

Drug Class Review

Nasal Corticosteroids

Final Report Update 1

June 2008

**The Agency for Healthcare Research and
Quality has not yet seen or approved this report**

The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

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EVIDENCE TABLES – Published in a separate document

Highlighting indicates new evidence.

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INTRODUCTION

Allergic rhinitis is a condition characterized by sneezing, watery rhinorrhea, nasal itching, congestion, itchy palate, and itchy, red, and watery eyes.¹ The prevalence of allergic rhinitis has increased significantly over the last 15 years and the disease currently affects twenty to forty million Americans.² It is estimated that in 2002, approximately 14 million medical office visits were attributed to allergic rhinitis.² Many suffering from allergic rhinitis are children and young adults, whom, if treated early, may avoid later stage complications.³ If left untreated, this condition could lead to the development or worsening of comorbidities including chronic or recurrent sinusitis, asthma, otitis media, and respiratory infections.^{4,5} Moderate to severe allergic rhinitis may also lead to sleep disorders, fatigue, and learning problems.^{3,5}

Rhinitis can be divided into 2 broad categories: allergic and non-allergic. Allergic rhinitis consists of seasonal and perennial rhinitis. Seasonal allergic rhinitis, also called hay fever, is characterized by symptoms that occur in response to specific seasonally occurring allergens. Allergens may include pollen from trees, grasses, and weeds. Perennial allergic rhinitis occurs throughout the year and is caused by allergens such as house dust mites, animal dander, cockroaches, and molds. In some geographic locations, pollen can play a role in perennial rhinitis. Patients are often sensitized to both seasonal and perennial allergens, which can be termed mixed allergic rhinitis.⁶

There is a prominent genetic component involved in the development of allergic rhinitis. Individuals with both parents suffering from atopic disease have a 50% or greater chance of affliction with allergic disease.⁵ The symptoms of allergic rhinitis are caused by an IgE-mediated immune response to a particular allergen. An antibody, called immunoglobulin E (IgE), represents a major component of this immunologic reaction. The binding of the allergen to IgE molecules leads to a chain of events that includes the release of mediators such as histamine and leukotrienes and culminates in the arrival of inflammatory cells to the region. These inflammatory cells are responsible for the clinical symptoms of allergic rhinitis.

In contrast, non-allergic rhinitis is often a diagnosis of exclusion and represents a diverse group of disorders. There are several different types of non-allergic rhinitis: drug induced, gustatory, hormonal, infectious, non-allergic rhinitis with eosinophilia syndrome, occupational, anatomic, and vasomotor.⁷ A classification according to the presence or absence of inflammatory cells in nasal scrapings has also been suggested in order to find the most effective treatment.⁸ The symptoms of non-allergic rhinitis are similar to allergic rhinitis and include nasal obstruction, rhinorrhea, and congestion. Nasal itch and conjunctival irritation may be less with non-allergic compared with allergic rhinitis.⁵

There are several types of treatments available for allergic and non-allergic rhinitis. Allergen avoidance is not always possible for patients with allergic rhinitis. These patients can use oral or nasal antihistamines and decongestants without a prescription. Nasal mast cell stabilizers, oral leukotriene modifiers, anticholinergic nasal spray, systemic and nasal corticosteroids, anti-IgE monoclonal antibodies, and immunotherapy can be obtained with a prescription from a healthcare provider. Treatment for non-allergic rhinitis focuses on symptom management and includes several of the aforementioned medications.

Nasal corticosteroids are a safe and effective treatment option for both allergic and non-allergic rhinitis. There are currently 8 different nasal corticosteroid preparations on the U.S. market (Table 1). The nasal sprays differ with respect to delivery device and propellant, as well as potency and dosing frequency. When used daily, nasal corticosteroids significantly reduce nasal congestion, sneezing, rhinorrhea, and other symptoms.⁶

Overall, the nasal preparations are well tolerated and patients experience few, if any, adverse effects. These include nasal irritation, nasal dryness, mild to moderate epistaxis, transient headache, and dizziness. More serious adverse effects include local fungal infections, potential growth inhibition, hypothalamic-pituitary-adrenal suppression, and ophthalmologic adverse effects, including cataract.

Table 1. Nasal corticosteroid FDA-approved indications and recommended doses

Generic name	Trade name	Nonallergic		Perennial AR	Seasonal AR	Dosage in adults	Dosage in children
		Nasal polyps	(vasomotor) rhinitis				
Beclomethasone	Beconase AQ [®] (42 mcg/spray)	X ^a	X	X	X	1-2 spray EN 2x/day Maximum dose: 2 sprays EN 2x/day	6-12 yrs old: 1 spray EN 2x/day Maximum dose: 2 sprays EN 2x/day
Budesonide	Rhinocort Aqua ^{®b} (32 mcg/spray)			X	X	1 spray EN 1x/day Maximum dose: 4 sprays EN 1x/day	≥ 6 yrs old: 1 spray EN 1x/day Maximum dose <12 yrs old: 2 sprays EN 1x/day
Ciclesonide	Omnaris [®] (50 mcg/spray)			X	X	2 sprays EN 1x/day Maximum dose: 2 sprays in each nostril (200 mcg/day)	≥6 yrs seasonal AR: 2 sprays EN 1x/day; Maximum dose: 2 sprays EN (200 mcg/day) ≥12 yrs perennial AR: 2 sprays EN 1x/day Maximum dose: 2 sprays EN (200 mcg/day)
Flunisolide	Generic flunisolide (25 mcg/spray) Nasarel [®] (29 mcg/spray)			X	X	2 sprays EN 2x/day; may increase to 2 sprays EN 3x/day Maximum dose: 8 sprays EN/day	6-14 yrs old: 1 spray EN 3x/day or 2 sprays EN 2x/day Maximum dose: 4 sprays EN 1x/day
Fluticasone furoate	Veramyst [®] (55 mcg/spray)			X	X	2 sprays EN 1x/day may decrease to 1 spray EN 1x/day once maximum benefit is achieved and symptoms are controlled	2 to 12 yrs: initial, 1 spray EN 1x/day; if adequate response is not achieved, may increase to 2 sprays EN 1x/day; reduce dosage to 1 spray EN 1x/day once maximum benefit is achieved and symptoms are controlled ≥12 yrs: 2 sprays EN 1x/day; may decrease to 1 spray EN 1x/day once

Generic name	Trade name	Nasal polyps	Nonallergic (vasomotor) rhinitis	Perennial AR	Seasonal AR	Dosage in adults	Dosage in children
							maximum benefit is achieved and symptoms are controlled
Fluticasone propionate	Generic fluticasone (50 mcg/spray)		X	X	X	2 sprays EN 1x/day or 1 spray EN 2x/day	≥4 yrs old: 1 spray EN 1x/day
	Flonase [®] (50 mcg/spray)					Maximum dose: 2 sprays EN 1x/day	Maximum dose: 2 sprays EN 1x/day
Mometasone	Nasonex [®] (50 mcg/spray)	X (≥18 years old)		X	X ^c	2 sprays EN 1x/day Nasal polyps: 2 sprays EN 2x/day	(2-11 years old): 1 spray EN 1x/day
Triamcinolone	Nasacort AQ [®] (55 mcg/spray)			X	X	2 sprays EN 1x/day Maximum dose: 2 sprays EN 1x/day	6-11 yrs old: 1 spray EN 1x/day Maximum dose: 2 sprays EN 1x/day

^a Indicated for the prevention of recurrence of nasal polyps following surgical removal.

^b FDA pregnancy category B, all others category C.

^c Treatment and prophylaxis: Prophylaxis of seasonal allergic rhinitis with mometasone (200 mcg/day) is recommended 2-4 weeks prior to anticipated start of pollen season.

EN= each nostril; AR= allergic rhinitis

Data source: Micromedex

Scope and Key Questions

The purpose of this review is to help policy makers and clinicians make informed choices about the use of nasal corticosteroids. Our goal is to summarize comparative data on efficacy, effectiveness, tolerability, and safety.

Report authors drafted preliminary key questions, identifying the populations, interventions, and outcomes of interest, and based on these, the eligibility criteria for studies. These were reviewed and revised by the Washington State Preferred Drug Program (PDP). Washington State PDP is responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The Washington State PDP approved the following key questions to guide this review:

1. For adults and children with seasonal or perennial (allergic and non-allergic) rhinitis, do nasal corticosteroids differ in effectiveness?
2. For adults and children with seasonal or perennial (allergic and non-allergic) rhinitis, do nasal corticosteroids differ in safety or adverse events?
3. Are there subgroups of patients based on demographics (age, racial groups, gender), other medications, or comorbidities, or in pregnancy and lactation for which one nasal corticosteroid is more effective or associated with fewer adverse events?

Inclusion Criteria

Population(s)

Adult patients and children (under age 18) in outpatient settings with the following diagnosis:

- Seasonal or perennial allergic or non-allergic rhinitis

Table 2. Interventions

Generic name	Trade name(s)	Forms
Beclomethasone	Beconase [®] , Beconase AQ [®] , Vancenase [®] , Vancenase AQ [®]	Nasal spray
Budesonide	Rhinocort [®] , Rhinocort Aqua [®]	Nasal spray
Ciclesonide	Omnaris [®]	Nasal spray
Flunisolide	Nasalide [®] , Nasarel [®]	Nasal spray
Fluticasone furoate	Veramyst [®]	Nasal spray
Fluticasone propionate ^a	Flonase [®]	Nasal spray
Mometasone	Nasonex [®]	Nasal spray
Triamcinolone	Nasacort [®] , Nasacort AQ [®]	Nasal spray

^a Unless otherwise stated, fluticasone propionate is referred to as 'fluticasone' or 'fluticasone aqueous' throughout this report; fluticasone furoate is always referred to as such.

Effectiveness outcomes

- Symptomatic relief
- Onset of action

Safety outcomes

- Overall adverse effect reports
- Withdrawals due to adverse effects
- Serious adverse events reported
- Specific adverse events (localized infection of nasal mucosa, hypersensitivity, hypercorticism, HPA suppression, growth suppression in pediatric population, headache, throat soreness, dry mouth, nasal irritation)

Study designs

1. For efficacy, controlled clinical trials and good-quality systematic reviews
2. For safety, controlled clinical trials and good-quality systematic reviews and observational studies.

METHODS

Literature Search

To identify relevant citations, we searched the Cochrane Central Register of Controlled Trials (4th Quarter 2005 Update 1: 3rd Quarter 2007), the Cochrane Database of Systematic Reviews (3rd Quarter 2007), and MEDLINE (1966 to October Week 3 2005; Update 1: September Week 1 2007) using terms for included drugs, indications, and study designs (see Appendix A for complete search strategies). Our literature search was limited to English-language publications. To identify additional studies, we also searched reference lists of included studies and reviews and FDA information.⁹ In addition, dossiers were requested from manufacturers of the included drugs. Dossiers were submitted by the following pharmaceutical companies: AstraZeneca (budesonide aqueous), GlaxoSmithKline (fluticasone furoate), Sanofi-Aventis (triamcinolone acetonide), and Schering-Plough (mometasone furoate).

All citations were imported into an electronic database (EndNote 9.0).

Study Selection

Two reviewers independently assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above. Disagreements were resolved using a consensus process. Full-text articles of potentially relevant abstracts were retrieved and a second review for inclusion was conducted by reapplying the inclusion criteria.

Data Abstraction

The following data were abstracted from included trials: study design, setting, population characteristics (including sex, age, ethnicity, diagnosis), eligibility and exclusion criteria, interventions (dose and duration), comparisons, numbers screened, eligible, enrolled, and lost to follow-up, method of outcome ascertainment, and results for each outcome. We recorded intention-to-treat results when reported. In cases where only per-protocol results were reported, we calculated intention-to-treat results if the data for these calculations were available. In trials with crossover, outcomes for the first intervention were recorded if available. This was because of the potential for differential withdrawal prior to crossover biasing subsequent results and the possibility of either a “carryover effect” (from the first treatment) in studies without a washout period, or “rebound” effect from withdrawal of the first intervention.

Data abstracted from observational studies included design, eligibility criteria duration, interventions, concomitant medication, assessment techniques, age, gender, ethnicity, number of patients screened, eligible, enrolled, withdrawn, or lost to follow-up, number analyzed, and results.

Quality Assessment

We assessed the internal validity (quality) of trials based on the predefined criteria listed in Appendix B. These criteria are based on the U.S. Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination (U.K.) criteria.^{10, 11} We considered the following factors when rating internal validity: methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; maintenance of comparable groups; adequate reporting of dropouts, attrition, crossover, adherence, and

contamination; loss to follow-up; and the use of intention-to-treat analysis. Trials that had a fatal flaw were rated “poor-quality”; trials that met all criteria were rated “good-quality”; the remainder were rated “fair-quality.” As the fair-quality category is broad, studies with this rating vary in their strengths and weaknesses: the results of some fair-quality studies are *likely* to be valid, while others are only *probably* valid. A poor-quality trial is not valid—the results are at least as likely to reflect flaws in the study design as the true difference between the compared drugs. A fatal flaw is reflected by failing to meet *combinations* of items of the quality assessment checklist. External validity of trials was assessed based on whether the publication adequately described the study population, how similar patients were to the target population in whom the intervention will be applied, and whether the treatment received by the control group was reasonably representative of standard practice. We also recorded the role of the funding source.

Appendix B also shows the criteria we used to rate observational studies. These criteria reflect aspects of the study design that are particularly important for assessing adverse event rates. We rated observational studies as good-quality for adverse event assessment if they adequately met 6 or more of the 7 predefined criteria, fair-quality if they met 3 to 5 criteria and poor-quality if they met 2 or fewer criteria.

Included systematic reviews were also rated for quality based on pre-defined criteria (see Appendix B), based on a clear statement of the question(s), inclusion criteria, adequacy of search strategy, validity assessment and adequacy of detail provided for included studies, and appropriateness of the methods of synthesis. Overall quality ratings for the individual study were based on internal and external validity ratings for that trial. A particular randomized trial might receive 2 different ratings: one for effectiveness and another for adverse events. The overall strength of evidence for a particular key question reflects the quality, consistency, and power of the set of studies relevant to the question.

Evidence Synthesis

Effectiveness compared with efficacy. When available, we highlight *effectiveness* studies conducted in primary care or office-based settings that use less stringent eligibility criteria, assess health outcomes, and have longer follow-up periods than most *efficacy* studies. The results of effectiveness studies are more applicable to the “typical” patient than results from highly selected populations in efficacy studies. Examples of “effectiveness” outcomes include quality of life, global measures of academic success, and the ability to work or function in social activities. These outcomes are more important to patients, family and care providers than surrogate or intermediate measures such as scores based on psychometric scales.

Efficacy studies provide the best information about how a drug performs in controlled settings that allow for better control over potential confounding factors and bias. However, the results of efficacy studies are not always applicable to many, or to most, patients seen in everyday practice. This is because most efficacy studies use strict eligibility criteria, which may exclude patients based on their age, sex, medication compliance, or severity of illness. For many drug classes severely impaired patients are often excluded from trials. Often, efficacy studies also exclude patients who have “comorbid” diseases, meaning diseases other than the one under study. Efficacy studies may also use dosing regimens and follow up protocols that may be impractical in other practice settings. They often restrict options, such as combining therapies or switching drugs that are of value in actual practice. They often examine the short-term effects of drugs that, in practice, are used for much longer periods of time. Finally, they tend to use

objective measures of effect that do not capture all of the benefits and harms of a drug or do not reflect the outcomes that are most important to patients and their families.

Data presentation. We constructed evidence tables showing the study characteristics, quality ratings, and results for all included studies. Studies that evaluated 1 nasal corticosteroid against another provided direct evidence of comparative benefits and harms. Outcomes of changes in symptom measured using scales or tools with good validity and reliability are preferred over scales or tools with low validity/reliability or no reports of validity/reliability testing. Where possible, head-to-head data are the primary focus of the synthesis. No meta-analyses were conducted in this review due to heterogeneity in treatment regimens, use of concomitant medications, outcome reporting and patient populations.

In theory, trials that compare these drugs to other interventions or placebos can also provide evidence about effectiveness. This is known as an indirect comparison and can be difficult to interpret for a number of reasons, primarily issues of heterogeneity between trial populations, interventions, and assessment of outcomes. Indirect data are used to support direct comparisons, where they exist, and are also used as the primary comparison where no direct comparisons exist. Such indirect comparisons should be interpreted with caution.

When analyses of statistical significance were not presented, Fisher's exact test was performed using StatsDirect (CamCode, U.K.) when adequate data were provided.

RESULTS

Overall results of literature search

We identified 1,404 (Update 1: 282) articles from literature searches and reviews of reference lists. This includes citations from dossiers submitted by the manufacturers of mometasone, fluticasone, and budesonide (Update 1: budesonide aqueous, fluticasone furoate, mometasone furoate, and triamcinolone acetonide.) After applying the eligibility and exclusion criteria to the titles and abstracts, we obtained copies of 489 (Update 1: 77) full-text articles. After re-applying the criteria for inclusion, we ultimately included 84 (Update 1: 29) publications, including 9 from submitted dossiers. The results of our literature search are detailed in Appendix C.

Overall summary of the evidence

Effectiveness

- No effectiveness trials were identified

Efficacy and adverse effects

Adults

Seasonal allergic rhinitis in adults:

- There were no significant differences between nasal corticosteroids in their effects on rhinitis symptoms overall in head-to-head trials. On average, 78% to 88% of adults with seasonal allergic rhinitis in head-to-head trials were rated by physicians as demonstrating significant global improvement.
- Based on evidence from placebo-controlled trials, both ciclesonide and fluticasone furoate were significantly better than placebo in improving seasonal allergic rhinitis symptoms and quality of life scores. Where reported, changes in RQLQ scores were similar to those in head-to-head trials of other nasal corticosteroids.

Perennial allergic rhinitis in adults:

- Very few differences in efficacy were reported in head-to-head trials involving beclomethasone, budesonide, fluticasone, or mometasone in adults with perennial allergic rhinitis.
 - Budesonide aqueous 256 mcg was associated with a significantly greater mean point reduction in a combined nasal symptom score relative to fluticasone aqueous 200 mcg (-2.11 compared with -1.65, $P=0.031$) in one 6-week trial of 273 patients.¹²
 - It is unknown how new form of flunisolide or triamcinolone compare to other nasal corticosteroids due to a lack of head-to-head trial evidence.
- Quality of life outcomes were rarely reported in head-to-head trials and beclomethasone, fluticasone, and triamcinolone were associated with similar levels of improvement.

- Results from placebo-controlled trials of ciclesonide found improved quality of life scores relative to placebo. The effect of fluticasone furoate on quality of life outcomes is unclear; results from 2 unpublished studies are mixed.
- No head-to-head trials of adults with non-allergic rhinitis were identified. No indirect comparisons were made across placebo-controlled trials of fluticasone and mometasone due to heterogeneous efficacy outcome reporting.
- There were generally no significant differences between nasal corticosteroids in rates of withdrawals due to adverse events, headache, throat soreness, epistaxis, and nasal irritation when used in adults with seasonal or perennial allergic rhinitis in head-to-head trials that compared similar dose levels.
 - The old form of flunisolide was associated with significantly higher rates of nasal burning/stinging than beclomethasone AQ and the newer form of flunisolide across 2 head-to-head trials of adults with perennial allergic rhinitis.
- Cataract development was only reported in 1 observational study and there were no significant differences in incidence rates associated with beclomethasone use compared to nonuse.
- No evidence of glaucoma-associated adverse events was identified.
- Mometasone *prophylaxis* was superior to beclomethasone *prophylaxis* in preventing rhinitis symptoms during pre- and peak-seasons, but mometasone *prophylaxis* was also associated with significantly higher rates of headache.

Children

- In children, head-to-head trials of seasonal and perennial allergic rhinitis are few and beclomethasone, fluticasone, and mometasone were associated with similar reductions in rhinitis symptoms and with similar rates of more common respiratory and nervous system adverse effects. Evidence from placebo-controlled trials was insufficient for further assessment of comparative effects.
- No trials of children with non-allergic rhinitis were identified.
- Growth retardation in children:
 - Beclomethasone was associated with significantly lower height increase over 12 months relative to placebo in 1 trial and was similar to expected height increases over 3 years in a retrospective observational study.
 - In placebo-controlled trials, neither fluticasone, mometasone, nor budesonide were associated with growth retardation after 12 months.

- Budesonide was associated with development of 2 cases of transient lenticular opacities in an uncontrolled retrospective study of 78 children over a 2-year period; the clinical significance of the opacities was not reported.

Subgroups

- Evidence is insufficient to draw any conclusions about comparative effectiveness, efficacy, or safety in subgroups based on demographics, concomitant use of other medications, comorbidities (e.g., asthma, daytime somnolence/sleep disturbances), or pregnancy.

Detailed assessment

Key Question 1. For adults and children with seasonal or perennial (allergic and non-allergic) rhinitis, do nasal corticosteroids differ in effectiveness?

Seasonal Allergic Rhinitis

I. Adults with seasonal allergic rhinitis

A. Description of trials in adults with seasonal allergic rhinitis

We included 15 head-to-head trials of nasal corticosteroids for the treatment of seasonal allergic rhinitis in adults (Table 3, Evidence Tables 1 and 2).¹³⁻²⁷

Table 3. Head-to-head trial comparisons in adults with seasonal allergic rhinitis

	Beclomethasone	Old flunisolide	New flunisolide	Triamcinolone	Fluticasone p.	Mometasone	Budesonide
Beclomethasone		3		1	2	2	1
Old flunisolide			2				
New flunisolide							
Triamcinolone					3 ^a		
Fluticasone p.							1
Mometasone							
Budesonide							

^a One trial used triamcinolone aerosol nasal spray propelled with CFC

The studies ranged from 2 to 8 weeks in duration and there were no open-label studies. Eight studies were single blind in design^{13-15, 18-20, 23, 26, 27} and the rest were double-blind. One study had a cross-over design²⁴ and was designed primarily to examine the adverse effects between 2 medications and thus efficacy was only a secondary measure.²⁴ Another trial used a double-dummy design²⁸ that presents a unique issue for interpretation with this particular class of medications. The patients in this type of trial were exposed to the active drug and the placebo vehicle of the comparator. This creates some uncertainty for interpretation of the adverse events as sometimes it is the vehicle and not the active ingredient that is responsible for certain adverse effects.

Patients were characterized by an overall mean age of 34.1 years (range 24 years²¹ to 66.7 years²⁰) and 46.1% were female (range 8.5%²⁹ to 66.7%²⁰). Only 40 percent of trials characterized trial populations by race and in those, the majority of patients were white (81.3-99%).^{14, 19, 23, 25-27} Eligibility criteria differed across trials with regard to symptom severity, verification, and history and this is a potential source of heterogeneity across patient populations (Table 4). Trials also differed in which, if any, concomitant treatments were allowed and whether use of these was recorded.

Table 4. Seasonal allergic rhinitis trial characteristics

Trial	Eligibility criteria			Allowed concomitant treatments	
	Symptom severity scores	24-month history	Positive skin prick test	Antihistamines	Immunotherapy
Kaiser, 2004	TNSS ≥ 42	√	√		
Gross, 2002	TNSS ≥ 42	√	√		√
Ratner, 1992	INSS ≥ 200	√	√	√	
Graft, 1996 ^a	TNSS ≤ 2	√	√		√
McArthur, 1994				√	
Langrick, 1984					√
Ratner, 1996	TSS = 2-7	√	√	√	√
Welsh, 1987		√	√	√	√
Stern, 1997		√	√	√	
Greenbaum, 1988		√	√	√	
Hebert, 1996	TSS ≥ 6; congestion ≥ 2 + one other symptom (INSS)	√	√	√	√
Lumry, 2003	RIS ≥ 24	√	√	√	√
Small, 1997	RIS ≥ 24	√	√		√
LaForce, 1994	INSS ≥ 200		√		√
Bronsky, 1987	EENT ≥ 8	√	√		

^a Prophylaxis trial

TNSS=Total Nasal Symptom Score; INSS=Individual Nasal Symptom Score; TSS=Total Symptom Score; RIS=Rhinitis Index Score; EENT=Eye, Ear, Nose & Throat

No seasonal allergic rhinitis trial was rated good quality. All but 1 trial was rated fair quality.²⁴ The only trial rated poor, Greenbaum 1988, suffered from multiple flaws including inadequately described randomization and allocation concealment methods, a complete lack of inclusion criteria and reporting of baseline demographics, and excluded a number of patients from the outcome assessment.²⁴ The majority of the trials were sponsored by the pharmaceutical industry. Sponsor information was not reported in 1 trial²⁰ and 3 trials^{24, 26, 29} did not acknowledge receiving funding but had authors employed by pharmaceutical companies.

No head-to-head trials in seasonal allergic rhinitis patients of the new drugs included in this update, ciclesonide and fluticasone furoate were identified through searches. One unpublished abstract of a head-to-head trial of fluticasone furoate 110 mcg/day compared with fluticasone 200 mcg/day provided by the manufacturer of fluticasone furoate suggested that fluticasone furoate was non-inferior to fluticasone in terms of efficacy and safety.³⁰ A published, peer reviewed report of these findings was not identified through literature searches, therefore these results should be considered inconclusive.

B. Results of trials of treatment in adults with seasonal allergic rhinitis

1. Direct comparisons

Similar proportions of patients experienced significant global improvements in rhinitis symptoms after 3 to 7 weeks of treatment based on physician assessment in head-to-head trials of nasal corticosteroids (Table 5). Physician assessment of global improvement was the most commonly reported outcome, was defined differently across trials, and was generally based on

patient diary ratings (0=none; 3=severe) of nasal symptom severity of rhinorrhea, stuffiness/congestion, nasal itching, and sneezing.

Three trials were associated with noticeably lower patient improvement rates.^{16, 20, 26} The lowest rates of patient improvement were observed in a 7-week trial of flunisolide 200 mcg compared with beclomethasone 400 mcg (29% compared with 34%, NS).²⁰ Reasons for why the rates in this trial differed from the others may have been that the mean age was noticeably higher at 66.7 years and the outcome definition of “total improvement” appeared to be more stringent than in the other trials. Rates of patient improvement were also quite low in the only trial to prohibit concomitant usage of both antihistamines and immunotherapy.²⁶ The third lowest patient improvement rates came from the trial with the shortest treatment period of only 2 weeks. Patient improvement rates may have been lower in this trial because the treatments may not have reached their maximum effect within that time.¹⁶

Only 2 trials pre-specified a primary outcome measure, which was the mean change in composite rhinitis symptom score.^{14, 15} Measurement of change in composite symptom scores was also the second most commonly reported outcome; however, these were defined differently across trials (Table 5). There were no significant differences between any 2 nasal corticosteroids in any of the trials that reported these outcomes for the treatment periods overall.^{13-15, 17, 19, 21-23, 29}

There was a difference in 1 trial when primary outcome scores were analyzed only on days when the pollen count was greater than 10 grains/m³.¹⁴ Results of this trial demonstrated that budesonide 256 mcg per day was superior in reducing combined symptom scores, as well as the individual scores for sneezing and runny nose when compared to fluticasone 200 mcg and budesonide 128 mcg daily.¹⁴

Table 5. Rhinitis symptom assessment outcomes in adults with seasonal allergic rhinitis

Study Sample size Trial duration	Age % female	Treatment A	Treatment B	Physician-rated global evaluation of improvement (% pts)	% Change in total symptom score
McArthur, 1994 N=77 3 weeks	27 years 51%	Budesonide 200 mcg	Beclomethasone 200 mcg	Noticeably, very or total effective: 85% compared with 82%, NS	NR
Langrick, 1984 N=60 7 weeks	66.7 years 37.5%	Flunisolide 200 mcg	Beclomethasone 400 mcg	Total improvement: 29% compared with 34%, NS	NR
Welsh, 1987 N=100 6 weeks	28 years 33%	Flunisolide 200 mcg	Beclomethasone 336 mcg	Substantial (patient-rated): 80% compared with 75%, NS	Total hay fever score: +13.1% compared with +96.4%, NS
Bronsky, 1987 N=151 4 weeks	29 years 52%	Flunisolide 200 or 300 mcg	Beclomethasone 168 or 336 mcg	Major improvement: 27% compared with 38% compared with 40% compared with 46%, NS	NR
Ratner, 1992 N=136 2 weeks	44 years 62%	Fluticasone 200 mcg	Beclomethasone 336 mcg	Significant or moderate: 53% compared with 59%, NS	NR
Laforce, 1994 N=238 4 weeks	24 years 29%	Fluticasone 200 mg BID or QD	Beclomethasone 336 mcg	Significant or moderate: 65% compared with 70% compared with 65%, NS	TNSS: -43% compared with -53% compared with -32%, NS

Study Sample size Trial duration	Age % female	Treatment A	Treatment B	Physician-rated global evaluation of improvement (% pts)	% Change in total symptom score
Hebert, 1996 N=477 4 weeks	32 years 8.5%	Mometasone 100 or 200 mcg	Beclomethasone 400 mcg	Complete/marked relief: 77% compared with 79% compared with 74%, NS	TNSS: -53% compared with -59% compared with -59%; NS
Lumry, 2003 N=147 3 weeks	37 years 51%	Triamcinolone AQ 220 mcg	Beclomethasone 336 mcg	Greatly or somewhat improved: 78.4% compared with 87%, NS	Nasal Index: -42.9% compared with -45.9%, NS
Stern, 1997 N=635 4-6 weeks	Age NR 51%	Budesonide 128 or 256 mcg	Fluticasone 200 mcg	Substantial or total control - patients: 85% compared with 88% compared with 82%, NS	Combined nasal symptom score ^a : -26.5% compared with -29.4% compared with -29.4%, NS
Kaiser, 2004 N=295 3 weeks	31.6 years 62%	Triamcinolone AQ 220 mcg	Fluticasone 200 mcg	NR	TNSS: -48% compared with -49.7%, NS
Gross, 2002 N=352 3 weeks	38.8 years 66.5%	Triamcinolone AQ 220 mcg	Fluticasone 200 mcg	NR	TNSS: -49.4% compared with - 52.7%, NS
Small, 1997 N=233 3 weeks	28 years 52%	Triamcinolone HFA 220 mcg	Fluticasone 200 mcg	NR	RIS**: -55% compared with -60%, NS
Ratner, 1996 N=218 6 weeks	44 years 62%	New flunisolide 200 mcg	Old flunisolide 200 mcg	NR	TNSS means: 3.81 compared with 3.55; NS
Greenbaum, 1988 N=122 4 weeks	NR NR	New flunisolide 200 mcg	Old flunisolide 200 mcg	NR	NR

^a Prespecified as primary outcome

Three trials reported quality of life outcomes based on assessments using the 28-item Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ).^{19, 23, 27} RQLQ items are organized into 7 dimensions (activities, emotions, eye symptoms, nasal symptoms, non-hay fever problems, practical problems, and sleep) and each are rated using a 7-point Likert Scale (0 to 6; lower scores indicate better QOL). Triamcinolone AQ 220 mcg was associated with similar mean reductions in RQLQ total score after 3 weeks relative to beclomethasone¹⁹ and fluticasone (Table 6).^{23, 27}

Table 6. Mean change in RQLQ total score

Study	Sample size	Age	Treatments	Point reductions
Trial duration	% female			
Lumry, 2003 N=147 3 weeks	37 years 51%	Triamcinolone AQ 220 mcg compared with beclomethasone 336 mcg	-1.71 compared with -1.79, NS	
Berger, 2003 N=295 3 weeks	31.6 years 62%	Triamcinolone AQ 220 mcg compared with Fluticasone 200 mcg	-2.4 compared with -2.5, NS	
Gross, 2002 N=352 3 weeks	38.8 years 66.5%	Triamcinolone AQ 220 mcg compared with Fluticasone 200 mcg	-2.4 compared with -2.5, NS	

RQLQ=Rhinoconjunctivitis Quality of Life Questionnaire

Nine trials included an analysis of the mean percentage change in severity of eye symptoms.^{13, 14, 17-20, 23, 25, 26} Out of those 9 trials, only 5 reported the raw data for comparison of numerical reduction in symptom severity and no differences between nasal corticosteroids were reported.^{13, 14, 17, 19, 26} When the reduction in eye symptoms is compared to the reduction for other symptoms of seasonal allergic rhinitis in these head-to-head trials it tends to be less dramatic.

2. Indirect comparisons

As no published head-to-head trials were identified through searches, the evidence on the effectiveness of ciclesonide and fluticasone furoate in seasonal allergic rhinitis patients is limited to placebo-controlled trials.

Two trials comparing ciclesonide 200 µg/day to placebo had similar patient populations and primary outcomes (Table 7 and Evidence Table 1a).^{31, 32} In both trials, ciclesonide 200 µg/day was associated with a significant improvement in morning and evening reflective TNSS relative to placebo. The sole trial that included other doses (25, 50, and 100 µg/day) of ciclesonide found it to be significantly more effective than placebo in improving TNSS only at the 100 µg/day dose.³¹ Physician-rated evaluation of symptom improvement was reported qualitatively in 1 trial and quantitatively in the other; both found that ciclesonide appeared to be associated with some symptom improvement when compared to placebo. One trial included quality of life outcomes.³² Patients taking ciclesonide experienced a mean change in RQLQ score of -1.17 at 4 weeks, which is similar to the change found in seasonal allergic rhinitis patients taking other nasal corticosteroids (shown in Table 6) but was not significantly different from placebo for this endpoint. However, at 2 weeks, RQLQ was significantly better with ciclesonide use relative to placebo ($P=0.002$). Ratner, et al. surmised this may have been due to reduced pollen counts during the time of the study rather than a true loss of effectiveness.³²

An additional small, short-term (7 day) placebo-controlled crossover trial in 24 asymptomatic seasonal allergic rhinitis patients comparing the effect on nasal symptoms following intranasal administration of pollen extracts found that there was less immediate nasal irritation (itching, rhinorrhea) following ciclesonide use relative to placebo.³³

Table 7. Efficacy outcomes in trials of ciclesonide compared with placebo

Study	Sample size	Mean age % female	Interventions	Change from baseline in total symptom score (TNSS) ^a	Physician-rated global evaluation of improvement	Change in RQLQ; point reductions
				Ciclesonide 25 µg/day: -4.8 (sum baseline score: 18.72)		
				Ciclesonide 50 µg/day: -4.8 (sum baseline score: 18.35)		
Ratner, 2006a	N=726	40 years 71% female	Ciclesonide 25 µg/day - 200 µg/day compared with placebo	Ciclesonide 100 µg/day: -5.3 (sum baseline score: 18.71) <i>P</i> =0.04 compared with placebo	Reported as 'somewhat better' than placebo for 100 and 200 µg/day doses	NR
				Ciclesonide 200 µg/day: -5.8 (sum baseline score 18.82) <i>P</i> =0.003 compared with placebo		
				Placebo: -4.2 (sum baseline score 17.80)		
Ratner, 2006b	N=327	40 years 75% female	Ciclesonide 200 µg/day compared with placebo	Ciclesonide 200 µg/day: -2.40 (mean baseline score 8.96) <i>P</i> <0.001 compared with placebo	Change in PANS: Ciclesonide 200 µg/day: -1.69 (SE 0.15) Placebo: -0.92 (SE 0.15); <i>P</i> <0.001	Ciclesonide 200 µg/day: -1.39; <i>P</i> =0.244 compared with placebo Placebo: -1.21
				Placebo: -1.50 (mean baseline score 8.83)		

^a The primary outcome in both trials was the mean change in reflective TNSS at day 14. Ratner 2006a used the *sum* of morning and evening scores as a baseline measurement, while Ratner 2006b used the *mean* of morning and evening scores as a baseline measurement.

Evidence regarding the efficacy of fluticasone furoate in seasonal allergic rhinitis patients comes from 3 well-designed placebo-controlled trials.³⁴⁻³⁶ In the 3 trials, fluticasone furoate was significantly better than placebo at ameliorating the nasal and ocular symptoms associated with seasonal allergic rhinitis based on reflective TNSS and TOSS and in improving RQLQ scores (Evidence Table 1a; Table 8).

Table 8. Efficacy outcomes in trials of fluticasone furoate compared with placebo

Study	Sample size	Duration	Mean age	% female	Interventions	Change from baseline in total symptom score (TNSS)	Change from baseline in total ocular symptom score (TOSS)	Proportion of patients reporting improvement in overall response to therapy	Change (improvement) in RQLQ
Fokkens, 2007	N= 285	2 weeks	30 yrs	53% female	Fluticasone furoate 100 µg/day compared with placebo	Fluticasone furoate -4.94 compared with placebo -3.18 (mean difference -1.757; $P<0.001$)	Fluticasone furoate -3.00 compared with placebo -2.26 (mean difference -0.741 (CI -1.14 to -0.34; $P<0.001$))	Fluticasone furoate 67% compared with placebo 39% ($P<0.001$)	Fluticasone furoate -2.23 compared with placebo -1.53 (mean difference -0.700; $P<0.001$)
Kaiser, 2007	N= 299	2 weeks	35 yrs	60% female	Fluticasone furoate 100 µg/day compared with placebo	Fluticasone furoate -3.55 compared with placebo -2.07 (mean difference: -1.473 (CI -2.01 to -0.94; $P<0.001$))	Fluticasone furoate -2.23 compared with placebo -1.63 mean difference: -0.600 (CI -1.01 to -1.19; $P=0.004$)	Fluticasone furoate 73% compared with placebo 52% ($P<0.01$)	Reported as 'significantly higher' in fluticasone furoate patients ($P<0.001$)
Martin, 2007	N= 641	2 weeks	39 yrs	66% female	Fluticasone furoate 55-440 µg/day compared with placebo	Fluticasone furoate 55 µg -3.5 Fluticasone furoate 110 µg -3.84 Fluticasone furoate 220 µg -3.19 Fluticasone furoate 440 µg -4.02 placebo -1.83 $P<0.001$ compared with placebo for all doses	Fluticasone furoate 55 µg -1.93 Fluticasone furoate 110 µg -2.08 Fluticasone furoate 220 µg -1.92 Fluticasone furoate 440 µg -2.43 placebo -1.34 $P<0.001$ compared with placebo for all doses	Fluticasone furoate 55 µg 16% Fluticasone furoate 110 µg 28% Fluticasone furoate 220 µg 23% Fluticasone furoate 440 µg 26% placebo 8% $P<0.001$ compared with placebo for all doses	All fluticasone doses: range -1.79 to -1.97 placebo -0.97; $P\leq 0.006$

C. Results of prophylaxis trials in adults with seasonal allergic rhinitis

Mometasone was associated with significantly lower levels of rhinitis symptom severity in the peak- and pre-seasons relative to beclomethasone in the only head-to-head trial of seasonal allergic rhinitis prophylaxis. This double-blind, parallel-group trial was conducted throughout 9 centers in the United States for adult and adolescent patients ranging in age from 12 to 69 years of age.²⁵ The patients were required to be free of symptoms (nasal and non-nasal) at the baseline visit in order to be randomized to receive either beclomethasone 168 mcg twice daily or mometasone 200 mcg once daily plus placebo in the evening for 8 weeks. The patients in this trial starting taking the nasal corticosteroids, on average, 23 days before the onset of ragweed season and recorded the severity of their symptoms twice daily in a diary. A physician evaluated the severity of the patient's symptoms at screening, day 1 (baseline), and days 8, 22, 29, 36, 50, and 57. The patients in the mometasone and beclomethasone groups had comparable severity scores at baseline; however, the mometasone group had a lower mean nasal symptom score from baseline to the start of the season when compared to beclomethasone treated patients. This is significant because the patients started taking the medication before the start of pollen season, so the mometasone may have conferred some early benefit for patients. The authors concluded that the proportion of minimal symptom days (total nasal symptom score ≤ 2) were similar between treatment groups at all time points assessed.

II. Children with seasonal allergic rhinitis

A. Direct comparisons

Physician-rated total nasal symptom score reductions were similar for mometasone and beclomethasone after 4 weeks in the only head-to-head trial of children with seasonal allergic rhinitis (N=679) (Evidence Tables 1 and 2).³⁷ This fair quality, double-blind, parallel group, placebo-controlled, RCT conducted in pediatric patients, compared 3 doses of mometasone to beclomethasone.³⁷ This was a 4-week trial that took place in 20 centers throughout the United States. Patients ranged in age from 6 to 11 years old and were randomized to receive mometasone 25, 100, or 200 mcg daily, beclomethasone 84 mcg twice daily, or placebo. The mean reduction in physician-rated total nasal symptom score at day 8 did not demonstrate any difference between the 3 mometasone doses nor between mometasone and beclomethasone. However, between days 16 and 29, patients treated with mometasone 100 and 200 mcg daily improved, whereas those treated with mometasone 25 mcg demonstrated little further reduction of symptoms. By day 29, mometasone 100 and 200 mcg daily and beclomethasone were significantly more effective at reducing symptoms than mometasone 25 mcg daily. Thirty-three patients withdrew from the study, 14 patients (2%) due to adverse events.

B. Indirect comparisons

Placebo-controlled trials were evaluated for potential indirect comparisons to address the dearth of head-to-head evidence in children (Evidence Tables 3 and 4). Fluticasone 100 or 200 mcg,³⁸⁻⁴² triamcinolone 110 or 220 mcg,^{43, 44} flunisolide 150 or 200 mcg,^{45, 46} and beclomethasone 42 mcg⁴⁷ were all associated with significantly greater levels of symptom relief relative to placebo in 2- to 4-week, fair-quality trials in pediatric patients with seasonal allergic rhinitis (Table 9). Patients were mostly male and mean ages ranged from 8.3 to 10.5 years in all but 1 trial.³⁸ One trial of fluticasone involved 243 adolescents with a mean age of 14.2 years.³⁸ Eligibility for all trials required positive skin prick tests to a variety of allergens. Extreme heterogeneity in outcome reporting methods across trials precluded any quantitative analyses of indirect comparative efficacy.

No published trials of the new drugs included in this update, fluticasone furoate and ciclesonide were identified through literature searches; evidence on the efficacy of these drugs is available from two 2-week unpublished studies provided by the manufacturers of each drug.^{48, 49} In both studies, there was a significant difference between the intervention group and placebo in reflective TNSS scores when the higher dose of each drug was used (110 mcg/day fluticasone furoate and 200 mcg/day ciclesonide) but not at the lower doses (55 mcg/day fluticasone furoate and 100 mcg/day ciclesonide.)

Table 9. Main results in placebo-controlled trials in children with seasonal allergic rhinitis

Study Sample size	NCS (total daily dose) x duration (weeks)	Main results
Kobayashi, 1989 N=101	Beclomethasone 168 mcg x 3	Significant decline in nasal obstruction, rhinorrhea, sneezing, and nasal itch as rated by physicians and patients (data NR)
Strem, 1978 N=48	Flunisolide 150 mcg x 4	All symptoms combined absent or questionably noted (# days): 5.6 compared with 1.2; $P<0.0001$ Patient felt spray achieved 'total control' (% pts): 16.7% compared with 4.2%; $P=0.0011$
Gale, 1980 N=35	Flunisolide 200 mcg x 4	Substantial or total control (% pts): 64% compared with 33%; $P<0.05$ Individual symptom relief: sneezing=NS; stuffy nose $P<0.05$; runny nose $P<0.05$; eye itch=NS
Boner, 1995 N=143	Fluticasone 100 or 200 mcg QD x 4	Percentage of symptom-free days: Sneezing=55% compared with 42% compared with 22%; $P<0.05$ Rhinorrhea=70% compared with 59% compared with 30%; $P<0.05$
Galant, 1994 N=249	Fluticasone 100 or 200 mcg QD x 4	'Significant improvement' (% pts; clinician-rated): 29% compared with 35% compared with 11%; $P<0.01$ 'Magnitude' of improvement (% reduction in pt-rated mean total nasal symptom scores): 50-57% compared with 37%; $P<0.05$
Grossman, 1993 N=250	Fluticasone 100 or 200 mcg QD x 2	'Significant improvement' (% pts; clinician-rated): 29% compared with 21% compared with 9%; $P<0.002$
Munk, 1994 N=243	Fluticasone 100 or 200 mcg QD x 2	'Significant improvement' (% pts; clinician-rated): 33% compared with 32% compared with 9%; $P<0.001$
Schenkel, 1997 N=223	Triamcinolone 110 or 220 mcg x 2	Adjusted mean change from baseline in Nasal Index: -2.62 compared with -2.50 compared with -1.78; $P<0.05$
Banov, 1996 N=116	Triamcinolone 220 mcg QD x 2	Adjusted mean change from baseline in Nasal Index: -2.30 compared with -1.16; $P<0.05$

Perennial Allergic Rhinitis

I. Adults with perennial allergic rhinitis

A. Results of literature search

We identified 19 head-to-head trials that compared efficacy of 2 nasal corticosteroids for perennial allergic rhinitis (Evidence Tables 5 and 6).^{12, 50-67} No good quality study was found. Eleven studies were rated fair quality^{12, 50-59} and 8 studies were rated as poor.⁶⁰⁻⁶⁷ Table 10 summarizes the combinations of comparisons.

Two recent systematic reviews were also identified through searches; both included studies with mixed AR populations. While these reviews focused largely on patient preference and cost, both also found little difference in effectiveness and safety among the nasal corticosteroids.^{68, 69}

Table 10. Head-to-head trial comparisons

	Beclomethasone	New flunisolide	Old flunisolide	Triamcinolone	Fluticasone p.	Mometasone	Budesonide
Beclomethasone		4		3	3	1	2
New flunisolide			1				
Old flunisolide							
Triamcinolone							
Fluticasone p.						1	2
Mometasone							2
Budesonide							

B. Description of trials in adults with perennial allergic rhinitis

The studies for perennial and mixed allergic rhinitis were generally similar in design, inclusion/exclusion criteria, population, and duration, but did vary greatly in size. No good quality study was found. Eleven studies were rated fair quality^{12, 38, 50-59} and 8 studies were rated as poor.⁶⁰⁻⁶⁷ Poor quality ratings were due to the presence of combinations of multiple serious flaws including inadequate reporting of methods of randomization and allocation concealment, differences between group demographic and prognostic factors at baseline, and exclusion of patients from outcome assessments.⁶⁰⁻⁶⁷

All but 1⁵¹ of the trials comparing beclomethasone to flunisolide were randomized. Six of these studies were double-blinded,^{12, 52, 53, 56, 57, 59} 3 were open-label,^{50, 51, 54} and 2 did not report blinding methods.^{55, 58} Most of these trials were multicentered, while 4 were performed at a single center.^{50, 51, 54, 55}

The populations studied were young to middle aged adults with mean ages mostly around 30-40 years and with balanced numbers of male/female subjects; 3 studies reported >60% females^{51, 55, 59} and 1 reported <30% females.⁵⁴ Several trials did, however, include adolescents between 12-18 years.^{52, 53, 55-57} All trials included patients with perennial rhinitis determined clinically or using various allergy tests and some also reported the proportion of participants with concomitant seasonal allergic rhinitis.^{50, 56, 57} The studies varied widely in size from as few as 24 patients to as many as 548 patients. Most studies involved over 300 patients.^{12, 52, 56-59} Duration of the trials ranged from 3 weeks to 1 year, with most around 4-8 weeks.

Most studies reported receiving financial or personnel support from pharmaceutical companies with the exception of 2 trials that did not report any source of external support.^{54, 55}

Nine out of the ten studies measured efficacy outcomes using a 4-point scale to describe the severity of individual nasal and non-nasal symptoms with 0=none and 3=severe and 1 trial used a visual analog scale from 1-100 for 2 separate individual symptoms.⁵² However, reporting methods for primary outcome measures varied widely among the trials, which prevents valuable indirect comparisons. These methods include reductions in points for individual symptoms and composite scores of individual symptoms, percent reduction of individual and/or composite scores and mean daily scores. The composite scores such as Nasal Index Score and Total Nasal Symptom Score include all or some of the measured individual symptoms. In addition, the trials reported physician assessments of symptoms, global evaluation of clinical efficacy and acceptability, onset of action, and amount of rescue medication required as secondary outcomes.

C. Results of trials of treatment in adults with perennial allergic rhinitis

1. Direct comparisons

The only evidence suggesting superiority of any 1 nasal corticosteroid over another comes from one 6-week trial of 273 patients with perennial allergic rhinitis in which budesonide aqueous 256 mcg was associated with a significantly greater mean reduction in a combined nasal symptom score relative to fluticasone aqueous 200 mcg (-2.11 compared with -1.65, $P=0.031$).¹² There were no significant differences between nasal corticosteroids in perennial allergic rhinitis symptom reductions when compared at *similar* dosages in most other trials (Tables 11 and 12).^{52, 56-58}

Fluticasone aqueous 400 mcg/day appeared superior to relatively lower dosages of beclomethasone aqueous (400 mcg/day) in reducing individual symptoms (nasal discharge, nasal blockage, eye watering and irritation, nasal itching, sneezing) over the duration of a year in the longest of the head-to-head trials.⁵³ The disparity of dosage levels between treatments used in this trial raise questions about how to interpret this finding, however.

Table 11. Reductions in nasal symptom scores in head-to-head trials of perennial allergic rhinitis patients

	Beclomethasone AQ	Budesonide AQ	Mometasone AQ	Fluticasone p. AQ
Beclomethasone AQ		No evidence	No differences ⁵⁶	Mixed ^{52, 53}
Budesonide AQ			No differences ⁵⁸	Budesonide superior ¹²
Mometasone AQ				No differences ⁵⁷
Fluticasone p. AQ				

It is unknown how the new⁵¹ or old⁵⁰ forms of flunisolide 200 mcg compare directly to the new aqueous form of beclomethasone because both have only been compared to the discontinued aerosol form of beclomethasone 400 mcg in 4-week trials. No other head-to-head trials comparing either form of flunisolide directly to any other nasal corticosteroid in perennial allergic rhinitis patients were identified. The new and old forms of flunisolide were compared directly to each other in one 4-week trial and both were associated with similar reductions in individual symptom scores (sniffing, stuffiness, sneezing, postnasal drainage).⁵⁹ No fair- to good-quality trial of the *direct* comparative efficacy of triamcinolone relative to other nasal corticosteroids was identified.

Beclomethasone compared with fluticasone

Mixed findings were reported across 2 head-to-head trials comparing efficacy of beclomethasone to fluticasone (Table 10).^{52, 53} While 1 study comparing standard doses of the 2 drugs found no significant differences in total symptom score,⁵² the other trial found that an above maximum daily dosage of fluticasone propionate (400 mcg) was superior to a maximum dosage of beclomethasone (400 mcg) in reducing most individual symptoms.⁵³

The British multicenter trial compared non-equivalent doses of the drugs (beclomethasone 200 mcg to fluticasone 200 mcg, both twice daily) for up to 1 year in 242 patients.⁵³ The population included adolescents aged 16 and over and adults with perennial

rhinitis based on clinical history, not an allergy test. There was no composite symptom score reported but only individual symptom scores for nasal and non-nasal symptoms. Results showed that fluticasone had significantly better symptom grades for nasal discharge, nasal blockage, and eye watering and irritation than beclomethasone.

The other study compared fluticasone 100 mcg either once or twice daily to beclomethasone 168 mcg or placebo twice daily in 466 adults and adolescents as young as 12 years for 6 months.⁵² The outcome measures were expressed as reduction of total symptom scores using a visual analog scale (0-100 for each of 4 nasal symptoms). The study found no significant differences in efficacy between any of active drugs, both of which showed at least 45% reduction in total symptom score. It was noted that equivalent dosages of beclomethasone (400 mcg) and fluticasone (200 mcg) also had similar efficacy and safety in an unpublished 4-week randomized double-blind placebo-controlled parallel group trial of 286 adult patients with perennial rhinitis that was identified in the dossier provided by the manufacturer of fluticasone.⁷⁰ Drop-out rates for beclomethasone, fluticasone 100 and 200 mcg, and placebo (28% compared with 23% compared with 14% compared with 28%) in the published trial were noted to be relatively higher than in other similar trials.

Mometasone

Mometasone was associated with generally similar reductions in rhinitis symptoms relative to beclomethasone⁵⁶ and fluticasone⁵⁷ across 2 head-to-head trials (Table 10). One double-blind RCT compared beclomethasone 400 mcg twice daily to mometasone 200 mcg once daily in 427 adults and adolescents as young as age 12 with perennial allergic rhinitis.⁵⁶ The study population included 45-54% patients with seasonal allergies and 18-24% with concomitant asthma. The primary outcome in this 12-week study was measured with mean percent reduction in total morning and evening symptom scores within the first 15 days.

A trial comparing fluticasone to mometasone revealed mixed results for differences in efficacy.⁵⁷ One double-blind multicenter RCT compared fluticasone 200 mcg to mometasone 200 mcg in 550 adults and adolescents as young as 12 years with confirmed perennial allergic rhinitis. This fair-quality 12-week study included 37.5% patients with concomitant seasonal allergies. The primary outcome of mean percent reduction in total nasal symptom score had to be estimated from figures provided in the article. Although mometasone resulted in greater reduction of the total nasal symptom score, this patient-rated outcome was not significantly different between the 2 drugs. There was, however, a significantly greater reduction in the same physician-rated secondary outcomes of nasal congestion, nasal discharge, and overall condition with mometasone.

Budesonide

One trial found budesonide to be more efficacious in treating combined nasal symptoms than fluticasone (Table 10).¹² This 6-week Canadian/Spanish study investigated budesonide 256 mcg compared with fluticasone 200 mcg compared with placebo in 273 adults with confirmed perennial allergic rhinitis.¹² There was a significantly greater reduction in combined nasal symptoms scores with budesonide (-2.11 compared with -1.65, $P=0.031$). Moreover, they found that budesonide was significantly better than placebo at reducing nasal blockage than was fluticasone, while improvement in all other individual symptom scores was similar for both drugs. The onset of action, measured in hours before significant step-score reductions, was

quicker for budesonide than fluticasone (36 h compared with 60 h). The secondary outcome of percentage of patients who reported substantial or total symptom control did not differ significantly between the 2 drugs.

The only head-to-head study investigating budesonide and mometasone for perennial rhinitis found the 2 drugs comparable for nasal symptom scores and overall symptom control. One fair-quality European RCT compared budesonide 256 mcg or 128 mcg to mometasone 200 mcg or placebo in 438 adults with confirmed perennial allergic rhinitis.⁵⁸ The primary efficacy outcome, nasal symptom score (morning and evening combined), was not significantly different in the 2 medications. Furthermore, there was no statistically significant difference for the secondary outcomes: percentage of patients experiencing no symptom control, consumption of rescue medication, and onset of action. We have identified unpublished quality of life data from this study in the dossier supplied by the manufacturer of budesonide that found no significant differences between treatments except that budesonide is superior to placebo for general health and vitality.

Flunisolide: New compared with old formulations

The randomized double-blind parallel-group study compared 2 different formulations of flunisolide aqueous in 215 patients with confirmed perennial allergic rhinitis and found similar efficacy in both treatments.⁵⁹ Dosages were equivalent in both the old and new formulations, which reduced propylene glycol from 20% to 5%, increased polyethylene glycol from 15% to 20%, and added 2.5% polysorbate in an effort to reduce nasal stinging and burning. There were no significant differences in mean reduction of total symptom and individual symptom scores between formulations. Further, patients rated acceptability of nasal burning/stinging on a 100-point visual analog scale. The original formulation had a mean score of 52 while the new formulation was rated as 87 ($P<0.001$).

Table 12. Outcomes in head-to-head trials of perennial allergic rhinitis patients

Study Sample size	Interventions (Total Daily Dose) Duration	Outcome	Results
Sahay, 1980 N=60	Flunisolide aerosol BID (200 mcg) Beclomethasone aerosol QID (400 mcg) 4 weeks	Reduction in mean symptom scores: (A) Sneezing (B) Stuffiness (C) Runny nose (D) Nose blowing (E) Post-nasal drip (F) Epistaxis	(A) -1.44 vs. -1.57 (B) -1.74 vs. 1.62 (C) -1.33 vs. 1.48 (D) -1.70 vs. -1.72 (E) -0.74 vs. -0.68 (F) -0.15 vs. -0.07 NS for all
Bunnag, 1984 N=45	Flunisolide BID (200 mcg) Beclomethasone aerosol QID (400 mcg) 4 weeks, then crossover	Overall symptom score	-2.91 compared with -4.96; $P<0.0005$
van As, 1993 N=466	Fluticasone p. aqueous BID (100 mcg) Fluticasone p. aqueous QD (200 mcg) Beclomethasone aqueous BID (168 mcg) 6 months	Reduction in Total Symptom Score (0-200)	$\geq 45\%$ for all (data NR), NS

Study Sample size	Interventions (Total Daily Dose) Duration	Outcome	Results
Haye, 1993 N=242	Fluticasone p. aqueous BID (200 mcg) Beclomethasone aqueous BID (200 mcg) ≤ 1 year	No overall score; only: (A) Nasal Discharge (B) Nasal Blockage (C) Eye watering and irritation (D) Nasal itching (E) Sneezing	Fluticasone > beclomethasone (data NR) (A) <i>P</i> =0.002 (B) <i>P</i> =0.002 (C) <i>P</i> =0.048 (D) <i>P</i> =0.052 (E) <i>P</i> =0.114
Al-Mohaimeid, 1993 N=120	Budesonide BID (400 mcg) Beclomethasone BID (400 mcg) 3 weeks	(A) Mean daily symptom scores (blocked nose, runny nose, itchy nose, sneezing, runny eyes, sore eyes) (B) % patients symptom free	(A) no differences for all but sneezing: 0.48 compared with 0.72, <i>P</i> =0.05 (B) 35% compared with 26%; NS
Day, 1998 N=273	Budesonide aqueous QD (256 mcg) Fluticasone p. aqueous QD (200 mg) 6 weeks	Reduction in combined nasal symptom scores	-2.11 compared with -1.65; <i>P</i> =0.031
Drouin, 1996 N=427	Mometasone aqueous QD (200 mcg) Beclomethasone aqueous BID (400 mcg) 12 weeks	Mean change in total AM + PM symptom diary scores over 15 days (estimated from figure)	46% compared with 51%, NS
Mandl, 1997 N=550	Mometasone aqueous QD (200 mcg) Fluticasone p. aqueous QD (200 mcg) 3 months	Mean change in total AM + PM symptom diary scores over 15 days (estimated from figure)	61% compared with 55%, NS
Bende, 2002 N=438	Mometasone aqueous QD (200 mg) Budesonide QD (256 mcg) Budesonide QD (128 mcg) 4 weeks	Reduction in Nasal Index Score (morning/evening)	-1.26/-1.44 compared with -1.45/-1.59 compared with -1.41/-1.50; NS
Meltzer, 1990 N=215	Flunisolide aqueous original formulation BID (200 mcg) Flunisolide aqueous new formulation BID (200 mcg) 4 weeks	Mean Reduction of Total Symptom Score, estimated from figure	-3.0 compared with -2.5, NS

Triamcinolone

Evidence was insufficient for analyzing the comparative efficacy of triamcinolone relative to any other nasal corticosteroids. The only head-to-head evidence identified for triamcinolone (220 mcg) comes from an open-label randomized parallel group 3-week trial of 175 perennial allergic rhinitis patients in which there were no differences in efficacy or safety endpoints when compared to fluticasone 200 mcg once daily.⁷⁰

2. Indirect comparisons

Placebo-controlled trials of triamcinolone were evaluated due to the dearth of head-to-head evidence available for this nasal corticosteroid. There were 4 large (N=178 to 305) fair

quality placebo-controlled trials that assessed triamcinolone in patients with perennial allergic rhinitis and 1 very small study of cat allergic patients (N=12).⁷¹⁻⁷⁵ All of the larger studies reported significantly lower nasal symptoms for the active drug in treatment of perennial rhinitis. Storms, et al. investigated 3 different doses of triamcinolone aerosol (110 mcg, 220 mcg, and 440 mcg/day) compared with placebo in 305 patients and found nasal index (composite of 4 symptoms on 4-point scale, maximum 12 points) values after 12 weeks (weekly mean change from baseline) of -2.9, -3.5, -3.35 and -2.2 respectively, $P<0.05$.⁷¹ Another study of 296 patients with mixed allergic rhinitis reported -4.80 compared with -3.55 ($P<0.001$), a significant reduction of mean score of daily total symptom score (maximum score 20 points, 5 symptoms on a 5-point scale) for triamcinolone aqueous 220 mcg and placebo respectively.⁷² Potter, et al. also reported significant improvements in a Rhinoconjunctivitis Quality of Life Questionnaire in the areas of sleep, nasal symptoms, emotional problems, and overall quality of life compared to placebo.⁷² The 12-week placebo-controlled trial of 205 perennial rhinitis subjects taking triamcinolone aerosol 200 mcg reported change from baseline nasal index (maximum 9 points) -3.16 compared with -2.36, $P<0.05$ for active drug and placebo, respectively.⁷⁴ A 4-week placebo-controlled trial of triamcinolone aqueous 220 mcg in 178 patients with perennial allergic rhinitis showed a significant overall reduction in nasal index (sum of 3 individual symptom scores, 4-point scale, 0=none and 3=severe) for triamcinolone compared with placebo, -2.07 compared with 1.27, $P<0.02$.⁷⁵ The 1-week crossover trial of triamcinolone 220 mcg followed by a 1-hour cat allergen challenge resulted in mean nasal symptoms (4-point scale, 0=none and 3=severe) of 0.65 compared with 1.0, $P=0.06$ for active drug and placebo, respectively.⁷³

The effect of ciclesonide use in perennial allergic rhinitis patients was evaluated in 2 placebo-controlled trials (see Evidence Tables 5a and 6a.)^{76, 77} Although inclusion criteria of these trials allowed enrollment of patients >12 years of age, the mean age was ~35 years in both trials. Other patient demographic characteristics were similar. Only 1 of the trials was designed to evaluate efficacy.⁷⁶ In that trial, patient-rated nasal symptoms (TNSS) and quality of life (RQLQ) were both significantly improved after 6 weeks of use in the ciclesonide group compared to the placebo group. There was a slight between-group difference in physician-rated symptoms favoring ciclesonide, although this difference did not reach statistical significance. In the longer trial (52 weeks) designed to evaluate safety outcomes rTNSS scores were significantly improved from baseline compared to placebo. There was also a statistically significant difference in RQLQ scores, favoring ciclesonide, at the study's endpoint. This difference was only clinically significant in the subset of patients who were more impaired at baseline (RQLQ scores ≥ 3.5).⁷⁷

No published effectiveness or efficacy trials of fluticasone furoate were identified. The only evidence on the efficacy of fluticasone furoate in perennial allergic rhinitis patients comes from the dossier provided by the drug's manufacturer, which includes reference to 2 unpublished studies (duration of 4 and 6 weeks) evaluating symptom relief and quality of life outcomes. Compared to placebo, those patients receiving fluticasone furoate had a significant improvement in reflective TNSS in both studies. Significant improvement in ocular symptoms was not observed in the 4-week study⁷⁸ although a statistically significant improvement was observed in the 6-week study.⁷⁹ Similarly, RQLQ was significantly improved in 1 study (mean between group difference -0.65 [CI -0.90 to -0.40; $P<0.001$]). The manufacturer also identifies this as a clinically significant improvement.⁷⁸ The other trial failed to show an either statistically or clinically significant difference in RQLQ.⁷⁹

II. Adolescents and children with perennial allergic rhinitis

A. Direct comparisons

Beclomethasone compared with fluticasone

The only head-to-head evidence in children and adolescents with perennial allergic rhinitis comes from a meta-analysis of combined data from a smaller (N=120) 12-week head-to-head trial comparing fluticasone 100 mcg once or twice daily with beclomethasone 200 mcg twice daily and a larger (N=415) 4-week placebo-controlled trial, which compared fluticasone 100 mcg or 200 mcg once daily with placebo.⁸⁰ There is no specific data reported for the comparator study, only the statement that fluticasone was as effective as beclomethasone in increasing the median percent of symptom-free days for all symptoms.

B. Indirect comparisons: Placebo-controlled trials

Since there was only 1 head-to-head comparison study involving children or adolescents that met review criteria, we looked at the available evidence from 10 placebo-controlled trials (Evidence Tables 7 and 8; Table 13).⁸¹⁻⁹⁰ Due to the heterogeneity of this evidence, no indirect comparisons of efficacy in children were possible.

A recent Cochrane review of placebo-controlled trials that included 3 older studies (Hill, Neuman, and Sarsfield; see Table 13 below) concluded that beclomethasone and flunisolide were likely more effective than placebo based on the very limited evidence available.⁹¹

No trials in children of the 2 new drugs included in this update (ciclesonide and fluticasone furoate) were identified. One published abstract of a 12-week placebo-controlled trial of fluticasone furoate in children aged 2 to 11 years was identified through the dossier provided by the drug's manufacturer. The limited results presented suggest that the 55µg dose is significantly better than placebo at reducing the nasal symptoms associated with perennial allergic rhinitis based on reflective TNSS.⁹²

Table 13. Placebo-controlled trials in children/adolescents with perennial allergic rhinitis

Study	Interventions (Total daily dose)	Mean age Age range % female	Outcome	Results
Day, 1990 N=51	Budesonide BID (200 mcg) Placebo 4 weeks	13.4 compared with 13.3 years, 7-18 compared with 6-18 years 53.4% compared with 40%	Difference in combined nasal symptom scores, including sneezing, blocked nose, itchy nose, runny nose	-0.95 ± 1.87 compared with -0.37 ± 1.38 P < 0.05
Fokkens, 2002 N=202	Budesonide aqueous QD (128 mcg) Placebo 6 weeks	10.5 compared with 10.7 years, 6-16 years, 34.3%	Difference in combined nasal symptom scores (evening), including sneezing, blocked nose, runny nose	-1.86 compared with -0.93; P<0.001

Study Sample size	Interventions (Total daily dose) Duration	Mean age Age range % female	Outcome	Results
Hill, 1978 N=22	Beclomethasone aerosol QD (300 mcg) Placebo 6 weeks then crossover	NR, 7-17 years, 50%	% children with improved nasal symptoms (lower mean daily diary score)	86.4% $P<0.01$ placebo results not reported
Shore, 1977 N=46	Beclomethasone aerosol (300 mcg) Placebo 3 weeks then crossover, followed by 3 months open label with active drug (200 mcg)	8 years, 4-12 years, 21.7%	Patient assessment that drug was effective	75% placebo results not reported
Neuman, 1978 N=30	Beclomethasone aerosol 4 times daily (200 mcg) Placebo 3 weeks then crossover	13.8 years, 9-18 years, 53.3%	Difference (baseline to end of study) in average daily symptom score on 4-point scale	Group I -2.5 compared with 0 Group II -2.5 compared with +2.65 (no washout period)
Ngamphaiboon, 1997 N=106	Fluticasone p. aqueous QD (100 mcg) Placebo 4 weeks	8.96 compared with 9.06 years, 5-11 years, 18.9% compared with 10.3%	Physician-rated mean total symptom score (sum of obstruction, rhinorrhea, sneezing and itching, scale 0-3)	-6.13 compared with -5.7, $P<0.05$
Todd, 1983 N=64	Flunisolide aqueous QD (150 mcg) Placebo 4 weeks then crossover	8.3 years, 3-17 years, 39%	Mean daily total symptom score (stuffy nose, sneezing, runny nose, nose blowing, and eye symptoms)	Significantly lower than placebo for Group II only for 11 of 28 days
Sarsfield, 1979 N=27	Flunisolide aqueous QD (150 mcg) Placebo 2 months then crossover	12.3 years, 7-16 years, 22%	Mean weekly symptom scores on 4-point scale (A) sneezing (B) stuffy nose (C) runny nose (D) nose-blowing	Week 4 (A) 0.64 vs. 1.17 (B) 1.04 vs. 1.00 (C) 0.62 vs. 0.85 (D) 1.10 vs. 1.45
Welch, 1991 N=210	Triamcinolone aerosol (165 mcg) Triamcinolone aerosol (82.5 mcg) Placebo 12 weeks	9 years, 4-12 years, 33%	Adjusted mean change from baseline total nasal symptom score in first 6 weeks (no escape medication allowed) and second 6 weeks (escape medication allowed)	Estimated from figure: first 6 weeks 2.65 compared with 2.2 compared with 1.65 second 6 weeks 3.35 compared with 2.75 compared with 2.05 $P<0.01$ for highest dose compared to placebo
Storms, 1996 N=137	Triamcinolone aerosol (220 mcg) Placebo 4 weeks	8.9 years, 6-11 years, 27% compared with 44%	Adjusted mean change from baseline nasal index: sum of symptom scores for nasal stuffiness, nasal discharge, and sneezing each on a 4-point scale	-2.27 compared with -1.36, $P<0.05$
Nayak, 1998 N=80	Triamcinolone aqueous (220 mcg) Triamcinolone aqueous (440 mcg) Placebo 6 weeks	9.5 years, 6-12 years, 37.5%	Outcome not eligible, for adverse events only	

Perennial Non-Allergic Rhinitis

I. Adults

A. Direct comparisons

There were no head-to-head efficacy trials that compared any nasal corticosteroids in adults with perennial non-allergic rhinitis that met the inclusion criteria of this review.

B. Indirect comparisons in placebo-controlled trials

We found 2 placebo-controlled studies of patients with non-allergic rhinitis that were not indirectly comparable due to heterogeneous efficacy outcome reporting (Evidence Tables 9 and 10). The first study of fluticasone reported efficacy for use in non-allergic rhinitis and the second study of mometasone revealed mixed results in this population.^{93, 94}

A pooled analysis from 3 randomized, double-blind, double-dummy, placebo-controlled trials examining fluticasone aqueous 200 mcg and 400 mcg compared with placebo in 983 patients with non-allergic rhinitis (NARES) and without eosinophilia (non-NARES) reported clinical improvement of symptoms in the total population.⁹³ Both doses of active drug showed significant improvement in total nasal symptom score (100-point visual analog scale for individual symptoms, maximum possible 300) after 4 weeks compared to placebo, -84, -85, and -64 for the lower dose, higher dose, and placebo respectively, $P < 0.002$. Differences for the individual subgroups, non-NARES and NARES, also favored active drugs, but did not report significance.

The fair quality multicenter, randomized, double-blind, placebo-controlled trial investigating mometasone 200 mcg found mixed results for the efficacy in 329 adult patients with non-allergic rhinitis.⁹⁴ The patient-rated improvement was numerically greater for mometasone than placebo, 56% compared with 49%; however this difference was not significant. The secondary efficacy variable of investigator-rated improvement was significantly greater for mometasone compared to placebo, 60% compared with 48% ($P = 0.03$). Efficacy was reported as improvement rate, which was defined as reduction of at least 1 point in overall symptom score, comprising 4 individual symptoms on a 4-point scale for a maximum total of 12 points. The study also reported no significant difference in quality of life, but did not report methods or specific results.

Based on the results of 2 unpublished studies provided by the drug's manufacturer, fluticasone furoate was not significantly better than placebo at improving daily reflective TNSS in patients with non-allergic rhinitis triggered by changes in weather or temperature.^{95, 96} Likewise, there was no significant difference in response to therapy between fluticasone furoate and placebo in either study. Full, published results of these studies were not identified through literature searches.

II. Children

No efficacy trials of nasal corticosteroids in children with perennial non-allergic rhinitis were identified.

Key Question 2. For adults and children with seasonal or perennial (allergic and non-allergic) rhinitis, do nasal corticosteroids differ in safety or adverse events?

All Rhinitis Types

I. Adults

A. Direct comparisons

Head-to-head trials served as the primary source of evidence for comparisons between nasal corticosteroids in incidence and severity of the more common adverse effects associated with shorter-term usage. No head-to-head trial was of sufficient duration to measure comparative risk of cataract development or worsening of glaucoma. Rates of withdrawals due to adverse events, headache, throat soreness, epistaxis, and nasal irritation were generally similar between nasal corticosteroids in head-to-head trials of adults/adolescents with either seasonal or perennial rhinitis (Appendix E).^{12-21, 23-27, 29, 50-54, 56-59, 94, 97-100} One exception is that the old formulation of flunisolide 200 or 300 mcg was associated with significantly higher rates of nasal burning/stinging than beclomethasone AQ 168 or 336 mcg (30% compared with 33% compared with 10% compared with 10%; $P < 0.05$)²⁶ and higher rates than the new formulation of flunisolide 200 mcg (13% compared with 0; $P < 0.001$)²⁴ in 4-week trials of adults with seasonal allergic rhinitis. It is not yet clear how the new formulation of flunisolide 200 mcg ranks relative to other nasal corticosteroids with regard to nasal irritation effects. To-date, nasal burning/stinging rates associated with the new formulation of flunisolide have only been directly compared to the discontinued form of beclomethasone (20% compared with 2.2%; $P = 0.0081$) in adults with perennial allergic rhinitis.⁵¹

The few other differences pertain to rates of headache and epistaxis. In the only trial of nasal corticosteroids used prophylactically, mometasone 200 mcg was associated with significantly higher rates of headache than beclomethasone 336 mcg in an 8-week trial of adults with seasonal allergic rhinitis (36% compared with 22%; $P = 0.02$ calculated here using the Fisher's Exact Test using StatsDirect, CamCode, UK).²⁵ Additionally, fluticasone 200 mcg was associated with a significantly higher rate of epistaxis than a relatively lower dosage of beclomethasone 200 mcg (14% compared with 5%; $P = 0.0285$) after a year or less in a trial of adults with perennial allergic rhinitis.⁵³ Fluticasone may have been at a disadvantage in this comparison due to the use of a relatively low dose of beclomethasone. This result was not consistent with 3 other trials using equivalent dosage comparisons.^{16, 21, 52}

Six head-to-head trials assessed how adverse sensory attributes of nasal corticosteroids use (e.g., overall comfort, medication run-off, irritation, odor, taste) affected patient preferences (Evidence Tables 5 and 6).¹⁰¹⁻¹⁰⁶ These studies reported no consistent differences between treatments. One trial compared single doses of budesonide aqueous (64 mcg) with fluticasone (100 mcg or 200 mcg) and found differences only in sensory outcomes that were not relevant for this review.¹⁰³ No comparative adverse events data were reported. Another trial comparing single doses of triamcinolone aqueous, beclomethasone aqueous, and fluticasone aqueous in 94 adult patients with mixed allergic rhinitis showed no significant differences for nasal irritation, urge to sneeze, or drug run-off between treatment groups.¹⁰⁵ Meltzer, et al. compared single doses of

mometasone and fluticasone in 100 patients with allergic rhinitis and found no significant difference in nasal irritation or product run-off into throat or nose.¹⁰⁶

The remaining 3 trials compared single doses of triamcinolone aqueous 220 mcg to fluticasone 200 mcg and mometasone 200 mcg^{101, 102, 104} and only Stokes and Bachert revealed a significant difference in a relevant outcome. It should be noted that Stokes used a pooled analysis of 2 studies and Bachert reported more thoroughly the data from 1 of these studies. This fair to poor quality study found that triamcinolone aqueous had significantly less nasal irritation in the immediate and delayed (2-5 minute) measurements.¹⁰² Bachert was the only study to report adverse events and found no significant difference between treatments.¹⁰⁴

B. Indirect comparisons

Placebo-controlled trials and observational studies provided evidence of the risk of cataract development and longer-term adverse effects of nasal corticosteroids, including ciclesonide and fluticasone furoate. Evidence is extremely limited and insufficient for indirect comparisons between nasal corticosteroids.

1. Cataract

We identified 1 retrospective cohort study of cataract incidence in 88,301 patients younger than 70 years of age taking intranasal steroids in England and Wales (Evidence Tables 11 and 12).¹⁰⁷ Seventy percent of these patients used beclomethasone. The study compared nasal steroid users to a non-exposed population to determine the incidence rate/1000 person years and the relative risk of developing cataract as a result of treatment. Evidence showed that there was no increase in the relative risk of cataract among all users of nasal corticosteroids (RR 1.0, 95% CI 0.6-1.4) or among beclomethasone users compared with the unexposed (RR 0.8, 95% CI 0.5-1.2).

Ocular changes, including the development of cataracts, were infrequent in one 52-week placebo-controlled trial of ciclesonide, with no difference between the ciclesonide and placebo groups.⁷⁷

We are aware of additional unpublished data from a comparative study of mometasone beclomethasone and placebo that found no clinically significant changes in results from ophthalmic exams during the 12-week study period. An unpublished 12-month open-label extension of the previously mentioned study reported no cataract and no significant differences in mean intraocular pressure between treatments groups.

2. Common adverse respiratory and nervous system effects of longer-term use

Triamcinolone

One open-label 12-month extension of a 4-week randomized placebo-controlled double-blind trial evaluated long-term safety and efficacy of triamcinolone aqueous (200 mcg with option to reduce to 100 mcg/day if symptoms are adequately controlled) in 172 patients with confirmed perennial rhinitis.¹⁰⁸ Adverse event rates potentially due to treatment were higher in the extension study than in the original controlled trial: Headache 22.1% compared with 6.8%, epistaxis 18 % compared with 6.8%, pharyngitis 32% compared with 14.8%, rhinitis 28.5 % compared with 6.8%, cough 8.1% compared with 0%, and sinusitis 15.7%. The authors note that

there is some overlap with the winter cold season and are not all clearly related to treatment with intranasal triamcinolone. The study also reports rates of adverse events related to topical effects possibly related to treatment that, although low, are higher in the long-term observation compared with the 4-week trial: nasal irritation 2.3% compared with 0%, naso sinus congestion 1.2% compared with 0%, throat discomfort and dry mucous membranes 0% in both studies, sneezing 0.6% compared with 0%, and epistaxis 12.8% compared with 4.5%.

Fluticasone propionate

A 12-month, randomized, double-blind, placebo-controlled parallel group trial of 42 patients with confirmed perennial allergic rhinitis treated with fluticasone aqueous 200 mcg/day reported only epistaxis as occurring more frequently in the active drug group.¹⁰⁹ There was 1 withdrawal due to an adverse event in the fluticasone group. Unpublished data from an open-label 52-week observational study of fluticasone 200 mcg twice daily in 60 patients with perennial rhinitis reported no serious or unexpected adverse events (http://www.fda.gov/cder/foi/nda/98/20121S009_Flonase.htm).

Fluticasone furoate

In a large (N=806) 12-month, placebo-controlled trial of fluticasone furoate most patients experienced an adverse event during time on trial (77% fluticasone furoate compared with 71% placebo). Patients treated with the active drug were more likely to experience epistaxis than those taking placebo (20% compared with 8%, respectively). While most of these were mild in the fluticasone furoate group, there were some moderate and severe episodes as well. All episodes of epistaxis in the placebo group were deemed mild. There was no difference between the 2 groups for other adverse event rates, including headache, cough, nasopharyngitis, and rhinitis.¹¹⁰

Ciclesonide

Evidence on the long-term safety on ciclesonide comes from 1 placebo-controlled trial of 663 patients. Mean duration of exposure to ciclesonide was 287.9 days. Rates of epistaxis were higher in the ciclesonide group (10% compared with 7.2% in the placebo group), as were rates of sinusitis and headache. Conversely, rates of nasopharyngitis and upper respiratory infection were higher in the placebo group. None of these differences were deemed to be clinically significant by the study's authors.⁷⁷

Mometasone

A well-designed, open-label 4-week trial of mometasone 200 mcg in seasonal allergic rhinitis patients was consistent with the data from head-to-head trials in adverse event rates.¹¹¹

II. Adolescents and children

A. Direct comparisons

Evidence of the comparative safety of nasal corticosteroids in adolescents and children is extremely limited and comes only from 3 head-to-head trials.^{80, 112, 113} Richards and Milton concluded that there were no clear differences in treatment-related adverse events between fluticasone aqueous, beclomethasone, and placebo.⁸⁰ There were some numerical differences in epistaxis occurring most frequently with fluticasone 100 mcg, but they could not be found clinically significant due to relative rarity and varying severity of symptoms. There were also no differences found in rates of withdrawal due to adverse events between treatment groups. The next controlled trial compared mometasone to budesonide in 22 children aged 7-12 years with confirmed perennial, seasonal, or mixed allergic rhinitis.¹¹² There were no withdrawals due to adverse events and no clear differences in rates of adverse events between treatments or active drug and placebo. The study did not report individual adverse events separately for treatment groups. A randomized controlled double/single-blind trial examined 2 doses of triamcinolone and fluticasone in 49 children between 4-10 years old.¹¹³ This trial studied short-term bone growth and effects of nasal steroids on the hypothalamic-pituitary-adrenal axis. These were not included in our adverse event review, but we were able to include the other clinical adverse events reported. There were no clear differences in all-cause adverse event rates among the treatment groups, triamcinolone 110 mcg (50%), triamcinolone 220 mcg (43.6%), fluticasone (43.6%), and placebo (49%). Fever was the only individual adverse event reported for all treatment groups and there were no clear differences among the groups for incidence of fever. There were 3 withdrawals due to adverse events in the triamcinolone 110 mcg group, 1 of which was treatment-related and 1 of which was due to adverse events in the placebo group.

B. Indirect comparisons

Due to the paucity of head-to-head trial evidence in adolescents/children, placebo-controlled trials were analyzed for further assessment of how nasal corticosteroids compare to one another, indirectly, in rates of more common adverse respiratory and nervous system effects and in effects on growth. The only evidence of the efficacy and safety of nasal corticosteroids in preschool-aged children also comes from a placebo-controlled trial.

1. Common adverse respiratory and nervous system effects

All eleven 2- to 12-week placebo-controlled trials reported miscellaneous tolerability outcomes such as nasal irritation, epistaxis/blood-tinged nasal secretions, headache, and others in children aged 8.3 to 12.3 years,^{81, 82, 86-90, 114-117} and only 3 studies additionally reported effects on standing height.^{114, 115, 117} The reporting of adverse effects in these trials was inconsistent across studies and thus, it is not possible to draw conclusive indirect comparisons. Day, et al. reported no significant difference in adverse effects between budesonide and placebo,⁸¹ a 4-week study found no adverse events with fluticasone or placebo,⁸⁶ and the remaining 9 studies reported no clear differences in adverse effects between the active drug and placebo groups.^{82, 87-90, 114-117}

The only evidence of safety in younger children between the ages of 2-5 years comes from a small (N=56) placebo-controlled trial of mometasone furoate. There were no serious adverse events found during the 6-week treatment period. Headache and rhinorrhea were more

common in the placebo group (7% mometasone furoate compared with 11% placebo for both AEs) while upper respiratory tract infection and skin trauma occurred in children using mometasone (7% for upper respiratory tract infection and 4% for skin trauma), although the latter adverse events were not reported in the placebo group.¹¹⁸

We identified 2 observational studies that included adolescent patients (12-18 yrs.). The first investigated open-label use of the new formulation of HFA propelled triamcinolone on 396 patients.¹¹⁹ The smaller study evaluated mometasone furoate in 61 subjects.¹²⁰ Both studies found no serious adverse events related to treatment drugs and similar tolerability events as previously described.

2. Lenticular opacities

We identified 1 observational study that examined long-term safety of budesonide in 78 children with confirmed perennial rhinitis between the ages of 5-15 years.¹²¹ There were 4 small lenticular opacities found; 2 were present before the study began and remained unchanged over 24 months of treatment and the other 2 were transient and disappeared upon discontinuation of budesonide treatment. There is no report of the clinical significance of these opacities.

3. Nasal carriage of staphylococcus aureus

We found 1 medium-sized fair quality observational study (N=196) of children (mean age 7.6 years) treated with fluticasone for allergic rhinitis for 2 months.¹²² Baysoy, et al. found no significant difference in pre- and post-treatment staphylococcus aureus carriage rates between active treatment and control groups.

4. Growth retardation in children

The evidence of clinical growth effects comes from 4 randomized double-blind placebo-controlled trials and 2 observational studies.^{114, 115, 117, 121, 123, 124} Changes were reported from baseline in statural growth, although the reporting methods varied somewhat among the studies. We excluded studies that only reported growth outcomes as measured using knemometry or hypothalamic-pituitary-adrenal (HPA) axis function. The use of short-term lower-leg growth rates measured with knemometry methods is less predictive of long-term growth due to the inconsistent and irregular timing of growth spurts in childhood.¹¹⁵ Many studies of nasal corticosteroids have included the assessment of hypothalamic-pituitary-adrenal (HPA) axis function in order to determine the systemic effects, however the FDA has suggested that childhood growth may be a more sensitive indicator of these systemic adverse effects than the HPA axis function.¹¹⁷

Growth effects of beclomethasone AQ 168 mcg, fluticasone AQ 200 mcg, and mometasone 100 mcg were each compared to placebo, respectively, in 12-month randomized controlled trials of children.^{114, 115, 117} Beclomethasone¹¹⁴ was associated with a significantly higher risk of growth reduction (Table 14). Allen et al. reported no significant difference in change in height from baseline between the fluticasone aqueous 200 mcg and placebo groups.¹¹⁵ The study of mometasone 100 mcg compared with placebo also showed no significant differences in mean height increase over 1 year.¹¹⁷ Murphy, et al. found no significant mean difference in growth velocity from baseline to 1 year between budesonide (64 mcg/day) and

placebo. Finally, Skoner, et al. found a reduction in growth rate for beclomethasone aqueous 168 mcg twice daily when compared to placebo after 12 months.¹¹⁴

We are aware of unpublished interim results from a randomized open-label 52-week comparison of budesonide aqueous to cromolyn sodium in children with perennial rhinitis that suggest some progressive slowing of growth in the budesonide group (http://www.fda.gov/cder/foi/nda/96/020233s003_rhinocort_toc.htm).

Evidence from observational studies is inconsistent with the placebo-controlled trials. A retrospective study of 60 children (Age 24-117 months, mean age 70 months) taking beclomethasone aqueous 336 mcg/day for confirmed perennial rhinitis investigated medium and long-term growth and found no adverse growth effects.¹²³ It should be noted that this study was unable to determine compliance rates from the clinical records and the children were allowed to take other antiallergic medication (antihistamines and decongestants) as needed.

Another observational study examined long-term growth rates in 73 children using budesonide over a period of 24 months.¹²¹ They assessed growth by comparing mean height to height predicted at entry. Changes in predicted mean heights after 12 and 24 months were not statistically significant.

Table 14. Summary of growth outcomes

Study	Interventions	Outcome	Results
Sample size	(Total daily dose)		
Mean age	Duration		
% female			
Skoner, 2000 N=80 7.5 years/7.1 years 31%	Beclomethasone aqueous (336 mcg) compared with placebo 12 months Randomized, double-blind, placebo-controlled	Mean change in height from baseline	5.0 cm compared with 5.9, <i>P</i> <0.01
Schenkel, 2000 N=98 6.3 years 32.7%	Mometasone aqueous (100 mcg) compared with placebo 12 months Randomized, double-blind, placebo-controlled	Mean change in height from baseline 3-5 years 6-9 years	7.65 cm compared with 7.26 cm 6.67 cm compared with 6.0 cm, both NS
Allen, 2002 N=150 6.2 years 34%	Fluticasone p. aqueous (200 mcg) compared with placebo 12 months Randomized, double-blind, placebo-controlled	Mean change in height from baseline 3 months completed 12 months completed	6.39 cm compared with 6.30 cm 6.32 cm compared with 6.20 cm, both NS
Mansfield, 2002 N=60 5.8 years 33%	Beclomethasone aqueous (168-336 mcg) Mean treatment duration: 3 years Retrospective observational	Comparison annual growth velocity with predicted growth velocity	Boys: 6.66 cm/y compared with 6.0 cm/y Girls: 4.66 cm/y compared with 5.25 cm/y, both NS
Moller, 2003 N=78 10.8 years 28%	Budesonide aerosol and aqueous (200-600 mcg) 24 months Prospective open observational	Mean height percent of predicted at entry compared with actual mean height percent First 12 months: aerosol Second 12 months: aqueous Mean change in height from baseline First 12 months: aerosol Second 12 months: aqueous	102.5% compared with 102.2% 102.1% compared with 101.9%, both NS 4.9 cm compared with 5.2 cm
Murphy, 2006 N=229 5.9 years 34%	Budesonide aqueous (64 mcg) compared with placebo 12 months Randomized, double-blind, placebo-controlled	Mean change in height from baseline Mean growth velocity Mean difference in growth velocity	5.83 compared with 6.17 cm, NS 5.91 compared with 6.19 cm/year, NS 0.27 +/-0.18 cm/year (95%CI, -0.07 to 0.62 cm/year)

Key Question 3. Are there subgroups of patients based on demographics (age, racial groups, gender), other medications, or comorbidities, or in pregnancy and lactation for which one nasal corticosteroid is more effective or associated with fewer adverse events?

No studies stratified or analyzed data by subgroups of patients based on demographics, use of concomitant medications, or comorbidities. Race was only reported in one-third of all head-to-head trials and was predominantly Caucasian.^{14, 19, 23, 25-27, 54, 97, 103, 113} Use of other concomitant nasal medications and/or presence of other concurrent nasal pathologies (e.g., sinusitis, viral infections, nasal structural abnormalities) were generally exclusionary. Given

these limitations, the demographic, concomitant medication usage, and comorbidity data provided can only be useful in determining the generalizability of results, but do not provide many insights into potential differences in efficacy or adverse events.

I. Demographics

Most head-to-head trials conducted in adults were comprised of comparable proportions of males (52%) and females (48%) and mean age overall was 33.5 years (range 24 years to 66.7 years). There were a few exceptions. One 4-week trial of mometasone 100 or 200 mcg and beclomethasone 400 mcg involved 477 adults with seasonal allergic rhinitis that were almost all male (91.5%).²⁹ Indirect comparisons suggest that physician ratings of improvement and changes in total symptom scores were similar in this trial to other similar trials with higher proportions of female participants. In another trial of flunisolide 200 mcg compared with beclomethasone 400 mcg in adults with seasonal allergic rhinitis and a noticeably higher mean age of 66.7, however, rates of physician-rated improvement were numerically lower than in other similar trials of younger patients.²⁰ It is not possible to draw conclusions about potential differential effects based on age using data from this trial, as the lower rates could also have been due to the use of a more stringent definition of improvement (“total” compared with “significant”).

With regard to race, 1 study compared the adverse sensory attributes of fluticasone, mometasone, and triamcinolone in 364 adults with perennial allergic rhinitis who were all of Asian descent.¹⁰¹ It is not possible to compare treatment effects in this trial to those reported in other similar head-to-head trials due to heterogeneity in outcome reporting. The only other evidence of safety and efficacy in an elderly population (65-87 years) with perennial allergic rhinitis was found in an unpublished 12-week placebo-controlled trial of mometasone identified in our dossier review. Mometasone 200 mcg/day was found to be significantly more effective than placebo in reducing total nasal symptom scores in the first 2 weeks. Local adverse effects such as headache, pharyngitis, coughing, and epistaxis occurred more frequently in the mometasone treatment group although statistical significance was not reported.¹²⁵

Trials in children were comprised of more males (65%) than females and the mean age overall was 9 years. Similarly, trials of adolescents were comprised of mostly males (90%) and the mean age was 14 years.^{38, 85, 88} The highest reported prevalence of male participants (97%) was reported in 1 of the trials of adolescents with seasonal allergic rhinitis that compared 2 weeks of treatment with fluticasone 100 or 200 mcg with placebo (N=243).³⁸ Rates of patients with significant improvement in this trial appear similar to those in other placebo-controlled trials of fluticasone and this evidence does not suggest that fluticasone has differential effects based on gender.

The only evidence of using nasal corticosteroids in very young children comes from placebo-controlled trials of fluticasone or mometasone. The first 6-week study found fluticasone safe and effective for 26 very young children between ages of 2 and 4 years with confirmed perennial rhinitis.¹²⁶ This randomized double-blind double-dummy placebo-controlled trial compared fluticasone 100 mcg and an oral placebo with ketotifen 1 mg (an antihistamine with mast-cell stabilizer activity) and a placebo nasal spray. The fluticasone treatment group showed statistically better efficacy for total nighttime and daytime symptom scores and for nasal blockage at 4-6 weeks. All other individual symptom scores revealed no significant differences between treatment groups. As a secondary outcome, investigators assessed 9 children using fluticasone to have experienced improvement or substantial improvement, while only 4 in the

ketotifen group had the same level of improvement. There were as well no significant differences in frequency of adverse events. Additional evidence of safety in young children between the ages 2-5 years comes from an unpublished placebo-controlled trial of mometasone that was revealed in our dossier review. There were no serious adverse events found during the 6-week treatment period and headache and rhinorrhea were more common in the placebo group, while upper respiratory tract infection and skin trauma occurred more frequently in children using mometasone.¹²⁵

With regard to race, 1 placebo-controlled trial examined the potential growth suppression effects of beclomethasone AQ 336 mcg over 1 year in 80 children that were 57% black.¹¹⁴ This data is only descriptive, however, and does not provide evidence of the comparative effects of beclomethasone relative to other nasal corticosteroids based on race.

II. Comorbidities

A. Asthma

Patients with comorbid asthma were included in 8 head-to-head trials in adults.^{13, 16, 20, 21, 24, 50, 51, 56} None reported analyses of rhinitis symptom outcome in the subgroups of patients with asthma, however. Only 1 trial conducted any subgroup analyses of the patients with comorbid asthma, but the focus was only on asthma symptom outcomes.¹³ This subgroup analysis involved patients with fall seasonal asthma and was conducted on 19 patients using flunisolide and 11 patients using beclomethasone nasal sprays.¹³ The authors reported that baseline scores for chest symptoms were similar for both groups. During the peak of ragweed season the placebo-treated patients reported a 10-fold increase in symptoms compared to patients treated with nasal corticosteroids. The expected symptoms of asthma did not occur in most of the active treatment patients. The study was not designed for rigorous evaluation of asthma symptoms and patients were not screened with pulmonary function tests, nor was the asthma monitored throughout the trial with peak flow meters or spirometry.

One small (N=28), fair quality, randomized, placebo-controlled, double-blind crossover trial examining intranasal beclomethasone aqueous in pediatric patients (mean age 10 years) with perennial allergic rhinitis and concomitant asthma showed positive effects on rhinitis symptoms and mixed effects on asthma symptoms.¹²⁷ After 4 weeks, the mean rhinitis symptom scores were lower for those taking beclomethasone in the morning ($P=0.06$) and in the evening ($P=0.03$). In contrast, the morning asthma symptom scores were lower for beclomethasone at end of the study ($P=0.07$) but the evening scores were temporarily significantly lower in week 2 and 3, only to be similar at study end.¹²⁷

Dahl, et al. investigated the cross effects of nasal and inhaled corticosteroids on both symptoms of pollen-induced rhinitis and asthma in a 6-week study with 262 patients receiving either only inhaled or nasal fluticasone, placebo, or combined therapy.¹²⁸ Results showed that nasal medication controlled nasal symptoms and inhaled medication controlled pulmonary symptoms but did not reduce reported symptoms in the untreated disease. The combined treatment did well in alleviating overall pollen-induced symptoms.

Another smaller 16-week active control study (N=59) looked at cross symptoms in patients with allergic rhinitis and mild-to-moderate asthma in 3 groups: nasal beclomethasone, inhaled beclomethasone, and combined treatment.¹²⁹ Results showed that self-assessed asthma symptom scores (from patient diaries) do improve significantly when treated with nasal

beclomethasone only ($P=0.0001$) and similarly for nasal symptoms treated with inhaled beclomethasone only ($P=0.002$). Using symptom scores from Asthma and Rhinitis Questionnaires, the asthma scores were significantly decreased ($P=0.009$) in all treatment groups, but not the rhinitis scores ($P=0.09$).

B. Daytime somnolence and/or sleep disorders

Five small ($N=22$ to 32) fair-quality, randomized, placebo-controlled, double-blind crossover trials examining patients with perennial allergic rhinitis and concomitant daytime somnolence and/or sleep disorders reported mixed efficacy of nasal corticosteroids in treating these comorbidities.¹³⁰⁻¹³⁴ Due to heterogeneity in outcome reporting, data from these trials were insufficient for analyzing the indirect comparative efficacy and safety of fluticasone and budesonide on rhinitis symptom outcomes in patients with comorbid sleep disturbances.

Three of the trials studied fluticasone 200 mcg/day; the first found the active drug to be significantly better at improving subjective nasal congestion and daytime alertness ($P=0.02$) but found no difference in subjective sleep quality or partner-reported snoring between treatment groups.¹³¹ The second fluticasone trial (Craig, et al.) reported significantly improved sleep as recorded by patients ($P=0.04$) but found no significant differences in nasal congestion, daytime sleepiness, and daytime fatigue between treatments.¹³² Craig, et al. also found no significant differences in any of the 9 items in the quality of life questionnaire or subjective analysis of quality of sleep assessment.¹³² The final study, Mansfield, et al., did not find any between-group differences in reaction time or daytime somnolence but did find a significant improvement in nasal congestion in the fluticasone group.¹³³

The other 2 trials studied the use of budesonide aqueous 128 mcg/day in patients with confirmed perennial allergic rhinitis. In the Gurevich study ($N=22$), significant improvement was seen in self-assessed daytime sleepiness between treatment and placebo ($P=0.01$) and in the total subjective sleep measures score ($P=0.04$).¹³⁴ However, there was no significant improvement for the Epworth Sleepiness Scale, the Functional Outcome of Sleep Questionnaire, or the Rhinoconjunctivitis Quality of Life Questionnaire. Hughes, et al., study subjects ($N=26$) also had symptoms of daytime fatigue and somnolence and reported significant differences in change of symptom severity (reported on 5-point scale, 0=none and 4=severe) in favor of active drug for daytime sleepiness ($P=0.02$), daytime fatigue ($P=0.03$), and sleep problems ($P=0.05$), however not for nasal congestion ($P=0.08$).¹³⁰ There was no significant differences between treatment groups in the items from the Juniper's Rhino-conjunctivitis Quality of Life Questionnaire and the Functional Outcome of Sleep Questionnaire, although there were some numerical differences favoring the active drug.

III. Pregnancy

Fluticasone AQ 200 mcg and placebo had similar effects on pregnancy rhinitis symptoms in 53 women after 8 weeks in the only trial of such patients identified for inclusion in this review.¹³⁵ Study authors defined pregnancy rhinitis as nasal congestion of more than 6 weeks duration during pregnancy without other known causes, such as respiratory tract infection or allergy, and disappearing within 2 weeks of delivery. The primary efficacy variable was the measurement of nasal peak expiratory flow, which is not included in this review. The secondary outcome of mean weekly morning symptom scores revealed no significant difference between

fluticasone and placebo, 1.5 compared with 1.9 on a 4-point scale (0=none and 3=severe symptoms). Measured safety outcomes included delivery week, birth weight, femur length, and biparietal diameter. There were no significant treatment group differences in any of the adverse events.

A recently published systematic review reported on budesonide use in pregnancy.¹³⁶ This review included data from multiple observational studies and 1 randomized controlled trial and included patients with allergic rhinitis and asthma. None of the included studies compared budesonide to another nasal corticosteroid. Among the included studies, pregnancy outcomes, including stillbirth, congenital malformations, birth weight, and gestational age were not significantly affected by budesonide use either in early pregnancy or throughout pregnancy.

SUMMARY

Table 15 summarizes the main findings of this review.

Table 15. Summary of the evidence by key question

Key Questions 1 and 2: Efficacy and safety	Strength of evidence	Conclusions
Adults: Efficacy and common adverse effects		
<i>Treatment of seasonal allergic rhinitis: Adults</i>	Beclomethasone compared with others: Moderate Fluticasone compared with others: Moderate Flunisolide old compared with new or beclomethasone: Low Ciclesonide: Low Fluticasone furoate: Low	Beclomethasone compared with budesonide, flunisolide, fluticasone, mometasone, triamcinolone: Differences in efficacy or adverse events not found Fluticasone compared with budesonide, triamcinolone: Differences in efficacy or adverse events not found. Flunisolide old compared with new, beclomethasone: Differences in efficacy not found; old flunisolide associated with higher rates of burning/stinging Ciclesonide and fluticasone furoate: No direct evidence; data from PCTs confirm the efficacy of these drugs compared to placebo
<i>Prophylaxis of seasonal allergic rhinitis: Adults</i>	Mometasone compared with beclomethasone: Low	Mometasone associated with lower rhinitis symptom severity during pre- and peak-seasons; but increased risk of headache with mometasone
<i>Treatment of perennial allergic rhinitis: Adults</i>	Budesonide compared with others: Low Beclomethasone compared with fluticasone: Low Mometasone compared with others: Low Flunisolide new compared with old: Low	Budesonide superior to fluticasone in reducing combined nasal symptom score in 1 fair-quality trial; no differences in adverse events Budesonide compared with mometasone: Differences in efficacy or adverse events not found Beclomethasone compared with fluticasone: Differences in efficacy or adverse events not found when compared at equivalent dosage levels Mometasone compared with beclomethasone, fluticasone: Differences in efficacy or adverse events not found Flunisolide new compared with old: Differences in efficacy or adverse events not found
<i>Treatment of non-allergic rhinitis</i>	Very low overall: No head-to-head trials; indirect comparisons of fluticasone, mometasone from placebo-controlled trials	Indirect comparisons from placebo-controlled trials: Provided no additional information about comparative efficacy/safety due to extreme heterogeneity
Adults: Serious harms		
<i>Cataracts</i>	Beclomethasone compared with non-use: Very low	No increase in the relative risk of cataract among all users of nasal corticosteroids (RR 1.0, 95% CI 0.6-1.4) or among beclomethasone users compared with the unexposed (RR 0.8, 95% CI 0.5-1.2) in 1 retrospective observational study

Other harms	Triamcinolone, mometasone, ciclesonide, fluticasone, fluticasone furoate: very low	No head-to-head studies compared long-term adverse event rates among the various nasal corticosteroids. Evidence is extremely limited and insufficient for indirect comparisons.
Children: Efficacy and common adverse effects		
<i>Treatment of seasonal allergic rhinitis: Children</i>	Mometasone compared with beclomethasone: Low Indirect comparisons from placebo-controlled trials of beclomethasone, flunisolide, fluticasone, triamcinolone: Very low	Mometasone compared with beclomethasone: Differences in efficacy or adverse events not found Indirect comparisons from placebo-controlled trials: Provided no additional information about comparative efficacy/safety due to extreme heterogeneity
<i>Treatment of perennial allergic rhinitis: Children</i>	Beclomethasone compared with fluticasone: Low Indirect comparisons from placebo-controlled trials of beclomethasone, budesonide, flunisolide, fluticasone, triamcinolone: Very low	Beclomethasone compared with fluticasone: Differences in efficacy or adverse events not found Indirect comparisons from placebo-controlled trials: Provided no additional information about comparative efficacy/safety due to extreme heterogeneity
<i>Treatment of non-allergic rhinitis: Children</i>	No evidence found	
Children: Serious harms		
<i>Growth retardation</i>	Beclomethasone, fluticasone, mometasone, budesonide: Low	Beclomethasone: Significantly lower height increase over 12 months relative to placebo in 1 trial; similar to expected height increases over 3 years in a retrospective observational study Fluticasone, mometasone, budesonide: Similar height increases over 12 months relative to placebo
<i>Lenticular opacities</i>	Budesonide: Very low	Budesonide was associated with development of 2 cases of transient lenticular opacities in an uncontrolled retrospective study of 78 children over a 2-year period; the clinical significance of the opacities was not reported
Key Question 3: Subgroups	Strength of evidence	Conclusions
Demographics, concomitant medication use, comorbidities (asthma, daytime somnolence/sleep disorders), pregnancy rhinitis:	Very low	No conclusions about comparative effectiveness, efficacy or safety can be made.

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Appendix A. Search strategies

Original searches

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <4th Quarter 2005>

Search Strategy:

-
- 1 mometasone.mp. (237)
 - 2 fluticasone.mp. (1428)
 - 3 budesonide.mp. or BUDESONIDE/ (1748)
 - 4 exp TRIAMCINOLONE/ or triamcinolone.mp. (694)
 - 5 beclomethasone.mp. or exp BECLOMETHASONE/ (1429)
 - 6 flunisolide.mp. (169)
 - 7 corticosteroid\$.mp. (5107)
 - 8 1 or 2 or 3 or 4 or 5 or 6 or 7 (8660)
 - 9 rhiniti\$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (2935)
 - 10 8 and 9 (757)
 - 11 limit 10 to yr="2000 - 2005" (230)
 - 12 from 11 keep 1-230 (230)
-

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <4th Quarter 2005>

Search Strategy:

-
- 1 mometasone.mp. (237)
 - 2 fluticasone.mp. (1428)
 - 3 budesonide.mp. or BUDESONIDE/ (1748)
 - 4 exp TRIAMCINOLONE/ or triamcinolone.mp. (694)
 - 5 beclomethasone.mp. or exp BECLOMETHASONE/ (1429)
 - 6 flunisolide.mp. (169)
 - 7 corticosteroid\$.mp. (5107)
 - 8 1 or 2 or 3 or 4 or 5 or 6 or 7 (8660)
 - 9 rhiniti\$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (2935)
 - 10 8 and 9 (757)
 - 11 from 10 keep 1-757 (757)
-

Database: Ovid MEDLINE(R) <1996 to October Week 1 2005>

Search Strategy:

-
- 1 mometasone.mp. (244)
 - 2 fluticasone.mp. (1388)
 - 3 budesonide.mp. or BUDESONIDE/ (1882)
 - 4 exp TRIAMCINOLONE/ or triamcinolone.mp. (1407)
 - 5 beclomethasone.mp. or exp BECLOMETHASONE/ (1182)

- 6 flunisolide.mp. (132)
- 7 1 or 2 or 3 or 4 or 5 or 6 (5171)
- 8 corticosteroid\$.mp. or exp adrenal cortex hormones/ [mp=title, original title, abstract, name of substance word, subject heading word] (45969)
- 9 exp ADMINISTRATION, INTRANASAL/ (3465)
- 10 8 and 9 (282)
- 11 7 or 10 (5291)
- 12 rhiniti\$.mp. or exp RHINITIS/ (7952)
- 13 11 and 12 (518)
- 14 limit 13 to (humans and english language) (467)
- 15 limit 14 to yr="2000 - 2005" (277)
- 16 from 15 keep 1-277 (277)

Database: Ovid MEDLINE(R) <1966 to October Week 2 2005>
Search Strategy:

- 1 mometasone.mp. (271)
- 2 fluticasone.mp. (1541)
- 3 budesonide.mp. or BUDESONIDE/ (2634)
- 4 exp TRIAMCINOLONE/ or triamcinolone.mp. (5443)
- 5 beclomethasone.mp. or exp BECLOMETHASONE/ (2761)
- 6 flunisolide.mp. (293)
- 7 1 or 2 or 3 or 4 or 5 or 6 (11520)
- 8 corticosteroid\$.mp. or exp adrenal cortex hormones/ [mp=title, original title, abstract, name of substance word, subject heading word] (164623)
- 9 exp ADMINISTRATION, INTRANASAL/ (6753)
- 10 8 and 9 (450)
- 11 7 or 10 (11730)
- 12 rhiniti\$.mp. or exp RHINITIS/ (19048)
- 13 11 and 12 (1049)
- 14 limit 13 to (humans and english language) (915)
- 15 limit 14 to yr="1966 - 1999" (630)
- 16 from 15 keep 1-630 (630)

Database: Ovid MEDLINE(R) <1966 to October Week 2 2005>
Search Strategy:

- 1 mometasone.mp. (271)
- 2 fluticasone.mp. (1541)
- 3 budesonide.mp. or BUDESONIDE/ (2634)
- 4 exp TRIAMCINOLONE/ or triamcinolone.mp. (5443)
- 5 beclomethasone.mp. or exp BECLOMETHASONE/ (2761)
- 6 flunisolide.mp. (293)
- 7 corticosteroid\$.mp. (44658)

- 8 exp adrenal cortex hormones/ (135755)
- 9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 (171616)
- 10 (nasal\$ or nose or intranasal\$.mp. [mp=title, original title, abstract, name of substance word, subject heading word] (80991)
- 11 (ae or po or to or ct).fs. (1100937)
- 12 (advers\$ adj5 effect\$.mp. (59983)
- 13 11 or 12 (1132475)
- 14 9 and 10 and 13 (681)
- 15 limit 14 to (humans and english language) (585)
- 16 limit 15 to yr="2000 - 2005" (190)
- 17 15 not 16 (395)
- 18 from 17 keep 1-395 (395)

Database: Ovid MEDLINE(R) <1996 to October Week 1 2005>
Search Strategy:

- 1 mometasone.mp. (244)
- 2 fluticasone.mp. (1388)
- 3 budesonide.mp. or BUDESONIDE/ (1882)
- 4 exp TRIAMCINOLONE/ or triamcinolone.mp. (1407)
- 5 beclomethasone.mp. or exp BECLOMETHASONE/ (1182)
- 6 flunisolide.mp. (132)
- 7 corticosteroid\$.mp. (20122)
- 8 exp adrenal cortex hormones/ (31448)
- 9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 (48857)
- 10 (nasal\$ or nose or intranasal\$.mp. [mp=title, original title, abstract, name of substance word, subject heading word] (33204)
- 11 (ae or po or to or ct).fs. (427255)
- 12 (advers\$ adj5 effect\$.mp. (34224)
- 13 11 or 12 (445407)
- 14 9 and 10 and 13 (351)
- 15 limit 14 to (humans and english language) (305)
- 16 limit 15 to yr="2000 - 2005" (185)
- 17 from 16 keep 1-185 (185)

Update #1 searches

Database: Ovid MEDLINE(R) <1996 to September Week 1 2007>
Search Strategy:

- 1 mometasone.mp. (308)
- 2 fluticasone.mp. (1769)
- 3 budesonide.mp. or BUDESONIDE/ (2273)
- 4 exp TRIAMCINOLONE/ or triamcinolone.mp. (2134)

5 beclomethasone.mp. or exp BECLOMETHASONE/ (1363)
 6 flunisolide.mp. (149)
 7 1 or 2 or 3 or 4 or 5 or 6 (6741)
 8 corticosteroid\$.mp. or exp adrenal cortex hormones/ [mp=title, original title, abstract, name
 of substance word, subject heading word] (93518)
 9 exp ADMINISTRATION, INTRANASAL/ (4327)
 10 8 and 9 (520)
 11 7 or 10 (6961)
 12 rhiniti\$.mp. or exp RHINITIS/ (10294)
 13 11 and 12 (647)
 14 limit 13 to (humans and english language) (579)
 15 (20051\$ or 2006\$ or 2007\$.ed. (1242454)
 16 14 and 15 (105)
 17 from 16 keep 1-105 (105)

 Database: EBM Reviews - Cochrane Central Register of Controlled Trials <3rd Quarter 2007>
 Search Strategy:

 1 mometasone.mp. (279)
 2 fluticasone.mp. (1586)
 3 budesonide.mp. or BUDESONIDE/ (1851)
 4 exp TRIAMCINOLONE/ or triamcinolone.mp. (777)
 5 beclomethasone.mp. or exp BECLOMETHASONE/ (1450)
 6 flunisolide.mp. (174)
 7 1 or 2 or 3 or 4 or 5 or 6 (5340)
 8 corticosteroid\$.mp. or exp adrenal cortex hormones/ [mp=title, original title, abstract, mesh
 headings, heading words, keyword] (11428)
 9 exp ADMINISTRATION, INTRANASAL/ (1478)
 10 8 and 9 (244)
 11 7 or 10 (5380)
 12 rhiniti\$.mp. or exp RHINITIS/ (3673)
 13 11 and 12 (792)
 14 limit 13 to yr="2005 - 2007" (54)
 15 from 14 keep 1-54 (54)

 Database: EBM Reviews - Cochrane Database of Systematic Reviews <3rd Quarter 2007>
 Search Strategy:

 1 mometasone.mp. (18)
 2 fluticasone.mp. (66)
 3 budesonide.mp. or BUDESONIDE/ (81)
 4 exp TRIAMCINOLONE/ or triamcinolone.mp. (74)
 5 beclomethasone.mp. or exp BECLOMETHASONE/ (66)
 6 flunisolide.mp. (41)

- 7 1 or 2 or 3 or 4 or 5 or 6 (131)
- 8 corticosteroid\$.mp. or exp adrenal cortex hormones/ [mp=title, abstract, full text, keywords, caption text] (642)
- 9 [exp ADMINISTRATION, INTRANASAL/] (0)
- 10 8 and 9 (0)
- 11 7 or 10 (131)
- 12 rhiniti\$.mp. or exp RHINITIS/ (103)
- 13 11 and 12 (18)
- 14 limit 13 to yr="2005 - 2007" (11)
- 15 from 14 keep 1-11 (11)

Appendix B. Quality criteria

Study quality is objectively assessed using predetermined criteria for internal validity, based on the combination of the US Preventive Services Task Force and the NNS Center for Reviews and Dissemination^{10, 11} criteria.

All studies regardless of design, that are included are assessed for quality, and assigned a rating of “good”, “fair” or “poor”. Studies that have a fatal flaw are rated poor quality. A fatal flaw is reflected in failing to meet combinations of criteria, which may be related in indicating the presence of bias. An example would be failure or inadequate procedures for randomization and/or allocation concealment combined with important differences in prognostic factors at baseline. Studies that meet all criteria are rated good quality and the remainder is rated fair quality. As the “fair” quality category is broad, studies with this rating vary in their strengths and weaknesses: the results of some fair quality studies are likely to be valid, while others are only probably valid. A “poor quality” trial is not valid-the results are at least as likely to reflect flaws in the study design as the true difference between the compared drugs.

Systematic Reviews:

1. Is there a clear review question and inclusion/exclusion criteria reported relating to the primary studies?

A good quality review should focus on a well-defined question or set of questions, which ideally will refer to the inclusion/exclusion criteria by which decisions are made on whether to include or exclude primary studies. The criteria should relate to the 4 components of study design, indications (patient populations), interventions (drugs), and outcomes of interest. In addition, details should be reported relating to the process of decision-making, i.e., how many reviewers were involved, whether the studies were examined independently, and how disagreements between reviewers were resolved.

2. Is there evidence of a substantial effort to search for all relevant research?

This is usually the case if details of electronic database searches and other identification strategies are given. Ideally, details of the search terms used, date and language restrictions should be presented. In addition, descriptions of hand-searching, attempts to identify unpublished material, and any contact with authors, industry, and research institutes should be provided. The appropriateness of the database(s) searched by the authors should also be considered, e.g. if MEDLINE is searched for a review looking at health education, then it is unlikely that all relevant studies will have been located.

3. Is the validity of included studies adequately assessed?

A systematic assessment of the quality of primary studies should include an explanation of the criteria used (e.g., method of randomization, whether outcome assessment was blinded, whether analysis was on an intention-to-treat basis). Authors may use either a published checklist or scale, or one that they have designed specifically for their review. Again, the

process relating to the assessment should be explained (i.e. how many reviewers involved, whether the assessment was independent, and how discrepancies between reviewers were resolved).

4. Is sufficient detail of the individual studies presented?

The review should demonstrate that the studies included are suitable to answer the question posed and that a judgement on the appropriateness of the authors' conclusions can be made. If a paper includes a table giving information on the design and results of the individual studies, or includes a narrative description of the studies within the text, this criterion is usually fulfilled. If relevant, the tables or text should include information on study design, sample size in each study group, patient characteristics, description of interventions, settings, outcome measures, follow-up, drop-out rate (withdrawals), effectiveness results and adverse events.

5. Are the primary studies summarized appropriately?

The authors should attempt to synthesize the results from individual studies. In all cases, there should be a narrative summary of results, which may or may not be accompanied by a quantitative summary (meta-analysis).

For reviews that use a meta-analysis, heterogeneity between studies should be assessed using statistical techniques. If heterogeneity is present, the possible reasons (including chance) should be investigated. In addition, the individual evaluations should be weighted in some way (e.g., according to sample size, or inverse of the variance) so that studies that are considered to provide the most reliable data have greater impact on the summary statistic.

Controlled Trials:

Assessment of Internal Validity

1. Was the assignment to the treatment groups really random?

Adequate approaches to sequence generation:

Computer-generated random numbers

Random numbers tables

Inferior approaches to sequence generation:

Use of alternation, case record numbers, birth dates or week days

Not reported

2. Was the treatment allocation concealed?

Adequate approaches to concealment of randomization:

Centralized or pharmacy-controlled randomization

Serially-numbered identical containers

On-site computer based system with a randomization sequence that is not readable until allocation

Other approaches sequence to clinicians and patients

Inferior approaches to concealment of randomization:

Use of alternation, case record numbers, birth dates or week days

Open random numbers lists

Serially numbered envelopes (even sealed opaque envelopes can be subject to manipulation)

Not reported

3. Were the groups similar at baseline in terms of prognostic factors?
4. Were the eligibility criteria specified?
5. Were outcome assessors blinded to the treatment allocation?
6. Was the care provider blinded?
7. Was the patient kept unaware of the treatment received?
8. Did the article include an intention-to-treat analysis, or provide the data needed to calculate it (i.e., number assigned to each group, number of subjects who finished in each group, and their results)?
9. Did the study maintain comparable groups?
10. Did the article report attrition, crossovers, adherence, and contamination?
11. Is there important differential loss to followup or overall high loss to followup? (give numbers in each group)

Assessment of External Validity (Generalizability)

1. How similar is the population to the population to whom the intervention would be applied?
2. How many patients were recruited?
3. What were the exclusion criteria for recruitment? (Give numbers excluded at each step)
4. What was the funding source and role of funder in the study?
5. Did the control group receive the standard of care?
6. What was the length of followup? (Give numbers at each stage of attrition.)

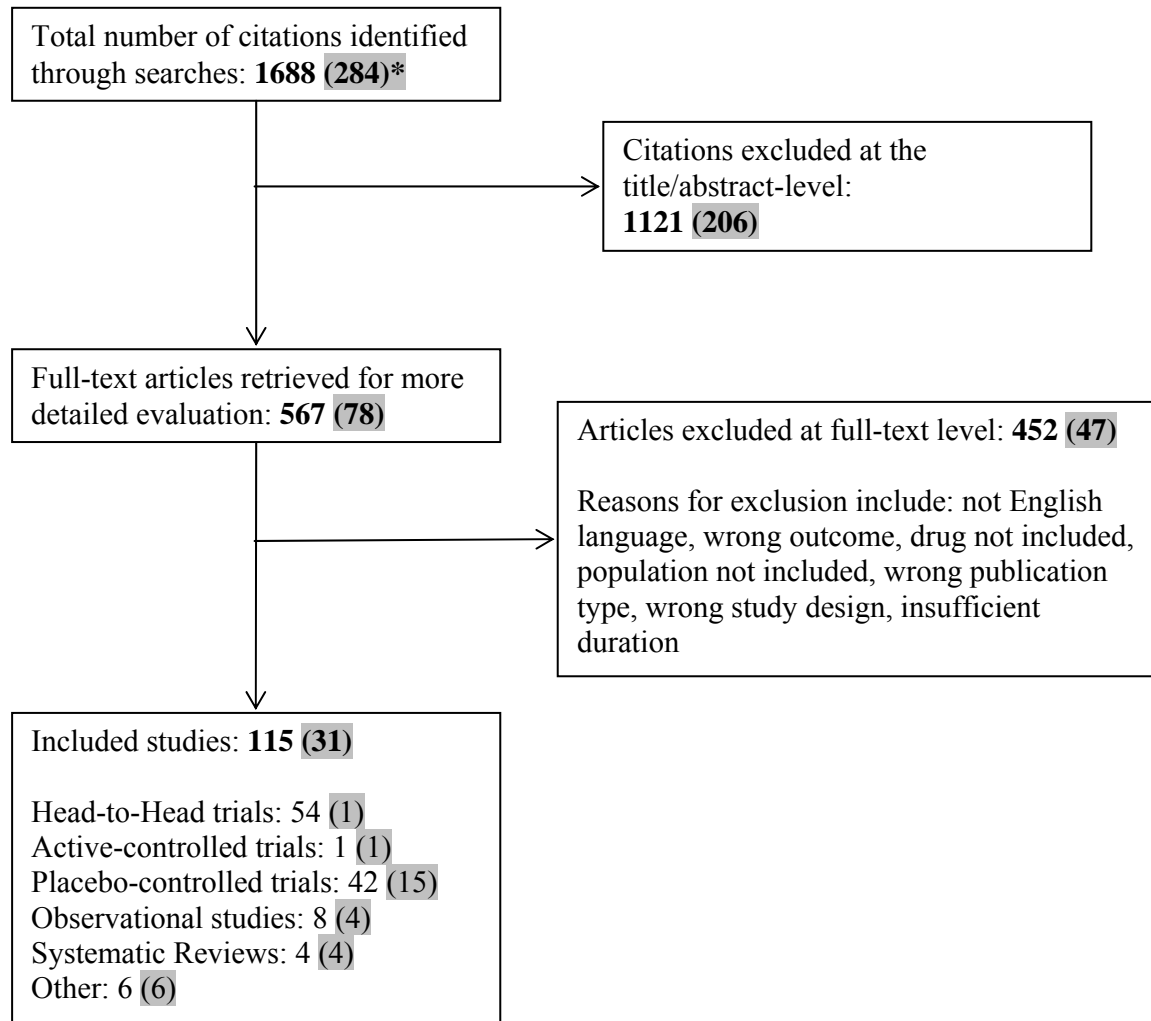
Non-randomized studies:Assessment of Internal Validity

1. Was the selection of patients for inclusion non-biased (Was any group of patients systematically excluded)?
2. Is there important differential loss to followup or overall high loss to followup? (Give numbers in each group.)
3. Were the events investigated specified and defined?
4. Was there a clear description of the techniques used to identify the events?
5. Was there non-biased and accurate ascertainment of events (independent ascertainers; validation of ascertainment technique)?
6. Were potential confounding variables and risk factors identified and examined using acceptable statistical techniques?
7. Did the duration of followup correlate to reasonable timing for investigated events? (Does it meet the stated threshold?)

Assessment of External Validity

1. Was the description of the population adequate?
2. How similar is the population to the population to whom the intervention would be applied?
3. How many patients were recruited?
4. What were the exclusion criteria for recruitment? (Give numbers excluded at each step)
5. What was the funding source and role of funder in the study?

Appendix C. Results of literature search



* Shaded totals in parenthesis reflect results of literature search specific to update 1

Appendix D. Listing of excluded studies

Excluded studies	Reasons for exclusion
<i>Active-controlled trials</i>	
Khanna P, Shah A. Assessment of sensory perceptions and patient reference for intranasal corticosteroid sprays in allergic rhinitis. <i>American Journal of Rhinology</i> . May-Jun 2005;19(3):316-321.	Outcome not included
Barnes ML, Biallostowski BT, Gray RD, Fardon TC, Lipworth BJ. Decongestant effects of nasal xylometazoline and mometasone furoate in persistent allergic rhinitis. <i>Rhinology</i> . Dec 2005;43(4):291-295.	Study design not included
Bhatia S, Baroody FM, deTineo M, Naclerio RM. Increased nasal airflow with budesonide compared with desloratadine during the allergy season. <i>Archives of otolaryngology--head & neck surgery</i> . Mar 2005;131(3):223-228.	Study design not included
Cordray S, Harjo JB, Miner L. Comparison of intranasal hypertonic dead sea saline spray and intranasal aqueous triamcinolone spray in seasonal allergic rhinitis. <i>Ear, Nose, & Throat Journal</i> . Jul 2005;84(7):426-430.	Study design not included
Das S, Gupta K, Gupta A, Gaur SN. Comparison of the efficacy of inhaled budesonide and oral choline in patients with allergic rhinitis. <i>Saudi medical journal</i> . Mar 2005;26(3):421-424.	Study design not included
Zieglmayer UP, Horak F, Toth J, Marks B, Berger UE, Burtin B. Efficacy and safety of an oral formulation of cetirizine and prolonged-release pseudoephedrine versus budesonide nasal spray in the management of nasal congestion in allergic rhinitis. <i>Treatments in Respiratory Medicine</i> . 2005;4(4):283-287	Study design not included
<i>Placebo-controlled trials</i>	
Barnes ML, Biallostowski BT, Fujihara S, Gray RD, Fardon TC, Lipworth BJ. Effects of intranasal corticosteroid on nasal adenosine monophosphate challenge in persistent allergic rhinitis. <i>Allergy</i> . Nov 2006;61(11):1319-1325.	Outcome not included
Agertoft L, Pedersen S. Short-term lower-leg growth rate and urine cortisol excretion in children treated with ciclesonide. <i>Journal of Allergy & Clinical Immunology</i> . May 2005;115(5):940-945.	Intervention not included
Gradman J, Caldwell MF, Wolthers OD. A 2-week, crossover study to investigate the effect of fluticasone furoate nasal spray on short-term growth in children with allergic rhinitis. <i>Clinical therapeutics</i> . Aug 2007;29(8):1738-1747.	Population not included
Nave R, Wingertzahn MA, Brookman S, Kaida S, Matsunaga T. Safety, tolerability, and exposure of ciclesonide nasal spray in healthy and asymptomatic subjects with seasonal allergic rhinitis. <i>Journal of Clinical Pharmacology</i> . Apr 2006;46(4):461-467.	Population not included

Excluded studies	Reasons for exclusion
Rowe-Jones JM, Medcalf M, Durham SR, Richards DH, Mackay IS. Functional endoscopic sinus surgery: 5 year follow up and results of a prospective, randomised, stratified, double-blind, placebo controlled study of postoperative fluticasone propionate aqueous nasal spray. <i>Rhinology</i> . Mar 2005;43(1):2-10.	Population not included
<i>Observational studies</i>	
Bousquet J, Neukirch F, Bousquet PJ, et al. Severity and impairment of allergic rhinitis in patients consulting in primary care. <i>Journal of Allergy & Clinical Immunology</i> . 2006;117(1):158-162.	Outcome not included
Meltzer EO, Hadley J, Blaiss M, et al. Development of questionnaires to measure patient preferences for intranasal corticosteroids in patients with allergic rhinitis. <i>Otolaryngology--head and neck surgery: Official journal of American Academy of Otolaryngology-Head and Neck Surgery</i> . Feb 2005;132(2):197-207.	Outcome not included
Bonfils P, Avan P, Malinvaud D. Influence of allergy on the symptoms and treatment of nasal polyposis. <i>Acta Oto-Laryngologica</i> . Aug 2006;126(8):839-844.	Population not included
Desrosiers M, Hussain A, Frenkiel S, et al. Intranasal corticosteroid use is associated with lower rates of bacterial recovery in chronic rhinosinusitis. <i>Otolaryngology - Head & Neck Surgery</i> . Apr 2007;136(4):605-609.	Population not included
Valera FCP, Anselmo-Lima WT. Evaluation of efficacy of topical corticosteroid for the clinical treatment of nasal polyposis: searching for clinical events that may predict response to treatment. <i>Rhinology</i> . Mar 2007; 45(1):59-62.	Population not included

Appendix E. Adverse effects in head-to-head trials

Study Sample size Trial duration	Age % female Rhinitis type	Treatments (total daily dose in mcg)	Withdrawals due to adverse events	Adverse effects			
				Headache	Throat soreness	Epistaxis	Nasarritation
Al-Mohaimeid 1993 N=120 3 wks	30 years 27.5% PAR	BUD 400 µg vs. BEC 400	5.2% vs. 1.7%; NS	NR	NR	NR	NR
Bende 2002 N=438 4 wks	31.0 years 57.7% PAR	MOM 200 vs. BUD 256/128	1.9% vs. 4.7% vs. 0.9%; NS	9% vs. 11% vs. 11%; NS	NR	6% vs. 9% vs. 6%; NS	NR
Berger 2003 3 wks N=295	31.6 yrs 62% SAR	TRI AQ 220 vs. FLUT 200	None	6.8% vs. 4.1%, NS	Pharyngitis: 0.7% vs. 2.7%; NS	2.7% vs. 4.8%, NS	NR
Bronsky 1987 N=151 4 wks	29 yrs 52% SAR	FLUN 200/300 vs. BEC 168/336	NR	10% vs. 10% vs. 12% vs. 10%, NS	8% vs. 5% vs. 5% vs. 0%, NS	8% vs. 8% vs. 7% vs. 8%, NS	Stinging/burning: 30% vs. 33% vs. 10% vs. 10%; <i>P</i> <0.05
Bunnag 1984 N=45 4 wks	28.5 years 66.7% PAR	FLUN 200 vs. BEC 400	2.2% vs. 0; NS	2.2% vs. 2.2%; NS	NR	NR	Burning sensation: 20% vs. 2.2%; <i>P</i> = 0.0081 Nasal irritation: 2.2% vs. 0; NS
Conley 1994 N=100 1 day	40.0 years 61% PAR	FLUN 50 vs. BEC 84	None	0 vs. 2%; NS	NR	NR	NR
Day 1998 N=273 6 wks	30.8 years 54.9% PAR	BUD 256 vs FLUT 200	1.8% vs. 1.8%; NS	9% vs. 10%; NS	NR	Bloody nasal discharge: 18% vs. 7%; NS	NR
Drouin 1996 N=427 12 wks	31.7 years 45.4% PAR	MOM 200 vs. BEC 400	5.6% vs. 4.1%; NS	10% vs. 7%; NS	Pharyngitis: 4% vs. 6%; p-value NR	19% vs. 23%; NS	Nasal irritation: 3% vs. 3%; NS Nasal Burning: 3% vs. 3%; NS

Study Sample size Trial duration	Age % female Rhinitis type	Treatments (total daily dose in mcg)	Withdrawals due to adverse events				
			Headache	Throat soreness	Epistaxis	Nasarritation	
Graft 1996† N=347 8 wks	34.7 yrs 47.3% SAR	MOM 200 vs. BEC 336	0.8% vs. 4.3%; NS	36% vs. 22%; P=0.02‡	Pharyngitis: 6% vs. 10%; NS	NR	NR
Greenbaum 1988 N=122 4 wks	NR NR SAR	New vs. old FLUN 200	2.4% vs. 4.1%; NS	<12% overall; NS between groups (data NR)	Throat irritation: 2% vs. 0; NS	NR	Severe nasal burning/stinging: 0 vs. 13%; P<0.001
Gross 2002 N=352 3 wks	38.8 yrs 66.5% SAR	TRI AQ 220 vs. FLUT 200	1.2% vs. 0; NS	11% vs. 11.7%; NS	Pharyngitis: 2.3% vs. 6.7%; NS	NR	NR
Haye 1993 N=242 ≤ 1 year	37.6 years 56.6% PAR	FLUT 200 vs. BEC 200	NR	8% vs. 4%; NS	NR	14% vs. 5%; P=0.0285	NR
Hebert 1996 N=477 4 wks	32 yrs 8.5% SAR	MOM 100/200 vs. BEC 400	3% vs. 4% vs. 0; NS	8% vs. 10% vs. 8%; NS	Pharyngitis: 3% vs. 2% vs. 4%, NS	3% vs. 6% vs. 5%, NS	NR
Laforce 1994 N=238 4 wks	24 yrs 29% SAR	FLUT 200 BID or QD vs. BEC 336	0 vs. 0 vs. 1.6%; NS	4.7% vs. 3.6% vs. 4.9%, NS	3.1% vs. 0 vs. 3.3%, NS	0 vs. 1.8% vs. 4.9%; NS	Burning: 1.6% vs. 1.8% vs. 6.5%; NS
Langrick 1984 N=60 7 wks	66.7 yrs 37.5% SAR	FLUN 200 vs. BEC 400	None	Dry throat: 2.9% vs. 0; NS Tickling sensation in nose: 0 vs. 2.8%; NS			
Lumry 2003 N=147 3 wks	37 yrs 51% SAR	TRI AQ 220 vs. BEC 336	None	Respiratory system: 15% vs. 10%; skin and appendages: 1% vs. 9%; digestive system: 5% vs. 5%; nervous system: 4% vs. 0; all P=NS			
Mandl 1997 N=550 3 mo	33.0 years 54.7% PAR	MOM 200 vs. FLUT 200	1% vs. 2%; NS	6% vs. 9%; NS	NR	17% vs. 17%; NS	Nasal burning: 3% vs. 3%; NS Nasal irritation: 2% vs. 3%; NS

Study Sample size Trial duration	Age % female Rhinitis type	Treatments (total daily dose in mcg)	Withdrawals due to adverse events	Withdrawals			
				Headache	Throat soreness	Epistaxis	Nasarritation
McArthur 1994 N=77 3 wks	27 yrs 51% SAR	BUD 200 vs. BEC 200	4% vs. 0; NS	2% vs. 0; NS	2% vs. 0; NS	0 vs. 2.6%; NS	Itchy nose: 0 vs. 2.6%; NS
Ratner 1992 N=136 2 wks	44 yrs 62% SAR	FLUT 200 vs. BEC 336	None	0 vs. 1%; NS	2% vs. 2%; NS	3% vs. 2%; NS	Nasal burning: 5% vs. 2%; NS
Ratner 1996 N=218 6 wks	44 yrs 62% SAR	New vs. old FLUN 200	NR	9% vs. 5%; NS	NR	NR	Irritation/tenderness: 4% vs. 4%; NS
Sahay 1980 N=60 4 wks	37 yrs 48% PAR	FLUN 200 vs. BEC 400	3.3% vs. 10%; NS	13.3% vs. 3.3%; NS	NR	0 vs. 10%; NS	Nasal irritation: 10% vs. 3.3%; NS Nasal dryness: 6.7% vs. 10%; NS
Small 1997 N=233 3 wks	28 yrs 52% SAR	TRI HFA 220 vs. FLUT 200	NR	5% vs. 9%; NS	NR	3% vs. 4%; NS	NR
Stern 1997 N=635 4-6 wks	Age NR 51% SAR	BUD 128/256 vs. FLUT 200	0.5% vs. 0.5% vs. 1.7%; NS	NR	NR	NR	NR
Synnerstad 1996 N=25 12 mo	44.1 years 16% NAR	BUD 256 vs. BEC 336	NR	NR	NR	0 vs. 25%	8.3% vs. 16.6%; p-value NR
Tai 2003 N=24 8 wks	40.9 years 62.5% PAR	BUD 400 vs FLUT 200	None	NR	NR	NR	NR
van As 1993 N=466 6 mo	36.3 years 51.3% PAR	FLUT 200 BID/200 QD vs. BEC 168	5% vs. 3% vs. 9%; NS	4% vs. 2% vs. 5%; NS		14% vs. 15% vs. 9%; NS	Nasal irritation: 0 vs. 2% vs. 0 Nasal dryness: 3% vs. 2% vs. 0; NS Nasal burning: 1% vs. 3% vs. 3%; NS
Welsh 1987 N=100 6 wks	28 yrs 33% SAR	FLUN 200 vs. BEC 336	6.7% vs. 0; NS	0 vs. 16.7%; P=0.0522	NR	Nosebleeds: 0 vs. 0	Sore nose: 3.3% vs. 3.3%; NS

Study	Age	Treatments	Withdrawals				
Sample size	% female	(total daily	due to	Headache	Throat	Epistaxis	Nasarritation
Trial duration	Rhinitis	dose in mcg)	adverse		soreness		
	type		events				
Zawisza 1992 N=43 4 wks	NR NAR	FLUN 200 vs. BEC 300	0% vs. 10%	NR	NR	NR	20% vs. 40%; p-value NR

†Prophylaxis trial; ‡Fisher’s exact test performed using StatsDirect (CamCode, U.K.)