥2 year history of moderate-to-severe SAR and current clinical rhinitis symptoms, a positive skin prick test response to relevant pollen	N=3,398 14 days	Primary: Change from baseline in the AM and PM sum rTNSS score Secondary: Change from baseline in iTNSS, rTOSS and RQLQ	Primary: Over the entire 14-day treatment period, combination treatment with azelastine/fluticasone propionate significantly reduced the mean rTNSS sum from baseline compared to azelastine, fluticasone propionate and placebo (-5.7 vs -4.1, -5.1 and -3.0, respectively; *P*<0.001 for all). Secondary: Patients randomized to receive combination therapy achieved significant reductions in iTNSS scores (-5.2) compared to azelastine (-4.1; *P*<0.001), fluticasone propionate (-4.8; *P*=0.022) and placebo (-2.6; *P*<0.001). More patients receiving combination therapy (12.4%) also exhibited complete or near-complete elimination of their symptoms (e.g., reduction in all nasal symptoms scores to <1) compared to those treated with fluticasone (9.3%; *P*=0.033), azelastine (7.1%; *P*<0.001), or placebo (4.2%; *P*<0.001). Over the entire 14-day treatment period, combination treatment significantly reduced the mean rTOSS score from baseline compared to fluticasone propionate (-3.2 vs -2.8; *P*=0.003) and placebo (-1.8; *P*<0.001), but not compared to azelastine (-2.9; *P*=0.196). By day 14 of treatment, all three active treatment groups significantly improved RQLQ scores compared to placebo (*P*<0.001 for all).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Meltzer et al[31] Azelastine/fluticasone propionate 137 µg/50 µg 1 spray in each nostril BID vs azelastine 137 µg 1 spray in each nostril BID (Astelin®) vs fluticasone propionate 50 µg 1 spray in each nostril BID vs placebo	AC, MC, PC, PG, RCT Patients 12 years of age and older with moderate-to-severe SAR and a positive skin prick test to a local, prevalent, seasonal allergen	N=770 14 days	Primary: 12-hour rTNSS Secondary: Change in individual symptom scores, onset of action, 12-hour rTOSS and the RQLQ overall score	Primary: Patients receiving combination treatment experienced significant reductions in the mean rTNSS (-5.54) compared to fluticasone propionate (-4.55; *P*=0.038), azelastine (-4.54; *P*=0.032) and placebo (-3.03; *P*<0.001). Combination therapy improved the rTNSS score by 39% compared to fluticasone propionate alone. Secondary: Patients receiving combination therapy achieved significant improvements in all individual symptoms (nasal congestion, runny nose, itchy nose and sneezing) compared to placebo (*P*<0.001 for all), In particular, combination therapy significantly improved nasal congestion compared to azelastine and fluticasone propionate (*P*≤0.046). The azelastine/fluticasone propionate combination demonstrated a rapid onset of action, with a statistically significant improvement in the TNSS compared to placebo at 30 minutes following the first dose. The significant improvements in the TNSS over placebo were sustained at each subsequent evaluation point during the four-hour observation period. The mean improvement from baseline in the 12-hour rTOSS was significantly greater with combination therapy (-3.56) compared to fluticasone propionate (-2.68; *P*=0.009); however, there was no statistically significant difference compared to azelastine (-2.96; *P*=0.069). There was a significant increase in RQLQ score with combination therapy compared to both azelastine and placebo (*P*<0.05 for both), but not compared to fluticasone propionate.
Hampel et al[32] Azelastine/fluticasone propionate 137 µg/50 µg 1 spray in each nostril BID vs	DB, MC, PC, PG, RCT Patients ≥12 years of age with a ≥2-year history of allergy to Texas mountain cedar	N=610 14 days	Primary: Change from baseline in 12-hour rTNSS Secondary: Change from baseline in	Primary: The mean improvement from baseline in rTNSS was -5.31 with combination therapy compared to -3.25 with azelastine alone (*P*<0.01), -3.84 with fluticasone propionate alone (*P*<0.01) and -2.2 with placebo. Both azelastine and fluticasone monotherapies were also significantly more effective compared to placebo (*P*≤0.02 for both). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
azelastine 137 µg 1 spray in each nostril BID (Astelin®) vs fluticasone propionate 50 µg 1 spray in each nostril BID vs placebo	pollen (*J ashei*), as confirmed by a positive prick-puncture skin test		individual symptom scores, rTNSS on each study day, TOSS, individual ocular symptom scores, RQLQ and safety	Combination therapy significantly improved the individual rTNSS symptoms of nasal congestion, itchy nose, and sneezing compared to azelastine, fluticasone, or placebo ($P<0.05$ for all). Combination therapy significantly improved runny nose compared to azelastine and placebo ($P<0.01$), but not compared to fluticasone. The combination treatment was associated with statistically significant improvements in rTNSS on all study days compared to azelastine and placebo ($P\leq0.01$ for both). Combination therapy improved TNSS compared to fluticasone propionate on all days except days 10 and 11 ($P\leq0.01$). Patients treated with combination therapy significantly improved overall TOSS scores compared to patients randomized to either fluticasone or placebo alone ($P<0.01$); however, the difference between combination therapy and azelastine alone was not statistically significant. Combination therapy significantly improved individual ocular symptoms compared to azelastine, fluticasone, or placebo alone, with the exception of azelastine for watery eyes ($P<0.05$). The combination of azelastine and fluticasone significantly improved the overall RQLQ score compared to azelastine ($P<0.05$) and placebo ($P<0.001$) but not fluticasone ($P=0.29$). The most commonly reported adverse events were bitter taste (2.0% with azelastine, 0.0% with fluticasone, and 7.2% with combination therapy). No significant changes in vital signs were reported.

* Agent not available in the United States.
Study abbreviations: AC=active-controlled, BID=twice daily, CC=case control, DB=double-blinded, DD=double dummy, MA=meta-analysis, MC=multicenter, PC=placebo-controlled, PG=parallel group, PRO=prospective, QD=once daily, R=randomized, RCT=randomized controlled trial, XO=cross over
Miscellaneous abbreviations: CGTSQ-AR= caregiver treatment satisfaction questionnaire for allergic rhinitis CI=confidence interval, ITT=intent to treat, LS=least squared, NNT=number needed to treat, PAR=perennial allergic rhinitis, PGA=patient global assessment, PRQLQ= pediatric rhinoconjunctivitis quality-of-life questionnaire, RQLQ=rhinoconjunctivitis quality of life questionnaire, SAR=seasonal allergic rhinitis, SSCS=secondary symptom complex score, rTNSS=reflective total nasal symptom score, iTNSS=instantaneous total nasal symptom score, TNSS=total nasal symptom score, TOSS=total ocular symptom score, rTOSS=reflective total ocular symptom score, TSC=total symptom complex score, TSQM=treatment satisfaction questionnaire for medication, TVSS=total VMR symptom score, rTVSS=reflective total VMR symptom score, VAS=visual analog scale, VMR=vasomotor rhinitis, WPAI-AS=work productivity and activity impairment questionnaire-allergy specific

Special Populations

Table 5. Special Populations[1-4,9]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Single-Entity Agents					
Azelastine hydrochloride	No dosage adjustment required in the elderly population. Astelin® is approved for use in children five years of age and older. Astepro® is approved for use in children 12 years of age and older.	No dosage adjustment required.	No dosage adjustment required.	C	Unknown
Olopatadine hydrochloride	No dosage adjustment required in the elderly population. Approved for use in children six years of age and older.	No dosage adjustment required.	No dosage adjustment required.	C	Unknown
Combination Products					
Azelastine hydrochloride/ fluticasone propionate	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 and older.	No dosage adjustment required.	No dosage adjustment required.	C	Unknown

Adverse Drug Events

Table 6. Adverse Drug Events (%)[1-4,9]

Adverse Event(s)	Single Entity Agents		Combination Products
	Azelastine Hydrochloride	Olopatadine Hydrochloride	Azelastine Hydrochloride/Fluticasone Propionate
Cardiovascular			
Atrial fibrillation	✔	-	✔
Angioedema	-	-	✔
Chest pain	✔	-	✔
Flushing	<2	-	-
Hypertension	<2	-	-
Palpitations	✔	-	✔
Tachycardia	<2	-	-
Central Nervous System			
Anxiety	<2	-	-
Confusion	✔	-	✔

Adverse Event(s)	Single Entity Agents		Combination Products
	Azelastine Hydrochloride	Olopatadine Hydrochloride	Azelastine Hydrochloride/Fluticasone Propionate
Depersonalization	<2	-	-
Depression	<2	-	-
Dizziness	2	-	-
Dysesthesia	7.9	-	-
Headache	1.0 to 14.8	4.4	2
Hyperkinesia	<2	-	-
Hypoesthesia	<2	-	-
Nervousness	<2	-	-
Paresthesia	✔	-	✔
Sleep disorder	<2	-	-
Somnolence	0.4 to 11.5	0.9	<1
Vertigo	<2	-	-
Dermatological			
Application site irritation	✔	-	✔
Hypersensitivity	-	-	✔
Nasal sores	-	-	✔
Nasal ulcers	-	-	✔
Pruritus	✔	-	✔
Rash	✔	1.3	✔
Gastrointestinal			
Abdominal pain	<2	-	-
Aphthous stomatitis	<2	-	-
Constipation	<2	-	-
Diarrhea	<2	-	✔
Gastroenteritis	<2	-	-
Glossitis	<2	-	-
Increased appetite	<2	-	-
Nausea	2.8	-	-
Ulcerative stomatitis	<2	-	-
Vomiting	<2	-	-
Laboratory Test Abnormalities			
Alanine aminotransferase elevation	<2	-	-
Creatine phosphokinase elevation	-	0.9	-
Musculoskeletal			
Back pain	<2	-	-
Involuntary muscle contractions	✔	-	✔
Myalgia	<2	-	-
Pain	-	-	✔
Pain in extremities	<2	-	-
Temporomandibular dislocation	<2	-	-
Rheumatoid arthritis	<2	-	-
Respiratory			
Anaphylactoid reaction	✔	-	✔
Asthma	4.5	-	-
Bronchitis	<2	-	-

Adverse Event(s)	Single Entity Agents		Combination Products
	Azelastine Hydrochloride	Olopatadine Hydrochloride	Azelastine Hydrochloride/Fluticasone Propionate
Bronchospasm	<2	-	✔
Cold symptoms	17	-	-
Cough	11.4	1.4	✔
Dry throat	<2	-	✔
Dyspnea	✔	-	✔
Dyspnea (nocturnal)	<2	-	-
Laryngitis	<2	-	-
Nasal burning	4.1	-	-
Nasal congestion	<2	-	✔
Nasal dryness	<2	-	-
Nasopharyngitis	<2	0.9	-
Paranasal sinus hypersecretion	<2	-	-
Parosmia	✔	-	✔
Paroxysmal sneezing	3.1	-	-
Pharyngitis	3.8	-	✔
Pharyngolaryngeal pain	<2	2.2	-
Postnasal drip	<2	1.5	-
Rhinitis	2.3 to 17	-	-
Sinusitis	3.2	-	-
Sneezing	1 to 2	-	-
Sore throat	-	-	✔
Throat burning	<2	0.9	-
Upper respiratory tract infection	-	2.6	✔
Wheezing	-	-	✔
Urogenital			
Albuminuria	<2	-	-
Amenorrhea	<2	-	-
Breast pain	<2	-	-
Hematuria	<2	-	-
Increased urinary frequency	<2	-	-
Urinary retention	✔	-	✔
Urinary tract infection	-	1.2	-
Other			
Allergic reaction	<2	-	-
Bitter taste	4.0 to 19.7	1.0 to 12.8	-
Blurred vision	-	-	✔
Cataracts	-	-	✔
Conjunctivitis	5.1	-	✔
Dry mouth	2.8	0.9	-
Dysgeusia	5	-	4
Epistaxis	1.0 to 3.2	3.2 to 5.7	2
Eye abnormality	<2	-	-
Eye irritation	-	-	✔
Eye pain	<2	-	-
Facial edema	✔	-	✔
Fatigue	2.3	0.9	-
Glaucoma	-	-	✔

Adverse Event(s)	Single Entity Agents		Combination Products
	Azelastine Hydrochloride	Olopatadine Hydrochloride	Azelastine Hydrochloride/Fluticasone Propionate
Herpes simplex	<2	-	-
Hoarseness	-	-	✔
Increased intraocular pressure	-	-	✔
Influenza	-	0.9	-
Malaise	<2	-	-
Nasal septal perforation	-	-	✔
Pyrexia	<2	1.3	✔
Sweet taste	✔	-	-
Taste loss	<2	-	✔
Tolerance	✔	-	✔
Tongue edema	-	-	✔
Viral infection	<2	-	✔
Vision abnormal	✔	-	✔
Voice changes	-	-	✔
Watery eyes	<2	-	-
Weight increase	2	-	-
Xerophthalmia	✔	-	✔

- Event not reported.
✔ Percent not specified.

Contraindications

Table 7. Contraindications[1-4,9]

Contraindication	Single Entity Agents		Combination Products
	Azelastine Hydrochloride	Olopatadine Hydrochloride	Azelastine Hydrochloride/ Fluticasone Propionate
Hypersensitivity to any component of the product	✔ (Astelin®)	-	-

Warnings/Precautions

Table 8. Warnings and Precautions[1-4,9]

Warnings/Precautions	Single Entity Agents		Combination Products
	Azelastine Hydrochloride	Olopatadine Hydrochloride	Azelastine Hydrochloride/ Fluticasone Propionate
Activities requiring mental alertness; somnolence has been reported by patients in clinical trials; exercise caution when using the product and operating potentially dangerous machinery.	✔	-	✔
Central nervous system depressants, including alcohol; avoid concomitant use of azelastine with these agents as additional impairment and	✔	-	✔

Warnings/Precautions	Single Entity Agents		Combination Products
	Azelastine Hydrochloride	Olopatadine Hydrochloride	Azelastine Hydrochloride/ Fluticasone Propionate
reduced alertness may result.			
Concurrent antihistamine use; concurrent use should be avoided unless instructed by a physician.	✔ (Astelin®)	-	-
Corticosteroids may cause a reduction in growth velocity when administered to pediatric patients.	-	-	✔
Epistaxis and nasal ulceration were reported in clinical trials; counsel on proper administration technique, monitor routinely, and/or avoid use until healing has occurred.	-	✔	✔
Hypothalamic-pituitary-adrenal axis effects are possible in susceptible individuals and in instances of higher than recommended dosing, resulting in systemic corticosteroid effects such as hypercorticism and adrenal suppression.	-	-	✔
Immunosuppression may occur in patients using corticosteroids, possibly resulting in a greater disease severity or death. Corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculosis infections of the respiratory tract, untreated local or systemic fungal or bacterial infections, systemic viral or parasitic infections, or ocular herpes simplex due to the potential for worsening infections.	-	-	✔
Localized infections of the nose and pharynx with *Candida albicans*; treat any infection accordingly, consider discontinuation of allergic rhinitis therapy, and/or monitor routinely for localized infection.	-	-	✔
Nasal and inhaled corticosteroids may result in the development of glaucoma and/or cataracts. Monitor closely in patients with a change in vision or in patients with a history of increased intraocular pressure, glaucoma, and/or cataracts.	-	-	✔
Nasal septal perforation; ensure patients are free of nasal disease other than allergic rhinitis via nasal examination prior to initiating therapy and monitor for the development of nasal ulcerations.	-	✔	✔
Use of strong CYP450 3A4 inhibitors (e.g., ritonavir, ketoconazole, etc.) may significantly increase fluticasone propionate exposure, potentially leading to systemic corticosteroid effects and significantly reduced serum cortisol levels.	-	-	✔

Drug Interactions

No significant drug interactions have been reported with the use of the intranasal formulation of azelastine hydrochloride. Drug interaction studies were not performed with olopatadine hydrochloride nasal spray or azelastine hydrochloride/fluticasone propionate. Drug interactions are not anticipated due to lack of inhibition or induction of CYP450 hepatic enzymes. Drug displacement when co-administered with drugs having high protein binding is not anticipated due to the relatively modest plasma protein binding of olopatadine hydrochloride.[1-4,9]

Dosage and Administration

Table 9. Dosing and Administration[1-4]

Generic Name	Adult Dose	Pediatric Dose	Availability
Single-Entity Agents			
Azelastine hydrochloride	Seasonal allergic rhinitis: Nasal spray: one to two sprays in each nostril BID (Astelin® and Astepro®) or two sprays in each nostril QD (Astepro® 0.15% only) Perennial allergic rhinitis: Nasal spray: two sprays in each nostril BID (Astepro®) Vasomotor rhinitis: Nasal spray: two sprays in each nostril BID (Astelin®)	Seasonal allergic rhinitis in children five to 11 years of age: Nasal spray: one spray in each nostril BID (Astelin®) Astepro® is approved for use in children 12 years of age and older.	Nasal spray: 137 µg/spray (Astelin®) 205.5 µg/spray (Astepro®)
Olopatadine hydrochloride	Seasonal allergic rhinitis: Nasal spray: two sprays in each nostril BID	Seasonal allergic rhinitis in children six to 11 years of age: Nasal spray: one spray in each nostril BID	Nasal spray: 665 µg/spray
Combination Products			
Azelastine hydrochloride/ fluticasone propionate	Seasonal allergic rhinitis: Nasal spray: one spray in each nostril BID	Dymista® is approved for use in children 12 years of age and older.	Nasal spray: 137 µg/50 µg/ spray

Clinical Guidelines

Table 10. Clinical Guidelines

Clinical Guidelines	Recommendations
Allergic Rhinitis and its Impact on Asthma and the Global Allergy and Asthma European Network: **Guideline Revisions (2010)[7]**	Diagnosis • 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. Treatment • The treatment of allergic rhinitis should consider the severity and

Clinical Guidelines	Recommendations
	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 H_1-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 may be reasonable. • Second-generation oral or intranasal H_1-antihistamines are recommended for the treatment of allergic rhinitis and conjunctivitis in adults and children. • First generation oral H_1-antihistamines are not recommended when second-generation ones are available, due to safety concerns. • Intranasal H_1-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 chromones 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 H_1-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.
Joint Task Force on Practice Parameters for Allergy and Immunology: **The Diagnosis and Management of Rhinitis: An Updated Practice Parameter (2008)**[33]	Diagnosis • 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.

Clinical Guidelines	Recommendations
	• Cytotoxic tests, provocation-neutralization, electrodermal testing, applied kinesiology, iridology, and hair analysis are not recommended diagnostic procedures. Treatment • 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. • 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 of rhinitis.
Institute for Clinical Systems Improvement: **Diagnosis and Treatment of Respiratory Illness in Children and Adults (2013)**[34]	Diagnosis • 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

Clinical Guidelines	Recommendations
	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 nonallergic rhinitis and to identify specific allergens causing allergic rhinitis. • 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. <u>Treatment of allergic rhinitis</u> • 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. • Intranasal corticosteroids reduce nasal blockage, itching, sneezing and rhinorrhea in allergic and non-allergic rhinitis. • 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. • Intranasal corticosteroids when given in recommended doses are not generally associated with clinically significant systemic side effects. • Growth suppression was detected in children with perennial allergic rhinitis treated with intranasal beclomethasone dipropionate, but not with intranasal fluticasone propionate and mometasone furoate; however, over the long term, the eventual adult height is unchanged. • Systemic corticosteroids should be reserved for refractory or severe cases of rhinitis. Oral steroids should be given as a short burst regimen (i.e., 3 to 5 days). 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 preferred as they are less sedating and cause less central nervous system impairment. • The leukotriene inhibitor, montelukast, is indicated for the management for seasonal allergic rhinitis in patients two years and older and for

Clinical Guidelines	Recommendations
	perennial allergic rhinitis in patients six months of age and older. It is as effective as loratadine and less effective than nasal steroids. • Montelukast is considered a third-line option to add after the failure of a nasal corticosteroid and an oral antihistamine. • Oral decongestants are effective in reducing nasal congestion. • Consider using topical decongestants for short-term or intermittent/episodic therapy. Routine daily use is not recommended because of the risk for the development of rhinitis medicamentosa. • Oral and topical decongestants should be used with caution in older adults, children under the age of six years, and in patients with a history of arrhythmia, angina, cerebrovascular disease, high blood pressure, bladder neck obstruction, glaucoma, or hyperthyroidism. • Cromolyn is less effective than intranasal corticosteroids and is most effective when used regularly prior to the onset of allergic symptoms. • Cromolyn is a good alternative for patients who are not candidates for corticosteroids. • Therapy adherence may be a concern, given the four times daily administration. • Intranasal cromolyn sodium is effective in some patients for prevention and treatment of allergic rhinitis and is associated with minimal side effects. • Ophthalmic medications are available as topical solutions/suspensions and contain antihistamines, decongestants, dual action antihistamine/mast cell stabilizers, combination antihistamines/decongestants, corticosteroids, or mast cell stabilizers (cromolyn sodium and lodoxamide). • Topical antihistamines can be used as needed for acute symptomatic relief and prophylaxis of allergic rhinitis with minimal systemic side effects. • Reserve immunotherapy for patients with significant allergic rhinitis in which avoidance activities and pharmacotherapy are insufficient to control symptoms. • Other candidates for immunotherapy include patients who have experienced side effects from medication or who cannot comply with a regular (or prescribed) pharmacotherapy regimen or who develop complications such as recurrent sinusitis. • Immunotherapy injections are most effective for allergic rhinitis caused by pollens and dust mites. They may be less effective for mold and animal dander allergies. • 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, a complete nasal examination, or a diagnosis of nonallergic rhinitis. <u>Treatment of non-allergic rhinitis</u> • Types of non-allergic rhinitis include hormonal, such as rhinitis of pregnancy; vasomotor rhinitis with sensitivity to smells and temperature changes; non-allergic rhinitic eosinophilic syndrome; rhinitis medicamentosa from regular use of topical nasal decongestants; and atrophic rhinitis.

Clinical Guidelines	Recommendations
	• Symptoms of non-allergic rhinitis are similar to those of allergic rhinitis (i.e., nasal congestion, postnasal drainage, rhinorrhea, and sneezing). • Treatment of obstructive symptoms due to non-allergic rhinitis include: o Azelastine hydrochloride nasal spray. o Intranasal corticosteroid spray, which are better suited for chronic symptoms (beyond four weeks). o Intranasal cromoglycate (cromolyn sulfate). o Oral decongestants. o Topical antihistamines.

Conclusions

Allergic rhinitis is a condition characterized by episodes of sneezing, rhinorrhea, nasal congestion, itchy and watery eyes, nose, and palate and may also include cough, past-nasal drip, and fatigue. Allergic rhinitis is a common condition associated with significant morbidity and economic impact; affecting 10 to 30% of children and adults in the U.S. Allergic rhinitis is generally classified according to the severity of symptoms as well as its intermittent or persistent pattern of symptom occurrence.[6,7]

Consensus guidelines offer multiple treatment options and do not offer a precise step-therapy approach for treating allergic rhinitis. Intranasal histamine-1 receptor antagonists (H_1-antihistamines) are effective therapies for managing the symptoms of allergic rhinitis; however, intranasal corticosteroids are generally recognized as the most effective single agents for controlling the broad spectrum of allergic rhinitis symptoms and are considered a first-line therapy in patients with moderate to severe symptoms. Intranasal H_1-antihistamines are an effective alternative to intranasal corticosteroids. The intranasal H_1-antihistamines are all considered equally effective treatment options in the management of allergic and vasomotor rhinitis, with no general preference given to one agent over another. [7,33,34]

The overall safety profile of the single-entity, intranasal H_1-antihistamines are comparable and are all generally well tolerated. Head to head studies have not demonstrated statistically significant differences between the agents with regard to efficacy. Azelastine hydrochloride (Astelin®) and olopatadine hydrochloride (Patanase®) are approved for use in children as young as five and six years of age, respectively; whereas both Astepro® and Dymista® are approved in children as young as 12 year of age.[1-4] Astelin® nasal spray is the only agent within the class that is available generically.[8] Dymista® (azelastine hydrochloride/fluticasone propionate) is a combination product that utilizes both an intranasal antihistamine and an intranasal corticosteroid to manage the symptoms of allergic rhinitis, and is indicated when treatment with both azelastine hydrochloride and fluticasone propionate are needed for symptomatic relief.[3] Treatment with the combination of azelastine hydrochloride and fluticasone propionate has consistently demonstrated significant improvement in allergy symptom scores compared to each agent administered alone.[29-31]

References

1. Astelin® [package insert]. Somerset (NJ): Meda Pharmaceuticals, Inc.; 2012 Jan.
2. Astepro® [package insert]. Somerset (NJ): Meda Pharmaceuticals, Inc.; 2010 Nov.
3. Dymista® [package insert]. Somerset (NJ): Meda Pharmaceuticals, Inc.; 2012 Sep.
4. Patanase® [package insert]. Fort Worth (TX): Alcon Laboratories, Inc.; 2012 Feb.
5. deShazo RD, Kemp SF. Pathogenesis of allergic rhinitis (rhinosinusitis). In: Basow DS (Ed). UpToDate [database on the internet]. Waltham (MA): UpToDate; 2013 [cited 2013 Jul 8]. Available at: http://www.utdol.com/utd/index.do.
6. deShazo RD, Kemp SF. Pharmacotherapy of allergic rhinitis. In: Basow DS (Ed). UpToDate [database on the internet]. Waltham (MA): UpToDate; 2013 [cited 2013 Jul 8]. Available at: http://www.utdol.com/utd/index.do.
7. Brozek J, Bousquet J, Baena-Cagnani C, Bonini S, Canonica GW, Casale TB, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision. J Allergy Clin Immunol. 2010;126:466-76.
8. Drugs@FDA [database on the Internet]. Rockville (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2013 [cited 2013 Jul 8]. Available from: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm.
9. Drug Facts and Comparisons 4.0 [database on the Internet]. St. Louis: Wolters Kluwer Health, Inc.; 2013 [cited 2013 Jul 8]. Available from: http://online.factsandcomparisons.com.
10. Lumry W, Prenner B, Corren J, Wheeler W. Efficacy and safety of azelastine nasal spray at a dose of 1 spray per nostril trice daily. Ann Allergy Asthma Immunol. 2007;99:267-72.
11. van Bavel J, Howland W, Amar NJ, Wheeler W, Sacks H. Efficacy and safety of azelastine 0.15% nasal spray administered once daily in subjects with seasonal allergic rhinitis. Allergy and Asthma Proceedings. 2009;30(5):512-18.
12. Howland WC, Amar NJ, Wheeler W, Sacks H. Efficacy and safety of azelastine 0.15% nasal spray administered once daily in patients with allergy to Texas mountain cedar pollen. Int Forum Allergy Rhinol. 2011 Jul-Aug;1(4):275-9.
13. Shah S, Berger W, Lumry W, La Force C, Wheeler, Sacks H. Efficacy and safety of azelastine 0.15% nasal spray and azelastine 0.10% nasal spray in patients with seasonal allergic rhinitis. Allergy and Asthma Proceedings. 2009;30(6):628-33.
14. Bernstein J, Prenner B, Ferguson B, Portnoy J, Wheeler W, Sacks H. Double-blind, placebo-controlled trial of reformulated azelastine nasal spray in patients with seasonal allergic rhinitis. American Journal of Rhinology & Allergy. 2009;23(5):512-7.
15. Shah S, Nayak A, Ratner P, Roland P, Wall GM. Effects of olopatadine hydrochloride nasal spray 0.6% in the treatment of seasonal allergic rhinitis: a phase III, multicenter, randomized, double-blind, active- and placebo-controlled study in adolescents and adults. Clin Therap. 2009;31(1):99-107.
16. Meltzer EO, Blaiss M, Fairchild CJ. Comprehensive report of olopatadine 0.6% nasal spray as treatment for children with seasonal allergic rhinitis. Allergy Asthma Proc. 2011 May-Jun;32(3):213-20.
17. Meltzer EO, Hampel FC, Rater PH, et al. Safety and efficacy of olopatadine hydrochloride nasal spray for the treatment of seasonal allergic rhinitis. Annals of Allergy and Asthma Immunology. 2005;95:600-6.
18. Ratner PH, Hampel F, Van Bravel J, Amar NJ, Daftary P, Wheeler W, Sacks H. Combination therapy with azelastine hydrochloride nasal spray in the treatment of patients with seasonal allergic rhinitis. Ann Allergy Asthma Immunol. 2008;100:74-81.
19. Fairchild C, Meltzer E, Roland P. Comprehensive report of the efficacy, safety, quality of life, and work impact of olopatadine 0.6% and olopatadine 0.4% treatment in patients with seasonal allergic rhinitis. Allergy and Asthma Proceedings. 2007;28:716-23.
20. Hampel FC, Ratner PH, Amar NJ, et al. Improved quality of life among seasonal allergic rhinitis patients treated with olopatadine HCL nasal spray 0.4% and olopatadine HCL nasal spray 0.6% compared to vehicle placebo. Allergy and Asthma Proceedings. 2006;27:202-7.
21. Patel P, Roland PS, Marple BF, et al. An assessment of the onset and duration of action of olopatadine nasal spray. Otolaryngology-Head and Neck Surgery. 2007;137:918-24.
22. Lee TA, Pickard AS. Meta-analysis of azelastine nasal spray for the treatment of allergic rhinitis. Pharmacotherapy. 2007;27(6):852-9.
23. Ghimire A, Das BP, Mishra SC. Comparative efficacy of steroid nasal spray vs antihistamine nasal spray in allergic rhinitis. NMCJ. 2007;9(1):17-21.

24. Patel D, Garadi R, Brubaker M, et al. Onset and duration of action of nasal sprays in seasonal allergic rhinitis patients: Olopatadine hydrochloride vs mometasone furoate monohydrate. Allergy and Asthma Proceedings. 2007;28:592-9.
25. Pipkorn P, Costantini C, Reynolds C, Wall M, Drake M, Sanico A, et al. The effects of the nasal antihistamines olopatadine and azelastine in nasal allergen provocation. Ann Allergy Asthma Immunol. 2008;101:82-9.
26. Meltzer EO, Garadi R, LaForce C, Chadwick SJ, Berger WE, Gross G, et al. Comparative study of sensory attributes of two antihistamine nasal sprays: olopatadine 0.6% and azelastine 0.1%. Allergy Asthma Proc. 2008;29:659-68.
27. Lieberman P, Meltzer EO, LaForce CF, Darter AL, Tort MJ. Two-week comparison study of olopatadine hydrochloride nasal spray 0.6% vs azelastine hydrochloride nasal spray 0.1% in patients with vasomotor rhinitis. Allergy Asthma Proc. 2011 Mar-Apr;32(2):151-8.
28. Berger W, Hampel F, Bernstein J, Shah S, Sacks H, Meltzer E. Impact of azelastine nasal spray on symptoms and quality of life compared to cetirizine oral tablets in patients with seasonal allergic rhinitis. Ann Allergy Asthma Immunol. 2006;97:375-81.
29. Ratner PH, Hampel FC, Amar NJ, Van Bavel JH, Mohar D, Marple BF, et al. Safety and efficacy of olopatadine hydrochloride nasal spray for the treatment of seasonal allergic rhinitis to mountain cedar. Annals of Allergy, Asthma, & Immunology. 2005;95(5):474-9.
30. Carr W, Bernstein J, Lieberman P, Meltzer E, Bachert C, et al. A novel intranasal therapy of azelastine with fluticasone for the treatment of allergic rhinitis. J Allergy Clin Immunol. 2012 May;129(5):1282-1289.e10.
31. Meltzer EO, Laforce C, Ratner P, Price D, Ginsberg D, Carr W. MP29-02 (a novel intranasal formulation of azelastine hydrochloride and fluticasone propionate) in the treatment of seasonal allergic rhinitis: A randomized, double-blind, placebo-controlled trial of efficacy and safety. Allergy Asthma Proc. 2012 Jul;33(4):324-32.
32. Hampel FC, Ratner PH, Van Bavel J, Amar NJ, Daftary P, Wheeler W, et al. Double-blind, placebo-controlled study of azelastine and fluticasone in a single nasal spray delivery device. Ann Allergy Asthma Immunol. 2010 Aug;105(2):168-73.
33. Wallace DV, Dykewicz MS, Bernstein DI, Blessing-Moore J, Cox L, Khan DA, et al. The diagnosis and management of rhinitis: An updated practice parameter of the joint task force on practice parameters for allergy and immunology. J Allergy Clin Immunol. 2008;122:S1-S84.
34. Snellman L, Adams W, Anderson G, Godfrey A, Gravley A, Johnson K, et al. Diagnosis and Treatment of Respiratory Illness in Children and Adults (Fourth edition; 2013 January). Institute for Clinical Systems Improvement. Available at: https://www.icsi.org/guidelines__more/.