VERMONT

Department of Vermont Health Access

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

Overview/Summary

The intranasal histamine H_1-receptor antagonists (antihistamines) work by preventing the binding of histamine to its receptor, thereby preventing or delaying smooth muscle contraction and nasal congestion.[1] Two products are available in this class- azelastine hydrochloride and olopatadine hydrochloride. Azelastine hydrochloride is Food and Drug Administration-approved for the treatment of the symptoms of seasonal (Astelin®, Astepro®) and perennial (Astepro®) allergic rhinitis and vasomotor rhinitis (Astelin®). There is no difference in the pharmacology of the two branded azelastine hydrochloride products, though differences do exist in formulation. Astelin® nasal spray contains 0.1% azelastine hydrochloride in an aqueous solution (pH 6.8±0.3), benzalkonium chloride (125 µg/mL), edetate disodium, hypromellose, citric acid, dibasic sodium phosphate, sodium chloride, and purified water. Astepro® nasal spray contains 0.1% azelastine hydrochloride in an isotonic aqueous solution, sorbitol, sucralose, hypromellose, sodium citrate, edetate disodium, benzalkonium chloride (125 µg/mL), and purified water (pH 6.4). The change in formulation is to minimize the potential for the adverse event of bitter taste that is associated with Astelin®.[2-4] A generic azelastine hydrochloride product is available in the 0.1% strength and is AB-rated to Astelin®. Astepro® is no longer available in a 0.1% strength, and is now formulated in a 0.15% strength for which no generic product is available.

Olopatadine hydrochloride (Patanase®) is indicated for the treatment of symptoms of seasonal allergic rhinitis in patients six years of age and older.[5] No generic olopatadine hydrochloride product is available.

According to the current clinical guidelines on the management of rhinitis, treatment should consist of patient education, allergen avoidance activities, and pharmacological therapies. 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.[6-9] Oral or intranasal antihistamines and cromolyn can be considered alternatives in patients who prefer not to use intranasal corticosteroids.[6-9]

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Azelastine hydrochloride (Astelin®*, Astepro®)	Intranasal histamine-1 (H_1)-receptor antagonist (antihistamine)	✔ *
Olopatadine hydrochloride (Patanase®)	Intranasal histamine H_1-receptor antagonist (antihistamine)	-

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

Indications

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

Indication	Azelastine Hydrochloride	Olopatadine Hydrochloride
Relief of the symptoms of seasonal allergic rhinitis	✔ (Astelin®, Astepro®)	✔
Relief of the symptoms of vasomotor rhinitis	✔ (Astepro®)	
Relief of the symptoms of perennial allergic rhinitis	✔ (Astelin®)	

Pharmacokinetics

There is no significant difference in the pharmacokinetics of the two branded intranasal azelastine hydrochloride products.

Table 3. Pharmacokinetics[2,3,5,10]

Generic Name	Bioavailability (%)	Metabolism	Excretion (%)	Active Metabolites	Half-Life (hours)
Azelastine hydrochloride	40	Oxidation by cytochrome P450 system	Feces (75)	Yes; des-methyl-azelastine	Azelastine: 22; des-methylazelastine: 52 to 54
Olopatadine hydrochloride	57	Not extensively metabolized	Feces (17); Urine (70)	6 minor metabolites	8 to 12

Clinical Trials

Overall, azelastine hydrochloride nasal spray has been found to be safe and effective in placebo controlled trials.[11-14] A meta-analysis of active comparators vs azelastine hydrochloride nasal spray in seasonal allergic rhinitis or perennial allergic rhinitis has been conducted. In the meta- analysis, comparators included a beclomethasone nasal spray and loratadine combination, terfenadine (not currently available in the United States), cetirizine, budesonide nasal spray, ebastine (not currently available in the United States), levocabastine (not currently available in the United States) and loratadine. Although multiple analyses between azelastine hydrochloride and the comparators were conducted, a statistically significant difference in response was not identified.[15] A trial by Berger et al showed that azelastine hydrochloride nasal spray was significantly more effective than cetirizine in various symptom scores and a trial by Ratner et al showed that the combination of azelastine hydrochloride nasal spray and fluticasone nasal spray was significantly more effective compared to the individual agents in various symptom scores.[16,17] Shah et al compared azelastine hydrochloride 0.1 and 0.15% in an active comparator and placebo controlled trial. Both azelastine hydrochloride groups showed significant improvement in Total Nasal Symptom Score from baseline and compared to placebo. There was a significant difference in favor of the azelastine hydrochloride 0.15% group compared to the azelastine hydrochloride 0.1% group in the 12-hour reflective Total Nasal Symptom Score when both groups were compared in a retrospective analysis.[13]

Olopatadine hydrochloride has been proven safe and effective in placebo controlled trials.[18-23] Overall, no significant differences in efficacy have been observed between olopatadine hydrochloride and azelastine hydrochloride.[18,24] Meltzer et al compared these two agents and found that significantly more patients favored/preferred olopatadine hydrochloride to azelastine hydrochloride.[25] Additionally olopatadine hydrochloride was found to be significantly more effective in a number of factors immediately post dose (smell, irritation etc).[25] However a number of these factors were no longer significant 45 minutes post dose.[25]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Lumry et al[11] Azelastine nasal spray, 1 spray in each nostril BID (Astelin®) vs placebo 1 spray in each nostril BID	2 DB, PC, RCT Patients 12 to 75 years of age with moderate-to-severe SAR who were still 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, 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 1 and 3.68 vs 2.50; *P*=0.02 for study 2). 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 1. 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 2. A significantly greater number of patients rated their symptom improvement as better with azelastine compared to placebo in study 1 (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 2 (74 vs 58%; *P*<0.01). The difference in the daily activity and nasal symptom domains of the RQLQ were significantly different in favor of azelastine vs placebo in both studies (*P*<0.05 for all). However the overall RQLQ was not significantly different between the two groups in study 1, but was in favor of azelastine in study 2 (*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[12] Azelastine 0.15%, 2 sprays in each nostril QD	DB, PC, PG, RCT Patients 12 years of age and older with moderate to severe SAR	N=536 14 days	Primary: 12-hour reflective TNSS Secondary: 24-hour	Primary: The LS mean improvement from baseline in the 12-hour TNSS was significantly greater in the azelastine group compared to placebo (*P*<0.001). The LS mean percentage change in the 12-hour TNSS was significantly greater in the azelastine group compared to placebo (*P*<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo			instantaneous TNSS, daily change from baseline in 12-hour reflective TNSS, 12-hour reflective SSCS, adult RQLQ	Secondary: The LS mean change from baseline in the 24-hour instantaneous TNSS was significantly greater in the azelastine group (*P*<0.001). The LS mean percent change from baseline in the 24-hour instantaneous TNSS was significantly greater in the azelastine group (*P*<0.001). The mean daily change from baseline in 12-hour reflective TNSS was significantly greater for the azelastine group (*P*<0.05) on all study days except day 10. The mean daily change from baseline in 24-hour instantaneous TNSS was significantly greater for the azelastine group (*P*<0.05). The LS mean change from baseline in the 12-hour reflective SSCS was significantly greater for the azelastine group (*P*<0.001). The LS mean percent change from baseline in the 12-hour reflective SSCS was significantly greater for the azelastine group (*P*<0.002). The overall score for the RQLQ was significantly improved from baseline in the azelastine group (*P*=0.023).
Shah et al[13] Azelastine 0.1%, 2 sprays in each nostril BID vs azelastine 0.15% in each nostril BID vs	AC, DB, PC, PG, RCT Patients 12 years of age and older with SAR	N=526 14 days	Primary: 12-hour reflective TNSS Secondary: Instantaneous TNSS, 12-hour reflective TNSS individual symptom scores, onset of action, 12-hour reflective SSCS, 12-hour	Primary: TNSS scores improved from baseline in both groups by day 14 (*P*<0.001). The LS mean improvement in the 12-hour TNSS 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 TNSS improvement in the azelastine 0.15% group was significantly greater than the azelastine 0.1% group (*P*=0.047). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo			reflective SSCS individual symptom scores, RQLQ	Both azelastine groups showed significant improvements in the LS mean and LS mean percent changes in the instantaneous TNSS compared with placebo. The LS mean and LS mean percent change from baseline in the 12-hour reflective TNSS for nasal congestion, rhinorrhea, itchy nose and sneezing showed significant differences from placebo in both azelastine groups ($P<0.05$). 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 ($P\leq0.002$). 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 ($P<0.05$). 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 with 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	DB, PC, RCT Patients with SAR	N=835 14 days	Primary: TNSS Secondary: Not reported	Primary: All azelastine groups produced comparable improvements in the TNSS. The percent changes from baseline in the 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 the 0.15% group and 8% in the 0.1% group at the two sprays/nostril dosage. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo 1 or 2 sprays in each nostril BID				
Shah et al[18] 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 reflective TNSS Secondary: RQLQ	Primary: The mean change from baseline in overall TNSS 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[19] Olopatadine 0.4%, 2 sprays in each nostril BID vs olopatadine 0.6%, 2 sprays in each nostril BID vs placebo 2 sprays in each nostril BID	DB, MC, PC, PG, RCT Patients, age 12 to 80 years of age, with SAR and positive allergic sensitivity test	N=565 2 weeks	Primary: Percent change from baseline in reflective TNSS Secondary: Percent change from baseline in instantaneous TNSS, individual symptoms (runny nose, itching nose, sneezing, stuffy nose, watery eyes and itchy eyes), and RQLQ	Primary: Treatment with 0.4 and 0.6% olopatadine resulted in significant improvement in reflective TNSS 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 and 0.6% olopatadine resulted in significant improvement in instantaneous TNSS as compared to placebo (*P*=0.02 and *P*=0.003 respectively). The average percent reductions were 31.6 and 33.3% respectively, compared to 23.6% for placebo. Treatment with 0.4 and 0.6% olopatadine resulted in significant improvement in reflective and instantaneous evaluation of most symptoms as 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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Reflective and instantaneous 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 and greater than placebo (*P*=0.02 and *P*<0.001 for respective strengths compared to placebo). The 0.6% strength score improved in all seven domains, while the 0.4% improved in four of the seven domains.
Ratner et al[20] Olopatadine 0.4%, 2 sprays in each nostril BID vs olopatadine 0.6%, 2 sprays in each nostril BID vs placebo 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 reflective TNSS Secondary: Percent change from baseline in instantaneous TNSS, individual symptoms (runny nose, itching nose, sneezing, stuffy nose, watery eyes and itchy eyes), and safety	Primary: Treatment with 0.4 and 0.6% olopatadine resulted in significant improvement in reflective TNSS as 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 and 0.6% olopatadine resulted in significant improvement in instantaneous TNSS as 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 and 0.6% olopatadine resulted in significant improvement in reflective and instantaneous evaluation of most symptoms as 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[21] Olopatadine 0.4%, 2 sprays in each nostril BID	DB, MC, PC, RCT Patients, 12 years and older, with a 2 year history of SAR	N=1,233 2 weeks	Primary: TNSS change from baseline Secondary:	Primary: Reflective TNSS absolute and percent change from baseline 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%]).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs olopatadine 0.6%, 2 sprays in each nostril BID vs placebo 2 sprays in each nostril BID	and positive skin test to relevant pollen		Safety, RQLQ, and WPAI-AS	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 TNSS (*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 (*P* value not significant). Changes in WPAI-AS scores for work impairment improvement and activity impairment improvement correlate with changes in TNSS (*P*<0.001 for both).
Hampel et al[22] Olopatadine 0.4%, 2 sprays in each nostril BID vs olopatadine 0.6%, 2 sprays in each nostril BID vs placebo 2 sprays in each nostril BID	DB, MC, RCT Patients, 12 years and older, with 2 year history of SAR and positive skin allergy test	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) as 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 with TNSS scores. Secondary: TNSS score improved for both treatment strengths as compared to placebo. The treatment strengths were not different from each other in RQLQ scores *(P* values not reported).
Patel et al[23] Olopatadine 0.2%, 2 sprays in each nostril	DB, PC, PG, RCT, single dose Patients, 17 to 65	N=320 12 hours	Primary: TNSS change from baseline	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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs olopatadine 0.4%, 2 sprays in each nostril vs olopatadine 0.6%, 2 sprays in each nostril vs placebo, 2 sprays in each nostril	years old, with a history of SAR during the fall season and allergic to short ragweed pollen; patients were exposed to pollen in an environmental exposure chamber and had to achieve a TNSS score of at least 6 of 12 to receive medication		Secondary: Patient global rating scale (7 unit scale: 0=very much better, 6=very much worse), individual symptoms, and safety	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 for the following: 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.
Lee et al[15] Azalstine nasal spray vs placebo or active comparators (budesonide nasal spray, certrizine, ebastine*,	MA Patients 12 years of age and older diagnosed with allergic rhinitis or nonallergic vasomotor rhinitis	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

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levocabastine*, loratadine, terfenadine*, and the combination of beclomethasone nasal spray and loratadine)				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[26] 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[27] Olopatadine 0.6%, 2 sprays in each nostril vs mometasone 50 µg nasal spray vs placebo	DB, PC, PG, RCT, single dose, environmental exposure study Patients, age 18 years and older, with moderate to severe SAR and sensitivity to ragweed	N=425 12 hours	Primary: TNSS change from baseline Secondary: Patient global rating scale (7 unit scale: 0=very much better, 6=very much worse) and individual symptoms	Primary: Olopatadine treatment resulted in a significant change in TNSS from baseline, at all 16 time points, between 0 and 720 minutes, compared to placebo (*P*<0.05) and at all time points between 60 and 600 minutes after dose when 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%;

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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[24] Study 1, phase 1: Olopatadine 0.1% nasal spray vs placebo Study 1, phase 2: olopatadine 0.2% nasal spray vs placebo Study 2: Azelastine nasal spray (Astelin®) vs olopatadine 0.1% nasal spray	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 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

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				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[25] Azelastine nasal spray (Astelin®) vs olopatadine nasal spray Patients recieved one administration of each treatment consisting of two sprays in each nostril. Each medication was seperated by a 24 hour washout period.	DB, MC, R, XO Patients ≥18 years of age 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 than 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 vs azelastine in smell, nasal congestion, urge to sneeze, dripping down nose, dripping down throat, and overall satisfaction (*P*≤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 than azelastine in nasal irritation, urge to sneeze and overall satisfaction (*P*≤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.
Berger et al[16] Azelastine nasal spray, 2 sprays in each nostril BID (Astelin®) vs cetirizine 10 mg tablets by mouth QD	DB, MC, R Patients 12 years of age and older with moderate-to-sever SAR	N=360 2 weeks	Primary: TNSS Secondary: RQLQ, individual symptoms, safety	Primary: Compared with the baseline score the combined morning and evening 12-hour reflective TNSS was significantly improved in both treatment groups (*P*<0.001). The mean improvement from baseline TNSS 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 TNSS in the evaluable population was

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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). Secondary: Compared with the baseline score the each individual RQLQ domain score and the overall RQLQ score was significantly improved in both treatment groups (*P*<0.001). Compared with cetirizine, azelastine significantly improved each domain of the RQLQ (*P*≤0.05) and the overall RQLQ score (*P*=0.002). For the four symptoms of the TNSS, compared with 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[17] 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	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 the azelastine and fluticasone there were absolute improvements of 11.0 (*P*=0.007) and 13.0% (*P*=0.02) with the combination, respectively. Secondary: Compared to either single treatment the combination was significantly more efficacious in treating the symptoms of congestion and itchy nose (*P*<0.05). Compared to fluticasone the combination was significantly more efficacious in

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
azelastine nasal spray, 2 sprays in each nostril BID (Astelin®) and fluticasone nasal spray, 2 sprays in each nostril QD in the morning				treating the symptom of runny nose (*P*<0.05). Compared to azelastine the combination was significantly more efficacious in treating the symptom of sneezing (*P*<0.05). On study days three to 14 the combination was significantly more efficacious than azelastine alone (*P*<0.05). On study days four and six to 11 the combination 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 (1.40). The difference was significant compared with 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). In 4.1% of the azelastine group, 4.0% of the fluticasone group and 5.8% of the combination group headache was 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: CI=confidence interval, LS=least squared, NNT=number needed to treat, PAR=perennial allergic rhinitis, RQLQ=Rhinoconjunctivitis Quality of Life Questionnaire, SAR=seasonal allergic rhinitis, SSCS=Secondary Symptom Complex Score, TNSS=Total Nasal Symptom Score, TSC=total symptom complex score, VAS=visual analog scale, WPAI-AS=Work Productivity and Activity Impairment Questionnaire-Allergy Specific

Special Populations

Table 5. Special Populations[2,3,5,10]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
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. Food and Drug Administration approved for use in children six years of age and older.	No dosage adjustment required.	No dosage adjustment required.	C	Unknown

Adverse Drug Events

Table 6 summarizes the most commonly reported adverse events associated with the intranasal antihistamines. The intranasal antihistamines are generally well-tolerated.

Table 6. Adverse Drug Events (%)[2,3,5,10]

Adverse Event(s)	Azelastine Hydrochloride	Olopatadine Hydrochloride
Cardiovascular		
Atrial fibrillation	✔	-
Chest pain	✔	-
Flushing	<2	-
Hypertension	<2	-
Palpitations	✔	-
Tachycardia	<2	-
Central Nervous System		
Anxiety	<2	-
Confusion	✔	-
Depersonalization	<2	-
Depression	<2	-
Dizziness	2	-
Dysesthesia	7.9	-
Headache	1.0 to 14.8	4.4
Hyperkinesia	<2	-
Hypoesthesia	<2	-
Nervousness	<2	-
Paresthesia	✔	-
Sleep disorder	<2	-
Somnolence	0.4 to 11.5	0.9

Adverse Event(s)	Azelastine Hydrochloride	Olopatadine Hydrochloride
Vertigo	<2	-
Dermatological		
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		
Involuntary muscle contractions	✔	-
Myalgia	<2	-
Temporomandibular dislocation	<2	-
Rheumatoid arthritis	<2	-
Respiratory		
Anaphylactoid reaction	✔	-
Application site irritation	✔	-
Asthma	4.5	-
Bronchitis	<2	-
Bronchospasm	<2	-
Cold symptoms	17	-
Dry throat	<2	-
Dyspnea	✔	-
Dyspnea (nocturnal)	<2	-
Laryngitis	<2	-
Nasal burning	4.1	-
Nasal congestion	<2	-
Nasal dryness	<2	-
Nasopharyngitis	<2	0.9
Pain in extremities	<2	-
Paranasal sinus hypersecretion	<2	-
Parosmia	✔	-
Paroxysmal sneezing	3.1	-
Pharyngitis	3.8	-
Pharyngolaryngeal pain	<2	2.2
Postnasal drip	<2	1.5
Pruritus	✔	-
Rhinitis	2.3 to 17	-
Throat burning	<2	0.9
Upper respiratory tract infection	-	2.6
Urogenital		
Albuminuria	<2	-

Adverse Event(s)	Azelastine Hydrochloride	Olopatadine Hydrochloride
Amenorrhea	<2	-
Breast pain	<2	-
Hematuria	<2	-
Increased urinary frequency	<2	-
Urinary retention	✔	-
Urinary tract infection	-	1.2
Other		
Allergic reaction	<2	-
Back pain	<2	-
Bitter taste	4.0 to 19.7	1.0 to 12.8
Conjunctivitis	5.1	-
Cough	11.4	1.4
Dry mouth	2.8	0.9
Epistaxis	1.0 to 3.2	3.2 to 5.7
Eye abnormality	<2	-
Eye pain	<2	-
Facial edema	✔	-
Fatigue	2.3	0.9
Herpes simplex	<2	-
Influenza	-	0.9
Malaise	<2	-
Pyrexia	<2	1.3
Sinusitis	3.2	-
Sneezing	1 to 2	-
Sweet taste	✔	-
Taste loss	<2	-
Tolerance	✔	-
Viral infection	<2	-
Vision abnormal	✔	-
Watery eyes	<2	-
Weight increase	2	-
Xerophthalmia	✔	-

- Event not reported.
✔ Percent not specified.

Contraindications/Precautions

The intranasal antihistamines are contraindicated in patients with a known hypersensitivity to any components of the respective medications.[2,3,5,10]

Azelastine hydrochloride may cause drowsiness, and somnolence has been reported. As such, the concurrent use of azelastine hydrochloride with alcohol or other central nervous system depressants should be avoided.[2,3,5,10] Patients should assess their individual responses to azelastine hydrochloride before engaging in activity requiring mental alertness.[2,3,10]

Epistaxis and nasal ulceration have been reported in olopatadine hydrochloride nasal spray clinical trials. Nasal septal perforation has occurred with a different formulation of olopatadine (povidone-containing) nasal spray (not commercially available). No reports of nasal septal perforation have been reported with Patanase®.[4-5] Patients should be cautioned that somnolence may occur with olopatadine hydrochloride. If present, activities requiring mental alertness, as well as concomitant use of alcohol and other central nervous system depressants known to cause somnolence, should be avoided while using olopatadine hydrochloride.[5]

Drug Interactions

There are no significant drug interactions reported with the use of the intranasal formulation of azelastine hydrochloride.[2,3,10] Drug interaction studies were not performed with olopatadine hydrochloride nasal spray.[5] 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.[5]

Dosage and Administration

Table 7. Dosing and Administration[2,3,5,10]

Generic Name	Adult Dose	Pediatric Dose	Availability
Azelastine hydrochloride	Seasonal allergic rhinitis: ≥12 years of age, 1 to 2 sprays in each nostril BID (Astelin® and Astepro® nasal spray) ≥12 years of age, 2 sprays in each nostril QD (Astepro® nasal spray) Perennial allergic rhinitis: ≥12 years of age, 1 to 2 sprays in each nostril BID (Astepro® nasal spray) Vasomotor rhinitis: 2 sprays in each nostril BID (Astelin® nasal spray)	Seasonal allergic rhinitis: 5 to 11 years of age, 1 spray in each nostril BID (Astelin® nasal spray) 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.	Nasal spray: 137 µg/spray (200 metered doses/ unit) 205.5 µg/spray (200 metered doses/unit, Astepro®)
Olopatadine hydrochloride	Seasonal allergic rhinitis: 2 sprays in each nostril BID	Seasonal allergic rhinitis: 6 to 11 years of age, 1 spray in each nostril BID	Nasal spray: 665 µg/spray (240 metered doses/ unit)

BID=two times daily, QD=once daily

Clinical Guidelines

According to the current clinical guidelines on the management of rhinitis, treatment should consist of patient education, allergen avoidance activities, and pharmacological therapies. Patients should be educated on how to avoid known triggers, such as aeroallergens, dust mites, molds and irritants, whenever possible. In addition to environmental control measures, pharmacological therapies may be used to control symptoms. 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.[6-9] Oral or intranasal antihistamines and cromolyn can be considered alternatives in patients who prefer not to use intranasal corticosteroids.[6-9]

Table 8. Clinical Guidelines

Clinical Guidelines	Recommendations
Allergic Rhinitis and its Impact on Asthma and the Global Allergy and Asthma European Network: **Guideline Revisions (2010)**[6]	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.

Clinical Guidelines	Recommendations
	Treatment • The treatment of allergic rhinitis should consider the severity and duration of the disease, the patient's preference, as well as the efficacy, availability and cost of the medication. • A stepwise approach depending on the severity and duration of rhinitis is proposed. • Not all patients with moderate/severe allergic rhinitis are controlled despite optimal pharmacotherapy. • Intranasal glucocorticoids are recommended over oral H1-antihistamines for the treatment of allergic rhinitis in adults and children. They are the most effective drugs for treating allergic rhinitis. In many patients with strong preferences for the oral route, an alternative choice may be reasonable. • Second-generation oral or intranasal H1-antihistamines are recommended for the treatment of allergic rhinitis and conjunctivitis in adults and children. • First generation oral H1-antihistamines are not recommended when second-generation ones are available, due to safety concerns. • Intranasal H1-antihistamines are recommended for the treatment of adults and children with seasonal allergic rhinitis, but data regarding their relative safety and efficacy is limited. Therefore, their use in persistent allergic rhinitis is not recommended. • Intramuscular glucocorticoids and long-term use of oral glucocorticoids are not recommended due to safety concerns. • Topical cromones are recommended in the treatment of allergic rhinitis but they are only modestly effective. • Montelukast is recommended for adults and children with seasonal allergic rhinitis, and in pre-school children with persistent allergic rhinitis. Montelukast has limited efficacy in adults with persistent allergic rhinitis. • Intranasal ipratropium is recommended for the treatment of rhinorrhea associated with allergic rhinitis. • Intranasal decongestants may be used for a short period (<5 days) for patients with severe nasal obstruction. Nasal decongestants should not be used in pre-school aged children. • Combination oral decongestants and oral H1-antihistamines may be used for the treatment of allergic rhinitis in adults, but should not be administered regularly due to adverse effects. • For patients experiencing ocular symptoms associated with allergic rhinitis intraocular antihistamines or chromones may be considered.
Joint Task Force on Practice Parameters for Allergy and Immunology: **The Diagnosis and Management of Rhinitis: An Updated Practice Parameter (2008)**[7]	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

Clinical Guidelines	Recommendations
	allergic rhinitis is in question. • The measurement of total IgE should not be routinely performed. • Cytotoxic tests, provocation-neutralization, electrodermal testing, applied kinesiology, iridology, and hair analysis are not recommended diagnostic procedures. 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 rhinitis.
Institute for Clinical Systems Improvement: **Diagnosis and Treatment of Respiratory Illness in Children and Adults**	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,

Clinical Guidelines	Recommendations
(2011)[8]	a family history of atopy or other allergy associated conditions make allergic rhinitis more likely. • The most common physical findings suggestive of rhinitis tend to be swollen nasal turbinates, rhinorrhea and pruritus however allergic conjunctivitis may also be present. • Symptoms suggestive of allergic etiology include sneezing, itching of the nose, palate or eyes, and clear rhinorrhea. Nasal congestion is the most significant complaint in patients with perennial rhinitis. • Diagnostic testing should be considered if the results would change management. • Skin tests and radioallergosorbent tests identify the presence of IgE antibody to a specific allergen and are used to differentiate allergic from 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</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. • Regular daily use of intranasal corticosteroids is required to achieve optimal results. • It may be best to start treatment one week prior to the start of the allergy season for prophylaxis. • Clinical response does not seem to vary significantly between the available intranasal corticosteroids. • Systemic corticosteroids should be reserved for refractory or severe cases of rhinitis. Injectable steroids are not generally recommended. • Antihistamines are effective at controlling all symptoms associated with allergic rhinitis except nasal congestion. • Antihistamines are somewhat less effective than intranasal corticosteroids but they can be used on a daily or as needed basis. • Second-generation antihistamines are recommended because they are less sedating and cause less central nervous system impairment. • Leukotriene inhibitors may be as effective as second-generation antihistamines for the treatment of allergic rhinitis and less effective than intranasal corticosteroids. • Oral decongestants are effective in reducing nasal congestion. Oral decongestants can be a useful addition to antihistamines. • Topical decongestants, which have the potential to induce rebound congestion after three days, are effective for the short-term relief of nasal congestion. • Cromolyn is less effective than intranasal corticosteroids and is most effective when used prior to the onset of allergic symptoms. • Cromolyn is a good alternative for patients who are not candidates for corticosteroids.

Clinical Guidelines	Recommendations
	• Intranasal anticholinergics are effective in relieving anterior rhinorrhea in allergic and nonallergic rhinitis. • Reserve immunotherapy for patients with significant allergic rhinitis in which avoidance activities and pharmacotherapy are insufficient to control symptoms. • If adequate relief is achieved appropriate follow-up should include further education on avoidance activities and medications. • If patients anticipate unavoidable exposure to known allergens they should begin the use of medications prior to exposure. • If adequate relief is not achieved within two to four weeks consider a trial of another medication, allergen skin testing by a qualified physician, a complete nasal examination, or a diagnosis of nonallergic rhinitis. • Treatment options for nonallergic rhinitis include intranasal corticosteroids, oral decongestants and antihistamines, topical antihistamines, and nasal strips.
American Academy of Family Physician: **Treatment of Allergic Rhinitis (2010)**[9]	• Treatment should be based on the patient's age and severity of symptoms. • Intranasal corticosteroids are the most effective treatment and should be first-line therapy for mild to moderate disease. • Moderate to severe disease not responsive to intranasal corticosteroids should be treated with second-line therapies, including antihistamines, decongestants, cromolyn, leukotriene receptor antagonists, and nonpharmacologic therapies (e.g., nasal irrigation). • Immunotherapy should be considered in patients with inadequate response to usual treatments. • Omalizumab has been shown to be effective in reducing nasal symptoms and improving quality of life scores in patients with allergic rhinitis. However, its high cost (average wholesale price of $679 to $3,395/month) and lack of Food and Drug Administration approval for home administration are the main limitations to its use.

Conclusions

The intranasal histamine H_1-receptor antagonists (antihistamines) work by preventing the binding of histamine to its receptor, thereby preventing or delaying smooth muscle contraction and nasal congestion.[1] Two products are available in this class- azelastine hydrochloride and olopatadine hydrochloride. Azelastine hydrochloride is Food and Drug Administration-approved for the treatment of the symptoms of seasonal and perennial allergic rhinitis and vasomotor rhinitis while olopatadine hydrochloride is approved for the treatment of seasonal allergic rhinitis.[2,3,5,10] Azelastine hydrochloride is available generically in a 0.1% formulation, which is AB rated to brand name Astelin®. Astepro® is available in a 0.15% azelastine hydrochloride formulation which does not have an AB-rated generic equivalent. Astepro® contains sorbitol and sucralose to potentially decrease the incidence of bitter taste associated with Astelin®.[2,3,4] Olopatadine hydrochloride is approved for the treatment of seasonal allergic rhinitis and no generic equivalent is currently available.[5]

Clinical trials have demonstrated that these agents are more effective than placebo and as effective as other alternatives in treating the symptoms of seasonal allergic rhinitis.[11-27] Azelastine hydrochloride 0.1 and 0.15% were evaluated in an active comparator and placebo controlled trial. Both azelastine hydrochloride groups showed significant improvement in Total Nasal Symptom Score from baseline and compared to placebo. There was a significant difference in favor of the azelastine hydrochloride 0.15% group compared to the azelastine hydrochloride 0.1% group in the 12-hour reflective Total Nasal Symptom Score when both groups were compared in a retrospective analysis.[13]

Olopatadine hydrochloride has been proven safe and effective in placebo controlled trials.[18-23] Overall, no significant differences in efficacy have been observed between olopatadine hydrochloride and azelastine hydrochloride. One study comparing these two agents found that significantly more patients favored/preferred olopatadine hydrochloride to azelastine hydrochloride. Additionally, olopatadine hydrochloride was found to be significantly more effective in a number of factors immediately post dose (smell, irritation etc). However, a number of these factors were no longer significant 45 minutes post dose.[25]

Consensus guidelines offer multiple treatment options and do not offer a precise step-therapy approach for treating allergic rhinitis. Although many drug classes are available for the treatment of allergic rhinitis, intranasal corticosteroids are the most effective agents in the treatment of symptoms.[6-9] Oral antihistamines are also an effective treatment option and all antihistamines appear to be equally effective, while the second-generation agents have a more favorable side effect profile.[6-9] For both allergic and nonallergic rhinitis intranasal antihistamines may be considered a first line treatment option.[6-9]

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

Medication	Unique utilizers	# of Rx's	Market Share (%)	Plan Cost $	Avg $/Rx
Azelastine	26	48	53.33%	$4,383.26	$91.32
Astepro	19	31	34.44%	$2,949.22	$95.14
Astelin	9	10	11.11%	$927.57	$92.76
Patanase	1	1	0.01%	$43.19	$43.19
Class Total:	**NA**	**90**	**100%**	**$8,303.24**	**$92.26**

Recommendations

In recognition of the following factors:

- That the safety and efficacy profile of the intranasal antihistamines is comparable to other agents routinely used for the treatment of seasonal allergic rhinitis symptoms and/or vasomotor rhinitis symptoms.
- The lack of a unique advantage over the other alternatives.
- The cost of all available products (including the generic) compared to alternative therapies.

…it is recommended that the current Department of Vermont Health Access (DVHA) approval criteria remain unchanged (see below).

Astelin, Astepro, azelastine, Patanase:

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

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

  AND
- If the request is for azelastine (generic), the patient has had a documented intolerance to brand Astelin.
- In addition, a quantity limit of 1 bottle/25 days is employed for all agents in the class.

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