Single Ingredient Nasal Corticosteroids

Beclomethasone dipropionate (*Qnasl*)
Beclomethasone dipropionate monohydrate (*Beconase AQ*)
Budesonide (*Rhinocort*)
Ciclesonide (*Omnaris, Zetonna*)
Flunisolide (*Generic*)
Fluticasone Furoate (*Flonase Sensimist*)
Fluticasone Propionate (*Flonase, Xhance*)
Mometasone Furoate (*Nasonex*)
Triamcinolone Acetonide (*Nasacort*)

AHFS Classification: 52.08.08 Corticosteroids (EENT)

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Review prepared by:
Valerie Gonzales, Pharm.D., Clinical Pharmacist
Elena Martinez Alonso, B.Pharm., MSc MTSI, Medical Writer
Vicki Frydrych, Pharm.D., Clinical Pharmacist
Joanita Lake, B.Pharm., MSc EBHC (Oxon), Research Assistant Professor
Joanne LaFleur, Pharm.D., MSPH, Associate Professor University of Utah College of Pharmacy

University of Utah College of Pharmacy, Drug Regimen Review Center
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Abbreviations

AAOHNS – American Academy of Otolaryngology Head and Neck Surgery
AQ – aqueous
AR – allergic rhinitis
CRS – chronic rhinosinusitis
CRSsNP – chronic rhinosinusitis without nasal polyps
CRSwNP - chronic rhinosinusitis with nasal polyps
FDA - U.S. Food & Drug Administration
INCS - intranasal corticosteroids
NAR – non-allergic rhinitis
OTC – over the counter
RCT - randomized control trial
Rx – formulation available by prescription
SR - systematic review
Executive Summary

Intranasal corticosteroids (INCS) are indicated and widely used for seasonal and perennial allergic rhinitis (AR). Mometasone furoate also has specific indications for nasal congestion and prophylaxis of seasonal AR symptoms. Three products are indicated for the management of nasal polyps (e.g. Beconase AQ [beclomethasone dipropionate monohydrate], Nasonex [mometasone furoate], and Xhance [fluticasone propionate]). Beconase AQ is indicated following surgical removal of polyps once healing has occurred, whereas Nasonex and Xhance can additionally be used prior to surgery. Several INCSs are available over-the-counter (budesonide, fluticasone furoate, fluticasone propionate, and triamcinolone), and others only by prescription (beclomethasone, ciclesonide, flunisolide, fluticasone propionate as the Xhance product, and mometasone). Two products are approved for non-allergic rhinitis, Beconase AQ and fluticasone propionate.

The majority of products are formulated as aqueous sprays. Upon administration, aqueous formulations tend to run down the back of the throat and have sensory attributes (scent, taste) which may influence patient compliance. Two products employ a hydrofluoroalkane (HFA) device to propel medication as an aerosol: Qnasl (beclomethasone dipropionate) and Zetonna (ciclesonide). When using INCSs for allergic rhinitis, products are to be administered once daily with the exception of beclomethasone dipropionate monohydrate (Beconase AQ) and generic flunisolide nasal sprays with twice daily dosing. The 3 products indicated for the management of nasal polyps (e.g. Beconase AQ, Nasonex, and Xhance) are dosed twice daily. Several agents have little systemic bioavailability (<2% bioavailable: ciclesonide, fluticasone furoate, fluticasone propionate, and mometasone furoate), considerably lower than that for beclomethasone, budesonide, flunisolide, and triamcinolone nasal sprays.

During rhinitis exacerbations, INCS treatment significantly improves nasal symptoms (itching, discharge, congestion, and sneezing) in adults and children, while also improving quality of life. Recommendation for the use of one INCS over another is not specified in guidelines for the treatment of allergic rhinitis, chronic rhinosinusitis (CRS), or for nasal polyps.

Following a systematic search we screened 313 systematic reviews (SR) and 634 randomized controlled trials (RCT) published from 2007 onward. A total of 5 systematic reviews were identified that addressed treatment-effect differences between INCSs. Three of these SRs found no available head-to-head RCTs for the following conditions: CRS without nasal polyps (Chong et al, Cochrane 2016), CRS following post-surgical intervention for nasal polyps (Fandino et al, 2013), and persistent AR in children (Al Sayyad et al, Cochrane 2007). One SR (Chong et al, Cochrane 2016) also investigated INCS treatment for CRS with nasal polyps and concluded that change in disease severity was not significantly different after treatment with fluticasone propionate versus beclomethasone or mometasone; no evidence was found for other head-to-head comparisons in the CRS setting.

Based on evidence from a high quality SR by Selover et al. (2008) comparing nasal corticosteroids for patients with allergic rhinitis or non-allergic rhinitis, there were few differences between agents. One head-to-head comparison stands out in particular (budesonide versus fluticasone propionate). An RCT (Day et al. 1998) reported a significant difference in the
reduction of the patient-rated total nasal symptom score (primary endpoint) in favor of budesonide 256 mcg/day versus fluticasone propionate 200 mcg/day for treatment of adults with perennial AR. In the setting of adult seasonal AR, one study (Stern et al. 1997) suggested budesonide 256 mcg/day improves patient-rated nasal symptoms better than fluticasone propionate 200 mcg/day only for days when the pollen count was greater than 10 grains/m$^3$. Products performed similarly when total nasal symptom scores were evaluated over all treatment days regardless of pollen count. It should be noted that the dosage form used in these studies was a budesonide 64mcg/actuation product; this strength is no longer available in the US.

There is conflicting evidence for the comparison of mometasone versus fluticasone propionate. In an RCT (Mandl et al. 1997) in patients older than 12 years, with perennial AR, the primary outcome of patient-rated total nasal symptom score reduction did not differ between the two treatment groups at any time period, yet a significantly greater reduction in physician-rated secondary outcomes of nasal congestion (at day 29 and week 8), nasal discharge (at week 8 and 12), and improved overall condition (at week 8 and 12) was observed in favor of the mometasone group. Another study assessing this comparison (Mak et al. 2013) in children 6 to 12 years of age with moderate to severe perennial AR found no differences in patient quality of life scores after 4 weeks of treatment.

Four additional RCTs published in the last 10 years, reported no significant differences in primary efficacy endpoints between certain treatment comparisons: fluticasone furoate versus mometasone furoate, and beclomethasone dipropionate monohydrate versus mometasone for perennial AR; fluticasone propionate versus mometasone for child dust mite AR; fluticasone furoate versus fluticasone propionate for seasonal AR.

Regarding safety comparisons, one RCT was identified (Fokkens et al, 2012) that assessed long-term treatment with fluticasone furoate 110 mcg once daily versus mometasone furoate 200 mcg once daily over 1 year on nasal epithelium. After 52 weeks, there was no difference in epithelial thickening (per nasal biopsy) between active treatment groups and respective placebo control groups, nor between each active arm. The authors concluded that long-term treatment with these agents does not induce nasal epithelium atrophy.

Intranasal corticosteroids are well tolerated with common mild adverse effects being headache, epistaxis, dizziness, and nasopharyngeal irritation. Serious, yet infrequent, adverse effects include fungal infection, growth inhibition, hypothalamic pituitary adrenal axis suppression, cataracts, increased intraocular pressure, nasal mucosal ulceration, and changes in taste and smell. Patients should be cautioned about possible brief lightheadedness/dizziness upon administration.

In summary, there is little RCT evidence suggesting that any one INCS agent is more efficacious than another. Moreover, the treatment guidelines reviewed recommend the INCS drug class as a whole, not specifying preference of one product over another. There are some product differences with respect to dosing frequency, delivery device, and systemic bioavailability that may be considered as previously discussed.
Introduction

Intranasal corticosteroids (INCS) are indicated and widely used for seasonal and perennial allergic rhinitis (AR). Mometasone furoate also has specific indications for nasal congestion and prophylaxis of seasonal AR symptoms.1 Three products are indicated for the management of nasal polyps (e.g. Beconase AQ [beclomethasone dipropionate monohydrate], Nasonex [mometasone furoate], and Xhance [fluticasone propionate]). Beconase AQ is indicated following surgical removal of polyps once healing has occurred, whereas Nasonex and Xhance can additionally be used prior to surgery.1-3 Several INCSs are available over-the-counter (budesonide, fluticasone furoate, fluticasone propionate, and triamcinolone), and others only by prescription (beclomethasone, ciclesonide, flunisolide, fluticasone propionate as the Xhance product, and mometasone). Two products are approved for non-allergic rhinitis, Beconase AQ and fluticasone propionate.2,4

The majority of products are available as aqueous sprays. Aqueous formulations tend to run down the back of the throat and have sensory attributes (scent, taste) which may influence patient compliance and the likelihood of systemic absorption via the stomach.5,6 Two products employ a hydrofluoroalkane (HFA) device to propel medication as an aerosol: Qnasl (beclomethasone) and Zetonna (ciclesonide).7,8

This report will discuss the head-to-head comparative evidence, following a systematic review methodology, available for the INCS products used within the FDA-approved dosing as listed in Table 1. Table 1 details the indications, and dosing for the eleven intranasal corticosteroid preparations available in the United States (US). The Utah Medicaid Preferred Drug List classifies Beconase AQ (beclomethasone dipropionate monohydrate), Omnaris (ciclesonide), generic flunisolide, generic fluticasone propionate, and generic mometasone furoate as preferred agents. Table 1 of Appendix A provides a shorter summary table of the approved indications for these products.
<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Available Formulations</th>
<th>Indication &amp; Dosage</th>
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</table>
| **Beclomethasone dipropionate**    | Qnasl [Aerosol; 24Hr]  | Rhinitis  
Qnasl: Relief of nasal symptoms from seasonal or perennial AR in patients ≥ 4yrs.  
Patients >12 years, using the 80mcg/actuation product: 2 actuations in each nostril once daily (320mcg total daily dose; this is also the maximum recommended dose)  
Patients 4 to < 12 years of age using the 40mcg/actuation product: 1 actuation in each nostril once daily (80mcg total daily dose; this is also the maximum recommended daily dose) |
|                                    | Beconase AQ [Spray]    | Beconase AQ: Relief of symptoms of seasonal or perennial AR and non-allergic (vasomotor) rhinitis in patients 6 years and older  
Patients > 12 years of age: 1 to 2 sprays per nostril twice daily (max 336 mcg/day)  
Patients 4 to 12 years of age: initial dose is 1 actuation in each nostril twice daily; may increase dose to 2 actuations per nostril for inadequate responders, however, dose should be reduced back to 1 actuation per nostril once control of symptoms is achieved |
|                                    |                         | **Nasal polyps**  
Beconase AQ only: Nasal polyps recurrence prevention following surgical removal. Same dosing as specified above |
| **Budesonide**                     | Rhinocort Allergy [Spray, 24Hr] | Allergic rhinitis  
Old Rx*: for the management of symptoms of seasonal or perennial allergic rhinitis in adults and children ≥6 years  
Patients 6 to 12 years of age: 64mcg/day to up to 128mcg/d  
Patients 12 years and older: 64mcg/day to up to 256mcg/d  
OTC*: For the relief of upper respiratory symptoms associated with hay fever or other respiratory allergies (e.g. nasal congestion, runny nose, itchy nose, sneezing) in adults and children ≥6 years of age  
Patients > 12 years of age: initially 2 sprays into each nostril once daily; decrease to 1 spray/nostril/day once allergy symptoms improve  
Patients 6 to < 12 years of age: initially 1 spray into each nostril once daily; inadequate responders may increase to 2 sprays/nostril/day, however, should decrease back to 1 spray/nostril/day once allergy symptoms improve  
OTC max dose is 128mcg/day |
| **Ciclesonide**                    | Omnaris [Spray; 24Hr]  | Allergic rhinitis  
Omnaris: for treatment of nasal symptoms associated with seasonal allergic rhinitis for patients > 6 years of age and for perennial allergic rhinitis in patients > 12 years of age  
For all ages/indications: 2 sprays per nostril once daily (max of 200mcg/day) |
|                                    | Zetonna [Aerosol; 24Hr] | Zetonna: for treatment of nasal symptoms associated with seasonal or perennial allergic rhinitis in patients > 12 years of age  
For all ages/indications: 1 spray per nostril once daily (max of 74mcg/day) |
<table>
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<tr>
<th>Generic Name</th>
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</table>
| **Flunisolide** | **Generic** [Spray] (Rx) | **Allergic rhinitis**  
For treatment of nasal symptoms associated with *seasonal* or *perennial* allergic rhinitis in patients >6 years of age  
**Adults:** 2 sprays per nostril twice daily; may increase to 2 sprays per nostril 3 times/day; after obtaining desired clinical effect, reduce maintenance dose to lowest amount necessary for symptom control  
**Patients 6 to 14 years:** 1 spray per nostril 3 times/day or 2 sprays per nostril 2 times/day; after obtaining desired clinical effect, use dose to lowest amount necessary for symptom control  
- Do not exceed 8 sprays in each nostril for adults (max 400mcg/day) and 4 sprays in each nostril for patients under 14 years (max 200mcg/day).  
Approximately 15% of patients with perennial rhinitis may be maintained on as little as 1 spray in each nostril per day |
| **Fluticasone Furoate** | **Flonase Sensimist** [Spray; 24Hr] (OTC) | **Allergic rhinitis**  
*OTC:* for the relief of upper respiratory symptoms associated with hay fever or other respiratory allergies (e.g. nasal congestion, runny nose, itchy nose, sneezing) in adults and children ≥ 2 years of age  
**Patients > 12 years of age:** For week 1, use 2 sprays in each nostril once daily. For week 2 to 6, use 1 to 2 spray(s)/nostril/day as needed per symptom response. After 6 weeks, ask your doctor if you can keep using this medication  
**Patients 2 to 11 years of age:** 1 spray in each nostril once daily; use for shortest duration necessary to achieve symptom relief. Consult a doctor if child needs the spray for longer than two months a year |
| **Fluticasone Propionate** | **Generic** [Spray; 24Hr] (Rx) | **Allergic rhinitis**  
*OTC Flonase:* for relief of upper respiratory symptoms due to hay fever or other respiratory allergies in adults and children ≥ 4 years of age  
**Patients > 12 years of age:** Week 1, use 2 sprays in each nostril once daily. Week 2 through 6 months, use 1 to 2 spray(s)/nostril/day as needed per symptom response. After 6 months, ask your doctor if you can keep using this medication  
**Patients 4 to 11 years of age:** 1 spray in each nostril once daily; only use for the shortest duration necessary to achieve symptom relief. Consult a doctor if the child seems to need the spray for longer than two months a year  
**Non-allergic rhinitis:**  
**Rx Generic Flonase:** For the management of nasal symptoms of perennial non-allergic rhinitis in adult and pediatric patients aged 4 years and older  
**Adult Dose:** Initially, 2 sprays per nostril once daily; alternatively, the same total daily dosage may be divided for twice daily administration. After the first few days and with symptom control, dosage may be reduced to 1 spray per nostril once daily for maintenance therapy. (max 2 sprays per nostril [200 mcg]/day)  
**Children 4 years and older:** 1 spray per nostril once daily; may increase to 2 sprays/nostril/day if initial response is inadequate, however the dosage should be decreased to 1 spray/nostril/day upon symptom control  
**Nasal polyps**  
**Xhance:** for treatment of nasal polyps in patients ≥18 years of age  
**Dose:** 1 spray per nostril twice daily; some patients may benefit from an increase in dose up to 2 sprays per nostril twice daily |
### Table 1. Nasal corticosteroid products

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Available Formulations</th>
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</table>
| Mometasone Furoate | Nasonex¹ [Spray, 24Hr] (Rx)  
  • 50 mcg/actuation  
  • Aqueous; pH 4.3-4.9 (generics available) | **Allergic rhinitis**: for the treatment of nasal symptoms of seasonal allergic and perennial allergic rhinitis in adults and pediatric patients ≥2 years  
  **Patients 12 years of age and older**: 2 sprays into each nostril once daily  
  **Patients 2 to 11 years of age**: 1 spray in each nostril once daily  
  **Nasal congestion**: for relief of nasal congestion associated with seasonal allergic rhinitis in adults and pediatric patients ≥2 years  
  **Patients 12 years of age and older**: 2 sprays into each nostril once daily  
  **Patients 2 to 11 years of age**: 1 spray in each nostril once daily  
  **Prophylaxis of seasonal allergic rhinitis**: Prophylaxis of nasal symptoms of seasonal allergic rhinitis in adults and pediatric patients ≥12 years  
  **Patients 12 years of age and older**: 2 sprays into each nostril once daily  
  **Nasal polyps**: Treatment of nasal polyps in patients ≥18 years old  
  **Patients 18 years of age and older**: 2 sprays into each nostril twice daily; 2 sprays into each nostril once daily may also be effective for some patients |
| Triamcinolone Acetonide | Nasacort Allergy¹⁸ [Spray, 24Hr] (OTC)  
  • 55 mcg/actuation  
  • Aqueous; pH unknown (generics available) | **Allergic rhinitis**  
  **OTC**: For the relief of upper respiratory symptoms associated with hay fever or other respiratory allergies in adults and children ≥ 4 years of age  
  **Patients > 12 years of age**: Initially use 2 sprays in each nostril once daily. Once symptoms improve, reduce to 1 spray/nostril/day. If allergy symptoms don’t improve after one week, consult a doctor  
  **Patients 6 to < 12 years of age**: 1 spray per nostril once daily; increase to 2 sprays/nostril/day if symptoms do not improve. Should reduce back to 1 spray/nostril/day upon symptom control  
  **Patients 2 to < 6 years of age**: 1 spray in each nostril once daily  
  **Old Rx Aerosol¹⁹ [DISC]²⁰**: Management of seasonal and perennial allergic rhinitis in adults and children 2 years and older |

* Some prescription brand products have been discontinued as the comparable OTC product was marketed. Old Rx dosing and information on product characteristics (e.g. pH) is provided where available.  
Abbreviations: 24Hr, [DISC], discontinued, signifies once daily dosing; AR, allergic rhinitis; HFA, hydrofluoroalkane; OTC, over the counter; Rx, prescription only
Allergic rhinitis (AR) is an inflammatory response, mediated by immunoglobulin E (IgE), following inhalation of allergens. The prevalence of AR, based on self-reporting, is estimated to be 10 to 30% of adults and up to 40% of children in the US. Hallmark symptoms include anterior and posterior nasal drip (rhinorrhea), nasal congestion, nasal itching, nasal polyps, and sneezing (in addition to cough and fatigue particularly in children). Allergic rhinitis may be accompanied by ocular symptoms including watery eye, itching, redness, conjunctiva swelling, and puffiness of the lower eyelids. This condition can exacerbate other chronic/recurrent respiratory conditions such as asthma and can lead to sleep and behavior disturbance, fatigue, and reduced learning performance. Other conditions such as viral/bacterial sinusitis, vasomotor rhinitis, and granulomatous diseases may present with similar symptoms, so must be ruled out (considering symptoms such as fever, myalgia, etc. that are not typically present in allergic rhinitis).

Exposure to the allergen may be seasonal (typically from plant pollens), perennial (e.g. from dust mites, animal dander, molds), or episodic (when not normally encountered) and ultimately determines the patient’s temporary or ongoing need for pharmacotherapy. Depending on geographic location, pollens and molds may be classified as perennial allergens. Some patients may suffer from concurrent AR to both perennial and seasonal influences or may have comorbidities that are directly exacerbated by the inflammatory reaction (e.g. asthma, sleep disturbances).

In 2015, the Centers for Disease Control and Prevention estimated that 20 million adults and 6.1 million children were diagnosed with hay fever in the prior year. The American Academy of Otolaryngology Head and Neck Surgery (AAOHN) describes that while symptoms can be classified by frequency (intermittent and persistent) and severity (mild or more severe), the classification system has limitations. They propose determining which category the patient falls into without use of the strict definitions, using a case-by-case consideration approach. Physicians can advise allergen avoidance, environmental controls, pharmacologic therapies, and immunotherapy desensitization. Table 2 lists recent guidelines regarding the treatment of allergic rhinitis and their recommendations for the use of INCS agents in particular.

There are five drug classes approved for the treatment of allergic rhinitis that are available as nasal sprays including the INCS products. Other classes include decongestants (e.g. phenylephrine, oxymetolazone); the anticholinergic, ipratropium; the mast cell stabilizer, cromolyn; and antihistamines (e.g. azelastine, olopatadine). Intranasal corticosteroids are considered to be the most effective for the management of nasal symptoms associated with allergic rhinitis compared to oral antihistamines and leukotriene receptor antagonists. Oral antihistamines, decongestants, and intranasal antihistamines, may be advantageous when a faster onset of action is desired. Intranasal corticosteroids are generally recommended for moderate to severe symptoms of allergic rhinitis (“defined as rhinitis accompanied by other troublesome symptoms and/or that affects quality of life”). The guidelines do not recommend one INCS over another for the treatment of allergic rhinitis.

Nasal polyps can occur with chronic allergic rhinitis or chronic rhinosinusitis. Chronic rhinosinusitis (CRS) is defined as inflammation of the nose and paranasal sinuses with 2
or more symptoms present, with at least one being nasal blockage or nasal discharge lasting more than 12 weeks; other symptoms may include facial pain and dysosmia.  

There are different underlying pathologies in chronic rhinosinusitis, however, the disease is characterized by inflammation and treatment with INCSs is recommended. Chronic rhinosinusitis is subtyped into CRS with nasal polyps (CRSwNP) and without nasal polyps (CRSsNP). An estimated 4% of patients with CRS have nasal polyps. Intranasal corticosteroids are recommended as a first line therapy for the treatment of nasal polyps and to reduce the risk of recurrence following polypectomy. There is ongoing research to better characterize the disease-causing pathology and potential treatment targets.

Non-allergic rhinitis (NAR) is characterized by an absence of IgE and has diverse etiologies, which may have some overlapping biological mechanism involved in chronic rhinosinusitis. Subtypes of this disease include NAR rhinopathy (previously known as vasomotor rhinitis), NAR with eosinophilia, drug-induced rhinitis, hormonal-induced rhinitis, atrophic rhinitis, senile rhinitis, gustatory rhinitis, and cerebral spinal fluid leak manifesting rhinorrhea. NAR triggers may include changes in the environment (temperature, humidity, and pressure), odors/fumes, and pollutants/chemicals. NAR is characterized by nasal obstruction and rhinorrhea; in contrast, AR is generally associated with more sneezing/conjunctivitis/nasal pruritis, and higher blood/nasal eosinophil counts. A detailed discussion pertaining to the complexity of diagnosing this disease state is addressed by Greiwe et al.

Table 2. Guidelines for the use of nasal corticosteroids in rhinitis conditions

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Recommendation</th>
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<tbody>
<tr>
<td><strong>Allergic Rhinitis</strong></td>
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<tr>
<td>Pharmacologic Treatment of Seasonal Allergic Rhinitis: Synopsis of Guidance From the 2017 Joint Task Force on Practice Parameters</td>
<td></td>
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<tr>
<td>American Academy of Allergy, Asthma and Immunology (AAAAI) and the American College of Allergy, Asthma and Immunology (ACAAI)</td>
<td><strong>Initial treatment of seasonal allergic rhinitis:</strong></td>
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<tr>
<td></td>
<td>• “The 2008 update of the Joint Task Force's rhinitis practice parameter (26) recommended intranasal corticosteroids as the most effective medication class for controlling symptoms, as did the original practice parameter from 1998 (27).”</td>
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<tr>
<td></td>
<td>• For persons aged 12 years or older, use monotherapy with an intranasal corticosteroid rather than the combination of an intranasal corticosteroid in combination with an oral antihistamine. (Strong recommendation)</td>
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<td></td>
<td>• For patients over 15, recommend an intranasal corticosteroid over a leukotriene receptor antagonist. (Strong recommendation)</td>
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<td><strong>Moderate to severe seasonal allergic rhinitis:</strong></td>
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<td>• For patients over 12 years of age, consider a combination of an intranasal corticosteroid and an intranasal antihistamine for initial treatment. (Weak recommendation)</td>
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<td><strong>Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines—2016 revision</strong></td>
<td>Choosing an intranasal corticosteroid: “ARIA guideline panel acknowledged that the choice of treatment would depend mostly on patient preferences and local availability and cost of treatment. Panel members assumed that in the majority of situations, potential net benefit would not justify spending additional resources.”</td>
</tr>
<tr>
<td><strong>Clinical Practice Guideline: Allergic Rhinitis 2015</strong></td>
<td>Recommendations for intranasal corticosteroids regarding choosing one drug class over another and combination therapy:</td>
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<tr>
<td><strong>American Academy of Otolaryngology Head and Neck Surgery (AAO-HNS)</strong></td>
<td>For patients with Seasonal Allergic Rhinitis:</td>
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<td></td>
<td>• Use an INCS rather than an inhaled antihistamine (conditional recommendation</td>
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<tr>
<td></td>
<td>• Use either a combination of an INCS with an intranasal antihistamine or an INCS alone (conditional recommendation</td>
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<tr>
<td></td>
<td>• Use either a combination therapy with an oral antihistamine + INCS or an INCS alone (conditional recommendation</td>
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<td></td>
<td>For patients with Perennial Allergic Rhinitis:</td>
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<td></td>
<td>• Use either an INAH or OAH (conditional recommendation</td>
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<td></td>
<td>• Use an INCS rather than an INAH (conditional recommendation</td>
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<tr>
<td></td>
<td>• Use an INCS alone rather than a combination of an INCS with an oral antihistamine (conditional recommendation</td>
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<tr>
<td></td>
<td>• Use either a combination of an INCS with an inhaled antihistamine or an INCS alone (conditional recommendation</td>
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**Classifications**

- **Intermittent**: exposure or symptoms that occur <4 days per week or <4 weeks per year
- **Persistent**: ongoing symptoms >4 days per week and >4 weeks per year
- **Episodic**: exposure that is not normally part of the individual’s environment
- **Mild**: symptoms don’t interfere with quality of life
- **More severe**: symptoms are bad enough to interfere with quality of life

**Recommendation definitions:**

- “Less frequent variation in practice is expected for a “strong recommendation” than might be expected with a “recommendation.” “Options” offer the most opportunity for practice variability.”
- Strong recommendation: benefits clearly exceed the harms; quality of supporting evidence is excellent (Grade A or B)
- Recommendation: benefits exceed the harms, but quality of evidence is not as strong (Grade B or C)
- Option: either the quality of evidence that exists is suspect (Grade D) or that well-done studies (Grade A, B, or C) show little clear advantage to one approach versus another
- Recommendation against: based on RCTs and systematic reviews, with a preponderance of benefit over harm
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<td><strong>Pharmacotherapy for Patients with Allergic Rhinitis</strong></td>
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<tr>
<td><strong>Topical steroids</strong>: “Clinicians should recommend intranasal steroids for patients with a clinical diagnosis of AR whose symptoms affect their quality of life.” (Strong recommendation)</td>
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<td>• Onset: “… it is reasonable to assume that efficacy would be reached after 1 week of therapy at the most and, if none is observed, the treatment might be considered ineffective.”</td>
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<tr>
<td><strong>Oral antihistamines</strong>: use oral second-generation/less sedating antihistamines for primary complaints of sneezing and itching. (Strong recommendation)</td>
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<tr>
<td><strong>Intranasal antihistamines</strong>: may consider for patients with seasonal, perennial, or episodic AR. (Option)</td>
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<tr>
<td><strong>Oral leukotriene</strong>: Do not offer oral leukotriene receptor antagonists as primary therapy for patients with AR (Recommendation against)</td>
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<td><strong>Combination therapy</strong>: consider for those who have inadequate response to pharmacologic monotherapy. (Option)</td>
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<td><strong>Allergy testing an immunotherapy</strong>: can be considered for patients with inadequate response to above pharmacotherapies (an adequate trial of medications is considered to be 2 to 4 weeks in duration), when the diagnosis is uncertain, or when knowing the culprit allergen will affect treatment decision making. (Recommendation)</td>
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**Sinusitis**

Clinical Practice Guideline (Update): Adult Sinusitis: 2015

AAO-HNS

**Topical intranasal therapy for chronic rhinosinusitis:**
“Clinicians should recommend saline nasal irrigation, topical intranasal corticosteroids, or both for symptom relief of CRS. Recommendation based on a preponderance of benefit over harm”

**Symptomatic relief of viral rhinosinusitis:**
“Clinicians may recommend analgesics, topical intranasal steroids, and/or nasal saline irrigation for symptomatic relief of VRS. Option based on randomized controlled trials with limitations and cohort studies with an unclear balance of benefit and harm that varies by patient.”
Table 2. Guidelines for the use of nasal corticosteroids in rhinitis conditions

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Recommendation</th>
</tr>
</thead>
</table>
| **Diagnosis and Management of Rhinosinusitis: A Practice Parameter Update; 2014**<sup>34</sup> | **Statements that apply to the use of intranasal corticosteroids:**
| | • Summary Statement 13: Treat allergic fungal rhinosinusitis with a combination of surgery and systemic and/or topical corticosteroids for optimal disease control. (Recommendation, B)
| | • Summary Statement 22: Use intranasal steroids for treatment of acute rhinosinusitis as monotherapy or with antibiotics. (Recommendation, B)
| | • Summary Statement 28: Use intranasal corticosteroid (sprays and aerosols) for the treatment of CRSwNP and CRSsNP. (Strong Recommendation, A)
| | • Summary Statement 41: Use an intranasal steroids as a potentially useful adjunct to antibiotics in the treatment of acute bacterial rhinosinusitis in children. (Strong Recommendation, A)
| | • Summary Statement 45: Use intranasal steroids in the treatment of chronic rhinosinusitis in children. (Recommendation, C)
| **Joint Task Force on Practice Parameters, representing the American Academy of Allergy, Asthma and Immunology, the American College of Allergy, Asthma and Immunology, and the Joint Council of Allergy, Asthma and Immunology** | Recommendation definitions:
| | • Strong recommendation: benefits clearly exceed the harms; quality of supporting evidence is excellent (Grade A or B).
| | • Recommendation: benefits exceed the harms, but quality of evidence is not as strong (Grade B or C).
| | • Option: either the quality of evidence that exists is suspect (Grade D) or that well-done studies (Grade A, B, or C) show little clear advantage to one approach versus another.
| **Topical Therapies in the Management of Chronic Rhinosinusitis: An Evidence-based Review with Recommendations; 2013**<sup>32</sup> | “There is overwhelming evidence from 5 meta-analyses that standard topical steroid therapy results in both patient based and objective clinical improvements in CRSwNP and CRSsNP. When combining an aggregate grade A of evidence with a preponderance of benefit over harm, we have produced a strong recommendation for the use of standard topical steroid therapy in patients with CRS. To optimize treatment effect, the evidence suggests that the delivery technique should focus on improving sinus penetration rather than simple nasal application.”<sup>32</sup>
| **Clinical Practice Guideline for the Diagnosis and Management of Acute Bacterial Sinusitis in Children Aged 1 to 18 Years; 2013**<sup>37</sup> | No recommendation is given for INCS for the treatment of bacterial sinusitis. “No recommendation indicates that there is a lack of pertinent published evidence and that the anticipated balance of benefits and harms is presently unclear.”<sup>37</sup>
| **American Academy of Pediatrics** | “Intranasal corticosteroids (INCSs) are recommended as an adjunct to antibiotics in the empiric treatment of ABRS, primarily in patients with a history of allergic rhinitis (weak, moderate).”<sup>38</sup>
| **Clinical Practice Guideline for Acute Bacterial Rhinosinusitis in Children and Adults; 2012**<sup>38</sup> | Abbreviations: CRS, chronic rhinosinusitis; CRSsNP, chronic rhinosinusitis without nasal polyps; CRSwNP, chronic rhinosinusitis with nasal polyps; INAH, inhaled antihistamine; INCS, intranasal corticosteroid; OAH, oral antihistamine
Administration of corticosteroids reduces inflammatory mediators including T-lymphocytes, basophils, eosinophils, neutrophils, mononuclear cells, cytokines (e.g. IL-2, IL-4, interferon-gamma, and TNF-alpha), and histamine release.\textsuperscript{5,6} Topical INCS administration to the nasal epithelium exerts anti-inflammatory/vasoconstrictor effects and reduces vascular permeability.\textsuperscript{2,5} During rhinitis exacerbations, INCS treatment significantly improves nasal symptoms (itching, discharge, congestion, and sneezing) in adults and children, while also improving quality of life.\textsuperscript{6}

They are most commonly used continuously during seasonal or perennial allergen exposure. On demand use is also being studied and has been shown to be as effective as regular use in some situations.\textsuperscript{39,40} Guideline authors highlight, “studies of as-needed use of intranasal fluticasone have shown that intermittent use is better than placebo,” in the setting of seasonal allergic rhinitis.\textsuperscript{6} When using INCS for allergic rhinitis, most products are to be administered once daily with the exception of beclomethasone dipropionate monohydrate (Beconase AQ) and generic flunisolide nasal sprays requiring twice daily dosing. The 3 products indicated for the management of nasal polyps (e.g. Beconase AQ, Nasonex, and Xhance) are each dosed twice daily.

Several agents have little systemic bioavailability (<2% bioavailable: ciclesonide, fluticasone furoate, fluticasone propionate, and mometasone furoate), lower than reported for beclomethasone, budesonide, flunisolide, and triamcinolone.\textsuperscript{41,42} The majority of these products are available as aqueous sprays. Aqueous formulations tend to run down the back of the throat and have sensory qualities (e.g. odor, nasal irritation), especially if formulated with alcohol, which can influence patient compliance.\textsuperscript{5} Two products employ a hydrofluoroalkane (HFA) device to propel medication as an aerosol: Qnasl (beclomethasone) and Zetonna (ciclesonide).\textsuperscript{7,8} Table 3 provides pharmacokinetic information the products.

Table 4 summarizes drug interaction warnings in product labeling for the intranasal corticosteroids. Since systemic exposure of INCSs is relatively low (especially with ciclesonide, fluticasone furoate, fluticasone propionate, and mometasone furoate), drug interactions are expected to be minimal. The first generation agents (beclomethasone, budesonide, and flunisolide), with higher bioavailabilities and metabolism pathways via cytochrome P450 3A4 enzyme (CYP3A4), are the most concerning with regard to potential systemic drug interactions with other molecules affecting CYP3A4 metabolism. In addition, drug monographs in Lexicomp cite a major interaction with INCS agents and desmopressin (may enhance hyponatremic effect of desmopressin exposure).\textsuperscript{16} Table 5 summarizes special population information for these products.
**Table 3. Pharmacokinetics of nasal corticosteroid products**

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Bio-availability</th>
<th>Half-life (hours)</th>
<th>Metabolism</th>
<th>Excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Beclomethasone dipropionate</em></td>
<td>Qnasl&lt;sup&gt;7&lt;/sup&gt; (Rx)</td>
<td>27.5%</td>
<td>2.8 (mean)</td>
<td>CYP3A4; Esterases (hydrolyze the prodrug)</td>
<td>Mainly excreted through feces; &lt;15% excreted in urine</td>
</tr>
<tr>
<td></td>
<td>Beclomethasone dipropionate</td>
<td>44%</td>
<td>0.5 to 2.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>monohydrate Beconase AQ&lt;sup&gt;2&lt;/sup&gt; (Rx)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Budesonide</em>&lt;sup&gt;16&lt;/sup&gt;</td>
<td>Rhinocort Allergy&lt;sup&gt;*10&lt;/sup&gt; (OTC available)</td>
<td>34%</td>
<td>2 to 3</td>
<td>CYP3A4</td>
<td>Mostly excreted through the urine (~66%)</td>
</tr>
<tr>
<td><em>Ciclesonide</em></td>
<td>Omnaris&lt;sup&gt;12&lt;/sup&gt; (Rx)</td>
<td>&lt;1%</td>
<td>NR</td>
<td>Esterases (hydrolysis); CYP3A4 &amp; 2D6</td>
<td>Predominantly excreted through the feces; &lt;20% through the urine</td>
</tr>
<tr>
<td></td>
<td>Zetonna&lt;sup&gt;8&lt;/sup&gt; (Rx)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Flunisolide</em></td>
<td>Generic&lt;sup&gt;13&lt;/sup&gt; (Rx)</td>
<td>50%</td>
<td>1 to 2</td>
<td>CYP3A4 minor (per Lexicomp monograph)&lt;sup&gt;16&lt;/sup&gt;</td>
<td>Half of the dose excreted in the urine and other half through the feces</td>
</tr>
<tr>
<td><em>Fluticasone Furoate</em></td>
<td>Flonase Sensimist&lt;sup&gt;*43&lt;/sup&gt; (OTC available)</td>
<td>&lt;1%</td>
<td>15.1</td>
<td>CYP3A4</td>
<td>Primarily excreted via bile; &lt;1% excreted through urine</td>
</tr>
<tr>
<td><em>Fluticasone Propionate</em></td>
<td>Generic (Rx)&lt;sup&gt;4&lt;/sup&gt; (OTC available)</td>
<td>&lt;2%</td>
<td>7.9</td>
<td>CYP3A4</td>
<td>Primarily excreted in the feces; &lt;5% excreted in the urine</td>
</tr>
<tr>
<td></td>
<td>Xhance&lt;sup&gt;3&lt;/sup&gt; (Rx)</td>
<td>NR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Mometasone Furoate</em></td>
<td>Nasonex&lt;sup&gt;4&lt;/sup&gt; (Rx)</td>
<td>&lt;1%</td>
<td>5.8</td>
<td>CYP3A4</td>
<td>Primarily excreted via bile</td>
</tr>
<tr>
<td><em>Triamcinolone Acetonide</em></td>
<td>Nasacort Allergy&lt;sup&gt;*19&lt;/sup&gt; (OTCs available)</td>
<td>34-49%&lt;sup&gt;42&lt;/sup&gt;</td>
<td>4</td>
<td>CYP3A4 minor (per Lexicomp monograph)&lt;sup&gt;16&lt;/sup&gt;</td>
<td>Feces (~60%); Urine (~40%)&lt;sup&gt;16&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

*Abbreviations: AQ, aqueous; CYP3A4, cytochrome P450 3A4; NR, not reported; OTC, over the counter; Rx, available by prescription only

*Pharmacokinetic information is from a product label with a different brand name, since PK data is not provided in OTC labeling
<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Drug Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Beclomethasone dipropionate</strong></td>
<td>Qnasl&lt;sup&gt;7&lt;/sup&gt; (Rx)</td>
<td>Qnasal labeling states that drug interaction studies have not been performed. Beconase AQ labeling does not discuss drug interactions. Note: drug interaction considerations should be taken into account since beclomethasone is a CYP3A4 substrate and has some systemic bioavailability.</td>
</tr>
<tr>
<td></td>
<td>Beclomethasone dipropionate monohydrate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Beconase AQ&lt;sup&gt;2&lt;/sup&gt; (Rx)</td>
<td></td>
</tr>
<tr>
<td><strong>Budesonide&lt;sup&gt;16&lt;/sup&gt;</strong></td>
<td>Rhinocort Allergy*&lt;sup&gt;10&lt;/sup&gt; (OTC available)</td>
<td>Prescription labeling for Rhinocort states that caution is advised when used with strong CYP3A4 inhibitors.</td>
</tr>
<tr>
<td><strong>Ciclesonide</strong></td>
<td>Omnaris&lt;sup&gt;12&lt;/sup&gt; (Rx)</td>
<td>No drug interactions are expected&lt;sup&gt;8,12&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Zetonna&lt;sup&gt;8&lt;/sup&gt; (Rx)</td>
<td></td>
</tr>
<tr>
<td><strong>Flunisolide</strong></td>
<td>Generic&lt;sup&gt;13&lt;/sup&gt; (Rx)</td>
<td>Labeling does not discuss drug interactions.&lt;sup&gt;13&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Fluticasone Furoate</strong></td>
<td>Flonase Sensimist*&lt;sup&gt;43&lt;/sup&gt; (OTC available)</td>
<td>Prescription labeling for Veramyst states that concomitant administration with ritonavir should be avoided and caution is advised with potent CYP3A4 inhibitor.&lt;sup&gt;15&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Fluticasone Propionate</strong></td>
<td>Generic (Rx)&lt;sup&gt;4&lt;/sup&gt; (OTC available)</td>
<td>Since fluticasone propionate is a substrate of CYP3A4, the use of strong CYP3A4 inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, ketoconazole, telithromycin, conivaptan, lopinavir, voriconazole) with Xhance of Flonase is not recommended, as systemic corticosteroid adverse effect risk may be increased.&lt;sup&gt;3,4&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Xhance&lt;sup&gt;3&lt;/sup&gt; (Rx)</td>
<td></td>
</tr>
<tr>
<td><strong>Mometasone Furoate</strong></td>
<td>Nasonex&lt;sup&gt;1&lt;/sup&gt; (Rx) (generics available)</td>
<td>Labeling states that drug interaction studies have not been performed.&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Triamcinolone Acetonide</strong></td>
<td>Nasacort Allergy*&lt;sup&gt;19&lt;/sup&gt; (OTCs available)</td>
<td>Drug interactions are not discussed in prescription product labeling.&lt;sup&gt;19&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Abbreviations: AQ, aqueous; CYP3A4, cytochrome P450 3A4; OTC, over the counter; Rx, available by prescription only
<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Pediatric Indication Age</th>
<th>Hepatic &amp; Renal Impairment</th>
<th>Pregnancy &amp; Nursing</th>
</tr>
</thead>
</table>
| Beclomethasone dipropionate        | Qnasl\(^7\): indicated for patients ≥ 4 years old for AR (seasonal/perennial) | No formal PK studies have been conducted in any special population | Pregnancy Category C  
May be excreted into breast milk          |
|                                    | Beconase AQ\(^7\): indicated for patients ≥ 6 years old for AR (seasonal/perennial), non-allergic rhinitis, and prevention of nasal polyp recurrence | No dosing adjustment recommendation provided in the prescribing information | Potential teratogenic and embryocidal effects; May be excreted into breast milk |
| Budesonide                         | Rhinocort Allergy: OTC indicated for seasonal AR in patients ≥ 6 year;\(^9\) | PK studies have not been conducted in renal impairment. Reduced liver function may affect the elimination of corticosteroids however, dosing adjustment recommendations are not provided*\(^{10}\) | Pregnancy Category B  
May be excreted into breast milk*\(^{10}\) |
|                                    | Ommaris\(^2\): labeled to treat seasonal AR in patients ≥ 6 years old and for the treatment of perennial AR in patients ≥ 12 years | No adjustment for liver impairment necessary; trials in renal impairment were not conducted since renal elimination is a minor excretion route per labeling | Pregnancy Category C  
May be excreted into breast milk |
|                                    | Zetonna\(^2\): labeled to treat AR (perennial/seasonal) in patients ≥ 12 years |  |  |
| Ciclesonide                        | Flunisolide                       | No dosing adjustment recommendation provided in the prescribing information | Potential teratogenic and fetotoxic effects; May be excreted into breast milk |
|                                    | Generic\(^3\): for AR (seasonal/perennial) in patients ≥6 years |  |  |
| Fluticasone Furoate                | Flonase Sensimist: OTC product labeled for seasonal AR in patients ≥ 2 years;\(^{14}\) | No dosing adjustment recommendation provided in the European prescribing information*\(^{43}\) | Pregnancy Category C *\(^{15}\)  
There are no adequate studies conducted in pregnant women |
|                                    | Rx product was labeled to treat AR (perennial/seasonal) in patients ≥ 2 years\(^{15}\) |  |  |
|                                    | Flonase: OTC product labeled for seasonal AR in patients ≥ 4 years old;\(^{17}\) | PK studies have not been conducted in renal and hepatic impairment |  |
|                                    | Rx product is labeled for age ≥4 to treat perennial nonallergic rhinitis*\(^4\) |  |  |
|                                    | Xhance\(^2\): only for use in patients ≥18 years of age to treat nasal polyps |  |  |
| Fluticasone Propionate             | Nasonex\(^1\): indicated for patients ≥ 2 years old for allergic rhinitis and nasal congestion; for those ≥ 12 years for seasonal AR prophylaxis; and for those ≥ 18 years old to treat nasal polyps | PK studies have not been conducted in renal impairment. Reduced liver function may increase exposure of corticosteroids however, the levels remain hardly detectable; dosing adjustment recommendations are not provided\(^{10}\) | Pregnancy Category C  
May be excreted into breast milk |
| Mometasone Furoate                 | Nasacort: OTC product is indicated for seasonal AR in patients ≥2 years;\(^{18}\) Rx formulation was approved for perennial and seasonal AR in patients over 6 years of age | No dosing adjustment recommendation provided in the prescribing information*\(^{19}\) | Pregnancy Category C  
May be excreted into breast milk*\(^{19}\) |

Abbreviations: AR, allergic rhinitis; AQ, aqueous; OTC, over the counter; Rx, prescription only product

*Information is from a product label with a different brand name, since data is not provided in OTC labeling
Methods

Literature Search

Search strategies were developed by an Informational Scientist for OVID Medline and EMBASE. Strategies consisted of controlled vocabulary, such as MeSH, and keyword phrases. Two methodological filters were used, one for systematic reviews (ad hoc) and another for randomized controlled trials (RCT) developed by the Cochrane Collaboration. Results were limited to English language. Databases were searched from date of inception forward. In EMBASE, we excluded conference abstracts. Searches were conducted in December, 2017. Articles were transferred to EndNote for deduplication and to limit the publication date from 2007 onward. The complete search strategies and terms are available in Appendix B.

We also screened the reference lists and other relevant websites for further information:

I. For guidelines addressing the treatment of rhinitis: websites of American Academy of Allergy, Asthma and Immunology (AAAAI) and the American College of Allergy, Asthma and Immunology, guidelins.gov; American Academy of Otolaryngology Head and Neck Surgery (AAO-HNS)

II. For prescribing information package inserts: The Food and Drug Administration website (Drugs@FDA: FDA Approved Drug Products: https://www.accessdata.fda.gov/scripts/cder/daf/)

III. Evidence-based drug information databases (Micromedex and Lexicomp)

Screening

Two reviewers screened titles and abstracts for articles identified with publications dates from 2007 onward. Full text for all citations receiving at least one inclusion or maybe vote were retrieved and reviewed; inclusion was determined by the lead author. Figure 1 shows the PRISMA flow chart for the review process.

Inclusion and Exclusion Criteria

Systematic reviews and RCTs providing head-to-head efficacy and safety comparisons (for the approved indications) among the intranasal corticosteroids sprays listed in Table 1 were included. For product comparisons where a systematic review provided robust data, we examined trials published after the search date of that systematic review. A list containing the excluded references is provided in Appendix C.
Figure 1. PRISMA Data

Identification

Screening

Eligibility

Included

Records after duplicates removed
(n = 947)
This represents RCTs and SRs published since 2007
• SRs 313
• RCTs 634

Records screened
(n = 947)

Records excluded
(n = 904)

Full-text articles assessed for eligibility
(n = 51)

Full-text articles excluded, with reasons
(n = 41)
Wrong intervention (2)
Wrong patient population (1)
Wrong comparator (15)
Wrong study design (16)
Wrong outcome (5)
Article withdrawn (2)

Studies included in qualitative synthesis
(n = 10)

Notes: (a) 3 of the 947 records in box 1 were found outside of the search strategy, (b) for the 10 studies included in the qualitative synthesis, 9 address efficacy and 1 addresses safety.

Abbreviations: RCT, randomized controlled trial; SR, systematic review
Efficacy

Systematic Reviews

Upon screening 313 systematic reviews (restricted to 2007 through 2017), a total of 5 systematic reviews (SR) were identified that addressed treatment effect differences between intranasal corticosteroids. Three of these SRs identified head-to-head RCT evidence: 2 publications for allergic rhinitis indications (Selover et al. and Herman et al.)\textsuperscript{45,46} and the other (Chong et al.)\textsuperscript{47} reviewed use in the setting of CRSwNP. Although searches were conducted by authors for head-to-head comparative evidence, none was identified for INCS treatment in the setting of CRSsNP (Chong et al.)\textsuperscript{47}, CRS following post-surgical intervention for nasal polyps (Fandino et al.)\textsuperscript{48}, and persistent allergic rhinitis in children (Al Sayyad et al.)\textsuperscript{49}. Findings from these systematic reviews are described below.

Allergic rhinitis

Selover et al. (2008) was a high quality systematic review searching Cochrane Central and Medline to September 2007 for controlled trials and systematic reviews comparing intranasal corticosteroids for patients with allergic rhinitis or non-allergic rhinitis.\textsuperscript{45}

- **Adults with seasonal allergic rhinitis**: No significant differences were found between agents with respect to total rhinitis symptom primary endpoints based on physician assessment, or when outcomes were assessed by patient-reported composite nasal symptom scores.\textsuperscript{45} Few selective secondary endpoint differences were found for budesonide versus fluticasone propionate.
  
  Head-to-head RCTs identified ranged between 2 and 8 weeks duration and included the following comparisons.
  
  a) Beclomethasone vs. triamcinolone (1 trial), fluticasone propionate (2 trials), mometasone (1 trial), budesonide (1 trial) and flunisolide (as the old chlorofluorocarbon formulation, 3 trials): no differences found in composite nasal symptom primary endpoints.
  
  b) Triamcinolone vs. fluticasone propionate (2 trials using aqueous forms): no differences found in composite nasal symptom primary endpoints.
  
  c) Budesonide vs. fluticasone propionate (1 trial): No differences found in composite nasal symptom endpoint over the whole time period.
  
  - **Note secondary endpoint differences**: While this trial found no difference in physician-rated global nasal symptom improvement between the budesonide and flunisolide treatment groups, there were significant differences found in secondary endpoints in favor of budesonide 256 mcg/day over fluticasone 200 mcg/day for the days analyzed when the pollen count was greater than 10grains/m\textsuperscript{3} and for the individual sneezing score.\textsuperscript{50}
Three trials were identified that assessed Rhinoconjunctivitis Quality of Life after 3 weeks of treatment comparing triamcinolone to beclomethasone and fluticasone propionate (2 trials). Similar mean reductions were found between the treatment groups.45

- **Adults with perennial allergic rhinitis:**
  Head-to-head RCTs ranged between 3 weeks to 1 year duration and included the following comparisons:
  
a) Beclomethasone vs. flunisolide (3 trials), triamcinolone (1 trial) fluticasone propionate (2 trials), and budesonide (1 trial)
  b) Budesonide vs. fluticasone propionate (1 trial)
  c) Mometasone vs. fluticasone propionate (1 trial); and budesonide (1 trial)

  An RCT by Day et al., assessed the efficacy difference between budesonide versus fluticasone propionate over 6-weeks and including 273 adults. A significant difference was found in favor of budesonide 256 mcg per day versus fluticasone propionate 200 mcg daily based on a combined patient-rated nasal score (-2.11 vs -0.65, p=0.031). Primary efficacy nasal symptoms included blocked nose, runny nose, and sneezing rated by patients using a 4 point scale.51 It should be noted that the dosage form used in the study was a 64 mcg/actuation product; this strength is no longer available in the US.

  A study by Mandl et al, assessed the efficacy difference between mometasone 200 mcg versus fluticasone propionate 200 mcg administer daily. 52 This study reported conflicting results between the primary patient-rated endpoint and the secondary physician rated endpoint. This was a 12 week, multicenter study including 550 adults and adolescents over 12 years old. The primary outcome of patient-rated total nasal symptom score reduction did not differ between the two groups at any time period, yet a significantly greater reduction in physician-rated secondary outcomes of nasal congestion (at day 29 and week 8), nasal discharge (at week 8 and 12), and overall condition (at week 8, and 12) was reported for the mometasone group. Primary efficacy nasal symptoms included sneezing, rhinorrhea, nasal itch, and congestion rated by patients using a 4 point scale. 52

  No other significant differences were found between agents when used at FDA-approved doses with respect to composite rhinitis symptoms.45

- **Children with seasonal allergic rhinitis:** Only 1 RCT was found for the pediatric population, which included children ages 6 to 11 years old (n=679).45 No significant differences were found with respect to physician-rated composite nasal symptom score reductions between groups treated with mometasone 100 or 200 mcg daily and beclomethasone 84 mcg twice daily after 4 weeks.53

- **Children with perennial allergic rhinitis:** One publication was found comparing beclomethasone 200 mcg twice daily to fluticasone 100 or 200 mcg once daily, including
children ages 4 to 11 years old (n=120). No significant differences were reported. In addition, the previous RCT by Mandl et al, discussed previously fits for this population.

Herman (2007) reviewed evidence from 1966 to January 2004 for RCTs in patients with allergic rhinitis comparing the once daily intranasal corticosteroid products. Findings are largely consistent with those by Selover et al.

- Several head-to-head studies were identified assessing once daily dosed INCSs for the treatment of seasonal allergic rhinitis: (a) triamcinolone vs. fluticasone propionate (2 trials), (b) budesonide vs. fluticasone propionate (1 trial), and mometasone (1 trial). No significant differences were found in terms of total nasal symptom score reduction for comparisons.
- Several head-to-head studies were identified assessing once daily dosed INCSs for the treatment of perennial allergic rhinitis: (a) budesonide vs. fluticasone propionate (1 trial), and mometasone (1 trial); and (b) mometasone vs. fluticasone propionate (1 trial). Similar to the SR by Selover et al, the head-to-head study showing a significant difference in favor of budesonide 256 mcg per day versus fluticasone propionate 200 mcg daily was identified. No significant differences were found in terms of total nasal symptom score reduction for other comparisons.

Chronic rhinosinusitis with nasal polyps

Chong et al, (Cochrane Review 2016) searched (up to August 11, 2015) for RCTs with a follow-up period of at least three months comparing different types of nasal corticosteroids for treatment of patients with or without nasal polyps. This SR included 3 RCTs evaluating head-to-head comparisons for the treatment of CRSwNP. No differences were reported for fluticasone propionate versus beclomethasone or mometasone furoate based on very low quality evidence.

- Fluticasone propionate nasal spray (400 mcg/day) versus beclomethasone dipropionate nasal spray (400mcg/day): 2 small studies (totaling 56 participants with polyps) evaluated disease severity and epistaxis which reported no differences between the two steroids. The evidence was graded as very low quality.
- Fluticasone propionate nasal spray (200 mcg/day) versus mometasone furoate nasal spray (200 mcg/day): 1 study was identified (including 100 participants with polyps) that evaluated disease severity by nasal symptoms scores, and reported no difference between the two steroids. The evidence was graded as very low quality.

No Head-to-head studies found for the following subpopulations & indications

CRSsNP

Chong et al, (Cochrane Review 2016) searched (up to August 11, 2015) for RCTs with a follow-up period of at least three months comparing different types of nasal corticosteroids used for patients with or without nasal polyps. No studies were found for the patient population without nasal polyps.
CRSwNP in adults post endoscopic sinus surgery and polypectomy

Fandino et al, (2013) searched (up to May 2012) for RCTs comparing INCSs with each other, versus placebo, or no treatment during the immediate postoperative period of endoscopic sinus surgery for at least 6 to 8 weeks continuously. No trial comparing INCs head-to-head were identified. Based on several placebo comparative studies, the authors concluded “INCS showed significant improvement in polyp score, patients’ symptoms and significant decrease in polyp recurrence in the first year postoperatively.”

Persistent allergic rhinitis in children

Al Sayyad et al, (Cochrane Review 2007) searched (up to September 5th, 2005) for randomized controlled trials comparing topical nasal steroid preparations against each other or placebo for the treatment of allergic rhinitis in children. No head-to-head trials were identified, only placebo controlled trials. The authors concluded that the three placebo controlled trials, “provided some weak and unreliable evidence for the effectiveness of Beconase AQ and flunisolide used topically intranasally for the treatment of intermittent and persistent allergic rhinitis in children.”

Randomized Controlled Trials

Following a systematic review of RCTs (published from 2007 through 2017), 4 additional RCTs were identified that addressed efficacy differences between intranasal corticosteroids. One trial was in regard to the indication for seasonal allergic rhinitis and the other 3 were conducted in the setting of perennial allergic rhinitis. Appendix D includes a table summarizing information from these trials described below.

Seasonal allergic rhinitis

Okubu et al, (2009), was a multicenter RCT taking place in Japan, comparing fluticasone furoate 110 mcg once daily versus fluticasone propionate 100 mcg twice daily (200mcg/day) in patients ≥16 year of age with a history of seasonal allergic rhinitis to Japanese ceder pollen for greater than 2 years. After treating patients for 2 weeks while symptoms were present during an active pollen season, no significant differences in primary or secondary endpoints were found at any time point between the treatment group. The primary efficacy end point was mean change from baseline over the entire treatment period in 3TNSS, defined as the sum (0 to 9) of three patient rated symptom scores for sneezing, rhinorrhea, and nasal congestion scored on a scale of 0 to 3 in the allergy diary. Secondary efficacy end points included (a) mean change from baseline over the entire treatment period in 4TNSS (sum of scores for sneezing, rhinorrhea, nasal congestion, and nasal itching), (b) mean change in the 3TNSS and 4TNSS in weeks 1 and 2; and over the entire treatment period in individual nasal symptom scores, (c) change from baseline in the individual nasal examination (rhinoscopy) score were also assessed,
(d) patients’ impression of the treatment effect, (e) change in the mean activities of daily living interference scores over the treatment period were also evaluated in this study. With regard to safety, the authors conclude that incidence of overall adverse events was comparable between treatment groups (17% for FFNS, and 18% for FPNS; 21% for placebo FFNS and 19% for placebo FPNS)

**Perennial Allergic Rhinitis**

Aneeza et al, (2013)\(^{55}\) was a single center RCT taking place in Malaysia, comparing fluticasone furoate NS 110 mcg once daily versus mometasone furoate NS 200 mcg once daily in patient \(\geq 12\) years of age \((n=63)\), who had both nasal and ocular symptoms of allergic rhinoconjunctivitis for 2 years or more. Both groups had significant improvement in patient rated nasal and ocular total symptom scores compared to baseline after 1 week of treatment, in addition to rhinoconjunctivitis quality of life scores after 1 month of treatment. No statistically significant differences between treatment groups were found for primary endpoints assessed at 4 and 8 weeks. Daily documentation of nasal (rhinorrhea, congestion, sneezing, and itching) and ocular (watering, itching, and redness) symptoms severity was based on a patient rated 4-point categorical scale from 0 to 3 for how patient felt at that moment.\(^{55}\)

Mak et al, (2013)\(^{56}\) was a single center RCT in Taiwan, comparing fluticasone propionate 100 mcg/day versus mometasone furoate 100 mcg/day in children 6 to 12 years of age \((n=83)\), diagnosed with moderate to severe perennial allergic rhinitis for at least 1 year, with a positive skin prick test response to house dust mites. After 4 weeks of treatment, there was no statistical difference found with respect to patient quality of life scores (based on 23 questions in five categories such as nasal symptoms, eye symptoms, practical problems, activity limitations, and other, recalled for the previous week, using a 7-point scale).\(^{56}\)

Ratner et al, (2009)\(^{57}\) compared an old product of beclomethasone aqueous nasal spray 0.084mg per actuation under the brand name Vancenase AQ, manufactured by Schering-Plough Corp, which has since been discontinued. This is a more concentrated form than the comparable beclomethasone aqueous product now on the market. This was a multicenter US study comparing the beclomethasone dipropionate monohydrate 168 mcg/day \((n=85)\) versus mometasone furoate 100 mcg/day \((n=166)\) in children 6 to less than 12 years old with established moderately severe perennial rhinitis at baseline. No efficacy difference was found between treatment groups over 8 to 52 weeks based on physician or subject rated condition scores using a 5 point rating scale to assessing nasal symptom severity (rhinorrhea, nasal congestions, nasal itch, and sneezing) and non-nasal symptom severity (itching/burning eyes, watery eye, eye redness, itching ears/or palate).\(^{57}\)
Safety

An RCT was identified (Fokkens et al, 2012) that assessed nasal epithelial atrophy following long-term treatment (for 1 year) of adults with perennial AR with fluticasone furoate 110 mcg versus mometasone furoate 200 mcg, each administered once daily. After 52 weeks, there was no difference in epithelial thickening (per nasal biopsy) between active treatment groups and their respective placebo control groups, nor between each active arm. The authors concluded that long-term treatment of fluticasone furoate and mometasone does not induce nasal epithelium atrophy. More recently, in 2015, Verkerk et al, concluded that “The concept of nasal mucosal atrophy is poorly defined and there is no histological evidence for deleterious effects from INCS use on human nasal mucosa,” upon performing a systematic review.

Intranasal corticosteroids are well tolerated with common mild adverse effects being headache, epistaxis, dizziness, and nasopharyngeal irritation. Serious, yet infrequent, adverse effects include fungal infection, growth inhibition, hypothalamic pituitary adrenal axis suppression, cataracts, increased intraocular pressure, nasal mucosal ulceration, and loss of taste and smell. Patients should be cautioned about possible brief lightheadedness/dizziness upon administration. Table 6 provides general warning considerations for all nasal corticosteroids.

Table 6. General warnings for INCS drug class

- Nasal discomfort, epistaxis, nasal ulceration, Candida albicans infection, nasal septal perforation, impaired wound healing: monitor for possible changes in the nasal mucosa with long-term use and avoid use in patients with recent nasal ulcers, nasal surgery, or nasal trauma.
- Eye Disorders: monitor for change in vision, increased intraocular pressure, blurred vision, glaucoma, and cataracts.
- Hypersensitivity
- Potential worsening of existing tuberculosis; fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex. More serious or even fatal course of chickenpox or measles in susceptible patients.
- Adrenal insufficiency and hypercorticism with very high dosages or at the regular dosage in susceptible individuals.
- Potential reduction in growth velocity in pediatric patients: monitor growth routinely

* Refer to prescribing information for full details and recommended monitoring with respect to warnings/precautions
Intranasal corticosteroids are recommended and widely used for the management of allergic rhinitis and for nasal polyps. When using approved INCSs for allergic rhinitis, most products are administered once daily with the exception of beclomethasone dipropionate monohydrate (Beconase AQ) and generic flunisolide nasal sprays, dosed twice daily. The 3 products indicated for the management of nasal polyps (e.g. Beconase AQ, Nasonex, and Xhance) are dosed twice daily. Preference for the use of one INCS over another is not specified in guidelines identified for the treatment of allergic rhinitis, chronic rhinosinusitis, or for nasal polyps.

Following a systematic search, we screened 313 systematic reviews and 634 randomized controlled trials published from 2007 onward. Where head-to-head studies were available, (a) no difference was reported in the change of CRSwNP disease severity comparing fluticasone propionate with beclomethasone or mometasone furoate; and (b) there was no difference in epithelial thickening after 52 weeks of treatment with fluticasone furoate versus mometasone (safety endpoint).

No head-to-head studies were found in systematic reviews designed to address INCS-head-to-head comparative evidence in the settings of CRS without nasal polyps (Chong et al, Cochrane 2016); CRS following post-surgical intervention for nasal polyps (Fandino et al, 2013); and persistent allergic rhinitis in children (Al Sayyad et al, Cochrane 2007). Additional RCTs published since 2007, reported no significant differences in primary efficacy endpoints between certain treatment comparisons: fluticasone furoate versus mometasone furoate and beclomethasone versus mometasone for perennial AR; fluticasone propionate versus mometasone for child dust mite AR; fluticasone furoate versus fluticasone propionate for seasonal AR.

The majority of evidence suggests that these products have similar efficacy profiles, with one head-to-head comparison standing out in particular (budesonide vs. fluticasone propionate). One RCT (Day et al.) reported a significant difference the reduction of the patient-rated total nasal symptom score (primary endpoint) in favor of budesonide 256 mcg/day versus fluticasone propionate 200 mcg/day for treatment of adults with perennial allergic rhinitis. In the setting of adult seasonal allergic rhinitis, one study (Stern et al.) suggested budesonide 256 mcg/day improves patient-rated nasal symptoms better than fluticasone propionate 200 mcg/day only for days when the pollen count was greater than 10 grains/m³; products performed similarly when total nasal symptom scores were evaluated over all treatment days regardless of pollen count.
# Appendix A: INCS Indication Comparison

Table 1. Indication comparisons for nasal corticosteroids

<table>
<thead>
<tr>
<th>Generic name (available brand names)</th>
<th>Nasal Polyps</th>
<th>Allergic Rhinitis</th>
<th>Non-allergic Rhinitis/or Vasomotor</th>
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<td></td>
<td></td>
<td>Perennial</td>
<td>Seasonal</td>
</tr>
<tr>
<td>Beclomethasone dipropionate (Qnasl Rx)</td>
<td></td>
<td>X</td>
<td>X</td>
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<tr>
<td>Beclomethasone dipropionate monohydrate (Beconase AQ Rx)</td>
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<td>X</td>
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<td>X (Rx)</td>
<td>X (OTC/Rx)</td>
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<tr>
<td>Ciclesonide (Omnaris, Zetonna)</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Flunisolide (Generic Rx)</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Fluticasone Furoate (Flonase Sensimist OTC)</td>
<td>X (per old Rx Veramyst labeling)</td>
<td>X (OTC)</td>
<td></td>
</tr>
<tr>
<td>Fluticasone Propionate (Generic Rx; Flonase OTC; Xhance Rx)</td>
<td>X (Xhance product only)</td>
<td>X (Flonase OTC)</td>
<td>X (Rx)</td>
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<tr>
<td>Mometasone Furoate (Nasonex Rx)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Triamcinolone Acetonide (Nasacort OTC)</td>
<td>X (per old Rx Nasacort labeling)</td>
<td>X (OTC)</td>
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</table>

*Note that the indication is specified for the drug moiety in general, however, depends on the specific product formulation/strength/age group. Refer to table 1 in text for the specific product that the indication applies to.

Abbreviations: OTC, over the counter formulation; Rx, prescription formulation
### Appendix B: Search Strategies

#### Table 1. Ovid Medline Literature Search Strategy

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<td>2  Budesonide/ or (acorspray or aerox or allercort or aquacort or “b cort” or bidien or budecol or budecort or budefat or budeflam or budek or budin or budlen or budonen or budonen or budosen or budlair or budo-san</td>
<td>(3670)</td>
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<tr>
<td>3  (ciclesonide or alvesco or “b 9207 015” or “b 9207015” or “b9207 015” or b9207015 or “by 9010” or by9010 or omnaris or zetona)</td>
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<td>4  (flunisolide or aerobid or aerobid-m or aerospan or bronalide or bronilide or cyntaris or flunisolide hemihydrate or fluinate or gilblu or inhaclor or locasyn or lokilan or lunis or nasalide or nasarel or rhinalar or “rs 3999” or rs3999 or sanergal or seractin or synaclyn or syntaris or “val 679” or val679)</td>
<td>(406)</td>
</tr>
<tr>
<td>5  (“fluticasone furoate” or alisade or allermist or arnuity or arnuity ellipta or avamys</td>
<td>(328)</td>
</tr>
<tr>
<td>6  Fluticasone/ or (“fluticasone propionate” or “armonair respicklick” or atmum or axotide or “beconase allergy 24 hour” or “cci 18781” or cci18781 or cultivat or cultivate or fixonase or fixolide or fixovate or flonase or fluspiral or “fluticasone 17 propionate” or flutivate or fluxonal or “gr 18781” or gr18781 or zoflüt)</td>
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<tr>
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Table 1. Ovid Medline Literature Search Strategy

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29
Table 2. EMBASE Literature Search Strategy

- EMBASE.com

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|  |  | (303) |
Table 2. EMBASE Literature Search Strategy

- EMBASE.com

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Table 2. EMBASE Literature Search Strategy

- **EMBASE.com**

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</tr>
<tr>
<td>#18</td>
<td>#9 OR #10 (326,425)</td>
</tr>
<tr>
<td>#19</td>
<td>'rhinitis' /exp/mj OR 'rhinosinusitis'/exp/mj OR 'sinusitis'/exp/mj OR 'nose polyp'/mj OR 'pollen all ergy' /mj OR rhinitis:ti,ab,de,lnk OR 100,392 rhinosinusitis:ti,ab,de,lnk OR naso sinusitis:ti,ab,de,lnk OR in usnitis:ti,ab,de,lnk OR p ansinusitis:ti,ab,de,lnk OR sphenoiditis:ti,ab,de,lnk OR 'nasal polyp*':ti,ab,de,lnk OR 'nose polyp* ':t i,ab,de,lnk OR 'nasal pap i lloma*':t i,ab,de,lnk OR [papilloma NEAR/2 nasi]:t i,ab,de,lnk OR 'polyposis nasi':ti,ab,de,lnk OR 'hay fever':t i,ab,de,lnk OR h ayfever*:ti,ab,de,lnk OR 'pollen allerg* ':ti,ab,de,lnk OR poll enos*:ti,ab,de,lnk OR polli nos*:ti,ab,de,lnk OR (((pollen* OR season* OR summer) NEAR/2 (allerg* OR hypersensitivity* OR bronchitis* OR rhinoconjunctivitis)):ti,ab,de,lnk ) OR catarrh: ti,ab,de,lnk</td>
</tr>
<tr>
<td>#20</td>
<td>#18 AND #11 [ Drugs + Drug class plus Nasal] (5,102)</td>
</tr>
<tr>
<td>#21</td>
<td>#18 AND #19 [ Drugs + Drug class plus Indications] (5,567)</td>
</tr>
<tr>
<td>#22</td>
<td>#20 AND #17 [ RCTs for Drugs + Drug class plus Nasal] (1,151)</td>
</tr>
<tr>
<td>#23</td>
<td>#21 AND #17 [ RCTs for Drugs + Drug class plus Indications] (1,204)</td>
</tr>
<tr>
<td>#24</td>
<td>#22 OR #23 (1,432)</td>
</tr>
<tr>
<td>#25</td>
<td>#24 NOT #16 [RCTs (Indication OR Nasal) not SR for last 5 yrs] (1,406)</td>
</tr>
</tbody>
</table>
Appendix C: Excluded Studies

Wrong intervention

   - Patient preference study (not efficacy study) that appears to use products not available in the US

Wrong patient population

Wrong comparator


   - Study used a fluticasone propionate product not available in the US (100 mcg/actuation)


Wrong study design

   - Literature search dates were too limited, only searching 1 years’ worth of studies
   - Randomization unclear
   - This is a descriptive review article without a systematic search methodology
   - This is a descriptive review article without a systematic search methodology
   - This is a descriptive review article without a systematic search methodology

Wrong outcome


**Other**

   - Article withdrawn by Cochrane and updated to publication by Chong et al. 2016

   - Article withdrawn by Cochrane and updated to publication by Chong et al. 2016
## Appendix D: Randomized Controlled Trials

### Table 1: Randomized Controlled Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Interventions &amp; Population</th>
<th>Results</th>
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<tbody>
<tr>
<td><strong>Informational: excluded due to wrong outcome</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yanez et al 2016: A patient preference study that evaluated fluticasone furoate and mometasone furoate nasal sprays for allergic rhinitis</td>
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<td></td>
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<tr>
<td>Multicenter, double blind Single dose cross-over study</td>
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<tr>
<td><strong>A)</strong> FFNS 27.5 mcg/actuation (Avamys GlaxoSmithKline, US trade name, Veramyst) with excipients (glucose anhydrous, dispersible cellulose, polysorbate 80, benzalkonium chloride, disodium edetate, and purified water): Dose: 2 sprays per nostril, 110mcg total dose</td>
<td>&quot;Overall, 56% of patients stated a preference for FFNS versus 32% for MFNS (p &lt; 0.001); the remaining 12% stated no preference. More patients stated a preference for FFNS versus MFNS for the attributes of “less drip down the throat” (p &lt; 0.001), “less run out of the nose” (p &lt; 0.05), “more soothing” (p &lt; 0.05), and “less irritating” (p &lt; 0.001). More patients responded in favor of FFNS versus MFNS for the immediate attributes, “run down the throat” (p &lt; 0.001), and “run out of the nose” (p &lt; 0.001), and, in the delayed attributes, “run down the throat” (p &lt; 0.001), “run out of the nose” (p &lt; 0.01), “presence of aftertaste” (p &lt; 0.01), and “no nasal irritation” (p &lt; 0.001).&quot;</td>
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<td>B) MFNS 50 mcg/actuation (Nasonex Merck Sharp &amp; Dohme Limited) with excipients (benzalkonium chloride, dispersible cellulose, glycerol, sodium citrate, citric acid monohydrate, polysorbate 80, and purified water) Dose: 2 sprays per nostril, 200mcg total dose</td>
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<td>Patients (n=300): adults, 18 – 65 years of age, with either seasonal or perennial allergic rhinitis confirmed by a positive allergen skin test result within 12 months of study treatment. Excluded women who were pregnant or breast-feeding; patients with an infection or structural abnormality of the respiratory system; patients who used an intranasal corticosteroid within 4 weeks of study participation, other intranasal medications within 1 week of study participation, or medications that could disturb taste or smell</td>
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<td></td>
<td>Author’s conclusion: “Patients with allergic rhinitis preferred FFNS versus MFNS overall and based on a number of individual attributes, including “less drip down the throat,” “less run out of the nose,” and “less irritating.” Greater preference may improve patient adherence and thereby improve symptom management of the patient’s allergic rhinitis.”</td>
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<tr>
<td>Study</td>
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<td>Informational: excluded due to wrong outcome</td>
<td>Patients were randomized to 2 weeks of treatment, then crossed over the next 2 weeks of treatment</td>
<td>“FNS was significantly preferred over MFNS. Significantly, fewer subjects perceived a bitter taste (p = 0.01), medication running down their throat (p = 0.033), and medication running out of their nose (p = 0.002) with FFNS. MFNS was more frequently reported to induce nasal irritation (p = 0.012), sneezing (p = 0.017), and rhinorrhea (p = 0.007) compared to FFNS. Interestingly, these findings were markedly observed in females. Medicine dripping out of the nose and nasal shooting were the most common problems reported for MFNS with a higher proportion of subjects who felt moderate-to-severe discomfort. Overall, 52.5% of patients expressed a preference for FFNS compared with 22.5% for MFNS.”</td>
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<tr>
<td>Yonezaki et al 2016: Preference evaluation and perceived sensory comparison of fluticasone furoate and mometasone furoate intranasal sprays in allergic rhinitis</td>
<td>A) FFNS (Allermist; GlaxoSmithKline K.K, Tokyo, Japan): Dose: 2 sprays per nostril, 110mcg total dose</td>
<td>Author’s Conclusion: “Several perceived sensory attributes of FFNS were rated significantly superior to MFNS. FFNS may contribute to enhanced treatment outcomes in AR patients due to improved treatment adherence”</td>
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<tr>
<td>Multicenter, (not blinded) cross-over study (2 weeks of treatment per intervention)</td>
<td>B) MFNS (Nasonex; MSD K.K, Tokyo, Japan): Dose: 2 sprays per nostril, 200mcg total dose</td>
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<th>Study</th>
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<td>Multicenter, (not blinded) cross-over study (2 weeks of treatment per intervention)</td>
<td>B) MFNS (Nasonex; MSD K.K, Tokyo, Japan): Dose: 2 sprays per nostril, 200mcg total dose</td>
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Table 1. Randomized Controlled Trials

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<tr>
<th>Study</th>
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</table>
| **Mak et al, 2013:** Comparison of Mometasone Furoate Monohydrate (Nasonex) and Fluticasone Propionate (Flixonase) Nasal Sprays in the Treatment of Dust Mite-sensitive Children with Perennial Allergic Rhinitis | Patients randomized to 4 weeks of treatment:  
A) **FPNS** (Flixonase): 1 spray per nostril, 100mcg total daily dose  
B) **MFNS** (Nasonex): 1 spray per nostril, 100mcg total daily dose  
Patients (n= 94): patients age 6 to 12 years old diagnosed with the following (a) moderate to severe (defined per ARIA classification as AR that occurs throughout the year) perennial allergic rhinitis for at least 1 year, (b) a positive reaction to mite-specific IgE, and (c) allergy to house dust mites confirmed by a skin-prick test response. Excluded individuals with a positive response to other allergens; deformities of the ear, nose, or throat, or infection in the 2 weeks preceding the initial visit; medications that may affect allergy symptoms (e.g oral antihistamines, decongestants, steroids, or leukotriene antagonists) within 2 weeks prior to the study or during the study period; respiratory-tract infection within 2 weeks prior to the study; intranasal corticosteroid use within 2 weeks prior to the study; or with nasal polyp disease.  
*Flixonase produced by GlaxoSmithKline  
The only between group differences that were tested for significance (with p values provided) include the finding for:  
1) Patient quality of life scores (based on 23 questions in five categories such as nasal symptoms, eye symptoms, practical problems, activity limitations, and other, recalled for the previous week, on a 7-point scale): there was not a significant difference between treatment groups at week 4  
• Although the authors concluded that the total symptom score analysis showed MFNS to be more effective for relieving nasal symptoms, and FPNS more effective for relieving non-nasal symptoms, a statistical significance test for the difference in baseline change between treatment groups was not performed (rather significance was only tested against baseline score) and there is clear overlap in the result intervals provided suggesting that differences between treatment groups were not significant. Thus one should not conclude that one agent is better than the other with this evidence. |
| **Aneeza et al, 2013:** Efficacy of mometasone furoate and fluticasone furoate on persistent allergic rhinoconjunctivitis investigator blinded, 8 week study | Patients were randomized to 8 weeks of treatment:  
A) **FFNS** (Avamys; GlaxoSmithKline): 110mcg total daily dose  
B) **MFNS** (Nasonex; Merck Sharp & Dohme Corp): 200mcg total daily dose  
• Patients allowed rescue medication (loratadine 10mg/day)  
Patients (n=78) 12 to 59 years old who had both nasal and ocular symptoms of allergic rhinoconjunctivitis for 2 years or more. Excluded patients pregnant; with other nasal obstructive conditions or nasal polyps; smokers; users of INCS or oral steroids for 4 weeks before the baseline period.  
Patients were dropped from the study if they did not complete 80% of their symptom scores in their diary or were noncompliant to treatment.  
• Endpoints assessed at 4 and 8 weeks  
1. Rhinoconjunctivitis QOLQ  
2. Daily documentation of nasal and ocular symptoms severity using a 4-point categorical scale from 0 to 3 (for how patient felt at that moment)  
• Total nasal symptom score (TNSS): tally of nasal symptoms (rhinorrhea, congestion, sneezing, and itching)  
• Total ocular symptoms score: tally of ocular symptoms TOSS(watering, itching, and redness)  
• 63 patients who were randomized completed the study: (MFNS n=36 and FFNS n=27); there was a 19.2% drop out rate mainly due to medication non-compliance and default of follow-up (per protocol assessments)  
**Results:** Both groups had significant improvement in nasal and ocular total symptom scores compared to baseline after 1 week of treatment, in addition to QOLQ scores after 1 month. **No statistically significant differences between groups were found for these scores.** |
<table>
<thead>
<tr>
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<tbody>
<tr>
<td><strong>Fokkens et al, 2012</strong></td>
<td>A) FFNS 110mcg total daily dose administered for 1 yr (n=56)</td>
<td>“Results: The nasal biopsy population comprised 96 participants (37 using FFNS, 42 using MFNS, and 17 healthy controls). Epithelial thickness did not change appreciably from baseline to week 52 in any of the groups and mean change from baseline did not differ between FFNS and MFNS (least square mean difference, &lt;0.001 mm, 95% confidence interval, -0.007, 0.006).”</td>
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<td></td>
<td>B) MFNS 200mcg total daily dose administered for 1 yr (n=60)</td>
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<td>Male or female subjects 18 years and older. The active treatment group (FFNS and MFNS) required a physician-confirmed greater than 2-year clinical history of treated perennial allergic rhinitis Excluded: pregnant adults; persons with severe physical obstruction of the nose, nasal injury or surgery in the past 3 months, asthma unless it was mild intermittent asthma, rhinitis medicamentosa, upper respiratory bacterial or viral infection within 4 weeks before screening, acute sinusitis or significant chronic sinusitis, and current or recent tobacco use, presence of glaucoma and/or cataracts or ocular herpes simplex, and use of the following medications within the following time periods before screening: subcutaneous omalizumab within 5 months; corticosteroids (intranasal form within 4 weeks and inhaled, intramuscular, i.v., and/or dermatologic forms, except ≤1% hydrocortisone cream/ointment, within 8 weeks); short-acting prescription or over-the-counter antihistamines, oral or intranasal decongestants, anticholinergics, or oral antileukotrienes within 3 days; long-acting antihistamines within 10 days (except astemizole, within 12 weeks); and intranasal antihistamines or intranasal ocular cromolyn within 14 days.</td>
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<td><strong>Informational: excluded due to wrong outcome</strong></td>
<td>A) FFNS (Veramyst; GlaxoSmithKline): 110mcg total daily dose administered for 7 days, then off (washed out) for 7 days prior to crossing over to FPNS (n=166)</td>
<td>58% vs 27% (P&lt;0.001) preferred fluticasone furoate compared with fluticasone propionate based on scent or odor; 15% of patients had no preference for either product based on scent or odor.</td>
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<td>B) FPNS (Fionase; GlaxoSmithKline): 200mcg total daily dose administered for 7 days (n=159)</td>
<td>Significantly more patients preferred fluticasone furoate compared with fluticasone propionate “because less medication leaked out of the nose or down the throat (59% vs 21%), because of the gentleness of the mist (57% vs 26%), and because of less aftertaste (60% vs 18%).”</td>
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<td></td>
<td>C) Placebo FFNS for 7 days</td>
<td>“No statistically significant differences were found in preferences for fluticasone furoate and fluticasone propionate with respect to attributes related to ease of use, consistency of medication delivered, the delivery method, or device comfort. Between 17%</td>
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<td>D) Placebo FPNS for 7 days</td>
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<td>Included adults with a history of seasonal AR and nasal symptoms during the 2 previous fall seasons (with a positive skin test to fall allergens appropriate to their region). Patient had to have an average 12-hour rTNSS of 6 or higher.</td>
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Table 1: Randomized Controlled Trials

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<tr>
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<tr>
<td>propionate in adults with seasonal allergic rhinitis: a randomized, placebo controlled, double-blind study</td>
<td>Excluded pregnant adults, clinically significant uncontrolled medical disorder, infection, or structural abnormality of the respiratory system, recent use of allergy or other medications, use of intranasal corticosteroids within 4 weeks of the study, use of oral or parenteral corticosteroids within 8 weeks of the study, and use of intranasal fluticasone propionate or fluticasone furoate within 1 year before the study.</td>
<td>and 31% of patients had no preference for either fluticasone furoate or fluticasone propionate with respect to the secondary and other attributes.</td>
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Non-inferiority study using 0.75 margin; multicenter study in Japan; investigator blinded; using per protocol assessment

Patients randomized to 2 weeks’ treatment of:

A) **FFNS** 110mcg once daily (n=147, 21% with PAR)
B) **FPNS** 200mcg twice daily (n=144, 17% with PAR)
C) Placebo FFNS once daily (n=70, 20% with PAR)
D) Placebo FPNS twice daily (n=72; 24% with PAR)

Patients aged 16 and older with a history of more than 2 years of seasonal allergic rhinitis with positive skin prick test to Japanese cedar pollen or a positive *in vitro* test for specific IgE antibody; diagnosis confirmed by either nasal challenge test or nasal eosinophil counting; required to be symptomatic at baseline during the Japanese cedar pollen season; with or without perennial allergic rhinitis

Excluded pregnant/lactating women; patients who had an interfering existing nasal disorder (e.g., acute/chronic sinusitis, nasal polyposis, vasomotor rhinitis, or drug-induced rhinitis) or a coexisting disease (e.g., serious hepatic/renal, cardiac, or pulmonary dysfunction; tuberculosis diseases; systemic mycosis; hypertension; diabetes mellitus; nasal or oropharynx candidiasis; asthma [except no significant differences found]

**Primary efficacy end point:** mean change from baseline over the entire treatment period in 3TNSS, defined as the sum (0 – 9) of three individual symptom scores for sneezing, rhinorrhoea, and nasal congestion scored on a scale of 0–3 in the allergy diary.

- Mean change from baseline in each active treatment group was similar and within the non-inferiority margin (mean difference upper limit 95% CI 0.17)

**Secondary efficacy end points:**

(a) mean change from baseline over the entire treatment period in 4TNSS (sum of scores for sneezing, rhinorrhoea, nasal congestion, and nasal itching)

- Mean change from baseline in each active treatment group was similar for all treatment periods and within the non-inferiority margin for FFNS and FPNS treatment groups (difference of adjusted means; week 1, -0.245; week 2, -0.279; over the entire treatment period, -0.249, 95% CI not reported)

(b) mean change in the 3TNSS and 4TNSS in weeks 1 and 2; and over the entire treatment period in individual nasal symptom scores
### Table 1: Randomized Controlled Trials

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<td><strong>Ratner et al, 2009:</strong> Mometasone furoate nasal spray is safe and effective for 1-year treatment of children with perennial allergic rhinitis</td>
<td>- Patients 6 to less than 12 years old were required to have perennial rhinitis of at least moderately severe at baseline. Excluded patients with asthma managed by inhaled or systemic corticosteroids; current condition or a history of clinically significant sinusitis or chronic purulent postnasal drip; rhinitis medicamentosa; multiple drug allergies or allergy to corticosteroids; nasal structural abnormalities affecting nasal air flow; upper respiratory infection or sinus infection requiring antibiotic therapy during the 2 weeks prior to screening; viral upper respiratory infection during the 7 days before screening; or receiving immunotherapy (desensitization).</td>
<td>- Similar mean changes were found for symptom scores (sneezing, rhinorrhea, nasal congestion, and nasal itching) in the FFNS and FPNS groups at each of the treatment period and the entire treatment period. &lt;br&gt;• No significant difference between active treatment groups &lt;br&gt;• Statistical significance testing not reported to assess difference between active treatment groups &lt;br&gt;• The number of days until onset of action, based on the significant change in 3TNSS compared with placebo &lt;br&gt;• Change in the mean activities of daily living interference scores over the treatment period were also evaluated in this study &lt;br&gt;• No significant difference between active treatment groups.</td>
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Safety: Authors conclude that incidence of overall adverse events was comparable between treatment groups (17% for FFNS, and 18% for FPNS, 21% for placebo FFNS and 19% for placebo FPNS). No efficacy difference between treatments over 8 to 52 weeks based on physician or subject rated condition scores using a 5 point rating scale (in which 1 = complete relief and 5 = treatment failure).
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<td>US between 1996 to 1998 Funded by Scheing-Plough</td>
<td>were excluded unless they had been on a stable maintenance schedule for at least 1 month prior to screening.</td>
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Abbreviations: AR, allergic rhinitis; BDPM, beclomethasone dipropionate monohydrate; FF, fluticasone furoate; FFNS, fluticasone furoate nasal spray; FPNS, fluticasone propionate nasal spray; INCS, intranasal corticosteroids; MF, mometasone furoate; MFNS, mometasone Furoate nasal spray; PAR, perennial allergic rhinitis; QOLQ, quality of life questionnaire
References


