

Intranasal Rhinitis Agents Review

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Intranasal Rhinitis Agents Review

FDA-Approved Indications

Drug	Manufacturer	Indication(s)
Nasal Corticosteroids		
beclomethasone * (Beconase AQ [®]) ¹	GSK	Relief of symptoms of seasonal or perennial allergic rhinitis and non-allergic (vasomotor) rhinitis in adults and children six years of age and older Prevention of recurrence of nasal polyps following surgical removal
budesonide (Rhinocort Aqua [®]) ²	AstraZeneca	Management of nasal symptoms of seasonal or perennial allergic rhinitis in adults and children six years of age and older
ciclesonide (Omnaris [™]) ³	Sepracor	Treatment of nasal symptoms of seasonal allergic rhinitis in adults and children six years of age and older Treatment of nasal symptoms of perennial allergic rhinitis in adults and children 12 years of age and older
flunisolide (Nasalide) ^{4**}	generic	Relief of nasal symptoms of seasonal or perennial allergic rhinitis in adults and children six years of age and older
flunisolide (Nasarel [®]) ⁵	generic	Relief of nasal symptoms of seasonal or perennial allergic rhinitis in adults and children six years of age and older
fluticasone furoate (Veramyst [®]) ⁶	GSK	Treatment of symptoms of seasonal and perennial allergic rhinitis in adults and children two years of age and older
fluticasone propionate (Flonase [®]) ⁷	generic	Management of nasal symptoms of seasonal and perennial allergic rhinitis and nonallergic rhinitis in adults and children four years of age and older
mometasone (Nasonex [®]) ⁸	Schering	Treatment of nasal symptoms of seasonal and perennial allergic rhinitis in adults and children two years of age and older Prophylaxis of nasal symptoms of seasonal allergic rhinitis in adults and children 12 years of age and older Treatment of nasal polyps in patients 18 years of age and older
triamcinolone (Nasacort AQ [®]) ⁹	Sanofi-Aventis	Treatment of nasal symptoms of seasonal and perennial allergic rhinitis in adults and children two years of age and older

* Another beclomethasone nasal formulation known as Vancenase[®] is no longer manufactured.

**Nasalide 0.025% was discontinued, but the generic is still available.

FDA-Approved Indications (continued)

Drug	Manufacturer	Indication(s)
Intranasal Antihistamines		
azelastine (Astelin [®]) ¹⁰	MEDA Pharm	Treatment of symptoms of seasonal allergic rhinitis such as rhinorrhea, sneezing, and nasal pruritus in adults and children five years of age and older Treatment of symptoms of vasomotor rhinitis such as rhinorrhea, nasal congestion, and postnasal drip in adults and children 12 years of age and older
azelastine (Astepro [®]) ¹¹	MEDA Pharm	Relief of symptoms of seasonal and perennial allergic rhinitis in adults and children 12 years of age and older
olopatadine (Patanase [™]) ¹²	Alcon Labs	Relief of symptoms of seasonal allergic rhinitis in adults and children 6 years of age and older
Others		
ipratropium nasal spray 0.03% (Atrovent [®]) ¹³	generic	Symptomatic relief of rhinorrhea associated with allergic and nonallergic perennial rhinitis in adults and children six years of age and older
ipratropium nasal spray 0.06% (Atrovent [®]) ¹⁴	generic	Symptomatic relief of rhinorrhea associated with the common cold or seasonal allergic rhinitis in adults and children five years of age and older

Overview

Allergic rhinitis is a constellation of symptoms affecting 30 to 60 million Americans annually.¹⁵ The condition is characterized by sneezing, itching of the eyes, nose, and palate; rhinorrhea, and nasal obstruction. It is often associated with post-nasal drip, cough, irritability, and fatigue. Symptoms develop when patients inhale airborne antigens to which they have previously been exposed and have made antibodies. The antibodies bind to receptors on mast cells in respiratory mucosa and to basophils in peripheral blood. Mast cells release pre-formed and granule-associated chemical mediators. In addition, mast cells generate other inflammatory mediators and cytokines, which lead to nasal inflammation, and with continued allergen exposure, chronic symptoms.¹⁶

Perennial allergic rhinitis is an IgE-mediated reaction to allergens with little or no seasonal variation. The condition is persistent, chronic, and generally less severe than seasonal allergic rhinitis. Allergic rhinitis is driven by the mucosal infiltration and action on plasma cells, mast cells, and eosinophils as part of an allergic response.

Vasomotor rhinitis, or irritant rhinitis, is a condition of unknown origin, which seems to be aggravated by fumes, odors, temperature, atmospheric changes, smoke, and other irritants. This form of rhinitis (generally a condition diagnosed in adults) causes year-round symptoms that include congestion and headache.

In 2008, the American Academy of Allergy, Asthma & Immunology (AAAAI) released an updated practice parameter for the management of rhinitis.¹⁷ These guidelines include the removal of the protocol for management of symptoms to a focus on tailoring treatment to patient specific guidelines. The selection of pharmacotherapy for a patient depends on multiple factors,

including the type of rhinitis present (e.g., allergic, nonallergic, mixed, episodic), most prominent symptoms, severity, and patient age. Response to previous treatment, patient and family preferences, compliance with therapy, and cost are additional factors that enter management decisions for the patient with rhinitis. Rhinitis medication management frequently will require consideration of a step-up approach, if therapy is inadequate, or a step-down approach, if symptom relief is achieved or maximized with other approaches, including avoidance measures.

According to these updated guidelines, intranasal corticosteroids are the most effective medications for treating allergic rhinitis. Second generation oral antihistamines are generally preferred over first generation oral antihistamines for treatment of allergic rhinitis because they have less of a tendency to cause sedation, performance impairment, and/or anticholinergic adverse effects. Intranasal antihistamines have demonstrated efficacy that is equal to or superior to oral second-generation antihistamines in the treatment of seasonal allergic rhinitis. These agents are also effective and have been associated with a clinically significant effect on nasal congestion for nonallergic rhinitis but are generally less effective than intranasal corticosteroids for treatment of allergic rhinitis. Combination therapy with intranasal corticosteroids may provide an added benefit.

Chronic, obstructive, nasal symptoms secondary to nonallergic rhinitis can be managed with intranasal corticosteroid sprays, oral decongestants, or a combination of both. In addition to conservative treatment measures (i.e., increased water intake, nasal saline irrigation, etc.), intranasal corticosteroids are recommended when medical treatment is necessary for symptomatic, non-purulent, chronic postnasal drip. For rhinorrhea due to nonallergic rhinitis, intranasal corticosteroids can be used if patients are unable to avoid offending irritants.¹⁸

Pharmacology

Following topical administration, corticosteroids produce anti-inflammatory and vasoconstrictor effects. They gain entry into the cell cytoplasm and interact with glucocorticoid receptors. The receptor complex undergoes a conformational change, becoming active prior to entering the cell nucleus. Gene expression is hypothesized to be the principal mechanism of modulating the inflammatory state. Direct effects may be a reduction in cytokine-induced production of pro-inflammatory mediators. Clinical benefits observed with corticosteroids can be attributed to wide-ranging suppressive effects on the immune system and anti-inflammatory mediator production.¹⁹

Azelastine (Astelin, Astepro) is a phthalazine derivative, which exhibits histamine (H₁) receptor antagonist activity. Olopatadine (Patanase) is an antihistamine with selective H₁ receptor antagonist activity.²⁰ Azelastine also demonstrates inhibitory effects on the release of inflammatory mediators from mast cells.²¹ The drug is 100 to 1,000 times more potent than cromolyn sodium, theophylline, astemizole, and verapamil in mast cell mediator release inhibition.²²

Ipratropium bromide (Atrovent) is an anticholinergic agent that blocks cholinergic receptors and reflex-mediated hypersecretion from nasal glands. Ipratropium bromide is a quaternary amine, which minimally crosses nasal and gastrointestinal membranes and the blood-brain barrier, resulting in a reduction of systemic anticholinergic effects.

Pharmacokinetics

Due to the route of administration, intranasal agents used to treat allergic rhinitis have very poor bioavailability. Pharmacokinetic information is limited and often extrapolated from other dosage forms.

Contraindications/Warnings

There are no specific contraindications for any of the intranasal corticosteroids, azelastine (Astelin, Astepro) or olopatadine (Patanase). Hypersensitivity to any of the ingredients in the nasal spray or inhaler contraindicates its use.^{23, 24, 25}

Nasal Corticosteroids^{26,27}

If a topical corticosteroid replaces a systemic corticosteroid, signs of adrenal insufficiency may appear.

Patients with immunosuppression are more susceptible to infections than healthy patients. Some patients who use immunosuppressive doses of corticosteroids can acquire more serious and even fatal responses to disseminated infections.

Patients using any of the nasal corticosteroids should be monitored periodically for adverse effects on the nasal mucosa. Instances of epistaxis, nasal ulceration, nasal septa perforations, impaired wound healing, and *Candida albicans* have all been reported. Avoid use in patients with recent nasal ulcers, nasal surgery, or nasal trauma.

The use of nasal corticosteroids could potentiate the development of posterior subcapsular cataracts or glaucoma. Patients should be monitored closely if they have an increase in intraocular pressure, cataracts, glaucoma, or experience any vision change.

Intranasal Antihistamines^{28,29}

Patients should be advised to assess their individual responses to azelastine (Astelin, Astepro) nasal spray or olopatadine (Patanase) nasal spray before engaging in any activity requiring mental alertness, such as driving a car or operating machinery. Patients should be advised that the concurrent use of azelastine nasal spray or olopatadine nasal spray with alcohol or other central nervous system (CNS) depressants may lead to additional reductions in alertness and impairment of CNS performance and should be avoided. Epistaxis and nasal ulceration has been reported in placebo-controlled clinical trials with olopatadine (Patanase).

Ipratropium (Atrovent) nasal spray should be used with caution in patients with narrow-angle glaucoma, prostatic hyperplasia, or bladder neck obstruction due to anticholinergic properties of ipratropium.

Drug Interactions

Fluticasone [propionate (Flonase) and furoate (Veramyst)] are substrates of cytochrome P450 3A4. Coadministration of fluticasone nasal spray (Flonase or Veramyst) and protease inhibitors is not recommended. A drug interaction study in healthy patients demonstrated that ritonavir can increase plasma fluticasone levels resulting in significantly reduced serum cortisol concentrations.^{30,31}

Drug-drug interaction studies were not conducted for olopatadine (Patanase) or ipratropium (Atrovent) nasal sprays.^{32,33,34} Based on *in vitro* metabolism data, olopatadine drug interactions involving P450 inhibition are not expected.³⁵

Adverse Effects

Nasal Corticosteroids

Drug	Pharyngitis	Epistaxis	Cough	Nasal Irritation
beclomethasone (Beconase AQ) ³⁶	nr	<3	nr	24
budesonide (Rhinocort Aqua) ³⁷ N=1,526; up to 400 mcg	4	8	2	2
ciclesonide (Omnaris) ³⁸ N= 546; up to 200 mcg	3.7	4.9	nr	>1
flunisolide (Nasalide) ³⁹	3 - 9	3 - 9	<3	44
flunisolide (Nasarel) ⁴⁰	<3	3 - 9	<3	13
fluticasone furoate (Veramyst) ⁴¹ N=768; 110 mcg	2	6	nr	1
fluticasone propionate (Flonase) ⁴² N=782; 200 mcg	7.8	6.9	3.8	3.2
mometasone (Nasonex) ⁴³ N=2,103; 200 mcg	12	11	7	reported
triamcinolone AQ (Nasacort AQ) ⁴⁴ N=857; 220 mcg	5.1	2.7	2.1	nr

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

Overall, intranasal corticosteroids are well tolerated in adult and pediatric patients. Serious adverse effects that may result in discontinuation include epistaxis and nasal septal perforation.

A 2004 study evaluated whether use of fluticasone propionate, mometasone furoate, or beclomethasone dipropionate for treatment of rhinitis produced an increase in intraocular pressure.⁴⁵ The authors conducted a comparative, double-blind, experimental, prospective, longitudinal study in which 360 patients were randomized into one of four groups. Ninety patients were given a placebo (control group). The other 270 were divided into three groups of 90 patients each. A different nasal corticosteroid was given to each group. All patients had intraocular pressure measured by Goldman's tonometry at three weeks, six weeks, three months, six months, and one year after using placebo or intranasal steroid. Fluticasone propionate, mometasone furoate, and beclomethasone dipropionate caused variations in intraocular pressure, but the variations were within normal limits.

Intranasal Antihistamines

Drug	Bitter taste	Headache	Myalgia	Nasal burning	Somnolence	Weight increase
azelastine (Astelin) ⁴⁶ N=391 placebo N=353	19.7 (0.6)	14.8 (12.7)	1.5 (0)	4.1 (1.7)	11.5 (5.4)	2 (0)
azelastine 0.1% (Astepro) ⁴⁷ N=146; vehicle N=138 azelastine 0.15% (Astepro) ⁴⁸ N=523; vehicle N=523	7 (2) 6 (1)	3 (<1) nr	nr nr	1 (0) 3 (2)	2 (0) <1 (<1)	nr nr
olopatadine (Patanase) ⁴⁹ N=587 vehicle N=593	12.8 (0.8)	4.4 (4.0)	nr	nr	0.9 (0.3)	nr

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive. Incidences for placebo group are in parentheses. nr = not reported

Others

Drug	Nasal dryness	Nasal Irritation	Epistaxis	Dry mouth/throat
ipratropium nasal 0.03% (Atrovent) ⁵⁰ N=356 perennial allergic rhinitis	5.1	2	9	<2
ipratropium nasal 0.06% (Atrovent) ⁵¹ N=352 common cold	4.8	Nasal burning <1	8.2	1.4

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive.

Monitoring

In children, intranasal corticosteroids should be used at the lowest effective dose, and the FDA recommends that height be routinely monitored due to potential reduction in growth velocity.^{52,53}

Special Populations

Pediatrics

Intranasal corticosteroids, azelastine (Astelin, Astepro), olopatadine (Patanase), and ipratropium (Atrovent) have been proven safe and effective for use in children. Please refer to the FDA-approved Indications Chart on page 1 and 2 or to the individual package inserts for specific age criteria.

Pregnancy

Azelastine (Astelin, Astepro), olopatadine (Patanase) and all of the intranasal corticosteroids except budesonide (Rhinocort Aqua) are Pregnancy Category C. Ipratropium (Atrovent) and budesonide (Rhinocort Aqua) are Pregnancy Category B.

Other considerations – renal, hepatic, race, etc.

Reduced liver function may affect the elimination of corticosteroids. The relevance of this finding to intranasal administration of corticosteroids has not been established. Ipratropium (Atrovent) and olopatadine (Patanase) have not been studied in patients with hepatic impairment. Ipratropium (Atrovent) has not been studied in patients with renal impairment.

Dosages

Drug	Adults (> 12 years)*	Children (<12 years)	Availability
Nasal Corticosteroids			
beclomethasone (Beconase AQ) ⁵⁴	1 - 2 sprays in each nostril twice daily	(≥ 6 years) 1 - 2 sprays in each nostril twice daily	42 mcg/spray 25 gm - 180 sprays
budesonide (Rhinocort Aqua) ⁵⁵	1 - 4 sprays in each nostril daily	(≥ 6 years) 1 - 2 sprays in each nostril daily	32 mcg/spray 8.6 gm - 120 sprays
ciclesonide (Omnaris) ⁵⁶	2 sprays in each nostril daily	(≥ 6 years) 2 sprays in each nostril daily	50 mcg/spray 12.5 gm – 120 sprays
flunisolide (Nasalide) ⁵⁷	2 sprays in each nostril twice daily	(≥ 6 years) 1 spray in each nostril three times daily or 2 sprays in each nostril twice daily	25 mcg aerosol 25 mL - 200 doses
flunisolide (Nasarel) ⁵⁸	2 sprays in each nostril twice daily up to 8 sprays in each nostril daily	(≥ 6 years) 1 spray in each nostril three times daily or 2 sprays in each nostril twice daily	25 mcg/spray 25 mL - 200 sprays
fluticasone furoate (Veramyst) ⁵⁹	2 sprays in each nostril daily	(≥ 2 years) 1 spray in each nostril daily	27.5 mcg/spray 10 gm – 120 sprays
fluticasone propionate (Flonase) ⁶⁰	Adults 18 years and older: 2 sprays in each nostril daily or 1 spray in each nostril twice daily	(≥ 4 years) 1 spray in each nostril daily May increase to a max of 2 sprays per nostril for severe symptoms	50 mcg/spray 16 gm - 120 sprays
mometasone (Nasonex) ⁶¹	2 sprays in each nostril daily Adults 18 years and older: Nasal polyps: 2 sprays in each nostril twice daily	(≥ 2 years) 1 spray in each nostril daily	50 mcg/spray 17 gm - 120 sprays
triamcinolone (Nasacort AQ) ⁶²	2 sprays in each nostril daily	(2-5 years) 1 spray in each nostril daily (6-12 years) 1 - 2 sprays in each nostril daily	55 mcg/spray 16.5 gm - 120 sprays

- * Unless otherwise specified.
- For fluticasone (Flonase), some patients 12 years of age and older have found as-needed usage of 200 mcg once daily (two sprays in each nostril) to be an effective treatment of seasonal allergic rhinitis.
- For all products listed above, the pump must be primed prior to first use and again if stored unused after a certain period of time (which are product specific). Consult package inserts.

Dosages (continued)

Drug	Adults (≥ 12 years)	Children (<12 years)	Availability
Intranasal Antihistamines			
azelastine (Astelin) ⁶³	Seasonal allergic rhinitis: 1 - 2 sprays in each nostril twice daily Vasomotor rhinitis: 2 sprays in each nostril twice daily	Seasonal allergic rhinitis: (≥ 5 years) 1 spray in each nostril twice daily	137 mcg/spray 30 mL - 200 sprays
azelastine (Astepro) ⁶⁴	Seasonal allergic rhinitis: 1 - 2 sprays in each nostril twice daily or 2 sprays in each nostril once daily (Astepro 0.15%) Perennial allergic rhinitis: 2 sprays in each nostril twice daily (Astepro 0.15%)	--	137 mcg/spray 30 mL - 200 sprays (Astepro 0.1%) 205.5 mcg/spray 30 mL - 200 sprays (Astepro 0.15%)
olopatadine (Patanase) ⁶⁵	2 sprays in each nostril twice daily	(≥ 6 years) 1 spray in each nostril twice daily	0.6% (665 mcg/100 mL spray) 30.5 gm – 240 sprays
Others			
ipratropium 0.03% (Atrovent) ⁶⁶	Perennial allergic rhinitis: 2 sprays in each nostril two or three times daily	(≥ 6 years) 2 sprays in each nostril two or three times daily	21 mcg/spray 30 mL - 345 sprays
ipratropium 0.06% (Atrovent) ⁶⁷	Seasonal allergic rhinitis: 2 sprays in each nostril four times daily	(≥ 5 years) 2 sprays in each nostril four times daily	42 mcg/spray 15 mL - 165 sprays
ipratropium 0.06% (Atrovent) ⁶⁸	Common cold: 2 sprays in each nostril three or four times daily not to exceed 4 days	(≥ 5 years) 2 sprays in each nostril three times daily not to exceed 4 days	

Clinical Trials

Search Strategy

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the use of all drugs in this class and allergic rhinitis. Randomized, controlled, comparative trials are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include

follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation.

Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance. Many of the trials with agents in this class were performed in an open-label manner; introduction of bias must be considered when evaluating study findings.

Seasonal Allergic Rhinitis

beclomethasone (Vancenase) versus mometasone (Nasonex)

A double-blind, placebo-controlled study enrolled 501 patients with moderate-to-severe seasonal allergic rhinitis.⁶⁹ Patients were treated for four weeks with either mometasone 100 mcg once daily in the morning, mometasone 200 mcg once daily in the morning, beclomethasone 200 mcg twice daily, or placebo. The study permitted patients to use oral loratadine (Claritin[®]) 10 mg once daily as rescue medication for intolerable symptoms. Based on physician-rated and patient-rated nasal symptom scores, total symptom scores, global evaluation of overall condition, and response to treatment, all active treatment regimens were more effective than placebo, although no differences among regimens were observed. Complete or marked relief, based on physician-evaluated response to treatment, was achieved by 77 percent of patients treated with mometasone 100 mcg once daily, 79 percent treated with mometasone 200 mcg once daily, 74 percent treated with beclomethasone, and 54 percent of placebo-treated patients ($p < 0.01$ for each active treatment compared to placebo). Use of rescue antihistamine was reduced in all three active treatment groups compared to the placebo group, with 41 percent of patients in the mometasone 100 mcg group, 34 percent in the mometasone 200 mcg group, and 35 percent in the beclomethasone group requiring rescue medication, compared with 55 percent of patients in the placebo group ($p < 0.05$ for all comparisons to placebo). Rate of adverse effects did not differ among active treatments.

budesonide (Rhinocort) versus mometasone (Nasonex)

In a double-blind, crossover design study, 38 patients with seasonal allergic rhinitis received treatment with spray formulations of placebo, budesonide 64 mcg, budesonide 256 mcg, and mometasone furoate 200 mcg.⁷⁰ Treatment was initiated for three days prior to allergen challenges administered daily for seven days while intranasal treatment continued. Active treatments reduced nasal symptoms and improved nasal peak inspiratory flow (PIF) ($p < 0.001$ to 0.05). Budesonide caused dose-dependent improvements in evening symptoms, morning nasal PIF, and nasal PIF recorded 10 minutes after allergen challenge ($p < 0.05$). Budesonide 256 mcg produced greater improvement than mometasone 200 mcg in nasal PIF 10 minutes after allergen challenge ($p < 0.05$).

azelastine (Astelin) versus placebo

Two studies were conducted in the United States with 554 patients with moderate-to-severe seasonal allergic rhinitis who were still symptomatic after a one-week placebo lead-in period.⁷¹ Patients were randomized to two weeks of double-blind treatment with azelastine nasal spray one spray per nostril twice daily or placebo nasal spray. The primary efficacy variable was change from baseline in total nasal symptom score consisting of sneezing, itchy nose, runny nose, and nasal congestion. Mean differences in total nasal symptom score between the

azelastine and placebo groups were significant in both studies: 2.69 versus 1.31 ($p=0.01$) in study-1 and 3.68 versus 2.50 ($p=0.02$) in study-2.

In another randomized, double-blind, placebo controlled trial, azelastine nasal spray 0.15% was tested to determine whether an increased concentration provided seasonal allergic rhinitis symptom relief without increasing adverse effects.⁷² The study included 536 patients who were randomized to either receive azelastine nasal spray 0.15% two sprays in each nostril once daily or placebo. A 12-hour reflective Total Nasal Symptom Score (TNSS) was performed indicating azelastine was statistically superior in improving seasonal allergic rhinitis symptoms compared to placebo, 19 percent versus 10 percent, respectively ($p\leq 0.001$). Additionally, a 24-hour instantaneous TNSS was measured which proved azelastine nasal spray 0.15% was superior to placebo and supported azelastine nasal spray 0.15% being effective as once daily dosing ($p\leq 0.001$). Patients treated in both groups had similar incidence of adverse effects with the exception of bitter taste and nasal discomfort being higher in the azelastine nasal spray 0.15% group. Overall, azelastine nasal spray 0.15% once daily treatment was well tolerated and effective in treating seasonal allergic rhinitis symptoms.

azelastine (Astelin) versus azelastine (Astelin) and fexofenadine (Allegra®)

In a two-week, multicenter, double-blind trial, 334 patients with moderate-to-severe seasonal allergic rhinitis were randomized to one of three treatments: 1) azelastine two sprays per nostril twice daily, 2) azelastine two sprays per nostril twice daily and fexofenadine 60 mg twice daily, or 3) placebo given twice daily.⁷³ All patients were given a one-week run-in with fexofenadine 60 mg twice daily. Patients who improved less than 33 percent were randomized to one of the three regimens. After 14 days of treatment, the azelastine and azelastine plus fexofenadine groups showed greater improvement in total nasal symptom score than placebo ($p=0.007$). Azelastine alone was as effective as azelastine plus fexofenadine.

azelastine (Astelin) versus azelastine (Astepro)

A randomized, double-blind, parallel-group study containing 835 patients with seasonal allergic rhinitis was performed comparing the efficacy of reformulated azelastine nasal spray (Astepro) to the original azelastine formulation (Astelin) and determined if a dose-response relationship existed.⁷⁴ The patients were randomized into six groups: original azelastine nasal spray one spray per nostril twice daily; reformulated azelastine one spray per nostril twice daily; placebo nasal spray one spray per nostril twice daily; original azelastine nasal spray two sprays per nostril twice daily; reformulated azelastine nasal spray two sprays per nostril twice daily; and placebo nasal spray two sprays per nostril twice daily. The study concluded the original and reformulated azelastine products had comparable improvements in the 12-hour reflective Total Nasal Symptom Score (TNSS) in both dosages after 14 weeks. Patients treated with original ($p\leq 0.01$) and reformulated azelastine ($p\leq 0.001$) nasal spray groups at dosages of two sprays per nostril twice daily had a change in TNSS baseline that was statistically superior to placebo, 23.5 percent, 27.9 percent, and 15.4 percent, respectively. However, the original and reformulated azelastine nasal spray groups dosed at one spray per nostril were not statistically significant compared to placebo which was attributed to an abnormally high placebo response rate (19 percent). The study further determined a TNSS dose-response difference favoring the higher dosages existed. The incidence of adverse effects were low in both dosage formulations. Both azelastine groups reported bitter taste as the most common adverse effect, and nasal discomfort was more prevalent in the original azelastine product. Overall, the study's results indicated both formulations are effective in treating seasonal allergic rhinitis symptoms and a dose-reponse difference was present.

fluticasone furoate (Veramyst) versus placebo

A double-blind, parallel-group, randomized trial was conducted in 299 patients aged 12 years or older with seasonal allergic rhinitis.⁷⁵ Patients were randomized to fluticasone furoate 110 mcg once daily or placebo. A four-point scale was used to evaluate ocular and nasal symptoms at baseline and at two weeks. Total nasal symptom score improvement was the primary endpoint. Fluticasone furoate produced significantly greater improvements than placebo in daily reflective total nasal symptom scores (-1.473, $p < 0.001$), morning predose instantaneous total nasal symptom score (-1.375, $p < 0.001$), daily reflective total ocular symptom score (-0.600, $p = 0.004$), and patient-rated overall response to therapy ($p < 0.001$). The mean onset of therapeutic effect occurred eight hours after initial administration. Fluticasone furoate was well tolerated. Active treatment resulted in sustained improvement in nasal and ocular symptoms over 24 hours.

Another randomized, double-blind, placebo-controlled, parallel-group study compared the efficacy of fluticasone furoate 55 mcg, 110 mcg, and placebo once daily in children ($n = 554$) with seasonal allergic rhinitis symptoms.⁷⁶ During the two week study, patients recorded their allergy symptoms and rated them using a categorical scale. Evaluators used the assessments to determine reflective and instantaneous Total Nasal Symptoms Scores. Each treatment group consisted of 25 percent of the children being ages two to less than six years old and 75 percent of the children being six to eleven years old. Due to the subjectivity of the assessment and difficulty assessing very young patients, examiners used efficacy data for the intent to treat patient population of ages six to eleven years old ($n = 448$) in the primary efficacy analysis. The entire intent to treat group (ages two through eleven) were used in supportive and safety data. The primary efficacy data concluded fluticasone furoate 110 mcg daily significantly improved seasonal allergic rhinitis symptoms compared to placebo. However, there was not a statistically significant improvement in efficacy in patients taking fluticasone furoate 55 mcg daily compared to placebo. When examining the entire intent to treat population, ages two through eleven, the same efficacy outcomes resulted. Furthermore, both doses of once daily fluticasone furoate were well tolerated in the pediatric population for the treatment of seasonal allergic rhinitis.

ciclesonide nasal (Omnaris) versus placebo

Four randomized, double-blind, parallel-group, multicenter, placebo-controlled clinical trials of two weeks to one year in duration conducted on adolescents and adults with allergic rhinitis evaluated safety and efficacy of ciclesonide.⁷⁷

Efficacy of ciclesonide was supported by three two- to six-week trials in 1,524 patients, including 79 adolescents. Results showed that ciclesonide nasal spray 200 mcg/day yielded significantly greater decreases in nasal symptom score, as evaluated by self-recorded severity of nasal symptoms (runny nose, nasal itching, sneezing, and nasal congestion; $p < 0.001$ for all trials). Statistically significant differences in morning predose total nasal symptom scores indicated that the effect was maintained for the full 24-hour dosing interval. In the trials, onset of effect occurred within 24 to 48 hours with further symptomatic improvement observed during one to two weeks in seasonal allergic rhinitis and five weeks in perennial allergic rhinitis.

The fourth trial was a 52-week, long-term safety trial that included 663 adults and adolescent patients (441 treated with ciclesonide: 227 males and 436 females). The trial showed that ciclesonide-treated patients achieved greater decreases in total nasal symptom scores compared with those receiving placebo; these decreases were maintained for the entire 52-week period. Adverse events were considered infrequent and generally mild.

olopatadine (Patanase) versus placebo

Safety and efficacy of olopatadine nasal spray were evaluated in three randomized, double-blind, parallel-group, multicenter, placebo-controlled clinical trials of two weeks duration in adult and adolescent patients, twelve years and older with symptoms of seasonal allergic rhinitis.⁷⁸

Three clinical trials were conducted in the United States and included 1,598 patients (556 male and 1,042 female) aged twelve years of age and older. In the three trials, 587 patients were treated with olopatadine nasal spray 0.6%, 418 patients were treated with olopatadine nasal spray 0.4%, and 593 patients were treated with a vehicle nasal spray. Assessment of efficacy was based on patient recording of four individual nasal symptoms, (congestion, rhinorrhea, itchy nose and sneezing), on a 0-to-3 categorical severity scale, (0=absent, 1=mild, 2=moderate, 3=severe), as reflective or instantaneous scores. Reflective scoring required patients to record symptom severity over the previous twelve hours; the instantaneous scoring required patients to record symptom severity at the time of recording. The primary efficacy endpoint was the difference from placebo in the percent change from baseline in the morning and evening reflective total nasal symptom score, (rTNSS), averaged for the two-week treatment period. In all three trials, patients treated with olopatadine nasal spray given as two sprays per nostril twice daily, exhibited statistically significant greater decreases in the rTNSS scores compared to the vehicle nasal spray group.

In the two-week seasonal allergic rhinitis trials, onset of action was also evaluated by assessing the instantaneous TNSS. The assessment was performed twice a day after the first dose of the study medication. In the trials, onset of action was seen after one day of dosing. Onset of action was evaluated in three environmental exposure studies with single doses of olopatadine nasal spray. In the studies, patients with seasonal allergic rhinitis were exposed to high levels of pollen in the environmental exposure unit. The patients were treated with olopatadine nasal spray or vehicle nasal spray two sprays in each nostril after which they self-reported allergy symptoms hourly as instantaneous scores for the subsequent twelve hours. Onset of action for olopatadine nasal spray 0.6% was thirty minutes after dosing in the environmental exposure unit.

olopatadine hydrochloride nasal spray 0.6% (Patanase) versus azelastine hydrochloride nasal spray 0.1% versus placebo

A study was conducted as a phase III, multicenter, randomized, double-blind, active and placebo controlled parallel group study.⁷⁹ It included 544 individuals who were ≥ 12 years with a history of seasonal allergic rhinitis and verified allergy to a prevalent local allergen. Efficacy was assessed by changes in mean daily total nasal symptom scores (TNSS). Tolerability was evaluated based on adverse events as well as nasal, physical, and cardiovascular parameters. Patients were randomly assigned olopatadine, azelastine or placebo given as two sprays in each nostril twice daily for 16 days. The mean reductions from baseline in reflective TNSS were 26.8 percent with olopatadine, 29.9 percent with azelastine, and 18.4 percent with placebo ($p=0.003$, for olopatadine versus placebo). The most commonly reported adverse effect of bitter taste was significantly lower with olopatadine than with azelastine (12.2 percent with olopatadine and 19.7 percent with azelastine, $p=0.05$). In conclusion, the total nasal symptom scores (TNSS) percentage reduction was greater with olopatadine than placebo but not significantly different from azelastine. Both active treatments were well tolerated.

olopatadine hydrochloride nasal spray 0.6% (Patanase) versus fluticasone propionate nasal spray 50 mcg (Flonase)

A two week double-blind, randomized, two-arm parallel-group, noninferiority trial was conducted comparing olopatadine nasal spray 0.6% (two sprays per nostril twice daily) to fluticasone nasal spray 50 mcg (two sprays per nostril once daily) for the treatment of seasonal allergic rhinitis.⁸⁰ Symptomatic patients (n=130) were equally divided between the two groups and required to record nasal and ocular symptoms twice daily throughout the study. The study found olopatadine nasal spray 0.6% provided a faster and greater onset of action compared to fluticasone nasal spray 50 mcg. However, at the end of the two week study, olopatadine nasal spray 0.6% compared to fluticasone nasal spray 50 mcg had no statistically significant difference in relief of seasonal allergic rhinitis symptoms with a mean reduction of 45.4 percent and 47.4 percent, respectively.

Perennial Allergic Rhinitis

ipratropium nasal spray 0.03% (Atrovent) versus beclomethasone nasal spray (Beconase AQ)

In a multicenter randomized trial, ipratropium nasal spray 0.03% (42 mcg three times daily) and beclomethasone nasal spray (84 mcg twice daily) were evaluated for efficacy and safety alone and in combination versus a vehicle placebo with perennial allergic rhinitis.⁸¹ The study enrolled 533 patients. Efficacy was evaluated by patient and physician assessment of severity and duration of rhinorrhea. Combination therapy was more effective than either agent alone in reducing average severity and duration of rhinorrhea during four weeks of treatment. During the first week of treatment, ipratropium had faster onset of action and reduced rhinorrhea more than beclomethasone. Beclomethasone was more effective in reducing the severity of congestion and sneezing than ipratropium nasal spray. Combination therapy and monotherapy showed similar adverse effects.

fluticasone (Flonase) versus mometasone (Nasonex)

In a double-blind, placebo-controlled study, 550 patients with perennial allergic rhinitis were randomized to receive intranasal mometasone 200 mcg, fluticasone 200 mcg, or placebo once daily for three months.⁸² Both drugs were better than placebo in controlling symptoms and decreasing nasal symptom scores. Reduction from baseline in patient-recorded nasal symptoms ranged from 37 to 63 percent with mometasone, 39 to 60 percent with fluticasone, and 22 to 39 percent with placebo. Physician-evaluated reduction of nasal discharge and congestion was greatest with mometasone, but both drugs showed greater reductions than placebo. The number of symptom-free days during the study was 10 days with mometasone, 11 days with fluticasone, and four days with placebo. At the end of the three-month treatment period, the percent of patients classified as having complete or marked relief was 69 percent with mometasone, 60 percent with fluticasone, and 36 percent with placebo.

fluticasone furoate (Veramyst) versus placebo

In a randomized, double-blind, placebo-controlled, parallel-group study, 806 patients with perennial allergic rhinitis were randomized to once daily fluticasone furoate nasal spray 110 mcg (n=605) or vehicle placebo spray (n=201) for 12 months to address the long term safety of fluticasone furoate.⁸³ Fluticasone furoate was well tolerated, and the incidence of adverse effects was similar to that of placebo, with the exception of epistaxis which was more common in those receiving active treatment. No differences between fluticasone furoate and placebo for

changes in ophthalmic parameters and 24-hour urine cortisol excretion were observed. Long-term use of fluticasone furoate 110 mcg daily over 12 months was found to have an adverse effect profile similar to other intranasal corticosteroids, and there was no evidence of clinically significant systemic corticosteroid exposure.

budesonide aqueous nasal (Rhinocort Aqua) versus placebo

In a one-year, double-blind, placebo-controlled, multicenter study, 229 prepubertal children (mean age of 5.9 years) were randomized to receive budesonide aqueous nasal spray 64 mcg once daily (32 mcg per nostril) or placebo.⁸⁴ Growth velocity was not significantly different between the two groups (5.91 +/- 0.11 cm per year for the budesonide group versus 6.19 +/- 0.16 cm for the placebo group). Treatment with budesonide for one year did not suppress the growth velocity compared with placebo and was well tolerated in prepubertal children with perennial allergic rhinitis.

triamcinolone acetate aqueous nasal (Nasacort AQ) versus placebo

A multicenter, double-blind, parallel-group study conducted over four weeks was performed to establish efficacy and safety of triamcinolone acetate aqueous nasal spray in children two to five years old.⁸⁵ Children (n=474) with perennial allergic rhinitis were randomized to receive either triamcinolone acetate aqueous nasal spray 110 mcg or placebo once daily. The instantaneous and reflective Total Nasal Symptom Score (TNSS) were used to compare triamcinolone acetate aqueous nasal spray to placebo. Patient treated with triamcinolone acetate aqueous nasal spray had a mean reduction in instantaneous TNSS of -2.28 whereas patients using placebo had a mean reduction of -1.92. Likewise, triamcinolone acetate aqueous nasal spray proved superior to placebo with a mean reduction in reflective TNSS of -2.31 and -1.87, respectively. The rates of adverse effects were similar between the triamcinolone acetate aqueous nasal spray and placebo groups. Furthermore, no serious adverse effects were reported in either group and discontinuation rates were low. Overall, the study results suggest that triamcinolone acetate aqueous nasal spray 110 mcg used once daily for six months in children ages two through five is an efficacious and safe choice when treating perennial allergic rhinitis symptoms.

Important to note is that a subset of children were later included in an open-label extension of this study.

Summary

With the exception of systemic corticosteroids, intranasal corticosteroids are the most effective single agents for controlling the spectrum of allergic rhinitis symptoms, according to the AAAAI. Intranasal corticosteroids are generally not associated with systemic adverse effects in adults. Local adverse effects such as nasal irritation and bleeding may occur, but incidence is minimized if patients are carefully instructed in the use of drugs in this class. The nasal septum should be periodically examined to assure that there are no mucosal erosions that may precede development of nasal septal perforations, a complication rarely associated with intranasal corticosteroids.

Clinical trials have shown intranasal corticosteroids are similar in efficacy. Differences among products include the number of sprays needed per day and dosing frequency. Patient preference for products may also differ.

The intranasal antihistamines, azelastine (Astelin, Astepro) and olopatadine (Patanase), offer an alternative to intranasal corticosteroids, oral antihistamines, and intranasal ipratropium for

treatment of allergic rhinitis. Azelastine has been shown to be as effective as oral antihistamines. Factors limiting use of intranasal azelastine and olopatadine include route of administration and taste perversion.

Ipratropium nasal spray (Atrovent) is safe and effective for treatment of rhinorrhea associated with perennial allergic rhinitis and the common cold. The primary indication for the agent is treatment of patients with nonallergic perennial allergic rhinitis with rhinorrhea as the predominant symptom.

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