Intranasal Rhinitis Agents
Therapeutic Class Review (TCR)

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FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indication(s)
Nasal Corticosteroids		
beclomethasone (Beconase AQ®)[1]	GlaxoSmithKline	▪ Relief of symptoms of seasonal or perennial allergic rhinitis and non-allergic (vasomotor) rhinitis in adults and children 6 years of age and older ▪ Prevention of recurrence of nasal polyps following surgical removal
beclomethasone (Qnasl®)[2]	Teva Specialty	▪ Treatment of nasal symptoms associated with seasonal and perennial allergic rhinitis in adults and adolescents 4 years of age and older
budesonide OTC (Rhinocort® Allergy)[3]	generic, Johnson & Johnson	▪ Temporary relief of hay fever or other upper respiratory allergies, including nasal congestion, runny nose, sneezing, and itchy nose, in adults and children 6 years of age and older
ciclesonide (Omnaris®)[4]	Covis	▪ Treatment of nasal symptoms of seasonal allergic rhinitis in adults and children 6 years of age and older ▪ Treatment of nasal symptoms of perennial allergic rhinitis in adults and children 12 years of age and older
ciclesonide (Zetonna®)[5]	Covis	▪ Treatment of symptoms associated with seasonal and perennial allergic rhinitis in adults and adolescents 12 years of age and older
flunisolide[6]	Bausch	▪ Relief of nasal symptoms of seasonal or perennial allergic rhinitis in adults and children 6 years of age and older
fluticasone furoate OTC (Flonase® Sensimist™)[7]	GlaxoSmithKline	▪ Temporary relief of symptoms of hay fever or other upper respiratory allergies, including nasal congestion, runny nose, sneezing, itchy nose, and itchy, watery eyes in adults and children 2 years of age and older
fluticasone propionate[8]	generic	▪ Management of nasal symptoms of perennial non-allergic rhinitis in adults and children 4 years of age and older
fluticasone propionate OTC (Flonase Allergy Relief®)[9]	generic, GlaxoSmithKline	▪ Temporary relief of symptoms of hay fever or other upper respiratory allergies, including nasal congestion, runny nose, sneezing, itchy nose, and itchy/watery eyes, in adults and children 4 years of age and older
fluticasone propionate (Xhance®)[10]	OptiNose	▪ Treatment of nasal polyps in patients 18 years of age or older
mometasone (Nasonex®)[11]	generic, Merck	▪ Treatment of nasal symptoms of seasonal and perennial allergic rhinitis in adults and children 2 years of age and older ▪ Treatment of nasal congestion associated with seasonal allergic rhinitis in adults and children 2 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
mometasone (Sinuva®)[12]	Intersect ENT	▪ Corticosteroid-eluting implant indicated for the treatment of nasal polyps in patients ≥ 18 years of age who have had ethmoid sinus surgery
triamcinolone OTC (Nasacort® Allergy 24HR)[13]	generic, Chattem	▪ Temporary relief of symptoms of hay fever or other upper respiratory allergies, including nasal congestion, runny nose, sneezing, and itchy nose, in adults and children 2 years of age and older

FDA-Approved Indications (continued)

Drug	Manufacturer	Indication(s)
Intranasal Antihistamines		
azelastine 0.1%[14]	generic	▪ Relief of symptoms of seasonal allergic rhinitis in adults and children 5 years of age and older ▪ Relief of symptoms of vasomotor rhinitis in patients 12 years of age and older
azelastine 0.15%[15]	generic	▪ Relief of symptoms of seasonal allergic rhinitis in adults and children 6 years of age and older ▪ Relief of symptoms of perennial allergic rhinitis in adults and children 6 years of age and older
olopatadine (Patanase®)[16]	generic, Alcon/Novartis	▪ Relief of symptoms of seasonal allergic rhinitis in adults and pediatric patients 6 years of age and older
Antihistamine and Intranasal Corticosteroid Combinations		
azelastine/fluticasone propionate (Dymista®)*[17]	generic, Meda/Mylan	▪ Relief of symptoms of seasonal allergic rhinitis in adult and pediatric patients 6 years of age and older
olopatadine/mometasone (Ryaltris™)*[18]	Hikma Specialty	▪ Treatment of symptoms of seasonal allergic rhinitis in adult and pediatric patients 12 years of age and older
Others		
hypromellose (Alzair™)[19]	Hudson Scientific	▪ Reduces the symptoms of allergic rhinitis
ipratropium nasal spray 0.03%[20]	generic	▪ Symptomatic relief of rhinorrhea associated with allergic and nonallergic perennial rhinitis in adults and children 6 years of age and older
ipratropium nasal spray 0.06%[21]	generic	▪ Symptomatic relief of rhinorrhea associated with the common cold or seasonal allergic rhinitis in adults and children 5 years of age and older

* Approved as a New Drug Application (NDA) via the 505(b)(2) pathway. A 505(b)(2) NDA is a Food and Drug Administration (FDA) approval pathway in which at least some of the information required for approval comes from studies not conducted by or for the applicant.[22,23]

Products packaged as kits are discussed in the FDA Indications and Dosages sections, and components are addressed in the Pharmacology section. For other information regarding these products, please refer to the primary component throughout the text.

Triamcinolone nasal spray (Nasacort Allergy 24HR), fluticasone furoate (Flonase Sensimist Allergy Relief), fluticasone propionate nasal spray (Flonase Allergy Relief), and budesonide nasal spray (Rhinocort Allergy) are available without a prescription. In June 2021, the FDA approved a partial switch to over-the-counter status for azelastine 0.15% nasal spray (Astepro Allergy, Children's Astepro Allergy) for the temporary relief of nasal congestion, runny nose, sneezing, and/or itchy nose due to hay fever or other upper respiratory allergies.[24] Generic azelastine 0.15% prescription only products remain available, and the 0.1% azelastine formulation remains prescription-only.

Regeneron Pharmaceuticals' dupilumab (Dupixent®) is an interleukin-4 receptor alpha antagonist indicated as an add-on to maintenance therapy in adult patients with inadequately controlled chronic rhinosinusitis with nasal polyposis (CRSwNP).[25] It is supplied as a 300 mg/2 mL solution in a single dose pre-filled syringe with a needle shield. The recommended dose for this indication is 300 mg given

subcutaneously every other week. The patients may self-inject the dose after proper training. Due to the route of administration of this medication, it will not be detailed in this therapeutic class review.

Genentech's omalizumab (Xolair®) is an anti-immunoglobulin E (anti-IgE) antibody indicated as add-on maintenance treatment for nasal polyps in adult patients ≥ 18 years of age with inadequate response to nasal corticosteroids.[26] It is supplied as a single-dose prefilled syringe in the strengths of 75 mg/0.5 mL and 150 mg/mL (patients or caregivers can administer) and as a lyophilized powder (150 mg) in a single-dose vial (for reconstitution and injection by a healthcare provider [HCP]). The recommended dose for this indication is 75 mg to 600 mg subcutaneously every 2 or 4 weeks based on body weight and serum total IgE level (IU/mL) measure prior to the start of therapy as described in the prescribing information (PI). Omalizumab is intended for use under the guidance of an HCP, and therapy is initiated in a healthcare setting. Once therapy has been established, the HCP may determine that self-administration by the patient or caregiver is appropriate (with the prefilled syringe) following a careful evaluation of the risk of anaphylaxis and mitigation strategies. Patients should be regularly reassessed for continued use based on disease severity and symptom control. Due to the route of administration of this medication, it will not be detailed in this therapeutic class review.

Products that are available as convenience kits are not included in this Therapeutic Class Review.

OVERVIEW

Allergic rhinitis (AR) is a constellation of symptoms affecting 7.7% of adults and 7.2% of children in the United States.[27] 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.[28] 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.

The American Academy of Allergy, Asthma and Immunology (AAAAI) 2017 focused evidence-based guideline update for Seasonal Allergic Rhinitis (SAR) provides guidance for the treatment of both adult and adolescent patients (≥ 12 to 15 years of age) with allergic rhinitis.[29] Pharmacological therapy for SAR may include intranasal and oral antihistamines, decongestants, and corticosteroids. Other therapies include intranasal cromolyn, intranasal anticholinergics, and leukotriene receptor antagonists (LTRAs). When specific monotherapy management is being considered, intranasal corticosteroids are more effective than LTRAs. If a patient is not adequately controlled on an intranasal corticosteroid or has moderate to severe symptoms, addition of an antihistamine may be considered, preferably an intranasal antihistamine agent versus an oral antihistamine product. The guidelines do not specify one agent from a specific drug class over another.

According to the 2008 AAAAI practice parameter for the diagnosis and management of rhinitis, the selection of pharmacotherapy for a patient depends on multiple factors, including the type of rhinitis present (e.g., allergic, non-allergic, 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 the management decision. Rhinitis medication management frequently requires 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.[30] 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 (SAR). These agents are also effective and have been associated with a clinically significant effect on nasal congestion for nonallergic rhinitis (NAR) but are generally less effective than intranasal corticosteroids for treatment of allergic rhinitis. According to the 2020 AAAAI practice parameter update on rhinitis, for intranasally administered treatment, they recommend inhaled antihistamines as first-line for seasonal allergic rhinitis (SAR)(high evidence), intermittent AR (conditional recommendation), and NAR (high evidence).[31] Intranasal corticosteroids are the preferred monotherapy for persistent AR (high evidence). AAAAI suggests combination of an intranasal corticosteroid and intranasal antihistamine for moderate-to-severe cases of SAR (patients ≥ 12 years of age) (high evidence), SAR and PAR that is resistant to monotherapy (moderate evidence), and resistant NAR (low evidence). An alternative option for rhinorrhea that persists while on intranasal corticosteroids is the addition of intranasal ipratropium (moderate evidence). If nasal congestion persists despite treatment with an intranasal corticosteroid with or without an intranasal antihistamine, addition of an intranasal decongestant for up to 4 weeks may be considered (low evidence). AAAAI also provides pharmacotherapy recommendation using oral agents, and strongly recommends use of an oral second-generation antihistamine and against prescribing an oral first-generation antihistamine for the treatment of AR (high evidence). Other oral alternatives are detailed in the 2020 guidance.

The 2015 American Academy of Otolaryngology – Head and Neck Surgery Clinical Practice Guideline for Allergic Rhinitis recommends the use of intranasal corticosteroids and oral antihistamines as key treatments for allergic rhinitis in adults and children over 2 years of age.[32] The panel issued a strong recommendation for use of intranasal corticosteroids in patients whose quality of life is affected by allergic rhinitis, as well as for oral second generation antihistamines for patients with sneezing and itching as their primary complaints. Clinicians may offer intranasal antihistamines for patients with seasonal, perennial, or episodic allergic rhinitis, although their more frequent dosing and adverse effect profile may guide clinicians and patients to initiate therapy with a different medication class.. The guideline also recommends combination therapy in patients who have had an inadequate response to monotherapy. The most effective addition to intranasal corticosteroid therapy is an intranasal antihistamine.

PHARMACOLOGY[33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55]

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.[56] Fluticasone propionate (Xhance) and mometasone (Sinuva) are specifically used for the treatment of nasal polyps in adult patients. However, the exact mechanism of action is unknown for this indication. Fluticasone propionate (Xhance) uses a bi-directional exhalation delivery system (EDS) designed to deliver drug higher and deeper in the nasal passages, compared to traditional nasal sprays.[57] However, clinical studies have not been conducted comparing effectiveness on nasal congestion, nasal obstruction symptoms, or nasal polyp grade of fluticasone propionate EDS (Xhance) with other nasal corticosteroids used to treat nasal polyps.

Azelastine (generics, Dymista) is a phthalazine derivative, which exhibits histamine (H_1) receptor antagonist activity. Azelastine also demonstrates inhibitory effects on the release of inflammatory mediators from mast cells.[58] The drug is 100 to 1,000 times more potent than cromolyn sodium, theophylline, astemizole, and verapamil in mast cell mediator release inhibition.[59] Olopatadine (Patanase, Ryaltris) is an antihistamine with selective H_1 receptor antagonist activity.

Ipratropium bromide 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.

Saline (sodium chloride 0.9%) nasal wash, a component of select product kits, is used to moisturize and lubricate dry nasal passages via a gentle mist. Large volume low pressure irrigation of nasal and sinus cavities may also be performed.

Hypromellose (Alzair) particles absorb moisture from the nasal mucosa and swell to create a protective gel-like barrier in the nasal tract. This gel barrier prevents allergens from making contact with the mucosa, thus stopping cell degranulation and the release of histamines from within the body.

PHARMACOKINETICS[60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77]

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.

After a single dose, the median time to peak exposure is 1 hour for both olopatadine and mometasone furoate (Ryaltris), and the mean elimination half-lives for each component is 9 and 18 hours, respectively. Any absorbed drug is excreted as metabolites with the majority excreted in the bile, and a limited amount, in the urine.

CONTRAINDICATIONS/WARNINGS[78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98]

There are no specific contraindications for any of the intranasal corticosteroids, azelastine (generics, Dymista), or olopatadine (Patanase, a component of Ryaltris). Hypersensitivity to any of the ingredients in the nasal spray, inhaler, or device contraindicates its use.

Nasal Corticosteroids

If a topical corticosteroid replaces a systemic corticosteroid, signs of adrenal insufficiency may appear. In susceptible individuals, systemic corticosteroid effects, such as hypercorticism and adrenal suppression, may appear. If this occurs, nasal corticosteroid therapy should be slowly discontinued. However, a 6-week clinical trial reported that serum cortisol weighted mean values were similar in patients treated with beclomethasone dipropionate 320 mcg once daily and placebo.[99]

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 septal perforations, impaired wound healing, and *Candida albicans* infections 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 (e.g., blurred vision). Consider referral to an ophthalmologist in patients who develop ocular symptoms. Central serous chorioretinopathy has occurred with select agents in this class in post-marketing reports.

Intranasal Antihistamines

Due to somnolence, patients should be advised to assess their individual responses to azelastine (generics, Dymista) nasal spray or olopatadine (Patanase, Ryaltris) 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 have been reported in placebo-controlled clinical trials with olopatadine (Patanase, Ryaltris).

Ipratropium 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[100,101,102,103,104,105,106,107,108,109,110,111,112,113,114,115,116,117,118]

Fluticasone propionate (Flonase Allergy Relief, Dymista), fluticasone furoate (Flonase Sensimist), and mometasone (Nasonex, Ryaltris) are substrates of cytochrome P450 3A4. Concurrent use with ketoconazole, a potent CYP 3A4 inhibitor, may increase the plasma concentrations of mometasone and associated adverse effects. In addition, co-administration of fluticasone nasal spray (Flonase Allergy Relief, Flonase Sensimist, Dymista) and protease inhibitors is not recommended. A drug interaction study in healthy patients demonstrated that ritonavir may increase plasma fluticasone levels resulting in significantly reduced serum cortisol concentrations.

Drug-drug interaction studies were not conducted for the following nasal sprays: olopatadine (Patanase, Ryaltris), ipratropium or mometasone (Sinuva, Ryaltris). Based on *in vitro* metabolism data, olopatadine drug interactions involving P450 inhibition are not expected. Evaluation of mometasone (Sinuva) with other commonly used nasal drugs did not exhibit any unusual adverse effects.

ADVERSE EFFECTS[119,120,121,122,123,124,125,126,127,128,129,130,131,132,133,134,135,136,137,138,139]

Nasal Corticosteroids

Drug	Pharyngitis	Epistaxis	Cough	Nasal Irritation/Discomfort
beclomethasone (Beconase AQ)	nr	< 3	nr	24
beclomethasone (Qnasl)	nr	1.9	nr	5.2
budesonide (Rhinocort Allergy) n=1,526; up to 400 mcg	4	8	2	2
ciclesonide (Omnaris) n=546; up to 200 mcg	3.7	4.9	nr	> 1
ciclesonide (Zetonna)	≥ 2	2.9	≥ 2	3.2
flunisolide	< 3–9	3–9	< 3	13–44
fluticasone furoate (Flonase Sensimist Allergy Relief) n=768; 110 mcg	2	6	nr	1
fluticasone propionate (Flonase Allergy Relief) n=782; 200 mcg	7.8	6.9	3.8	3.2
fluticasone propionate (Xhance)	≥ 2	≥ 2	< 1	≥ 2
mometasone (Nasonex) n=2,103; 200 mcg	12	11	7	reported
mometasone (Sinuva) n=254; 200 mcg	3	6	nr	nr
triamcinolone (Nasacort Allergy 24HR) 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 study evaluated whether use of fluticasone propionate, mometasone furoate, or beclomethasone dipropionate for treatment of rhinitis produced an increase in intraocular pressure.[140] The authors conducted a comparative, double-blind, experimental, prospective, longitudinal study in which 360 patients were randomized into 1 of 4 groups. Ninety patients were given a placebo (control group). The other 270 were divided into 3 groups of 90 patients each. A different intranasal corticosteroid was given to each group. All patients had intraocular pressure measured by Goldman's tonometry at 3 weeks, 6 weeks, 3 months, 6 months, and 1 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.

The safety of repeat administration of the mometasone sinus implant was evaluated in an open-label, single-arm, multicenter study in 50 patients. All patients were followed for 365 days after bilateral implant placement and used mometasone furoate nasal spray once daily through the entire 365 days. The implants were removed at day 90. Repeat placement of an implant was permitted in patients with ethmoid sinus polyps grade ≥ 1, which occurred in 41 patients. The most common adverse events occurring after the repeat implantation were acute sinusitis (29%), upper respiratory infection (17%), epistaxis (12%), nasal discomfort/rhinalgia (12%), and headache (7%).

Intranasal Antihistamines

Drug	Bitter Taste/ Taste Disturbance	Headache	Myalgia	Nasal Burning	Somnolence	Weight Increase
azelastine 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% n=146; vehicle n=138 azelastine 0.15% 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) n=587 vehicle n=593	12.8 (0.8)	4.4 (4)	nr	nr	0.9 (0.3)	nr
azelastine / fluticasone propionate (Dymista)	4 (< 1)	2 (1)	nr	nr	< 1	nr
olopatadine/ mometasone (Ryaltris)	3 (0.3)	nr	nr	1 (0.8)	<1 (0)	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% n=356 perennial allergic rhinitis	5.1	2	9	< 2
ipratropium nasal 0.06% 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 Food and Drug Administration (FDA) recommends that height be routinely monitored due to potential reduction in growth velocity.[141,142]

SPECIAL POPULATIONS[143,144,145,146,147,148,149,150,151,152,153,154,155,156,157,158,159,160,161,162,163]

Pediatrics

With the exception of mometasone (Sinuva) and fluticasone propionate (Xhance), which are approved for patients ≥ 18 years, all other agents in this class are approved in pediatrics. Please refer to the FDA-Approved Indications chart or to the individual package inserts for specific age criteria.

Controlled clinical studies have shown that intranasal corticosteroids may cause a reduction in growth velocity in pediatric patients; however, the impact on final adult height is unknown.[164] Olopatadine/mometasone (Ryaltris) is approved for use in patients 12 years and older for seasonal allergic rhinitis. Over-the-counter (OTC) use of an intranasal corticosteroid should be limited to ≤ 2 months in children 2 to 11 years of age. A prescriber should be consulted for use beyond 2 months.

Pregnancy

Other than described below, all of the intranasal corticosteroids are Pregnancy Category C. Labeling for ciclesonide (Omnaris) and olopatadine (Patanase) were updated to comply with the Pregnancy and Lactation Labeling Rule (PLLR). For ciclesonide, there are no data for use in pregnant women to assess a drug-associated risk to the mother or fetus; however, there is low systemic drug exposure with the recommended dose. Human studies have not been conducted with olopatadine, although post-marketing surveillance with antihistamines similar to olopatadine has not demonstrated a drug-associated risk of adverse fetal or maternal outcomes. Labeling for mometasone spray (Nasonex), mometasone implant (Sinuva), and olopatadine/mometasone (Ryaltris) states that there are no adequate data for their use in pregnant women. Data available for fluticasone propionate (Xhance) do not suggest that there is an association for risks to the fetus nor adverse developmental outcomes.

Ipratropium and budesonide are Pregnancy Category B.

Labeling for azelastine (Dymista) was updated to comply with the PLLR. Limited data from post-marketing experience have not identified any drug-associated risks of miscarriages, birth defects, or other adverse maternal or fetal outcomes.

Other Considerations

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

DOSAGES[165,166,167,168,169,170,171,172,173,174,175,176,177,178,179,180,181,182,183,184,185]

Drug	Adults (≥ 12 years)	Children (< 12 years)	Availability
Nasal Corticosteroids			
beclomethasone (Beconase AQ)	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
beclomethasone (Qnasl)	2 sprays in each nostril once daily (Qnasl 80 mcg) (maximum 4 sprays per day)	(4–11 years) 1 spray in each nostril daily (Qnasl 40 mcg) (maximum 2 sprays per day)	40 mcg/spray; 6.8 gm – 60 actuations; 80 mcg/spray; 10.6 gm – 120 actuations
budesonide OTC (Rhinocort Allergy)	2 sprays in each nostril daily	(≥ 6 years) 1–2 sprays in each nostril daily; A physician should be consulted for use beyond 2 months	32 mcg/spray; 8.43 mL – 120 sprays
ciclesonide (Omnaris)	2 sprays in each nostril daily	(≥ 6 years) 2 sprays in each nostril daily	50 mcg/spray; 12.5 gm – 120 sprays
ciclesonide (Zetonna)	1 spray in each nostril daily	--	37 mcg/spray; 6.1 gm –6 0 actuations
flunisolide	2 sprays in each nostril twice daily up to 8 sprays in each nostril daily	(≥ 6 years) 1 spray in each nostril 3 times daily or 2 sprays in each nostril twice daily	25 mcg aerosol; 25 mL – 200 doses
fluticasone furoate (Flonase Sensimist Allergy Relief)	Week 1: use 2 sprays in each nostril once daily; Week 2 through 6 months: use 1–2 sprays in each nostril once daily, as needed for symptoms; A physician should be consulted for use beyond 6 months	(2–11 years) 1 spray in each nostril daily; A physician should be consulted for use beyond 2 months	27.5 mcg/spray; 9.9 mL–60 sprays and 15.8 mL – 120 sprays
fluticasone propionate	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
fluticasone propionate OTC (Aller-Flo®*, ClariSpray®*, Flonase Allergy Relief)	Week 1: 2 sprays in each nostril once daily; Week 2 through 6 months: 1 – 2 sprays in each nostril once daily as needed	(4–11 years) 1 spray in each nostril daily	50 mcg/spray; 16 gm – 120 sprays*
fluticasone propionate (Xhance)†	1 spray in each nostril twice daily	(≥ 18 years) 2 sprays in each nostril daily	93 mcg/spray; 16 mL – 120 sprays

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.

* A branded generic product approved under an abbreviated new drug application (ANDA).

† Xhance uses a bi-directional exhalation delivery system (EDS) to dispense the dose of fluticasone propionate. To administer Xhance, the tip of the nosepiece is inserted deep into 1 nostril to form a tight seal between the nosepiece and the nostril. Next, the patient blows into the mouthpiece, while simultaneously actuating the spray pump.[186]

Dosages (continued)

Drug	Adults (≥ 12 years)	Children (< 12 years)	Availability
Nasal Corticosteroids *(continued)*			
mometasone (Nasonex)	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
mometasone (Sinuva)	Adults 18 years of age and older: 1,350 mcg of mometasone furoate can be delivered over 90 days	--	Implant system contains 1,350 mcg of mometasone furoate within a sterile delivery system
triamcinolone OTC (Nasacort® Allergy 24 HR, Aller-Cort™*)	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 A physician should be consulted for use beyond 2 months	55 mcg/spray; 16.5 gm – 120 sprays
Intranasal Antihistamines			
azelastine 0.1%	Seasonal allergic rhinitis: 1–2 sprays in each nostril twice daily Vasomotor rhinitis: 2 sprays in each nostril twice daily	Seasonal allergic rhinitis (2 to 11 years): 1 spray in each nostril twice daily	137 mcg/spray; 30 mL – 200 sprays Discard once spray capacity has been reached even if not empty
azelastine 0.15%	Seasonal allergic rhinitis: 1–2 sprays in each nostril twice daily or 2 sprays in each nostril once daily Perennial allergic rhinitis: 2 sprays in each nostril twice daily	Seasonal allergic rhinitis (6 to 11 years): 1 spray in each nostril twice daily Perennial allergic rhinitis (6–11 years): 1 spray in each nostril twice daily	205.5 mcg/spray; 30 mL – 200 sprays Discard once spray capacity has been reached even if not empty
olopatadine (Patanase)	2 sprays in each nostril twice daily	(≥ 6 years) 1 spray in each nostril twice daily	0.6% (665 mcg/100 mcL spray); 30.5 gm – 240 sprays

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.

*A branded generic product approved under an abbreviated new drug application (ANDA).

Dosages (continued)

Drug	Adults (≥ 12 years)	Children (< 12 years)	Availability
Antihistamine and Intranasal Corticosteroid Combinations			
azelastine/fluticasone propionate (Dymista®)	1 spray in each nostril twice daily	(≥ 6 years) 1 spray in each nostril twice daily	137 mcg/50 mcg per spray 23 gm – 120 sprays
olopatadine/ mometasone (Ryaltris)	2 sprays in each nostril twice daily	2 sprays in each nostril twice daily	665 mcg/25 mcg per spray 29 gm – 240 sprays
Others			
hypromellose (Alzair)	Firmly squeeze a 6-inch plume at least 3 times daily (minimum) or as needed	Gently squeeze a 2-inch plume at least 3 times daily (minimum) or as needed	Nasal powder spray bottle
ipratropium 0.03%	Perennial allergic rhinitis: 2 sprays in each nostril 2 or 3 times daily	(≥ 6 years) 2 sprays in each nostril 2 or 3 times daily	21 mcg/spray 30 mL – 345 sprays
ipratropium 0.06%	Seasonal allergic rhinitis: 2 sprays in each nostril 4 times daily	(≥ 5 years) 2 sprays in each nostril 4 times daily	42 mcg/spray 15 mL – 165 sprays
	Common cold: 2 sprays in each nostril 3 or 4 times daily not to exceed 4 days	(≥ 5 years) 2 sprays in each nostril 3 times daily not to exceed 4 days	

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.

For fluticasone, some patients 12 years of age and older have found as-needed usage of 200 mcg once daily (2 sprays in each nostril) to be an effective treatment of seasonal allergic rhinitis.

The mometasone sinus implant (Sinuva) can by removed by day 90 or earlier as deemed appropriate by the physician. The safety of repeat administration of the mometasone sinus implant was demonstrated in an open-label, single-arm, multicenter study in 50 patients.

CLINICAL TRIALS

Search Strategy

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved 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% 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 and/or 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.

Several agents in this class have demonstrated efficacy versus placebo.[187,188,189,190,191,192,193,194,195,196,197,198,199,200,201,202] Comparative trials regarding use for rhinitis are included in more detail below. There are no comparative trials for agents approved for the treatment of nasal polyps; however, efficacy has been demonstrated in placebo-controlled trials.[203,204,205]

Seasonal Allergic Rhinitis

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.[206] Treatment was initiated for 3 days prior to allergen challenges and administered daily for 7 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 versus azelastine plus fexofenadine (Allegra®)

In a 2-week, multicenter, double-blind trial, 334 patients with moderate-to-severe seasonal allergic rhinitis were randomized to 1 of 3 treatments: 1) azelastine 2 sprays per nostril twice daily, 2) azelastine 2 sprays per nostril twice daily and fexofenadine 60 mg twice daily, or 3) placebo given twice daily.[207] All patients were given a 1-week run-in with fexofenadine 60 mg twice daily. Patients who improved < 33% were randomized to 1 of the 3 regimens. After 14 days of treatment, the azelastine and azelastine plus fexofenadine groups showed greater improvement in Total Nasal Symptom Score (TNSS) than placebo ($p=0.007$). Azelastine alone was as effective as azelastine plus fexofenadine.

azelastine versus azelastine (Astepro)

A randomized, double-blind, parallel-group study containing 835 patients with seasonal allergic rhinitis was performed to compare the efficacy of reformulated azelastine nasal spray (Astepro) to the original azelastine formulation (Astelin®) and to determine if a dose-response relationship existed.[208] The patients were randomized into 6 groups: original azelastine nasal spray, 1 spray per nostril twice daily; reformulated azelastine, 1 spray per nostril twice daily; placebo nasal spray, 1 spray per nostril twice daily; original azelastine nasal spray, 2 sprays per nostril twice daily; reformulated azelastine nasal spray, 2 sprays per nostril twice daily; and placebo nasal spray, 2 sprays per nostril twice daily. The study concluded the original and reformulated azelastine products had comparable improvements in the 12-hour reflective TNSS in both dosages after 14 weeks. Patients treated with original ($p\leq0.01$) and reformulated azelastine ($p\leq0.001$) nasal spray groups at dosages of 2 sprays per nostril twice daily had a change in TNSS baseline that was statistically superior to placebo (23.5%, 27.9%, and 15.4%, respectively). However, the original and reformulated azelastine nasal spray groups dosed at 1 spray per nostril were not statistically significant compared to placebo which was attributed to an abnormally high placebo response rate (19%). The study further determined a TNSS dose-response difference favoring the higher dosages existed. The incidence of adverse effects was low for 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-response difference was present.

azelastine versus fluticasone propionate

In a double-blind, placebo-controlled, parallel-group trial, 610 patients (≥ 12 years old) with moderate-to-severe SAR were randomized to receive azelastine (137 mcg/spray) or fluticasone propionate (50 mcg/spray), both given as 1 spray/nostril twice daily.[209] The primary efficacy measure was change from baseline in reflective TNSS (rTNSS) (morning and evening) over 14 days. Reflective total ocular symptom score (rTOSS), reflective total of seven symptom scores (rT7SS [nasal plus ocular symptoms]), and time to ≥ 50% reduction from baseline in these parameters were secondary measures. Both drugs reduced rTNSS from baseline by a similar degree (-3.25 versus -3.84; p=0.2014). Patients experienced comparable improvement in rTOSS (-2.62 versus -2.17; p=0.2371) and rT7SS (-5.83 versus -6.05; p=0.7820). Fluticasone propionate was favored over azelastine in alleviating rhinorrhea (-1.15 versus -0.87; p=0.0433), but azelastine showed comparable efficacy for all other nasal and ocular symptoms. There was no clinically or statistically significant difference between azelastine (-1.17) and fluticasone propionate (-1.43) for reduction in the overall rhinitis quality of life questionnaire score, although fluticasone propionate, but not azelastine, significantly differed from placebo. A similar proportion of patients in the azelastine and fluticasone propionate groups achieved a 50% reduction in rTNSS. However, more azelastine patients (53%) exhibited a 50% reduction in rTOSS by day 14 than FP patients (40%), and this endpoint occurred at least 3 days earlier with azelastine (p=0.028).

azelastine / fluticasone propionate (Dymista) versus azelastine versus fluticasone versus placebo

Adults and children 12 years and older (n=853) with seasonal allergic rhinitis were enrolled in 3 randomized, double-blind, placebo- and active-controlled, parallel-group trials.[210] Patients were randomized to 1 spray twice daily of azelastine/fluticasone propionate combination nasal spray, azelastine nasal spray, fluticasone propionate nasal spray, or vehicle placebo. In all 3 trials, combination therapy demonstrated statistically significant greater decreases in rTNSS (-5.6 versus -4.3 versus -4.7 versus -2.9, respectively; p≤0.002 for all) and instantaneous TNSS (iTNSS) (-5.2 versus -3.9 versus -4.5 versus -2.7, respectively; p<0.001 for all) as compared to azelastine hydrochloride and to fluticasone propionate, as well as to placebo.

fluticasone furoate (Flonase Sensimist Allergy Relief) versus fluticasone propionate (Flonase)

A randomized, placebo-controlled, double-blind, crossover study was conducted in 360 patients with seasonal allergic rhinitis symptoms to compare patient preference for fluticasone furoate and fluticasone propionate nasal sprays after 1 week of treatment.[211] Patients were randomized to active treatment (fluticasone furoate 110 mcg or fluticasone propionate 200 mcg, followed by crossover treatment for 1 week each) or matched placebo sequence with a 1-week washout before crossover dosing. The primary efficacy endpoints were measured by change from baseline during 1 week in daily rTNSS that assessed severity of rhinorrhea, nasal congestion, nasal itching, and sneezing. Patient preference was assessed at the end of the study by questionnaire. Both fluticasone furoate and fluticasone propionate reduced the daily rTNSS compared with their respective placebos (least squares mean [SD] difference, -0.8 [0.24], p<0.001, and -0.6 [0.24], p=0.01, respectively). More patients (p<0.001) preferred fluticasone furoate to fluticasone propionate based on attributes of scent or odor

(58% versus 27%), aftertaste (60% versus 18%), leaking out of the nose and down the throat (59% versus 21%), and mist gentleness (57% versus 26%). However, there were no statistically significant differences seen in preferences regarding ease of use, delivery method, or device comfort.

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

A study was conducted as a phase 3, multicenter, randomized, double-blind, active and placebo-controlled parallel group study.[212] It included 544 individuals who were ≥ 12 years of age with a history of seasonal allergic rhinitis and verified allergy to a prevalent local allergen. Efficacy was assessed by changes in mean daily 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 2 sprays in each nostril twice daily for 16 days. The mean reductions from baseline in reflective TNSS were 26.8% with olopatadine, 29.9% with azelastine, and 18.4% 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% versus 19.7%, respectively; p=0.05). Both active treatments were well tolerated.

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

A 2-week double-blind, randomized, 2-arm parallel-group, noninferiority trial was conducted comparing olopatadine nasal spray 0.6% (2 sprays per nostril twice daily) to fluticasone nasal spray 50 mcg (2 sprays per nostril once daily) for the treatment of seasonal allergic rhinitis.[213] Symptomatic patients (n=130) were equally divided between the 2 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 2-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% and 47.4%, respectively.

olopatadine hydrochloride/mometasone furoate nasal spray (Ryaltris)

The efficacy of olopatadine/mometasone nasal spray was evaluated in 2 similarly designed double-blind, placebo-and active-controlled clinical studies in a total of 2,352 patients ≥ 12 years of age with seasonal allergic rhinitis.[214,215] In both studies (Study 1 [NCT02631551] and Study 2 [NCT02870205]) patients randomized 1:1:1:1 to one of 4 treatment groups: olopatadine/mometasone (665 mcg/25 mcg per spray), olopatadine hydrochloride nasal spray (665 mcg per spray), mometasone furoate (25 mcg per spray), or vehicle placebo, each administered as 2 sprays per nostril twice daily for 2 weeks. The olopatadine hydrochloride and mometasone furoate comparators used the same device and vehicle as the combination product but were non-US approved drugs. The primary endpoint for both studies was the change from baseline in average morning (AM) and evening (PM) patient-reported 12-hour reflective total nasal symptom score (rTNSS) over the 2-week treatment period. In Study 1, olopatadine/mometasone significantly improved average AM and PM rTNSS compared to placebo (least squares mean difference [LSMD], -0.98 [95% CI, -1.38 to -0.57]; p<0.001) and olopatadine monotherapy (LSM difference, -0.61 [95% CI, -1.01 to -0.21]; p=0.003), and approached statistical significance versus mometasone (LSM difference, -0.39 [95% CI, -0.79 to 0.01]; p=0.059). The combination therapy also significantly improved average AM and PM the instantaneous Total Nasal

Symptom Score (iTNSS) over the 2-week period compared to placebo and both monotherapies (p<0.05 for all). In Study 2, olopatadine/mometasone significantly improved average AM and PM rTNSS compared to placebo (LSMD, -1.09 [95% CI, -1.49 to -0.69]; p<0.001) and olopatadine monotherapy (LSM difference, -0.44 [95% CI, -0.84 to -0.05]; p=0.03), and mometasone monotherapy (LSM difference, -0.47 [95% CI, -0.86 to -0.08]; p=0.02). The combination therapy also significantly improved average AM and PM the iTNSS over the 2-week period compared to placebo and both monotherapies (p<0.05 for all). Across both studies, onset of action for olopatadine/mometasone was seen within 15 minutes of administration and maintained for up to 4 hours.

Perennial Allergic Rhinitis

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

In a multicenter randomized trial, ipratropium nasal spray 0.03% (42 mcg 3 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.[216] 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 4 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 propionate (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 3 months.[217] 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% with mometasone, 39% to 60% with fluticasone, and 22% to 39% 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 4 days with placebo. At the end of the 3-month treatment period, the percentage of patients classified as having complete or marked relief was 69% with mometasone, 60% with fluticasone, and 36% with placebo.

In a prospective, controlled study, 94 patients aged 6 to 12 years were randomized to receive 100 mcg mometasone nasal spray (1 spray/nostril) daily or 100 mcg fluticasone propionate nasal spray (1 spray/nostril) daily for 4 weeks.[218] The patients, with parental assistance as needed, completed the Pediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ). Physical examinations, nasal smears for eosinophil percent, and nasal-peak expiratory flow rate (nPEFR) tests were performed. Patients' total symptom score (TSS) was the sum of the 8 recorded symptom scores. An independent-sample *t* test was used to compare the rate of improvement in the mean nasal PEFR, the mean PRQLQ score (for each question), and the mean TSS for the 2 groups. Baseline TSS and each symptom score were calculated as the mean of the daily scores during the baseline period of 7 days. Patients in the mometasone group exhibited a significant improvement in their TSS (t = -2.65, p<0.05). A detailed TSS analysis showed mometasone to be more effective for relieving nasal symptoms, whereas fluticasone propionate was more effective for relieving non-nasal symptoms. Patient questionnaire scores

suggested a significant reduction in symptoms for both the mometasone (t = -7.23, p<0.01) and fluticasone propionate (t = -5.43, p<0.01) groups.

META-ANALYSES

A Cochrane review of 18 randomized, controlled trials compared the use of intranasal corticosteroids to placebo or no intervention in patients with chronic rhinosinusitis (n=2,738).[219] Fourteen studies included participants with nasal polyps and only 1 study evaluated the benefit in children. In general, available data were heterogenous, limiting conclusions. One study reported no significant difference in health-related quality of life (HRQoL) as measured by the Rhinosinusitis Outcome Measures 31 (RSOM-31). Another study found no significant difference in disease severity as measured by the Chronic Sinusitis Survey (range, 0 to 100; mean difference [MD], 2.84; 95% CI, -5.02 to 10.7). However, another study did find an improvement in disease severity as measured by proportion of improvement on global symptom score (relative risk [RR], 2.78; 95% CI, 1.76 to 4.4). Regarding symptoms measured by the European Position Paper on Rhinosinusitis (nasal blockage, rhinorrhea, loss of sense of smell, and facial pain/pressure), 2 studies evaluated all 4 symptoms with an average MD from baseline of -0.26 with inhaled corticosteroids compared to placebo (95% CI, -0.37 to -0.15). When only rhinorrhea and nasal blockage were considered, the authors found a MD of -0.31 (95% CI, -0.38 to -0.24; 2 studies). Significant differences were also found in the effect size of the individual symptoms; however, the overall quality of evidence was considered moderate to low. Notably, the authors also found an increased risk in epistaxis (risk ratio [RR], 2.74; 95% CI, 1.88 to 4; 13 studies). No statistically significant difference was found in local irritation. No studies provided meaningful data regarding the risk of osteoporosis or stunted growth in children. The authors concluded that there was little information regarding the effect of intranasal corticosteroids on quality of life and moderate- to low-quality data on disease severity impact.

A second Cochrane review of 9 randomized, controlled trials assessed the comparative efficacy of intranasal corticosteroids (n=911). No studies evaluated disease-specific HRQoL.[220] Regarding studies comparing fluticasone propionate to beclomethasone dipropionate, no numerical data were sufficient to find differences in 2 small studies. Regarding studies comparing fluticasone propionate to mometasone furoate, no numerical data were sufficient to find a difference in 1 study. Five studies compared low versus high dose corticosteroids (3 mometasone furoate, 2 fluticasone propionate) reporting greater improvement in nasal polyp score with high-dose intranasal corticosteroids; however, the improvements were small in size and may not be clinically significant. Likewise, epistaxis (defined broadly across studies) was more common in those treated with high-dose intranasal corticosteroid (RR, 2.06; 95% CI, 1.2 to 3.54). The authors concluded that there was no sufficient evidence to suggest that any 1 intranasal corticosteroid is superior to another for the treatment of chronic rhinitis.

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 American Academy of Allergy, Asthma and Immunology (AAAAI), American Academy of Otolaryngology – Head and Neck Surgery, and the Institute for Clinical Systems Improvement (ICSI). 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 (generics) and olopatadine (Patanase), offer an alternative to intranasal corticosteroids, oral antihistamines, and intranasal ipratropium for treatment of allergic rhinitis. Intranasal products that combine an antihistamine with a corticosteroid are also available and include azelastine/fluticasone (Dymista) and olopatadine/mometasone (Ryaltris). Factors limiting use of intranasal azelastine and olopatadine include route of administration and taste perversion.

Ipratropium nasal spray 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 allergic and nonallergic perennial rhinitis with rhinorrhea as the predominant symptom.

Triamcinolone nasal spray (Nasacort Allergy 24HR), fluticasone furoate (Flonase Sensimist Allergy Relief), fluticasone propionate nasal spray (Flonase Allergy Relief), and budesonide nasal spray (Rhinocort Allergy) are intranasal corticosteroids available without a prescription. In 2021, the FDA approved an over-the-counter version of azelastine nasal spray 0.15% (Astepro Allergy). Once available, it will be the only intranasal antihistamine available without a prescription. Generic prescription formulations of the 0.15% strength remain available, and the 0.1% strength remains prescription only.

Other therapies available include hypromellose (Alzair) which provides a gel-like barrier against air borne allergens and may be used as primary or adjunctive therapy in allergic rhinitis. Additionally, mometasone (Sinuva) corticosteroid-eluting agent is approved for use in adult patients with nasal polyps.

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