

Intranasal Rhinitis Agents Review

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Intranasal Rhinitis Agents Review

Overview

Allergic rhinitis is a constellation of symptoms affecting 40 million Americans.¹ 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.²

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 which 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.

The American Academy of Allergy, Asthma and Immunology (AAAAI) recommends a stepwise approach for managing allergic rhinitis. For patients with persistent, mild to moderate allergic rhinitis, an oral, minimally sedating antihistamine (with or without a decongestant) and/or an intranasal corticosteroid are recommended.³ For severe allergic rhinitis, combination therapy with an intranasal corticosteroid and a minimally sedating antihistamine (with or without a decongestant) is recommended.

For children or adult patients with perennial allergic rhinitis, azelastine (Astelin[®]) intranasal antihistamine and nasal cromolyn sodium may be considered alternative therapies. Because montelukast (Singulair[®]), a leukotriene antagonist, was not approved for seasonal allergic rhinitis at the time of publication, the AAAAI guidelines do not specifically address this agent. It is anticipated montelukast will find a therapeutic niche in patients with concurrent seasonal allergic rhinitis and asthma.

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.⁴

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.⁵

Azelastine (Astelin[®]) is a phthalazine derivative which exhibits histamine (H₁) receptor antagonist activity. Azelastine also demonstrates inhibitory effects on the release of inflammatory mediators from mast cells.⁶ The drug is 100 to 1,000 times more potent than cromolyn sodium, theophylline, astemizole, and verapamil in mast cell mediator release inhibition.⁷

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

FDA-Approved Indications

Drug	Manufacturer	Indication(s)
Nasal Corticosteroids		
beclomethasone (Beconase AQ [®]) ⁸	GSK	Relief of symptoms of seasonal or perennial allergic rhinitis and non-allergic (vasomotor) rhinitis Prevention of recurrence of nasal polyps following surgical removal
budesonide (Rhinocort Aqua [®]) ⁹	AstraZeneca	Management of nasal symptoms of seasonal or perennial allergic rhinitis in adults and children ages six years and older
flunisolide (Nasalide)*	generic	Relief of nasal symptoms of seasonal or perennial allergic rhinitis in adults and children ages six and older
flunisolide (Nasarel [®]) ¹⁰	generic	Relief of nasal symptoms of seasonal or perennial allergic rhinitis in adults and children ages six and older
fluticasone fuorate (Veramyst [®]) ¹¹	GSK	Treatment of symptoms of seasonal and perennial allergic rhinitis in adults and children two years of age and older
fluticasone propionate (Flonase [®]) ¹²	generic	Management of nasal symptoms of seasonal and perennial allergic rhinitis and nonallergic rhinitis in adults and children ages four and older
mometasone (Nasonex [®]) ¹³	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 pediatric patients 12 years of age and older Treatment of nasal polyps in adults
triamcinolone (Nasacort AQ [®]) ¹⁴	Sanofi-Aventis	Treatment of nasal symptoms of seasonal and perennial allergic rhinitis in adults and children ages six and older

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

Drug	Manufacturer	Indication(s)
Others		
ipratropium nasal spray 0.03% (Atrovent) ¹⁵	generic	Symptomatic relief of rhinorrhea associated with allergic and nonallergic perennial rhinitis in adults and children ages six years and older
ipratropium nasal spray 0.06% (Atrovent) ¹⁶	generic	Symptomatic relief of rhinorrhea associated with the common cold or seasonal allergic rhinitis in adults and children ages five and older
azelastine (Astelin) ¹⁷	MedPointe	Treatment of symptoms of seasonal allergic rhinitis such as rhinorrhea, sneezing, and nasal pruritis in adults and children ages five and older Treatment of symptoms of vasomotor rhinitis such as rhinorrhea, nasal congestion and postnasal drip in adults and children 12 years and older

Pharmacokinetics

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

Clinical Trials

Search Strategy

Articles were identified through searches performed on PubMed, www.ifpma.org/clinicaltrials, and review of information sent by manufacturers. Search strategy included the use of all drugs in this class 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)

Five hundred one patients with moderate-to-severe seasonal allergic rhinitis were enrolled in a double-blind, placebo-controlled study.¹⁸ Patients were treated for four weeks with either

mometasone (Nasonex) 100 mcg once daily in the morning, mometasone (Nasonex) 200 mcg once daily in the morning, beclomethasone (Vancenase) 200 mcg twice daily, or placebo. Patients were allowed to use 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 difference between regimens was observed. Complete or marked relief, based on physician-evaluated response to treatment, was achieved by 77 percent of patients treated with mometasone (Nasonex) 100 mcg once daily, 79 percent treated with mometasone (Nasonex) 200 mcg once daily, 74 percent treated with beclomethasone (Vancenase), and 54 percent of placebo-treated patients ($p < 0.01$ for each active treatment compared to placebo). The use of rescue antihistamine was also reduced in all three active treatment groups compared to the placebo group, with 41 percent of patients in the mometasone (Nasonex) 100 mcg group, 34 percent in the mometasone (Nasonex) 200 mcg group, and 35 percent in the beclomethasone (Vancenase) group requiring rescue medication, compared with 55 percent of patients in the placebo group ($p < 0.05$ for all comparisons to placebo). Side effects did not differ between 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 (Rhinocort) 64 mcg, budesonide (Rhinocort) 256 mcg, and mometasone furoate (Nasonex) 200 mcg.¹⁹ 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 (Rhinocort) caused dose-dependent improvements in evening symptoms, morning nasal PIF, and nasal PIF recorded 10 minutes after allergen challenge ($p < 0.05$). Budesonide (Rhinocort) 256 mcg produced greater improvement than mometasone (Nasonex) 200 mcg in nasal PIF 10 minutes after allergen challenge ($p < 0.05$).

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

In this two-week, multicenter, double-blind trial, 334 patients with moderate-to-severe seasonal allergic rhinitis were randomized to one of three treatments: 1) azelastine (Astelin) two sprays per nostril twice daily, 2) azelastine (Astelin) two sprays per nostril twice daily and fexofenadine (Allegra) 60 mg twice daily, or 3) placebo given twice daily.²⁰ All patients were given a one-week run-in with fexofenadine (Allegra) 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 (Astelin) and azelastine (Astelin) plus fexofenadine (Allegra) groups showed greater improvement in total nasal symptom score than placebo (p value here). Azelastine (Astelin) alone was as effective as azelastine (Astelin) plus fexofenadine (Allegra).

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.²¹ Patients were randomized to fluticasone furoate (Veramyst) 110 micrograms once daily or placebo. A four-point scale was used to evaluate the ocular and nasal symptoms at baseline and at two weeks. Total nasal symptom score improvement was the primary endpoint. Fluticasone furoate (Veramyst) produced significantly greater improvements than placebo in daily reflective total nasal symptom scores (-1.473 , $p < 0.001$), morning predose instantaneous total nasal 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 (Veramyst) was well tolerated. Active treatment resulted in sustained improvement in nasal and ocular symptoms over 24 hours.

Perennial Allergic Rhinitis

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

In a multicenter randomized trial, ipratropium nasal spray (Atrovent) 0.03% (42 mcg three times daily) and beclomethasone nasal spray (Beconase AQ) (84 mcg twice daily) were evaluated for efficacy and safety alone and in combination versus a vehicle placebo with perennial allergic rhinitis.²² 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 the average severity and duration of rhinorrhea during four weeks of treatment. During the first week of treatment, ipratropium (Atrovent) had faster onset of action and reduced rhinorrhea more than beclomethasone (Beconase AQ). Beclomethasone (Beconase AQ) was more effective in reducing the severity of congestion and sneezing than ipratropium (Atrovent) nasal spray. Combination therapy and monotherapy showed equal adverse effects.

fluticasone (Flonase) versus mometasone (Nasonex)

In a double-blind, placebo-controlled study, 550 patients with perennial allergic rhinitis were randomized to receive either intranasal mometasone (Nasonex) 200 mcg, fluticasone (Flonase) 200 mcg, or placebo once daily for three months.²³ Both drugs were better than placebo in controlling symptoms and decreasing nasal symptom scores. The reduction from baseline in patient-recorded nasal symptoms ranged from 37 to 63 percent with mometasone (Nasonex), 39 to 60 percent with fluticasone (Flonase), and 22 to 39 percent with placebo. The physician-evaluated reduction of nasal discharge and congestion was greatest with mometasone (Nasonex), but both drugs showed greater reductions than placebo. The number of symptom-free days during the study was 10 days with mometasone (Nasonex), 11 days with fluticasone (Flonase), 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 (Nasonex), 60 percent with fluticasone (Flonase), and 36 percent with placebo.

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.²⁴ Growth velocity was not significantly different between the two groups (5.91 +/- 0.11 cm per year for the budesonide (Rhinocort Aqua) group versus 6.19 +/- 0.16 cm for the placebo group). Treatment with budesonide (Rhinocort Aqua) for one year did not suppress the growth velocity compared with placebo and was well tolerated in prepubertal children with perennial allergic rhinitis.

Special Populations

Pediatrics

The intranasal corticosteroids and azelastine (Astelin) have been proven safe and effective for use in children. Please refer to the package inserts for specific age criteria.

Pregnancy

Azelastine (Astelin) 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. However, the relevance of this finding to intranasal administration of corticosteroids has not been established.

Contraindications/Warnings

There are no specific contraindications for any of the intranasal corticosteroids or azelastine (Astelin).

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. Children or adults taking immunosuppressive doses of corticosteroids can have more serious or fatal responses to disseminated infections.

Patients should be advised to assess their individual responses to azelastine (Astelin) nasal spray before engaging in any activity requiring mental alertness, such as driving a car or operating machinery.²⁵ Patients should be advised that the concurrent use of azelastine nasal spray with alcohol or other CNS depressants may lead to additional reductions in alertness and impairment of CNS performance and should be avoided.

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.

Patients using fluticasone furoate (Veramyst) should be monitored periodically for adverse effects on the nasal mucosa. Avoid use in patients with recent nasal ulcers, nasal surgery or nasal trauma.

Drug Interactions

Fluticasone [propionate (Flonase) and furoate (Veramyst)] are substrates of cytochrome P450 3A4. Coadministration of either fluticasone nasal spray (Flonase or Veramyst) and ritonavir 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.²⁶

Adverse Effects

Nasal Corticosteroids

Drug	Pharyngitis	Epistaxis	Cough	Nasal Irritation
beclomethasone (Beconase AQ) ²⁷	nr	<3	nr	24
budesonide (Rhinocort Aqua) ²⁸ N=1,526; up to 400 mcg	4	8	2	2
flunisolide (Nasalide) ²⁹	3 - 9	3 - 9	<3	44
flunisolide (Nasarel) ³⁰	<3	3 - 9	<3	13
fluticasone furoate (Veramyst) ³¹ N=768; 110 mcg	2	6	nr	1
fluticasone propionate (Flonase) ³² N=782; 200 mcg	7.8	6.9	3.8	3.2
mometasone (Nasonex) ³³ N=2,103; 200 mcg	12	11	7	reported
triamcinolone AQ (Nasacort AQ) ³⁴ N=857; 220 mcg	5.1	2.7	2.1	nr

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

Overall, intranasal corticosteroids are well tolerated in adult and pediatric patients. The most serious effects impacting continued therapy are nose bleed 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.³⁵ The authors conducted a comparative, double-blind, experimental, prospective, and 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.

Others

Drug	Bitter taste	Headache	Myalgia	Nasal burning	Somnolence	Weight increase
azelastine (Astelin) ³⁶ N=391	19.7 (0.6)	14.8 (12.7)	1.5 (--)	4.1 (1.7)	11.5 (5.4)	2 (--)
placebo N=353						

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

Drug	Nasal dryness	Nasal Irritation	Epistaxis	Dry mouth/throat
ipratropium nasal (Atrovent) 0.03% ³⁷ N=356 perennial allergic rhinitis	5.1	2	9	<2
ipratropium nasal (Atrovent) 0.06% ³⁸ N=352 common cold	4.8	Nasal burning <1	8.2	1.4

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

Monitoring

In children, intranasal corticosteroids should be used at the lowest effective dose, and the FDA recommends that height be routinely monitored.^{39,40}

Dosages

Drug	Adults	Children (<12 years)	Availability
Nasal Corticosteroids			
beclomethasone (Beconase AQ)	1 - 2 sprays twice daily	1 - 2 sprays twice daily	42 mcg spray 25 gm - 180 sprays
budesonide (Rhinocort Aqua)	1 - 4 sprays daily	1 - 2 sprays daily	32 mcg spray 8.6 gm - 120 sprays
flunisolide (Nasalide)	2 sprays twice daily	1 spray three times daily or 2 sprays twice daily	25 mcg aerosol 25 mL - 200 doses
flunisolide (Nasarel)	2 sprays twice daily up to 8 sprays daily	1 spray three times daily or 2 sprays twice daily	25 mcg spray 25 mL - 200 sprays
fluticasone furoate (Veramyst)	2 sprays once daily	1 spray once daily	27.5 mcg spray 10 gm – 120 sprays
fluticasone propionate (Flonase)	2 sprays daily or 1 spray twice daily	1 - 2 sprays daily	50 mcg spray 16 gm - 120 sprays
mometasone (Nasonex)	2 sprays daily Nasal polyps: 2 sprays twice daily	1 spray daily	50 mcg spray 17 gm - 120 sprays
triamcinolone (Nasacort AQ)	2 sprays daily	1 - 2 sprays daily	55 mcg spray 16.5 gm - 120 sprays
ipratropium 0.03% (Atrovent Nasal)	Perennial allergic rhinitis: 2 sprays twice or three times daily	2 sprays twice or three times daily	21 mcg/spray 30 mL - 345 sprays
Others			
ipratropium 0.06% (Atrovent Nasal)	Seasonal allergic rhinitis: 2 sprays four times daily	2 sprays four times daily	42 mcg/spray 15 mL - 165 sprays
ipratropium 0.06% (Atrovent Nasal)	Common cold: 2 sprays three or four times daily not to exceed 4 days	2 sprays three times daily not to exceed 4 days	
azelastine (Astelin)	1 spray twice daily (12 and older)	1 spray twice daily	137 mcg/spray 2 x 17 mL - 200 sprays; 30 mL - 200 sprays

- For fluticasone (Flonase), some patients greater than or equal to 12 years of age have found as-needed usage of 200 mcg once daily to be effective in seasonal allergic rhinitis.
- For mometasone (Nasonex), triamcinolone (Nasacort AQ), fluticasone furoate (Veramyst) and ipratropium nasal spray (Atrovent), the pump must be primed prior to first use and again if stored unused after specified periods of time (which are product specific). Consult package inserts.

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.⁴¹ Intranasal corticosteroids are generally not associated with systemic side effects in adults. Local side 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 between products are found in number of sprays needed per day and dosing frequency. Patient preference for products may also differ.

Azelastine (Astelin) nasal spray offers an alternative to intranasal corticosteroids, oral antihistamines and intranasal ipratropium for treatment of allergic rhinitis. The drug has been shown to be as effective as oral antihistamines, but no published trials to date are available comparing azelastine to intranasal corticosteroids. Factors limiting use of azelastine include route of administration, incidence of sedation and taste perversion.

Ipratropium nasal spray (Atrovent) appears 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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