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Topical nasal steroids for intermittent and persistent allergic rhinitis in children (Review)

Al Sayyad JJ, Fedorowicz Z, Alhashimi D, Jamal A

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TABLE OF CONTENTS

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[Intervention Review]

Topical nasal steroids for intermittent and persistent allergic rhinitis in children

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ABSTRACT

Background

Allergic rhinitis is a very common chronic illness affecting 10% to 40% of children worldwide. There has been a significant increase in prevalence among children over the last two decades and this increase has been accompanied by a parallel increase in comorbid illnesses such as asthma.

Objectives

To evaluate the therapeutic effectiveness and adverse event profiles of topical nasal steroids for intermittent and persistent allergic rhinitis in children.

Search methods

We searched the Cochrane Ear, Nose and Throat Disorders Group Trials Register, the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* Issue 3, 2005), MEDLINE (1950 onwards) and EMBASE (1974 onwards) on 5th September 2005. CINAHL, *m*RCT(a meta-database of controlled trials), NRR (the National Research Register), LILACS, MedCarib, KOREAMED, IndMed, Samed, Panteleimon, Zetoc, ISI Proceedings, the GlaxoSmithKline Clinical Trials Database and the websites of AstraZeneca, Schering Plough and Aventis were also searched.

Selection criteria

Randomised controlled trials comparing topical nasal steroid preparations against each other or placebo, prescribed for allergic rhinitis in children.

Data collection and analysis

Two authors independently assessed trial quality and extracted data from the included trials. The limited and variable quality of reported data precluded any pooling of results and only a descriptive summary is presented.

Main results

Three trials involving a total of 79 participants were included. All three trials, which compared topical nasal steroids against placebo for perennial rhinitis, provided some, albeit limited data, relevant to our primary outcomes; but in two of the trials the data analysis was flawed and in the third trial it was incomprehensible. None of the trials provided data relevant to our secondary outcomes. There were no adverse events reported from any of the interventions.

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Authors' conclusions

The three included trials provided some weak and unreliable evidence for the effectiveness of Beconase® and flunisolide used topically intranasally for the treatment of intermittent and persistent allergic rhinitis in children. The reduction of severity in symptoms as assessed by the trialists could not be confirmed with the data provided and decisions on the use of these medications should, until such time as more robust evidence is available, be guided by the physician's clinical experience and patients' individual circumstances and preferences.

PLAIN LANGUAGE SUMMARY

Topical nasal steroids for intermittent and persistent allergic rhinitis in children

Allergic rhinitis is a very common chronic illness affecting 10% to 40% of children worldwide. There has been a significant increase in prevalence among children over the last two decades and this increase has been accompanied by a parallel increase in comorbid illnesses such as asthma. Symptoms include sneezing, itching, runny nose and nasal congestion. Allergic rhinitis may be defined as 'persistent' or 'intermittent'. These classifications loosely correspond to perennial (all year round) allergic rhinitis and seasonal allergic rhinitis ('hay fever'). There are a wide range of drug treatments available including topical and oral decongestants, topical and oral antihistamines, topical and systemic corticosteroids, leukotriene antagonists and a number of over the counter preparations. Topical steroids (nasal sprays) are often prescribed, and act directly on the nasal mucosa to reduce symptoms.

The authors of the review identified a large number of randomised controlled trials, however many were excluded due to the use of 'rescue' (additional) medication, which may have confounded the results.

The three included trials provided some weak and unreliable evidence for the effectiveness of Beconase® and flunisolide used topically in the nose for the treatment of intermittent and persistent allergic rhinitis in children. The review authors concluded that until more research is available, decisions on the use of topical steroids should be guided by the physician's clinical experience and patients' individual circumstances and preferences.

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BACKGROUND

Epidemiology

Allergic rhinitis is a very common chronic illness affecting 10% to 40% of children worldwide (Fireman 2000; AHRQ 2002). There has been a significant increase in prevalence among children over the last two decades and this increase has been accompanied by a parallel increase in comorbid illnesses such as asthma. Studies have consistently shown that the UK has one of the highest levels of allergic rhinitis in the world but the true prevalence may be difficult to assess as symptoms vary and patients with mild symptoms may self-medicate with over the counter medicines. Incidence and severity are related to age, with children of school age most commonly affected. The mean age of onset is 10 years and the incidence peaks between the ages of 13 and 19 years.

Clinical symptoms

Allergic rhinitis is clinically defined as a symptomatic disorder of the nasal membranes and surrounding tissues induced by an IgE mediated inflammation after the exposure of the nasal membranes to allergen (ARIA 2001). It is a mucosal allergic reaction which occurs in genetically predisposed individuals in whom cells, which were previously sensitised by an antigen, are triggered to release chemical mediators (Ledford 1998). The immediate response to an antigen is known as the early-phase allergic reaction, in which histamine and other inflammatory mediators are released from mast cells in the nasal mucosa. The released histamine acts on nerve endings to cause the characteristic nasal symptoms which include sneezing, pruritus (itching), rhinorrhoea (runny nose) and nasal congestion. A late-phase allergic reaction occurs approximately 4 to 12 hours after antigen exposure with nasal congestion as the predominant symptom. Children may exhibit other signs such as allergic salute (the rubbing of the hand against the nose in response to pruritus and rhinorrhoea), allergic shiner (bruised appearance on the skin under one or both eyes) and allergic crease (a wrinkle across the bridge of the nose caused by repeated allergic salute).

Quality of life

Although allergic rhinitis is not life threatening it is often associated with a significant reduction in quality of life (Bousquet 1994; Meltzer 2001). By limiting daily activity, allergic rhinitis may have a negative impact on social behaviour and the emotional well-being of children, and may be responsible for absenteeism and inefficient performance at school (Spector 1999).

Classification

Allergic rhinitis has been defined as seasonal or perennial based on the duration of exposure to the allergen. The more recent ARIA guidelines of the World Health Organisation include a classification which utilises symptoms and quality of life parameters (ARIA 2001). It is based on the duration of symptoms, which are either 'intermittent' or 'persistent', and is further subdivided into either 'mild' or 'moderate to severe', depending on the degree of severity and the impact on quality of life. The classification is defined as intermittent if the symptoms last for less than four days per week or for less than four weeks per year, whereas symptoms which last in excess of four days per week and for more than four weeks per year are classified as persistent. The severity of the symptoms can be classified as mild if daily activities such as sport and leisure are normal and there is no disruption to work, school or sleep patterns. Moderate to severe symptoms would be indicated by an impact on one or more of the following; sleep, daily activities such as sport and leisure, and work or school.

Diagnosis

A diagnosis of allergic rhinitis is based on a typical history of allergic symptoms. However, as some of these symptoms may not necessarily be of allergic origin the diagnosis may additionally be confirmed through a combination of in vivo and in vitro diagnostic tests. These may include both serological testing for IgE in conjunction with skin-prick testing (Johansson 1997). The evaluation of skin tests can be as valuable as the assessment of allergen-specific IgE in serum but caution should be exercised when interpreting results as a positive result may not mean that the allergen is the specific cause of the illness. Serological testing is directed towards the detection of free or cell-bound IgE using enzyme allergosorbent tests (EAST) or a radioallergosorbent test (RAST). The immediate hypersensitivity skin tests made with the suspected allergens or other aeroallergens can be used to demonstrate an IgE-mediated allergic reaction.

Nasal challenge tests with allergens have been used extensively in research but may also prove useful in the diagnosis of occupation related allergic rhinitis.

Treatment

Persistent rhinitis is most commonly due to an allergy to the house dust mite. Allergen avoidance is the first line of treatment and there are a variety of measures used to reduce dust mite exposure. Some of the 'environmental' methods include physical changes (heating, ventilation, freezing, washing, barrier methods, air filtration, vacuuming, and ionisers) or chemical treatments (acaricides). There is, however, considerable uncertainty regarding the efficacy and effectiveness of these interventions in treating allergic rhinitis (Sheikh 2007; Gelfand 2005).

Pharmacological treatments include a wide range of topical and oral decongestants, topical and oral antihistamines, anticholinergic agents, topical sodium cromoglycate, topical and systemic corticosteroids, leukotriene antagonists and a number of over the counter preparations. However, environmental control (allergen avoidance) measures are often recommended before or in association with pharmacological treatment.

The first line pharmacological approach will largely depend on the frequency, severity and duration of symptoms. For example, in the early phase of the allergic reaction, when histamine and inflammatory mediators are released, antihistamines may be considered the most appropriate treatment. In the late phase corticosteroids appear to be more effective in dealing with the inflammatory response, however some of their side effects are well documented (Skoner 2000).

The ARIA guidelines for treatment of allergic rhinitis base their recommendations for the appropriate treatment on randomised controlled trials carried out on studies performed using the historical classification of rhinitis. The clinical recommendations associated with these guidelines have now been adapted to the new classification (ARIA 2001; van Cauwenberge 2000).

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Topical nasal steroids

Topical nasal corticosteroids are frequently prescribed by paediatricians, rhinologists and allergists for the treatment of children with allergic rhinitis. They act directly on the nasal mucosa where they can produce their optimal effect (Spector 1999). Dexamethasone, betamethasone, beclomethasone dipropionate, flunisolide, budesonide, fluticasone propionate, triamcinolone and mometasone furoate are the most commonly available.

Topical steroids are capable of almost complete inhibition of late-phase nasal symptoms, although they have a limited effect on the early phase of the allergic response in sensitised patients (Rak 1994). There is also evidence that in patients with persistent allergic rhinitis the regular use of nasal steroid sprays can reduce rhinorrhoea and overall long-term symptom scores (Weiner 1998; Waddell 2003). The developmental vulnerability of children, however, means that the risk/benefits of topical steroids need to be assessed on an individual basis (Gelfand 2005).

Disadvantages associated with topical corticosteroids are local irritation of the mucosa, nasal burning and sneezing after administration. Bloody nasal discharge and septal perforations have been reported in a few cases (LaForce 1985; Naclerio 1993). Although rare, delayed hypersensitivity reactions can occur (Bircher 1996) and systemic effects are generally uncommon but some studies have shown that dexamethasone, beclomethasone and betamethasone may induce moderate adrenal suppression (Michels 1967; Norman 1967; Gazis 1999) and growth retardation in children (Skoner 2000). In addition some of the side effects may be indistinguishable from the symptoms of allergic rhinitis.

Economic costs

The possible association between allergic rhinitis and other comorbidities needs to be considered when evaluating the socio-economic impact of the disease (Spector 1997). The direct economic cost can be fairly high and this is of particular importance in under-resourced countries (Spector 1999; Nash 2000; Santos 1999). The direct cost of physician visits and medication expenses is at least $1.8 billion annually, or nearly 2.5 percent of the $47 billion annual direct cost for respiratory treatment in the United States. Moreover, the estimated cost of lost productivity to employers and society as a result of allergic rhinitis approaches nearly $3.8 billion annually. In the mid-1990s, according to the US Agency for Healthcare Research and Quality, the resulting total annual cost for allergic rhinitis amounted to $5.6 billion (AHRQ 2002).

A systematic review has shown some benefit of using intranasal corticosteroids over either sedating or non-sedating antihistamines (Yanez 2002). Another recent systematic review (Long 2002) assessed the efficacy of treatments for non-allergic and allergic rhinitis which included antihistamines, nasal corticosteroids, immunotherapy, sedating and non-sedating antihistamines, cromolyn sodium, anticholinergic agents, leukotriene inhibitors and sympathomimetics. The review included male and female children and adults, minorities, people on low incomes and elderly patients. It did not provide explicit inclusion and exclusion criteria for the outcomes assessed and searched only one English language database. Significantly, most of the clinical trials were supported by pharmaceutical companies and the majority of included studies reported no major adverse events.

A number of clinical trials have studied topical corticosteroids for the treatment of allergic rhinitis in children. A systematic review is now required to evaluate the evidence for safety and effectiveness

OBJECTIVES

To evaluate the therapeutic effectiveness and adverse event profiles of topical nasal steroids for intermittent and persistent allergic rhinitis in children.

METHODS

Criteria for considering studies for this review

Types of studies

Only randomised controlled trials (RCTs) were included in this review.

Types of participants

Children under the age of 18 with a history of allergic rhinitis, with or without allergic conjunctivitis or asthma were included. The diagnosis must have been confirmed by the clinical history or the allergen to have been identified and the sensitivity proven by positive skin prick test or high circulating levels of allergen-specific IgE antibody detected by radioallergosorbent test (RAST).

Types of interventions

Active interventions

Administration of any topical nasal steroid preparations prescribed for allergic rhinitis, at any dosage over any period of time. We also considered any comparisons between individual steroid preparations.

Control

Placebo.

Types of outcome measures

Primary outcomes

Improvement of global symptoms recorded in validated daily or weekly dairies and any scores from validated visual analogue scales. Individual symptom scores which included any appropriate measures of nasal obstruction, runny nose, sneezing, itching and eye symptoms. Parent rated rhinitis symptom scores were considered acceptable but all scores were to have been confirmed and investigator rated.

Secondary outcomes

- Nasal assessment scores of inspiratory peak flow levels
- Assessment of allergen sensitivity in either the eye or nose
- Measurement of serum IgE antibodies

In addition we considered any outcomes which utilised quality of life instruments to measure any of the following domains; performance at school, absenteeism, social behaviour, emotional well-being and social relationships.

Adverse events

We reported on any specific adverse effects which were described in any of the included trials; whether systemic or local, and any

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clinically diagnosed hypersensitivity or other adverse reactions to the topical nasal steroid medications.

Search methods for identification of studies

We searched the Cochrane ENT Group Trials Register, the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* Issue 3, 2005), MEDLINE (1950 onwards) and EMBASE (1974 onwards) on 5th September 2005.

The following databases were also searched: CINAHL, *m*RCT (a meta-database of controlled trials), NRR (the National Research Register), LILACS, MedCarib, KOREAMED, IndMed, Samed, Panteleimon, Zetoc, ISI Proceedings, GlaxoSmithKline Clinical Trials Database and the AstraZeneca, Schering Plough and Aventis websites.

The following search strategies were used in each of the main databases. Other databases were searched using free text terms. In MEDLINE, EMBASE and CINAHL, the search strategy was used in conjunction with the randomised controlled trial filter validated by the Cochrane Collaboration. MeSH terms appear in upper case and are all exploded, free text terms appear in lower case.

The Cochrane Central Register of Controlled Trials (CENTRAL) and NNR were searched using the search terms shown in Appendix 1

Search strategies for MEDLINE, EMBASE and CINAHL are shown in Appendix 2.

References of retrieved articles from electronic searches were searched. A search for existing meta-analyses and non-Cochrane systematic reviews was performed and their reference lists were scanned for additional trials. One author of an ongoing trial was contacted but this trial included only adult patients. Although we searched their websites, we did not contact any pharmaceutical companies or manufacturers but will consider doing so if appropriate and based on the further evaluation of any of the trials still awaiting assessment. There were no language, publication year or publication status restrictions on searching.

Data collection and analysis

Selection of studies

Two authors (JS & ZF) independently assessed the abstracts of studies resulting from the searches. Full copies of all relevant and potentially relevant studies, those appearing to meet the inclusion criteria, or for which there were insufficient data in the title and abstract to make a clear decision, were obtained. All irrelevant records were excluded and details of the studies and the reasons for their exclusion were noted in the 'Characteristics of Excluded Studies' table.

Data extraction and management

Study details from randomised controlled clinical trials meeting the inclusion criteria were entered into the 'Characteristics of included studies' table in RevMan 4.2.2 by each author separately and cross checked. The following details were extracted:

(1) Study methods: method of allocation, masking of participants and outcomes, exclusion of participants after randomisation and proportion of follow-up losses;
(2) Participants: country of origin, sample size, age, sex, inclusion and exclusion criteria;
(3) Intervention: type of topical nasal steroid;
(4) Control: placebo or nil;
(5) Outcomes: both primary and secondary which are mentioned in the 'outcome measures' section of the protocol for this review.

Outcomes data were collected using a predetermined form designed for this purpose. Zbys Fedorowicz (ZF) held the master copy.

Assessment of risk of bias in included studies

Each author graded the remaining studies, using a simple contingency form, according to the criterion grading system described in the Cochrane Reviewers' Handbook 4.2.0 (Clarke 2003). The gradings were compared and any inconsistencies between the authors in the interpretation of inclusion criteria and their significance to the selected studies were discussed and resolved.

We assessed the following parameters of methodological quality:

- Randomisation was graded as adequate (A), unclear (B) or inadequate (C). Adequate (A) included any one of the following methods of randomisation: computer generated or table of random numbers, drawing of lots, coin-toss, shuffling cards or throw of a dice. Inadequate method of randomisation (C) utilising any of the following: case record number, date of birth or alternate numbers was judged as inadequate.
- Concealment of allocation was graded as adequate (A), unclear (B) or inadequate (C). Adequate (A) methods of allocation concealment included either central randomisation or sequentially numbered sealed opaque envelopes. This criterion was considered inadequate (C) if there was an open allocation sequence and the participants and trialists were able to foresee the upcoming assignment.
- Blinding of outcomes assessment (whether persons assessing the outcome of care were aware of which treatment the participant received) was graded as yes, no or unclear (detection bias).
- Handling of withdrawals and losses (whether there was a clear description given of the difference between the two groups of losses to follow up) was graded as yes (A), unclear (B) or no (C) (attrition bias).

Data synthesis

We followed the Cochrane Ear, Nose and Throat Disorders Group statistical guidelines, however the somewhat limited and variable quality of data in the three included studies precluded any pooling of results or a meta-analysis of their data and therefore this review only provides a descriptive summary of these trials.

In view of the small number of included trials we were not able assess publication bias or to conduct any subgroup analyses.

Further information on what data were available and our reservations concerning some of the data reported in the included trials can be found in the 'Results' and 'Discussion' sections.

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Sensitivity analysis

Sensitivity analyses to assess the robustness of our review results were not conducted due to the lack of included studies.

RESULTS

Description of studies

Results of the search

The search strategy identified 3259 references which, after initial evaluation for relevancy and discarding of all duplicate references, yielded 1061 studies for further consideration. The abstracts of these were then further assessed independently by two of the authors (JS/ZF) resulting in 79 references to studies for potential inclusion. Full text copies of these studies were obtained and were then subjected to further analysis by both authors.

After consultation and discussion with the Cochrane Ear, Nose and Throat Disorders Editorial Group it was agreed that the use of rescue or concomitant medication in any of the included trials might confound outcomes assessment and therefore these trials were to be excluded from this review. Thus a further sixty-one trials, which had permitted the use of rescue medications during the treatment phase, were excluded.

We arranged to translate one trial (Wahn 1978), which was in the German language, but it was subsequently excluded as it permitted the use of rescue medications. Studies in which some of the participants were under the age of 18 but the mean age of all the participants was greater than 18 years were also excluded. All of these excluded trials and the reasons for their exclusion can be found in the 'Characteristics of excluded studies' table.

We were unable to obtain full text copies of Dash 1984 or McGivern 1985 and these studies together with Aasand 1982, Becher 1994, Erin 2003, Gorski 2000, Holmstrom 1999, Okuda 1986, Stern 1994, Turkeltaub 1976, Turkeltaub 1982, which were not explicit about the age of trial participants, are awaiting further assessment. Three other trials Banov 1996, Gale 1980 and Schenkel 1997 required participants to provide details of any concomitant medications they had taken during the course of the trial but no data were reported. As it could not be established from the text if and which rescue medications were taken, these trials are awaiting assessment and the trialists have been contacted and requested to provide details of any concomitant or rescue medications used by the participants.

Three trials which evaluated the effectiveness of two different topical nasal steroids for perennial rhinitis were included in this review, and a further 14 trials, which are currently awaiting assessment, are listed in 'Characteristics of studies awaiting classification'.

Included studies

Hill 1978

The Hill 1978 trial was a randomised double blind placebo controlled cross-over trial which had been conducted in the ENT Clinic at the Royal Children's Hospital Melbourne Australia. The participants were 22 children (11 girls, 11 boys) aged 7 to 17 years with severe perennial rhinitis. The study was conducted just before and during the grass pollen season. All of the participants were chronic mouth breathers, had gross hypertrophy of the nasal mucosa, excessive rhinorrhea and had failed to respond to antihistamines and adrenergic drugs for their rhinitis symptoms. Nineteen of the participants had evidence of marked systemic reaginic allergy to house dust mite and/or rye grass which had been previously assessed by radioallergosorbent test (RAST).

Randomisation was to either Beconase® (beclomethasone dipropionate aerosol spray) 300 mg/day or placebo, and no concomitant medications were permitted during the course of the study. The intervention or placebo were continued for six weeks and were then crossed over. Patients or their parents completed a daily symptom diary which rated the degree of nasal obstruction, sneezing, itching, nasal discharge and eye irritation. These scores were used to calculate a mean daily nasal and eye symptom score for both placebo and active treatment periods. In addition one of the trialists, who was blinded to the symptom scores and medication used, rated the participants nasal physical signs for patency; mucosal swelling, colour, and mucoid and purulent discharge at the start of the trial and the end of each treatment period.

Neuman 1978

The Neuman 1978 study was a double blind cross-over trial conducted over a six month period, through the summer and autumn of 1975, in a General Hospital in Israel . The participants consisted of 30 patients (14 males and 16 females) with an age range of 9 to 18 years (mean 13.8 years) and a history of perennial rhinitis with daily symptoms of sneezing, rhinorrhea and nasal obstruction of at least five years duration. All participants exhibited a positive skin-prick test with standard airborne allergens. None had previously used steroid therapy but all had daily symptoms which were poorly controlled by antihistamines and decongestants. Randomisation was to beclomethasone dipropionate 50 mg inhaled into each nostril four times a day or placebo, details of the cross-over and wash out segments of the trial were not reported. The trialists indicated that the study was conducted over a six-month period yet only provided data for "two three week periods" and were not clear about the follow-up period.

The mode of administration of the treatment or placebo was checked by the trialists at each of the weekly visits. All other medications were withdrawn one week before the start of the trial.

Diary cards, which recorded symptoms of sneezing, rhinorrhea, blocked or itchy nose and throat, cough and headache were completed by the patients. The severity of the symptoms was rated on a 4-point ordinal scale; 0 = no symptoms, 1 = symptoms of less than 30 minutes duration, 2 = symptoms between 30 minutes and two hours, 3 = symptoms lasting longer than two hours. These cards were reviewed weekly when the patients returned for physical examination and the daily scores were used to calculate mean daily and weekly symptom scores as well as a final score at the end of each test period.

Sarsfield 1979

The Sarsfield 1979 study was a double blind cross-over study conducted in the UK. Twenty-seven children (21 boys and six girls), age range from 7 to 16 years (mean 12.3) and with a mean duration of perennial allergic rhinitis of 7.4 years, were enrolled in the study, but there was one withdrawal during the placebo period because of nasal irritation. All participants exhibited a positive skin-prick test

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to the most common allergens and none of them were taking any oral corticosteroids or using any local nasal treatment at the start of the trial. Randomisation was to either, nasal spray consisting of flunisolide as an aqueous propylene glycol solution (0.025% w/v) supplied in a glass bottle fitted with a mechanical pump which was capable of delivering 0.1 ml per actuation, or placebo (vehicle only) in an identical glass bottle.

One group received active nasal spray for four weeks followed by placebo for four weeks and the other group received the same treatment but in reverse order. Participants were instructed to use one spray up each nostril three times daily at eight hourly intervals which provided a total daily dose of 150 mg. Diary cards were filled in at the end of each week by either participants or their parents. These recorded the severity of sneezing, stuffy nose, runny nose and nose blowing which were rated on a four-point scale where 0 = none, 1 = mild, 2 = moderate, 3 = severe. Clinical assessments were made on admission to the study and at the end of each treatment period. The severity of allergic symptoms (sneezing, stuffy nose, runny nose, nose blowing, post nasal drip, epistaxis and throat itch) during the previous month was recorded by direct questioning and scored according to the four-point scale. Any adverse effects from either intervention or placebo were noted and an overall assessment of the control of symptoms was made at the end of each four-week trial period and was rated as total, good, minor, none or worse. At the end of the eight-week treatment period the trial concluded with an assessment of the preferences of the participants to one or neither of the treatments. Seven of the children who had achieved some benefit with flunisolide were encouraged to continue using the spray for a further six months and were followed up with bi-monthly open assessment of their symptoms which included the reporting of any side effects to the medication.

Further trial details can be found in the 'Characteristics of included studies' table.

Risk of bias in included studies

The Hill study was a small sample trial in which the participants were randomised to the intervention (Beconase®) and control (placebo) groups but the method of randomisation was not specified (Hill 1978). However the trialists indicated that the randomisation code was only broken and revealed to the assessors at the conclusion of the trial. The trialists did not provide any details on how blinding of the medication and placebo was achieved. Randomisation was graded as unclear (B) whilst allocation concealment was graded as adequate (A). There were no losses to follow up and therefore this criterion was graded as yes (A).

The Neuman study reported that the participants were allocated at random in a double blind fashion to intervention and control, but the method used to randomise participants was not mentioned by the trialists and therefore this criterion was graded as (B) unclear (Neuman 1978). No details were provided on how blinding of medications was achieved or how the allocation sequence was concealed from participants and trialists and thus this criterion was graded (B) unclear. Two early drop outs were replaced and all participants completed the trial and therefore this criterion was graded as (A) clear.

The Sarsfield study provided no details of the method used to randomise the participants or how the allocation sequence was concealed from trialists or participants and thus both criteria were graded as unclear (B) (Sarsfield 1979). Blinding of intervention and placebo was achieved through the use of identical glass bottles containing either placebo or medication and was graded 'yes'. Only one child, in the placebo group, withdrew and was excluded from the analysis. There were no losses to follow up and therefore this criterion was graded as (A) clear.

Effects of interventions

In view of the scarcity and poor quality of their data none of the three included trials were able to provide any reliable evidence regarding the effectiveness of either Beconase® or flunisolide used topically intranasally for the treatment of intermittent and persistent allergic rhinitis in children. Therefore we present a descriptive summary of some of the results and include a commentary on the analysis and interpretation of the outcomes data reported in these trials.

Primary outcomes

The primary outcomes as reported in one of the trials (Neuman 1978) consisted of a free-hand drawn graph of the mean daily nasal symptom scores. It was not possible to decipher any precise values from this graph and thus no inferences could be drawn from it nor from the rather limited data in the accompanying text. The trialists reported that the diary cards indicated that runny and stuffed noses as opposed to cough and sneezing showed the most marked improvements, but it was not possible to confirm these outcomes from the data that were provided. The daily nasal symptom scores, which had been collected from an ordinal rating scale, were transformed into mean daily nasal symptom scores. However, the transformation of this ordinal data into means and mean change scores, and its further analysis and interpretation would appear to be more appropriate to observations measured on a continuous rating scale. Furthermore, the narrow range of possible answers on this type of short symptom scale is likely to make interpretation of an "average score" difficult and thus the data reported in this trial were not particularly useful.

Data showing lowered mean daily nasal symptom scores ($P < 0.01$) within five days of starting treatment were reported in the Hill trial. The trialists indicated that nasal signs were improved in 15 of the children and that in 13 of the children mean daily eye symptoms scores were decreased during the active treatment phase of the study ($P < 0.05$). At the completion of this study (Hill 1978), only three children out of the total appeared to show no improvement in their daily diary symptom scores and 14 of them expressed a preference for Beconase® over placebo. However, it was not clear from the study details whether a continuous or ordinal rating scale was used to assess the eye and nasal symptoms and thus we were uncertain whether the transformation of the daily symptom scores into means was plausible and therefore advise caution in the interpretation of this data.

The Sarsfield 1979 study provided three sets of data relevant to our primary outcomes; mean weekly self assessed symptom scores, physician's assessment of changes in symptom scores from baseline (admission) values to the end point and, patient's subjective assessments of overall control after each four-week treatment period. The data reported in the first table were the means of daily scores recorded in the diary cards, the second table listed the mean and (SD) of changes in symptom scores

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from baseline (admission) to the end of the treatment period. All of the daily symptom scores, which had been obtained from a short ranked ordinal scale, were transformed into mean and standard deviation of weekly symptom scores. As in the Neuman trial, the investigators in this trial assessed symptoms on an ordinal rating scale and presented outcomes data as means and standard deviations (SD), however the differences between these measured values cannot be considered interpretable in a quantitative sense and therefore the conclusions reached may be suspect. Moreover, to ensure that this trial provided information on the effects of the intervention, a comparison should have been made using the Wilcoxon paired sign-rank test of the differences in score for treatment versus control and not solely the difference in the treatment group (or the control group) from baseline to end point as was done in the analysis. In the absence of any reliable data reflecting treatment outcomes for the active intervention in this trial we have not included any of its data in our review.

Secondary outcomes

None of the three included trials provided any data relevant to these outcomes.

Adverse events

No adverse events from Beconase® or flunisolide were reported and there was no evidence of candidiasis during the study period or in the long term follow up, in either the Neuman or Hill trials. Although the Sarsfield study did not provide any evidence of adrenal suppression with flunisolide, it was considered that this was most probably due to the low dose used and the rapid metabolism of the drug in the liver.

DISCUSSION

The comprehensive search used in this review provided a large number of references to trials, however the number of relevant randomised controlled trials that were retrieved proved to be somewhat disappointing. It is clearly apparent that the selection of trials to ensure a pure comparison between intervention and placebo by excluding trials which permitted access to rescue medicines may have resulted in a lower number of included trials than expected, and all of which were over 25 years old. However, this absence of more recent clinical trials may reflect contemporary changes, current trends and more stringent requirements in the ethical conduct of clinical trials.

The lack of any robust evidence to support or refute the effectiveness of either Beconase® or flunisolide in reducing the symptoms of allergic rhinitis was largely attributable to poor methodological quality and the scarcity and flawed analysis of the data in all three of the included trials. Advancements in theoretical formulation of test statistics now allow for a more plausible analysis and interpretation of outcomes which are based on ordinal data. However, the lack of a wash-out period and absence of important trial details such as the type of measurement scale used in one of the trials has compromised the internal and external validity of the included trials and further diminished any confidence in the applicability and generalisability of their results to any potential clinical applications.

Even though no adverse events were reported, the apparent lack of effectiveness and seemingly low side effect profile of these medications should not be seen as a recommendation for the use of stronger dosage regimens.

It is known that the steroid group of drugs are capable of almost complete inhibition of late-phase nasal symptoms in allergic rhinitis, and it was regrettable that our searches proved unsuccessful in finding any trials which differentiated between the early or late stage of allergic response and thus we were unable to test our null hypothesis; that there is no difference in the relief of symptoms for patients who have taken nasal topical steroids for early as compared to late-phase allergic rhinitis.

As the included trials were conducted before the advent of the more recent classifications of allergic rhinitis, based on 'intermittent' or 'persistent' symptoms, we were also unable to assess the impact of these interventions on patient relevant outcomes such as quality of life, social behaviour and emotional well being.

AUTHORS' CONCLUSIONS

Implications for practice

The three included trials provided some weak and unreliable evidence for the effectiveness of topical nasal steroids for intermittent and persistent allergic rhinitis in children. The reduction of severity in symptoms as assessed by the trialists could not be confirmed with the data provided and decisions on the use of these types of medications should, until such time as more robust evidence is available, be guided by a physician's clinical experience and patients' individual circumstances and preferences.

Although the three studies were conducted in the developed world the relevance and cost implications of the results of this review for resource poor developing countries, where low dose intranasal corticosteroids are prescribed as the first line treatment for mild or persistent allergic rhinitis, cannot be underestimated.

Implications for research

Future research should ensure that all new trials are well designed randomised controlled trials and reported according to the Consolidated Standards of Reporting Trials (CONSORT) statement (http://www.consort-statement.org). These should also include a larger sample, a longer intervention and follow-up period, and if a cross-over design is used, ensure that there is a sufficiently long enough wash out period between intervention and placebo. Outcomes data, particularly if generated from an ordinal rating scale, should be analysed appropriately and interpreted in such way that meaningful conclusions can be reached.

The re-classification of allergic rhinitis into persistent and intermittent categories, based on the duration and severity of symptoms, aligns the assessment of outcomes more closely with those outcomes of relevance to patients and therefore future trials should focus more on these patient assessed outcomes and quality of life measures.

Changing requirements for the ethical conduct of clinical trials are likely to lead to a more permissive use of rescue medications, therefore future trials should more closely monitor and report on rescue medication use and trialists should investigate and test for potential confounding by examining differences between groups through the use of modelling techniques i.e. ANOVA, or multi-variate regression analysis.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Hill 1978

Methods	A randomised double blind placebo controlled cross-over trial, in Australia.
Participants	22 children (11 girls and 11 boys) aged 7-17 years with severe perennial rhinitis assessed by RAST.
Interventions	Randomisation to Beconase (beclomethasone dipropionate aerosol spray) 300 mg/day or placebo. Treatment or placebo for 6 weeks and then crossed over.
Outcomes	Patients or parents completed a daily symptom diary; nasal obstruction, sneezing, itching, nasal discharge and eye irritation. Mean daily nasal and eye symptom score compared for both placebo and Beconase treatment periods. Blinded outcomes assessment: symptoms scores, type of medication, nasal physical signs for patency; mucosal swelling, colour, and mucoid and purulent discharge at start of the trial and end of each treatment period.
Notes	No concomitant medications permitted during the trial. Exact method of administration of intervention or placebo, other than "in an identical manner" not described. No details of 'wash out' period.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Neuman 1978

Methods	A double blind cross over trial, in Israel for a six month period.
Participants	30 patients (14 males and 16 females) age 9-18 years (average 13.8 years) with perennial allergic rhinitis, daily symptoms of sneezing, rhinorrhoea and nasal obstruction of at least five years duration.
Interventions	Beclomethasone dipropionate 50 mg inhaled into each nostril four times a day or placebo. The intervention/placebo exposure times and cross-over periods unspecified.
Outcomes	Diary cards: symptoms of sneezing, rhinorrhea, blocked nose, itchy nose and throat, cough and headache. Rated as; 0 = no symptoms, 1 = symptoms <30 minutes duration, 2 = symptoms between 30 minutes and two hours, 3 = symptoms >2 hours. Average daily and weekly scores and final score at the end of each test period. Patients' preferences for one or neither intervention or placebo were recorded at the end of the trial.
Notes	All medications including antihistamines withdrawn one week prior. Study design unclear, wash out period unspecified. The data very sparse, one poorly annotated graph. Stated "success rate of 83%" no data to confirm results.

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Neuman 1978 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Sarsfield 1979

Methods	A double blind cross over study in the UK.
Participants	27 children (21 boys, 6 girls) 7-16 years. Mean:12.3 years with perennial rhinitis.
Interventions	Nasal spray of flunisolide as an aqueous propylene glycol solution (0.025% w/v) in a glass bottle fitted with a mechanical pump delivering 0.1 ml per actuation, or placebo. Intervention or placebo for 4 weeks and crossed over. One spray in each nostril three times per day at 8-hourly intervals. A total daily dose of 150 micrograms.
Outcomes	Weekly diary cards by participants or parents, severity of : sneezing, stuffy nose, runny nose and nose blowing rated: 0 = none, 1 = mild, 2 = moderate, 3 = severe. Clinical assessments at enrollment and the end of each treatment period. Severity of allergic symptoms (sneezing, stuffy nose, runny nose, nose blowing, post nasal drip, epistaxis, and throat itch) during the previous month was recorded by direct questioning and scored 0-3.
Notes	No indication of whether concomitant or rescue medications were prohibited during the trial, and no wash out period was specified.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Agertoft 1993	Inhaled glucocorticosteroids and other anti-asthma treatment was allowed to continue unchanged during the study and rescue medicines were also permitted.
Andersson 1995	Adult participants aged > 35yrs.
Anon 1980	Participants 16 years or more with no upper age limit specified.
Berkowitz 1999	Age 12 to 60 [Mean 32].
Boner 1994	Use of rescue anthistamines was permitted.
Boner 1995	Rescue medicines consisting of antihistamine syrup or tablets and sodium cromoglycate eye drops were provided to participants.
Cockcroft 1976	Mean age 34.2 years.

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Study	Reason for exclusion
de Graaf Veld 1995	Age range 21 to 50 [Mean 34].
Dolovich 1990	Adults and rescue medications.
Drouin 1996	Age range 13 to 65 [Mean 33].
Dunn 1984	Adults and children 14 to 53 [Mean 27.8].
Dykewicz 2003	Participants aged 12 to 70 [Mean 34]. No individualised data.
Fokkens 2002	Patients were provided with anthistamine rescue medication.
Friedman 1962	A comparison against an antibiotic.
Galant 1994	Anthistamine rescue medicines were provided.
Gawchik 2003	Participants aged 12 to 74 [Mean 34.2].
Girard 1978	Age range 16 to 53 [Mean 31.4].
Grossman 1993	Anthistamine rescue medicines were provided throughout the treatment phase.
Grubbe 1996	Age range 12 to 70 [Mean 33.8].
Gupta 2004	Adult participants. Age range 15 to 45 [Mean 24].
Hebert 1996	Adult participants. Age range 18 to 87 [Mean 31].
Hofman 1995	No control only a comparative study.
Holopainen 1977	Age range 13 to 67 [Mean 32].
Horan 1978	Age range 13 to 65 [Mean 37.6].
Irander 1984	Age range 16 to 66 [Mean 30.1].
Joubert 1983	Age range 14 to 51 [Mean 28].
Kobayashi 1989	Antihistamine rescue medicines were dispensed and permitted.
McAllen 1980	Men and women 16 to 60 years.
Meltzer 1999	Antihistamine rescue medication was permitted throughout the treatment phase of the study.
Moesgaard 1983	Age range 16 to 58 [Mean 32.9].
Munch 1982	Age range 29 to 58 [Mean 39].
Munk 1994	Anthistamine rescue medication was permitted during the study.
Munk 1996	Age range 20 to 65 [Mean 37].
Ngamphaiboon 1997	Anthistamine rescue medicines were permitted during the treatment phase of this study.
Nuutinen 1987	Adult patients.

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Study	Reason for exclusion
Pedersen 1991	Age range 18 to 59 [Mean 30.5].
Pedersen 1994	Adult patients.
Pedersen 1995	Age 12+ [Mean 29.6].
Pedersen 1998	Use of the ß2 agonist inhaler was permitted.
Pintus 1979	Age range 15 to 47 [Mean 33].
Pipkorn 1980	Age range 17 to 56 [Mean 29.5].
Pipkorn 1982	Age range 16 to 57 [Mean 29.4].
Pipkorn 1983	Age range 16 to 49 [Mean 29.6].
Pipkorn 1984	Age range 17 to 64 [Mean 29].
Rudolph 1976	Supplementary anthistamines permitted during the study.
Rusnak 1981	Age range 20 to 56 [Mean 36].
Scadding 1995	Age range 12 to 65 [Mean 34.8].
Schulz 1978	Age range 15 to 71.
Shore 1977	Anthistamine decongestant therapy was permitted during the study.
Sipila 1983	Mean age 22.7. Rescue medicines were permitted.
Spector 1990	Age range 16 to 65 [Mean 36.93].
Steensen 1981	Age range 17 to 53 [Mean 29.8].
Storms 1996	Concomitant medications were not restricted.
Strem 1978	Additional concomitant medications were permitted.
Tarlo 1977	Age range 15 to 61 [Mean 34].
Wahn 1978	Antihistamine rescue medication was permitted during the study.
Warland 1981	Age range 12 to 74 [Mean 25].
Warland 1982	Age range 16 to 76 [Mean 32.5].
Welch 1991	Anthistamine rescue medicines were permitted during part of the treatment phase of this study.
Welch 1994	Age range 12 to 65 [Mean 25.5].
Yang 1998	Age range 19 to 74.
Zhang 1995	A comparison of the bio-equivalence of Beclomethasone Dipropionate manufactured by Chongqing Glaxo Limited and Glaxo UK.

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APPENDICES

Appendix 1. Search strategy for CENTRAL

#1 STEROIDS explode all trees (MeSH)
#2 ANTI-INFLAMMATORY-AGENTS explode all trees (MeSH)
#3 ANTI-INFLAMMATORY-AGENTS-NON-STEROIDAL explode all trees (MeSH)
#4 #2 NOT #3
#5 GLUCOCORTICOIDS single term (MeSH)
#6 STEROID* OR CORTICOSTEROID*
#7 GLUCOCORTICOID* OR CORTICOID*
#8 BECLOMETHASON* OR BECLAMET OR BECLOCORT OR BECOLMETASONE OR BECOTIDE
#9 BETAMETHASON* OR BETAMETASONE OR BETADEXAMETHASONE OR FLUBENISOLONE OR CELESTO*
#10 HYDROCORTISON* OR CORTISOL
#11DEXAMETHASON* OR DEXAMETASON* OR HEXADECADROL OR DECADRON OR DEXASONE OR HEXADROL OR METHYLFLUORPREDNISOLONE OR MILLICORTEN OR ORADEXON
#12 BUDESONID* OR HORACORT OR PULMICORT OR RHINOCORT
#13 FLUNISOLID* OR NASALIDE
#14 FLUTICASON* OR FLONASE OR FLOUNCE
#15 MOMETASON* OR NASONEX
#16 TRIAMCINOLON* OR NASACORT OR TRI ADJ NASAL OR ARISTOCORT OR VOLON
#17 #1OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11OR #12 OR #13 OR #14 OR #15 OR #16
#18 RHINITIS-ALLERGIC-PERENNIAL single term (MeSH)
#19 HAY-FEVER single term (MeSH)
#20 HAYFEVER OR HAY ADJ FEVER OR POLLINOSIS OR POLLENOSIS OR PAR OR SAR
#21 RHINITI*
#22 ALLERG* OR SEASON* OR PERENNIAL OR POLLEN OR MITE*
#23 #21 AND #22
#24 #18 OR #19 OR #20 OR #23
#25 #17 AND #24

Appendix 2. Search strategies for other databases

MEDLINE (DataStar)

1. STEROIDS#.W..DE.
2. ANTI-INFLAMMATORY-AGENTS#.W..DE.
3. ANTI-INFLAMMATORY-AGENTS-NON-STEROIDAL#.W..DE. 4. 2 NOT 3
5. GLUCOCORTICOIDS.W..DE.
6. (STEROID$2 OR CORTICOSTEROID$2).TI,AB.
7. (GLUCOCORTICOID$2 OR CORTICOID$2).TI,AB.
8. BECLOMETHASONE OR 4419-39-0.RN. OR BECLAMET OR BECLOCORT OR BECOLMETASONE OR BECOTIDE OR BECONASE OR VANCENASE
9. BETAMETHASONE OR 378-44-9.RN. OR BETAMETASONE OR BETADEXAMETHASONE OR FLUBENISOLONE OR CELESTO$4
10. HYDROCORTISONE OR CORTISOL OR 50-23-7.RN.
11. DEXAMETHASONE OR 50-02-2.RN. OR DEXAMETASONE OR HEXADECADROL OR DECADRON OR DEXACORT OR DEXASONE OR HEXADROL OR METHYLFLUORPREDNISOLONE OR MILLICORTEN OR ORADEXON
12. BUDESONIDE OR 51333-22-3.RN. OR HORACORT OR PULMICORT OR RHINOCORT
13. FLUNISOLIDE OR 3385-03-3.RN. OR NASALIDE OR NASAREL OR RHINALAR
14. FLUTICASONE OR 90566-53-3.RN. OR 80474-14-2.RN. OR FLONASE OR FLOUNCE OR FLIXONASE
15. MOMETASONE OR 105102-22-5.RN. OR NASONEX 16. TRIAMCINOLONE OR 124-94-7.RN. OR NASACORT OR TRI ADJ NASAL OR ARISTOCORT OR VOLON
17. 1 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16
18. RHINITIS-ALLERGIC-PERENNIAL.W..DE. OR HAY-FEVER.W..DE.
19. (HAYFEVER OR HAY ADJ FEVER OR POLLINOSIS OR POLLENOSIS OR PAR OR SAR).TI,AB.
20. RHINITI$1.TI,AB.
21. (ALLERG$3 OR SEASON$2 OR PERENNIAL OR POLLEN OR MITE$1).TI,AB.
22. 20 AND 21
23. 18 OR 19 OR 22
24. 17 AND 23

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EMBASE (DataStar)

1. CORTICOSTEROID#.DE.
2. ANTIINFLAMMATORY-AGENT#.W..DE.
3. NONSTEROID-ANTIINFLAMMATORY-AGENT#.W..DE. OR OCULAR-ANTIINFLAMMATORY-AGENT#.W..DE. 4.2 NOT 3
5. (STEROID$2 OR CORTICOSTEROID$2).TI,AB.
6. (GLUCOCORTICOID$2 OR CORTICOID$2).TI,AB.
7. BECLOMETHASONE OR 4419-39-0.RN. OR BECLAMET OR BECLOCORT OR BECOLMETASONE OR BECOTIDE OR BECONASE OR VANCENASE
8. BETAMETHASONE OR 378-44-9.RN. OR BETAMETASONE OR BETADEXAMETHASONE OR FLUBENISOLONE OR CELESTO$4
9. HYDROCORTISONE OR CORTISOL OR 50-23-7.RN.
10. DEXAMETHASONE OR 50-02-2.RN. OR DEXAMETASONE OR HEXADECADROL OR DECADRON OR DEXACORT OR DEXASONE OR HEXADROL OR METHYLFLUORPREDNISOLONE OR MILLICORTEN OR ORADEXON
11. BUDESONIDE OR 51333-22-3.RN. OR HORACORT OR PULMICORT OR RHINOCORT
12. FLUNISOLIDE OR 3385-03-3.RN. OR NASALIDE OR NASAREL OR RHINALAR
13. FLUTICASONE OR 90566-53-3.RN. OR 80474-14-2.RN. OR FLONASE OR FLOUNCE OR FLIXONASE
14. MOMETASONE OR 105102-22-5.RN. OR NASONEX
15. TRIAMCINOLONE OR 124-94-7.RN. OR NASACORT OR TRI ADJ NASAL OR ARISTOCORT OR VOLON
16. 1 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15
17. ALLERGIC-RHINITIS.DE. OR HAYFEVER.DE. OR PERENNIAL-RHINITIS.DE. OR CHRONIC-RHINITIS.DE.
18. (HAYFEVER OR HAY ADJ FEVER OR POLLINOSIS OR POLLENOSIS OR PAR OR SAR).TI,AB.
19. RHINITI$1.TI,AB.
20. (ALLERG$3 OR SEASON$2 OR PERENNIAL OR POLLEN OR MITE$1).TI,AB.
21. 19 AND 20
22. 17 OR 18 OR 21
23. 16 AND 22

CINAHL (DataStar)

1. STEROIDS#.W..DE.
2. ANTIINFLAMMATORY-AGENTS#.DE.
3. ANTIINFLAMMATORY-AGENTS-NON-STEROIDAL.DE.
4. 2 NOT 3
5. GLUCOCORTICOIDS.W..DE.
6. (STEROID$2 OR CORTICOSTEROID$2).TI,AB. 7. (GLUCOCORTICOID$2 OR CORTICOID$2).TI,AB.
8. BECLOMETHASONE OR 4419-39-0.RN. OR BECLAMET OR BECLOCORT OR BECOLMETASONE OR BECOTIDE OR BECONASE OR VANCENASE
9. BETAMETHASONE OR 378-44-9.RN. OR BETAMETASONE OR BETADEXAMETHASONE OR FLUBENISOLONE OR CELESTO$4
10. HYDROCORTISONE OR CORTISOL OR 50-23-7.RN.
11. DEXAMETHASONE OR 50-02-2.RN. OR DEXAMETASONE OR HEXADECADROL OR DECADRON OR DEXACORT OR DEXASONE OR HEXADROL OR METHYLFLUORPREDNISOLONE OR MILLICORTEN OR ORADEXON
12. BUDESONIDE OR 51333-22-3.RN. OR HORACORT OR PULMICORT OR RHINOCORT
13. FLUNISOLIDE OR 3385-03-3.RN. OR NASALIDE OR NASAREL OR RHINALAR
14. FLUTICASONE OR 90566-53-3.RN. OR 80474-14-2.RN. OR FLONASE OR FLOUNCE OR FLIXONASE
15. MOMETASONE OR 105102-22-5.RN. OR NASONEX
16. TRIAMCINOLONE OR 124-94-7.RN. OR NASACORT OR TRI ADJ NASAL OR ARISTOCORT OR VOLON
17. 1 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16
18. RHINITIS#.DE.
19. (HAYFEVER OR HAY ADJ FEVER OR POLLINOSIS OR POLLENOSIS OR PAR OR SAR).TI,AB.
20. RHINITI$1.TI,AB.
21. (ALLERG$3 OR SEASON$2 OR PERENNIAL$2 OR POLLEN OR MITE$1).TI,AB.
22. 20 AND 21
23. 18 OR 19 OR 22
24. 17 AND 23

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FEEDBACK

Comment received June 2007

Summary

We acknowledge receipt of a criticism/comment from Professor Fokkens, June 2007. We are awaiting further clarification from the contributor before publishing this and the authors' response.

WHAT'S NEW

Date	Event	Description
30 October 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 4, 2005
Review first published: Issue 1, 2007

Date	Event	Description
1 November 2006	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

JS was the guarantor for the review.

ZF was responsible for co-ordinating the review, organising retrieval of papers, writing to authors of papers for additional information and providing additional data about papers.

JS & ZF were responsible for screening search results, screening retrieved papers against inclusion criteria, appraising quality of papers, abstracting data from papers, data management for the review, obtaining and screening data on unpublished studies, entering data into RevMan and interpretation of data.

JS, DAH, ZF and AJ were responsible for writing the review.

DECLARATIONS OF INTEREST

There are no financial conflicts of interest and the reviewers declare that they do not have any association with any manufacturers or promoters of pharmaceutical products or any parties who may have vested interests in the results of this review.

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Intranasal; Glucocorticoids [*therapeutic use]; Randomized Controlled Trials as Topic; Rhinitis, Allergic, Perennial [*drug therapy]

MeSH check words

Child; Humans

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