Therapeutic Class Overview
Intranasal Allergic Rhinitis Agents

INTRODUCTION

- Allergic rhinitis (AR) is an inflammatory, immunoglobulin E (IgE)-mediated disease characterized by nasal congestion, rhinorrhea, sneezing, and/or nasal itching. It is generally viewed as either seasonal AR (SAR) or perennial AR (PAR). SAR is caused by seasonal aeroallergens, such as pollens, and PAR is caused by year-round environmental aeroallergens such as dust mites, mold, animal allergens, or occupational allergens (*Seidman et al 2015*). AR is common, affecting 10% to 30% of adults and up to 40% of children in the United States (US) (*Wallace et al 2008*).
- Pharmacologic therapy for AR includes antihistamines (intranasal [IN] and oral), decongestants (IN and oral), corticosteroids (IN and oral), IN cromolyn, IN anticholinergics, and oral leukotriene receptor antagonists (LTRAs) (*Dykewicz et al 2017*).
- IN treatments are often selected over oral therapies based on their high effectiveness and targeted local effects (*Wallace et al 2008, Seidman et al 2015*).
  - IN corticosteroids are generally considered the most effective class of medications for controlling AR symptoms.
  - IN antihistamines are an additional option for the treatment of AR and may be considered for first-line use.
  - IN anticholinergics reduce rhinorrhea but are not effective for other AR symptoms.
  - Clinicians may offer combination therapy to patients with an inadequate response to monotherapy.
- Vasomotor rhinitis is a type of nonallergic (non-IgE-mediated) rhinitis (*Wallace et al 2008*). Symptoms are similar to those of AR and include sneezing, congestion, and runny nose, although itchy nose, eyes, and throat are typically absent. Symptoms of vasomotor rhinitis can be triggered by airborne pollutants or odors, certain foods and medications, changes in the weather, or underlying health problems (*American Academy of Allergy, Asthma & Immunology [AAAAI] 2019*). IN corticosteroids, IN antihistamines, and IN anticholinergics are effective for vasomotor rhinitis (*Wallace et al 2008*).
- Nasal polyps are soft, painless growths on the lining of nasal passages or sinuses, which result from chronic inflammation due to asthma, infection, allergies, drug sensitivity, or immune disorders (*Mayo Clinic 2018*). Nasal polyps often occur in the setting of chronic rhinosinusitis. Larger polyps may lead to symptoms such as blocked nasal passages, breathing problems, reduced sense of smell, and infections. Medications such as IN corticosteroids can shrink or eliminate nasal polyps; however, surgical removal is sometimes necessary. Nasal polyps often return after treatment.
- Effectiveness is often evaluated with the use of the total nasal symptom score (TNSS). Although there is some variability in specific studies, the TNSS is typically the sum of individual symptom scores for nasal itching, rhinorrhea, sneezing, and nasal congestion. Symptoms are often rated on a scale of 0 (none) to 3 (severe), and twice-daily scores may be summed or averaged, so the score range may be 0 to 12 or 0 to 24 depending on the study design. A minimum clinically important difference in TNSS has not been definitively established (*Glacy et al 2013, Meltzer et al 2016*).
- This therapeutic class overview includes IN corticosteroids, IN antihistamines, and IN anticholinergics. Specific products are listed in Table 1. Note that in some cases, there is more than one brand name for the same chemical entity.
- Most products are formulated as aqueous nasal sprays. One product, Xhance (fluticasone propionate), uses a novel delivery system containing a nosepiece and a mouthpiece; it uses the patient's exhaled breath to facilitate delivery of drug deep into the nasal passages. Two products, Qnasl (beclomethasone dipropionate) and Zetonna (ciclesonide), are formulated as nasal aerosols.
- Several products formerly available by prescription are now available solely as over-the-counter (OTC) products. These products include: fluticasone furoate (Flonase Sensimist, formerly marketed as the prescription product Veramyst), budesonide (Rhinocort Allergy, formerly marketed as the prescription product Rhinocort Aqua), and triamcinolone acetonide (Nasacort Allergy 24hr, formerly marketed as the prescription product Nasacort AQ). Fluticasone propionate is available as a prescription product (generic only; the brand is no longer marketed) and an OTC product (Flonase Allergy Relief).
- Medispan classes: Nasal Steroids; Nasal Antiallergy; Nasal Agent Combination; Nasal Anticholinergics

Table 1. Medications Included Within Class Review

Drug	Generic Availability
IN corticosteroids	
Beconase AQ (beclomethasone dipropionate monohydrate)	-
Flonase Sensimist (fluticasone furoate)*	-
Flonase Allergy Relief (fluticasone propionate)†‡	✔
Flunisolide†	✔
Nasacort Allergy 24 hr (triamcinolone acetonide)*	✔
Nasonex (mometasone furoate monohydrate)	✔
Omnaris (ciclesonide)	-
Qnasl (beclomethasone dipropionate)	-
Rhinocort Allergy (budesonide)*	✔
Xhance (fluticasone propionate)	-
Zetonna (ciclesonide)	-
IN antihistamines	
Astepro (azelastine§)	✔
Azelastine†‖	✔
Patanase (olopatadine hydrochloride)	✔
IN antihistamine/corticosteroid combination	
Dymista (azelastine hydrochloride/fluticasone propionate)	-
IN anticholinergics	
Ipratropium†	✔

*The following products are currently available as nonprescription/OTC products only: fluticasone furoate (Flonase Sensimist, formerly marketed as the prescription product Veramyst), budesonide (Rhinocort Allergy, formerly marketed as the prescription product Rhinocort Aqua), and triamcinolone acetonide (Nasacort Allergy 24hr, formerly marketed as the prescription product Nasacort AQ).
† Brand prescription product no longer marketed, but generic is available. The reference brand names were Astelin (azelastine 0.1%), Atrovent (ipratropium bromide), Flonase (fluticasone propionate), and Nasalide (flunisolide).
‡ Fluticasone propionate is available both as a prescription product (fluticasone propionate) and as an OTC product (Flonase Allergy Relief). Both the prescription and OTC products are available generically.
§ The 0.15% strength of Astepro is available as a brand and a generic; a 0.1% strength was also FDA-approved but is not currently marketed.
‖ Generic Astelin (azelastine 0.1%)

(*Drugs@FDA 2019, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2019*)

INDICATIONS

- An overview of the indications for the prescription IN corticosteroids, antihistamines, and anticholinergics is provided in Table 2. Additional detail on the indication(s) for each product is provided in the box following the table. Information from the Pediatric Use section of the prescribing information was included when the recommended age range was not specified in the indication.

Table 2. Indications for IN Corticosteroids, Antihistamines, and Anticholinergics*

Indication	Corticosteroids												Antihistamines			Other	
	Beconase AQ	Flonase Sensimist†	Flunisolide	Flonase Allergy Relief	Fluticasone propionate	Nasacort Allergy 24 hr†	Nasonex	Omnaris	Qnasl	Rhinocort Allergy†	Xhance	Zetonna	Astepro	Azelastine	Patanase	Dymista	Ipratropium
Seasonal Allergic Rhinitis (SAR)	✔		✔				✔	✔	✔			✔	✔	✔	✔	✔	✔
Perennial Allergic Rhinitis (PAR)	✔		✔				✔	✔	✔			✔	✔				✔
Vasomotor/Nonallergic Rhinitis	✔				✔									✔			✔
Nasal Polyps (Treatment or Prevention)	✔						✔				✔						
Rhinorrhea Associated with Common Cold																	✔
Relief from symptoms of hay fever or other upper respiratory allergies		✔		✔		✔				✔							

† Available as OTC only

***Notes: Additional Detail on Indications**

- **Beconase AQ (beclomethasone dipropionate monohydrate):**
  - Relief of the symptoms of seasonal or perennial allergic and nonallergic (vasomotor) rhinitis
  - Prevention of recurrence of nasal polyps following surgical removal
  - Safety and effectiveness established in children aged ≥ 6 years
- **Flunisolide:**
  - Treatment of the nasal symptoms of seasonal or perennial rhinitis
  - Not recommended for use in pediatric patients aged < 6 years as safety and efficacy have not been assessed in this age group
- **Flonase Allergy Relief (fluticasone propionate OTC):**
  - Relief of symptoms of hay fever or other upper respiratory allergies
  - Not recommended for use in pediatric patients aged < 4 years
- **Flonase Sensimist (fluticasone furoate OTC):**
  - Relief of symptoms of hay fever or other upper respiratory allergies
  - Not recommended for use in pediatric patients aged < 2 years
- **Fluticasone propionate:**
  - Management of the nasal symptoms of perennial nonallergic rhinitis in adults and pediatric patients aged ≥ 4 years
- **Nasacort Allergy 24 hr (triamcinolone acetonide OTC):**
  - Relief of symptoms of hay fever or other upper respiratory allergies
  - Not recommended for use in pediatric patients aged < 2 years
- **Nasonex (mometasone furoate monohydrate):**
  - Treatment of the nasal symptoms of SAR and PAR in adults and pediatric patients aged ≥ 2 years
  - Relief of nasal congestion associated with SAR in adults and pediatric patients aged ≥ 2 years

- Prophylaxis of the nasal symptoms of SAR in adult and adolescent patients aged ≥ 12 years
- Treatment of nasal polyps in patients aged ≥ 18 years

- **Omnaris (ciclesonide):**
  - Treatment of nasal symptoms associated with SAR in adults and children aged ≥ 6 years
  - Treatment of nasal symptoms associated with PAR in adults and adolescents aged ≥ 12 years
- **Qnasl (beclomethasone dipropionate):**
  - Treatment of the nasal symptoms associated with SAR and PAR in patients aged ≥ 4 years
- **Rhinocort Allergy (budesonide OTC):**
  - Relief of symptoms of hay fever or other upper respiratory allergies
  - Not recommended for use in pediatric patients aged < 6 years
- **Xhance (fluticasone propionate):**
  - Treatment of nasal polyps in patients aged ≥ 18 years
- **Zetonna (ciclesonide):**
  - Treatment of symptoms associated with SAR and PAR in adults and adolescents aged ≥ 12 years
- **Astepro (azelastine):**
  - Relief of the symptoms of SAR and PAR in patients aged ≥ 6 years
    - The prescribing information for brand-name Astepro notes that the approved age range is ≥ 2 years for SAR and ≥ 6 months for PAR; however, the lower, 0.1% strength is recommended for patients aged < 6 years and this strength is no longer marked as a brand.
    - An authorized generic for Astepro 0.15% is marketed by Wallace Pharmaceuticals; its indication is for the relief of the symptoms of SAR and PAR in patients aged ≥ 6 years.
- **Azelastine (0.1%; generic Astelin):**
  - Treatment of the symptoms of SAR in adults and pediatric patients aged ≥ 5 years, and for the treatment of the symptoms of vasomotor rhinitis in adults and adolescent patients aged ≥ 12 years
- **Patanase:**
  - Relief of the symptoms of SAR in adults and children aged ≥ 6 years
- **Dymista (azelastine hydrochloride/fluticasone propionate):**
  - Relief of symptoms of SAR in patients aged ≥ 6 years who require treatment with both azelastine hydrochloride and fluticasone propionate for symptomatic relief
- **Ipratropium:**
  - **0.03% spray**: Symptomatic relief of rhinorrhea associated with allergic and nonallergic perennial rhinitis in adults and children aged ≥ 6 years
  - **0.06% spray**: Symptomatic relief of rhinorrhea associated with the common cold or SAR for adults and children aged ≥ 5 years

(*Prescribing information: Astepro 2018, Azelastine [Amneal] 2018, Azelastine [Wallace] 2015, Beconase AQ 2019, Dymista 2018, Flonase Allergy Relief 2018, Flonase Sensimist 2018, Flunisolide 2016, Fluticasone propionate 2019, Ipratropium [0.03%] 2016, Ipratropium [0.06%] 2016, Nasacort Allergy 24 hr 2018, Nasonex 2018, Omnaris 2018, Patanase 2015, Qnasl 2018,Rhinocort Allergy 2016, Xhance 2018, Zetonna 2018)*

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

IN Corticosteroids

- Daily administration of IN corticosteroids is associated with statistically significant improvements in allergy-related TNSS and health-related quality of life (QoL) scores. Numerous head-to-head clinical trials comparing the available IN corticosteroids have generally demonstrated no significant clinical differences among the available IN corticosteroids with regard to efficacy. Some studies have reported differences in sensory perceptions and patient preference with 1 agent compared to another. Patients administering the agents noted differences in odor, aftertaste, and severity of irritation; however, these differences were not associated with differences in efficacy between the agents (*Aasand et al 1982, Al-Mohaimeid 1993, Andersson et al 1995, Bachert et al 2002, Berger et al 2003, Day et al 1998, Drouin et al*

1996, Graft et al 1996, Gross et al 2002, Haye et al 1993, Hebert et al 1996, Khanna et al 2005, Karaulov et al 2019, LaForce et al 1994, Langrick 1984, Lumry et al 2003, Mak et al 2013, Mandl et al 1997, McAllen et al 1980, McArthur 1994, Meltzer et al 2005, Meltzer et al 2008, Meltzer et al 2010, Naclerio et al 2003, Ratner et al 1992, Sahay et al 1980, Shah et al 2003, Sipila et al 1983, Small et al 1997, Stern et al 1997, Stokes et al 2004, Svendsen et al 1989, Van As et al 1993, Vanzieleghem et al 1987, Varshney et al 2012, Welsh et al 1987, Winder et al 1993, Yonezaki et al 2016).

- IN corticosteroid aerosol formulations have been demonstrated to be significantly more effective compared to placebo. Aerosol formulations may be associated with increased retention of medication in the nasal cavity and decreased dripping from the nose and deposition in the back of the throat compared to aqueous formulations (*Leach et al 2015*). However, data on effectiveness vs traditional spray formulations are lacking.
  - Beclomethasone:
    - In a 6-week study of patients with PAR, aerosolized beclomethasone significantly improved reflective TNSS compared to placebo (-2.46 vs -1.63; p < 0.001). Furthermore, beclomethasone was associated with a statistically significant improvement in QoL score compared to placebo (p = 0.001) (*Meltzer et al 2012[a]*).
    - A 2-week study of beclomethasone nasal aerosol 80 mcg daily in pediatric patients 6 to 11 years of age with SAR also demonstrated improvement in reflective TNSS compared to placebo (-1.9 vs -1.2; p < 0.001) (*Storms et al 2013*).
    - A 12-week study of beclomethasone nasal aerosol 80 mcg daily in pediatric patients 4 to 11 years of age with PAR demonstrated improvement in both reflective and instantaneous TNSS compared to placebo (mean treatment differences, -0.53 [p = 0.009] and -0.52 [p = 0.008], respectively) (*Berger et al 2015*).
  - Ciclesonide:
    - A meta-analysis of 8 studies (4,039 patients) evaluating ciclesonide vs placebo for PAR found that ciclesonide was associated with significant reductions in the reflective and instantaneous TNSS,as well as the reflective nasal symptom score (rNSS) subtotal compared to placebo, with no difference in treatment-emergent adverse events (AEs) (*Yang et al 2018*).
    - Ciclesonide administered at a daily dose of 80 mcg or 160 mcg reduced reflective TNSS by 15.1 and 16%, respectively, compared to 3.7% with placebo (p < 0.001 for both). In addition, significant improvements were observed with both doses of ciclesonide compared to placebo with regard to ocular symptom scores and QoL (p < 0.001 for both) (*Ratner et al 2010*).
    - Similar improvements in outcomes were reported in additional studies of up to 26 weeks duration (*Berger et al 2012, LaForce et al 2009, Mohar et al 2012, Ratner et al 2012*).
- The approval of Xhance (fluticasone propionate) for the treatment of nasal polyps was based on two 16-week, randomized, placebo-controlled trials (*Leopold et al 2019, Sindwani et al 2019*). Adults with nasal polyps and associated moderate to severe nasal congestion showed improvement in nasal congestion/obstruction and bilateral polyp grade when treated with fluticasone propionate using the Xhance delivery device. Published data from 1 of the 2 studies demonstrated that improvements in symptoms and polyp grade continued to increase with an additional 8 weeks of open-label treatment (*Leopold et al 2019*). Use of Xhance was also shown to improve chronic rhinosinusitis symptoms and polyp grade in a 12-month open-label trial, and the product was well tolerated over this time period (*Palmer et al 2018*). However, data are not available comparing Xhance to fluticasone propionate (or other corticosteroids) in a traditional nasal spray formulation.
- Two meta-analyses have reviewed information on the use of IN corticosteroids for treatment of chronic rhinosinusitis with or without nasal polyps.
  - A meta-analysis of 18 randomized trials (N = 2738) reviewed the use of IN corticosteroids vs placebo or no intervention, and demonstrated that IN corticosteroids improved symptoms, including a moderate-sized benefit for nasal blockage and a small benefit for rhinorrhea (*Chong et al 2016[a]*). Little information on QoL was available.
  - A meta-analysis of 9 randomized trials (N = 911) found insufficient evidence to suggest differences in efficacy among different IN corticosteroids or between a spray and an aerosol (*Chong et al 2016[b]*). Lower doses appeared to have similar effectiveness and fewer side effects than higher doses.

IN Antihistamines

- IN azelastine has been shown to be safe and effective over 14 days of treatment in placebo-controlled trials (*Howland et al 2011, Lumry et al 2007, van Bavel et al 2009*).
- When azelastine 0.1% and azelastine 0.15% were compared to placebo in a 2-week trial, there was a significantly greater improvement in TNSS for both concentrations vs placebo (p < 0.001). In a retrospective analysis, there was a

statistically significant difference in favor of azelastine 0.15% compared to azelastine 0.1% (p = 0.047) (*Shah et al 2009[a]*).

- IN olopatadine has been proven safe and effective in placebo-controlled trials across a range of doses (*Fairchild et al 2007, Hampel et al 2006, Meltzer et al 2005, Meltzer et al 2011, Patel et al 2007, Ratner et al 2005*).
- Head-to-head studies have not demonstrated any statistically significant differences in efficacy between azelastine and olopatadine (*Lieberman et al 2011, Shah et al 2009[b]*).
  - In patients with SAR, azelastine 0.1% and olopatadine 0.6% reduced symptom scores to a similar extent in a 16-day trial. Tolerability was similar between agents, with the exception of the prevalence and intensity of bitter taste, which were lower with olopatadine (*Shah et al 2009[b]*).
  - In patients with vasomotor rhinitis, both azelastine 0.1% and olopatadine 0.6% significantly reduced symptom scores from baseline in a 2-week clinical trial; the difference between treatments was not statistically significant. The overall incidence of AEs was similar between the 2 groups. The most common AE was taste disturbance, which was reported in 10.3% and 5.3% of patients in the azelastine and olopatadine groups, respectively (*Lieberman et al 2011*).
- In a single-dose crossover study evaluating sensory attributes, 60.6% of patients favored olopatadine, 30.3% favored azelastine, and 9.2% had no preference. Mean patient preference was significantly greater with olopatadine than azelastine for overall aftertaste, overall preference, and likelihood of use (*Meltzer et al 2008*).

IN Anticholinergics

- For the common cold, ipratropium bromide nasal spray has been shown to reduce the severity of rhinorrhea compared to placebo or no treatment, although it had no effect on nasal congestion. Overall, nasal dryness was the most common AE reported (*AlBalawi et al 2013, Diamond et al 1995, Dockhorn et al 1992, Eccles et al 2007, Hayden et al 1996*).
- For the treatment of perennial allergic or nonallergic rhinitis, ipratropium bromide has been shown to significantly reduce the severity and duration of rhinorrhea compared to no treatment or placebo (*Bronsky et al 1995, Dockhorn et al 1999, Georgitis et al 1994, Kaiser et al 1998, Meltzer et al 1997*). Nasal congestion was not significantly improved.

Combination Therapy and Comparisons Among Different Drug Classes

- The Agency for Healthcare Research and Quality (AHRQ) published a comparative effectiveness review of pharmacological therapies for the treatment of SAR (*Glacy et al 2013*). A total of 59 randomized controlled trials met inclusion criteria to compare agents of 6 classes for relative efficacy. Agents included oral and IN antihistamines and decongestants, IN corticosteroids, leukotriene modifiers, cromolyn, ipratropium, and normal saline. Overall, there was insufficient evidence to draw a conclusion about relative efficacy among most of the agents used for the treatment of SAR. For a few comparisons, sufficient evidence was available to draw a conclusion. Oral selective antihistamines and montelukast were equivalent for efficacy in reducing nasal and eye symptoms. Montelukast was superior to oral selective antihistamines for controlling asthma symptoms. IN antihistamines and IN corticosteroids had equivalent efficacy for nasal and eye symptoms. Similarly, montelukast was comparable to IN corticosteroids for nasal symptoms. The combination of IN antihistamines and IN corticosteroids demonstrated equivalent efficacy in nasal and eye symptom resolution compared to either monotherapy. For children, conclusions about relative efficacy were not determined due to insufficient evidence.
- A systematic review and meta-analysis evaluated results from 5 randomized trials that compared IN corticosteroids to oral antihistamines in patients with AR (*Juel-Berg et al 2017*). Results demonstrated that IN corticosteroids were superior to oral antihistamines for improving TNSS (difference, -0.70; 95% CI, -0.93 to -0.47). There was no difference in relief of ocular symptoms. Four additional trials were included in a narrative review, and results were consistent with studies in the meta-analysis.
- A meta-analysis compared azelastine hydrochloride nasal spray to other agents used in the management of SAR and PAR which included beclomethasone nasal spray and loratadine combination, terfenadine (not available in the US), oral cetirizine, budesonide nasal spray, ebastine (not available in the US), levocabastine (not available in the US), and oral loratadine (*Lee et al 2007*). Azelastine was demonstrated to improve symptoms compared to placebo. The analysis did not identify a statistically significant difference in treatment response for azelastine compared to active comparators, despite multiple analyses.
- A meta-analysis of 8 RCTs in patients with allergic rhinitis found that combination therapy with intranasal fluticasone propionate and azelastine led to significantly greater reductions in TNSS from baseline compared to placebo or monotherapy with either agent (*Debbaneh et al 2019*).

- The combination of azelastine hydrochloride with fluticasone propionate nasal spray was significantly more effective compared to the individual agents in various symptom scores in a 2-week, multicenter, double-blind, randomized trial (*Ratner et al 2008*). The improvement in TNSS from baseline was 37.9% for combination therapy compared to 27.1% and 24.8%, respectively, with single-entity fluticasone and azelastine ($p < 0.05$ for the combination vs either agent alone).
- Other randomized trials comparing the combination of azelastine hydrochloride nasal spray and fluticasone propionate nasal spray have also demonstrated significant improvements in TNSS, individual symptom scores, and QoL ratings compared to each agent administered as monotherapy (*Carr et al 2012, Hampel et al 2010, Meltzer et al 2012[b], Ilyina et al 2019*).
- A randomized, active-controlled, open-label study demonstrated that long-term treatment with combination azelastine hydrochloride and fluticasone propionate nasal spray was well tolerated in adults and adolescents over a 1-year period (*Berger et al 2014*). Another randomized, active-controlled, open-label study demonstrated that this combination was safe and well tolerated in pediatric patients aged 4 to 11 years over a 3-month period (*Berger et al 2018*).

CLINICAL GUIDELINES

- The American Academy of Allergy, Asthma and Immunology (AAAAI) and the American College of Allergy, Asthma and Immunology (ACAAI) jointly published guidelines on the diagnosis and management of rhinitis in 2008, and a focused update on the treatment of SAR was published by these groups in 2017.
  - The 2008 guidelines note that (*Wallace et al 2008*):
    - IN corticosteroids are the most effective medication class for controlling symptoms of AR. They may also be useful in the treatment of some forms of nonallergic rhinitis.
    - When comparing the available IN corticosteroids, the overall clinical response does not appear to vary significantly between products.
    - IN antihistamines may be considered for use as first-line treatment for allergic and nonallergic rhinitis. However, IN antihistamines are generally less effective than IN corticosteroids for treatment of AR.
    - IN anticholinergics may effectively reduce rhinorrhea but have no effect on other nasal symptoms.
    - The concomitant use of ipratropium bromide nasal spray and an IN corticosteroid is more effective than administration of either drug alone in the treatment of rhinorrhea.
  - The 2017 focused update on treatment of SAR notes that, for the initial treatment of nasal symptoms of SAR (*Dykewicz et al 2017*):
    - For patients aged ≥ 12 years, clinicians should routinely prescribe monotherapy with an IN corticosteroid rather than a combination of an IN corticosteroid with an oral antihistamine.
    - For patients aged ≥ 15 years, clinicians should recommend an IN corticosteroid over an LTRA.
    - For moderate to severe symptoms in patients aged ≥ 12 years, clinicians may recommend the combination of an IN corticosteroid and an IN antihistamine.
- Guidelines on AR from the American Academy of Otolaryngology-Head and Neck Surgery Foundation note that (*Seidman et al 2015*):
  - Clinicians should recommend IN corticosteroids for patients with a clinical diagnosis of AR whose symptoms affect their QoL.
    - There are no significant differences in efficacy between the available agents. Sensory attributes, including aftertaste, nose runout, throat rundown, and smell, are an important factor in patient preference and adherence to therapy. Aerosol preparations may address some of these concerns.
    - Comparative studies have shown that IN corticosteroids are superior to oral antihistamines in controlling nasal symptoms, including nasal congestion, with no significant difference in the relief of ocular symptoms. IN corticosteroids are more effective than LTRAs across the range of allergy symptoms. However, IN antihistamines have a more rapid onset of action than IN corticosteroids in comparison studies.
    - In addition to improving nasal symptoms, IN corticosteroids have beneficial effects on allergic eye symptoms such as itching, tearing, redness, and puffiness.
  - Clinicians should recommend oral second-generation/less-sedating antihistamines for patients with AR and primary complaints of sneezing and itching.
  - Clinicians should not offer oral LTRAs as primary therapy for patients with AR.
  - Clinicians may offer IN antihistamines for patients with seasonal, perennial, or episodic AR.
    - IN antihistamines are an effective treatment for AR and can be used as first- or second-line therapy.

    - For the treatment of nasal symptoms, IN antihistamines have shown equality or superiority to oral antihistamines in numerous studies.
    - Azelastine and olopatadine have equal efficacy in head-to-head, placebo-controlled comparison studies.
  - Clinicians may offer combination pharmacologic therapy in patients with AR who have an inadequate response to pharmacologic monotherapy.
    - The most effective addition to an IN corticosteroid is an IN antihistamine.
- According to the International Consensus Statement on Allergy and Rhinitis for AR (*Wise et al 2018*):
  - IN corticosteroids:
    - Benefits: IN corticosteroids are effective in reducing nasal and ocular symptoms of AR. They have superior efficacy compared to oral antihistamines and LTRAs.
    - Harms/disadvantages: IN corticosteroids have undesirable local AEs such as epistaxis with prolonged administration. There might be some negative effects on short-term growth in children, but it is unclear whether these effects translate into long-term growth suppression.
    - Recommendation: IN corticosteroids are strongly recommended and should be used as first-line therapy for AR.
  - IN antihistamines:
    - Benefits: IN antihistamines have a rapid onset, are more effective for nasal congestion than oral antihistamines, are more effective for ocular symptoms than IN corticosteroids, and show consistent reduction in symptoms and improvement in QoL compared to placebo.
    - Harms/disadvantages: There are concerns for patient tolerability, especially due to taste. IN antihistamines are less effective for congestion than IN corticosteroids.
    - Recommendation: IN antihistamines are recommended and may be used as first-line or second-line therapy for AR.
  - IN anticholinergic (ie, ipratropium):
    - Benefits: Use of an IN anticholinergic reduces rhinorrhea.
    - Harms/disadvantages: Local side effects include nasopharyngeal irritation, burning, headache, pharyngitis, epistaxis, nasal dryness, nasal congestion, and dry mouth. Care should be taken to avoid overdosage leading to systemic side effects.
    - Recommendation: An IN anticholinergic is an option for the treatment of AR and may be considered as an adjunct to IN corticosteroids in PAR patients with uncontrolled rhinorrhea.
  - The combination of an IN corticosteroid and an IN antihistamine is strongly recommended when monotherapy fails to control AR symptoms.
  - Combinations of an oral antihistamine and an IN corticosteroid are an option, with the combination equivocal over either drug alone.
- Guidelines from Allergic Rhinitis and its Impact on Asthma (ARIA), a part of the European Forum for Research and Education in Allergy and Airway Diseases (EUFOREA), suggest the use of an IN corticosteroid over an IN antihistamine in patients with AR (SAR and PAR). No preference is stated for IN corticosteroid monotherapy vs IN corticosteroid/ IN antihistamine combination therapy or for IN antihistamine vs oral antihistamine (*Brozek et al 2017*).
- Joint guidelines on the diagnosis and management of rhinosinusitis are available from the AAAAI, the ACAAI, and the Joint Council of Allergy, Asthma, and Immunology (JCAAI) (*Peters et al 2014*). According to these guidelines:
  - IN corticosteroids (sprays and aerosols) have been extensively studied as a treatment for chronic rhinosinusitis with nasal polyps. Several different IN corticosteroids have been shown to be effective at decreasing nasal polyp size or preventing the regrowth of nasal polyps after surgical removal; however, head-to-head studies comparing different IN corticosteroids are not available.
  - The published studies have consistently shown IN corticosteroids to be superior to placebo for improving nasal patency, lessening nasal symptoms, decreasing polyp size, and improving QoL when used for 1 to 12 months; however, the magnitude of effect is variable.
  - The extent to which the use of IN corticosteroids prevents the need for sinus surgery or regrowth of nasal polyps is not well established.
- Joint guidelines from the European Rhinologic Society (ERS) and the European Academy of Allergy and Clinical Immunology (EAACI) also support the use of IN corticosteroids in the management of chronic rhinosinusitis with nasal polyps (*Fokkens et al 2012*). These guidelines state that “modern” IN corticosteroids (mometasone, fluticasone, and ciclesonide) do not have greater efficacy vs “first-generation” IN corticosteroids (budesonide, beclomethasone, betamethasone, triamcinolone, and dexamethasone), although they may have fewer AEs.

SAFETY SUMMARY

- IN corticosteroids
  - Key warnings and precautions among the IN corticosteroids include the following:
    - Local nasal effects, such as epistaxis, nasal ulceration, nasal septal perforation, *Candida albicans* infection of the nose or pharynx, and impaired wound healing
    - Development of glaucoma or cataracts
    - Hypersensitivity reactions, including angioedema, anaphylaxis, urticaria, contact dermatitis, hypotension, bronchospasm, and rash
    - Immunosuppression: potential worsening of existing tuberculosis; fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex; or more serious or even fatal course of chicken pox or measles in susceptible individuals
    - Hypercorticism and adrenal suppression
    - Potential reduction in growth velocity in children
  - Common AEs include cough, pharyngitis, nasal discomfort, headache, and epistaxis.
- IN antihistamines
  - Key warnings and precautions among the IN antihistamines include the following:
    - Local nasal effects, such as epistaxis and nasal ulcerations (olopatadine)
    - Activities requiring mental alertness: somnolence has been reported in some patients using olopatadine or azelastine
  - Common AEs with olopatadine include bitter taste, headache, epistaxis, pharyngolaryngeal pain, post-nasal drip, cough, urinary tract infection, upper respiratory tract infection, pyrexia, and rash.
  - Common AEs with azelastine include bitter taste, pyrexia, dysgeusia, nasal discomfort/burning, epistaxis, headache, sneezing, fatigue, somnolence, upper respiratory infection, cough, pharyngitis, rhinalgia, rhinitis, sinusitis, nausea/vomiting, dry mouth, fatigue, dizziness, otitis media, contact dermatitis, oropharyngeal pain, dysesthesia, and weight gain.
- IN anticholinergics
  - Key warnings and precautions for ipratropium nasal spray include the following:
    - Immediate hypersensitivity reactions, including urticaria, angioedema, rash, bronchospasm, anaphylaxis, and oropharyngeal edema
    - Anticholinergic effects; should be used with caution in patients with narrow-angle glaucoma, prostatic hyperplasia, or bladder neck obstruction, particularly if they are receiving an anticholinergic by another route
    - Temporary blurred vision, acute eye pain, and other ophthalmic or vision-related AEs may occur if ipratropium comes into direct contact with the eyes
    - Dizziness, accommodation disorder, mydriasis, and blurred vision may occur with use; patients should be cautioned about engaging in activities requiring balance and visual acuity
    - Has not been studied in patients with hepatic or renal insufficiency; should be used with caution in these populations
  - Common AEs with ipratropium bromide nasal spray include upper respiratory tract infection, epistaxis, pharyngitis, nasal symptoms (including dryness, congestion, and irritation), dry mouth/throat, and nausea.
- Dymista (azelastine hydrochloride and fluticasone propionate) contains an antihistamine and a corticosteroid; safety information for both classes applies to this product. The most common AEs are dysgeusia, epistaxis, and headache.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
IN corticosteroids				
Beconase AQ (beclomethasone dipropionate monohydrate)	Spray	Nasal	Twice daily	42 mcg/actuation

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Flonase Sensimist (fluticasone furoate)	Spray	Nasal	Once daily	27.5 mcg/actuation
Flunisolide	Spray	Nasal	2 or 3 times daily	25 mcg/actuation
Flonase Allergy Relief (fluticasone propionate)	Spray	Nasal	Once or twice daily	50 mcg/actuation
Nasacort Allergy 24 hr (triamcinolone acetonide)	Spray	Nasal	Once daily	55 mcg/actuation
Nasonex (mometasone furoate monohydrate)	Spray	Nasal	Once or twice daily	50 mcg/actuation
Omnaris (ciclesonide)	Spray	Nasal	Once daily	50 mcg/actuation
Qnasl (beclomethasone dipropionate)	Aerosol	Nasal	Once daily	Available in 2 strengths, 40 mcg/actuation (children aged 4 to 11 years) and 80 mcg/actuation (adults/adolescents)
Rhinocort Allergy (budesonide)	Spray	Nasal	Once daily	32 mcg/actuation
Xhance (fluticasone propionate)	Spray	Nasal	Twice daily	93 mcg/actuation; delivered into the nose by actuating the pump spray into 1 nostril while simultaneously blowing into the mouthpiece of the device
Zetonna (ciclesonide)	Aerosol	Nasal	Once daily	37 mcg/actuation
IN antihistamines				
Astepro (azelastine)	Spray	Nasal	Once or twice daily	Available in a 0.15% strength supplying 205.5 mcg/actuation (0.1% strength is not marketed)
Azelastine*	Spray	Nasal	Twice daily	0.1% strength supplying 137 mcg/actuation
Patanase (olopatadine hydrochloride)	Spray	Nasal	Twice daily	665 mcg/actuation
IN antihistamine/corticosteroid combination				
Dymista (azelastine hydrochloride/fluticasone propionate)	Spray	Nasal	Twice daily	137 mcg azelastine/50 mcg fluticasone propionate/actuation
IN anticholinergic				
Ipratropium	Spray	Nasal	2 to 4 times daily	Available in a 0.03% strength supplying 21 mcg/actuation and a 0.06% strength supplying 42 mcg/actuation; the 0.03% strength is given 2 or 3 times daily and the 0.06% strength is given 3 or 4 times daily

*Generic Astelin
See the current prescribing information for full details

CONCLUSION

- For the management of AR, IN therapies are often selected over oral therapies based on their high effectiveness and targeted local effects (*Seidman et al 2015*). IN corticosteroids are generally considered the most effective class of medications for controlling AR symptoms (*Wallace et al 2008*). IN antihistamines are an additional option for the treatment of AR and may be considered for first-line use. IN anticholinergics reduce rhinorrhea but are not effective for other AR symptoms (*Wallace et al 2008*).
- IN corticosteroids, antihistamines, and anticholinergics have demonstrated efficacy for their respective FDA-approved indications. Patients may have a preference for certain products based on sensory attributes, such as aftertaste, nose

runout, throat rundown, and smell. However, available evidence does not suggest that any specific agent is more effective than others within the same therapeutic class.

- Clinicians may offer combination therapy to patients with an inadequate response to monotherapy (*Wallace et al 2008*).

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Publication Date: June 25, 2019