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Antihistamines used in addition to topical nasal steroids for intermittent and persistent allergic rhinitis in children (Review)

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[Intervention Review]

Antihistamines used in addition to 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 and its prevalence among children has significantly increased over the last two decades. Prevalence and severity are related to age, with children of school age most commonly affected.

Objectives

To assess the effectiveness and adverse event profile of antihistamines (oral or topical) used as an adjunct to 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); MEDLINE; EMBASE; CINAHL; Web of Science; BIOSIS Previews; Cambridge Scientific Abstracts; mRCT and additional sources for published and unpublished trials. The date of the most recent search was 21 September 2009.

Selection criteria

Randomised controlled trials (RCTs) in children under the age of 18 with a history of allergic rhinitis, with or without allergic conjunctivitis or asthma, comparing topical nasal steroids with antihistamines to topical nasal steroids only.

Data collection and analysis

Two review authors independently screened studies, extracted data and assessed risk of bias.

Main results

One study including 24 participants met the inclusion criteria for this review. This study compared the administration of topical nasal steroids with oral antihistamines to topical nasal steroids only in children, but it did not provide sufficient data to address the clinical question of this review.

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Authors' conclusions

In view of the lack of evidence for the benefit or lack of benefit of antihistamine add-on therapy with topical nasal steroids for children with intermittent or persistent allergic rhinitis, it is important that clinicians are mindful of the adverse effects of antihistamines and the additional costs that may be incurred.

PLAIN LANGUAGE SUMMARY

Antihistamines as an addition to topical nasal steroids for allergic rhinitis in children

Allergic rhinitis is a very common chronic illness affecting 10% to 40% of children worldwide. Seasonal allergic rhinitis (hay fever) is most common around springtime. The symptoms are mostly sneezing, a runny nose and watery eyes. We looked for trials that compared antihistamines (either oral or topical) in addition to a topical nasal steroid with a topical nasal steroid alone in children who had allergic rhinitis. We wanted to know whether adding antihistamines (oral or topical) in the therapy of children with allergic rhinitis who already use topical nasal steroids would have additional benefits for them. We found one trial that had been carried out in children comparing oral antihistamines in addition to topical nasal steroids with topical nasal steroids alone but it did not provide sufficient data to draw any conclusions. Most of the trials focused only on adults or included a small number of children. Unfortunately, the trials which included children along with adults did not report whether there were any differences in the effect of treatment or adverse effects in children in comparison with adults. We are therefore unable to draw a conclusion as to whether or not this combination therapy has beneficial effect in children with allergic rhinitis or whether the benefits are acceptable in terms of the adverse effects.

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BACKGROUND

Description of the condition

Epidemiology

Allergic rhinitis is a very common chronic illness affecting 10% to 40% of children worldwide (AHRQ 2002; Fireman 2000) and its prevalence has significantly increased among children over the last two decades. Prevalence and severity are related to age, with children of school age most commonly affected.

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 an allergen (ARIA 2008). In the immediate response to an antigen (the early-phase allergic reaction) histamine and other inflammatory mediators are released from mast cells in the nasal mucosa which were previously sensitised by an antigen. This causes the characteristic nasal symptoms which include sneezing, pruritus (itching), rhinorrhoea (runny nose) and nasal congestion. A late-phase allergic reaction occurs approximately four 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).

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 Organization include a classification which utilises symptoms and quality of life parameters (ARIA 2008). It is based on the duration of symptoms, which are either 'intermittent' (lasting for less than four days per week or for less than four weeks per year) or 'persistent' (lasting in excess of four days per week and for more than four weeks per year). The classification is further subdivided into either 'mild' or 'moderate to severe', depending on the degree of severity and the impact on quality of life.

The ARIA guidelines for the treatment of allergic rhinitis base their recommendations for the appropriate treatment on randomised controlled trials performed using the historical classification of rhinitis. The clinical recommendations associated with these guidelines have now been adapted to the new classification (ARIA 2008; van Cauwenberge 2000).

Diagnosis

A diagnosis of allergic rhinitis is based on a typical history of allergic symptoms and in vivo and in vitro diagnostic tests. These may include both serological testing for IgE which is directed towards the detection of free or cell-bound IgE using enzyme allergosorbent tests (EAST) or a radioallergosorbent test (RAST) in conjunction with skin-prick testing (Johansson 1997).

Description of the intervention

As well as being recommended concurrently with pharmacological treatment, allergen avoidance is the first-line treatment. There is, however, considerable uncertainty regarding the efficacy and effectiveness of allergen avoidance in treating allergic rhinitis (Marinho 2006) and it is not always possible (Selover 2008). A Cochrane Review suggests that while the use of bedroom-based environmental control programmes may be of some benefit in reducing rhinitis symptoms, the isolated use of house dust mite impermeable bedding is unlikely to prove effective (Sheikh 2010).

Pharmacological treatments include a wide range of topical and oral decongestants, topical and oral H_1 antagonists (antihistamines), anticholinergic agents, topical sodium cromoglycate, topical and systemic corticosteroids and leukotriene antagonists (Weiner 1998).

The first-line pharmacological approach will largely depend on the frequency, severity and duration of symptoms. 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 they include some well-documented side effects (Skoner 2000; Spector 2003). Abuse of over the counter preparations may lead to long-term damage to nasal function.

How the intervention might work

Topical nasal steroids

Topical nasal corticosteroids are frequently prescribed for the treatment of children with allergic rhinitis and 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). However, due to the developmental vulnerability of children, the risks and benefits of topical steroids use need to be assessed on an individual basis (Gelfand 2005).

Disadvantages and side effects associated with topical corticosteroids are local irritation of the mucosa, nasal burning and sneezing after administration, possible bloody nasal discharge and septal perforations (BNF 2004). Some studies have shown that dexamethasone, beclomethasone and betamethasone may induce moderate adrenal suppression (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. Overdosage and side effects are more likely to occur with topical drops the dosage of which is more difficult to self-monitor, and these preparations should be used with extreme caution in children.

A Cochrane Review provided some weak and unreliable evidence for the effectiveness of topical nasal steroids (Beconase® and flunisolide) for the treatment of intermittent and persistent allergic rhinitis in children (Al Sayyad 2007). A recent evidence report from the Center for Evidence-Based Policy looking both at direct and indirect comparisons concluded that beclomethasone, fluticasone and mometasone are associated with similar reductions in rhinitis symptoms (Selover 2008).

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Topical antihistamines

Topical H_1 receptor antagonists (antihistamines) are prescribed to treat the nasal itch, sneezing and rhinorrhoea which are caused by the release of histamine and inflammatory mediators due to the allergic reaction. Currently, the most commonly available antihistamines include intranasal sprays such as azelastine and levocabastine, and oral drugs such as cetirizine, loratadine, fexofenadine and mizolastine.

Topical antihistamines are recommended by some as an alternative to oral antihistamines to alleviate the early-phase allergic symptoms. They also have a faster onset of action for both nasal and ocular symptoms (van Cauwenberge 2000). Usually, a low dose (i.e. twice-daily intranasal and once-daily oral) of antihistamines is recommended to prevent the onset of allergic symptoms.

Known disadvantages of the use of current non-sedating second-generation antihistamines include the side effects of mild drowsiness, fatigue, headache, nausea and dry mouth (Rossi 2004). However, they do not have the adverse sedative effects associated with first-generation antihistamines (Weiner 1998; Yanez 2002). While all antihistamines act through the same mechanism, each type has different advantages and disadvantages. A further consideration is the likelihood of better treatment compliance with once-daily dosage regimes. Despite the availability of studies evaluating the safety profile of antihistamines in adults, there is insufficient evidence on the comparative safety of antihistamines in children (OEPC 2006).

Why it is important to do this review

Although allergic rhinitis is not life-threatening, it can have a substantial socioeconomic impact and be associated with a significant reduction in quality of life (Marinho 2006). 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. The direct economic cost can also be fairly high and this is of particular importance in under-resourced countries and economically disadvantaged populations (Spector 1999).

A systematic review in 1998 found reliable evidence suggesting that intranasal corticosteroids are more effective in relieving sneezing and reducing total nasal symptoms than oral antihistamines (Weiner 1998). A more recent 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. 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.

As mentioned above, there is currently limited evidence available on the effectiveness of topical nasal steroids used alone for children with intermittent and persistent allergic rhinitis (Al Sayyad 2007; Selover 2008). The findings have cost and resource implications for developing countries where low-dose intranasal corticosteroids are prescribed as the first-line treatment for mild or persistent allergic rhinitis. A number of clinical trials have studied topical corticosteroids in conjunction with antihistamines for the treatment of allergic rhinitis in children and this Cochrane Review has been conducted to evaluate the evidence for the safety and effectiveness of this method of treatment.

OBJECTIVES

To assess the effectiveness and adverse event profile of antihistamines used as an adjunct to topical nasal steroids for intermittent and persistent allergic rhinitis in children.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs).

Types of participants

Children under the age of 18 with a history of allergic rhinitis, with or without allergic conjunctivitis or asthma, in whom topical nasal steroids are being used. The diagnosis will have been confirmed by the clinical history or the allergen will 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: oral or topical antihistamine preparations at any dosage over any time period along with the administration of any topical nasal steroid preparation prescribed for allergic rhinitis, at any dosage, over any period of time.

Control intervention: administration of any topical nasal steroid preparation prescribed for allergic rhinitis alone, at any dosage, over any period of time.

Types of outcome measures

Primary outcomes

1. Improvement of global symptoms. Recorded in validated daily or weekly diaries and any scores from validated visual analogue scales (VAS). Individual symptom scores may have included any appropriate measures of nasal obstruction, runny nose, sneezing, itching and eye symptoms. Depending on the age of the child, parent-rated rhinitis symptom scores were acceptable but all scores had to be confirmed and investigator rated.
2. Adverse events. We planned to report on any specific adverse effects, systemic or local, and any clinically diagnosed hypersensitivity or other adverse reactions to the topical nasal steroid medications.

Secondary outcomes

- Nasal assessment scores of inspiratory peak flow levels.
- Rhinomanometry or other objective measurement of nasal airflow.
- Assessment of allergen sensitivity in either the eye or nose.
- Measurement of serum IgE antibodies.

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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.

Search methods for identification of studies

We conducted systematic searches for randomised controlled trials. There were no language, publication year or publication status restrictions. The date of the last search was 21 September 2009.

Electronic searches

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, 2009); PubMed; EMBASE; CINAHL; LILACS; KoreaMed; IndMed; PakMediNet; China National Knowledge Infrastructure; CAB Abstracts; Web of Science; BIOSIS Previews; UKCRN; ICTRP (International Clinical Trials Registry Platform); *m*RCT (Current Controlled Trials) and Google.

We modelled subject strategies for databases on the search strategy designed for CENTRAL. Where appropriate, we combined subject strategies with adaptations of the highly sensitive search strategy designed by the Cochrane Collaboration for identifying randomised controlled trials and controlled clinical trials (as described in the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.0.1, Box 6.4.b. (Handbook 2008)).

Search strategies for all key databases including PubMed are shown in Appendix 1.

Searching other resources

We scanned reference lists of identified studies for further trials. We also searched PubMed, TRIPdatabase, NLH ENT & Audiology Specialist Library and Google to retrieve existing systematic reviews possibly relevant to this systematic review, in order to search their reference lists for additional trials.

Data collection and analysis

Selection of studies

Two authors (MN and ZF) independently assessed the abstracts of studies resulting from the searches. We obtained 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. Two authors assessed the full-text papers independently and resolved any disagreements on the eligibility of included studies through discussion and consensus, or if necessary through a third party. We excluded all irrelevant records and noted details of the studies and the reasons for their exclusion in the 'Characteristics of excluded studies' table in RevMan 5 (RevMan 2008).

Data extraction and management

We collected study details from randomised controlled clinical trials meeting the inclusion criteria using a pre-determined form designed for this purpose and entered these into the 'Characteristics of included studies' table. The authors only included data if there was an independently reached consensus; any disagreements were resolved by consulting with a third author, Hamad Aljufairi (HA).

The following details were extracted:

(1) Trial methods
(a) method of allocation
(b) masking of participants and outcomes
(c) exclusion of participants after randomisation and proportion of losses at follow up

(2) Participants
(a) country of origin
(b) sample size
(c) age
(d) sex
(e) inclusion and exclusion criteria as described in the 'Criteria for considering studies for this review'.

(3) Intervention
(a) type
(b) dose
(c) frequency
(d) duration and length of time in follow up

(4) Control
(a) control or placebo

(5) Outcomes
(a) primary and secondary outcomes outlined in the outcome measures section

The authors used this information to help them assess heterogeneity and the external validity of the trials.

Assessment of risk of bias in included studies

Each review author graded the selected trials and assessed every trial using a simple contingency form following the domain-based evaluation described in the *Cochrane Handbook for Systematic Reviews of Interventions* 5.0.0 (Handbook 2008). We compared the evaluations and discussed and resolved any inconsistencies and disagreements.

We assessed the following domains as 'Yes' (i.e. low risk of bias), 'Unclear' (uncertain risk of bias) or 'No' (i.e. high risk of bias):

1. sequence generation;
2. allocation concealment;
3. blinding (of participants, personnel and outcome assessors, data analysts);
4. incomplete outcome data; and
5. selective outcome reporting.

We reported this assessment in the 'Risk of bias' table ('Characteristics of included studies').

In view of the paucity of trials and the limited amount of data reported in the one included trial, pooling of results of extracted data was not feasible and therefore only data relevant to some of the primary and secondary outcomes and a descriptive summary of results is presented.

For future updates, when studies are identified for inclusion in this review, the following methods will be applied.

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Measures of treatment effect

We will conduct analysis at the same level as the allocation.

We will calculate risk ratios (RR) and their 95% confidence intervals (CIs) for all dichotomous data and as weighted mean difference (WMD) (with 95% confidence intervals) for continuous outcomes, using the Peto fixed-effect method.

Unit of analysis issues

In parallel group RCTs, the analysis will be at individual allocation level. For cross-over trials, if possible, we will undertake a paired analysis of the data obtained to allow a within-individual comparison of the treatment interventions as recommended by Elbourne (Elbourne 2002).

Dealing with missing data

We will make attempts to retrieve missing data from the investigators of any of the included trials, and if unsuccessful or the discrepancies are significant, we will provide a narrative synthesis of the data as reported.

Assessment of heterogeneity

The authors will assess clinical heterogeneity by examining the characteristics of the studies, the similarity between the types of participants, the interventions and the outcomes. Statistical homogeneity will be assessed using a Chi^2 test in addition to the I^2 statistic, where I^2 values over 50% indicate moderate to high heterogeneity (Higgins 2003).

Pooling of the results of any clinically homogeneous trials to provide estimates of the efficacy of the interventions will only be done if the studies have similar interventions received by similar participants. We will calculate relative risks for outcomes and odds ratios for adverse effect outcomes. The risk ratio (relative risk) is the ratio of the risk of an event in the two groups whereas the odds ratio is the ratio of the odds of an adverse event in the intervention group to the odds of an event in the control group.

For the synthesis and meta-analysis of any quantitative data, we will use the fixed and random-effects models as appropriate. We will use the fixed-effect model if we establish that the each study is estimating the same quantity, otherwise we will use the random-effects model (e.g. the identified studies use different types of nasal topical corticosteroids and different types of antihistamines). In the event that there are clinically heterogenous trials (e.g. reporting different outcomes) or insufficient data for pooling, we will perform a descriptive analysis only.

Assessment of reporting biases

To assess publication bias we will follow the recommendations on testing for funnel plot asymmetry as described in section 10.4.3.1 of the *Cochrane Handbook for Systematic Reviews of Interventions* 5.0.0 (Handbook 2008), and we will explore these in the Discussion if appropriate.

Data synthesis

The authors will follow the Cochrane Ear, Nose and Throat Disorders Group statistical guidelines for data synthesis. Two authors (MN and ZF) will analyse the data using RevMan as suggested in Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* version 5.0.0 (Handbook 2008).

Sensitivity analysis

If there are sufficient included trials, the authors plan to conduct sensitivity analyses to assess the robustness of their review results by repeating the analysis excluding trials with unclear or inadequate allocation concealment and unclear or lack of blinding. In addition, the authors will undertake sensitivity analyses to examine the effect of allocation concealment, blind outcome assessment and completeness of follow up.

RESULTS

Description of studies

Results of the search

We carried out searches in November 2008, December 2008 and September 2009 which retrieved a total of 1584 reports. After de-duplication 1082 remained. Two authors (MN and ZF) independently examined the titles and abstracts of these references and excluded studies which did not match the inclusion criteria and were deemed ineligible. After the initial screening, 35 articles remained from 30 studies and we obtained their full-text copies (Albernaz 2007; Andy 2002; Anolik 2008; Barnes 2006; Benincasa 1994; Berger 1999; Berger 2005; Brooks 1996; Brooks 1997;Can 2006; Chao 2003; Cox 1997; D'Ambrosio 1998; Di Lorenzo 2004; Drouin 1995 ; Filipovic 2001; Gupta 1999; Juniper 1989; Kamenov 2003;Kessel 2008; Kotwani 2001; Lee 2003; Ozcan 2002; Paunovic 2007; Pinar 2008; Ratner 1998; Schenkel 1997; Snyman 2004; Stricker 1998; Waddell 2003).

We were unable to find the full text of two studies (Brooks 1997; Kotwani 2001) and one study did not report the age of the patients (Brooks 1996). We have listed and reported these three studies in the 'Studies awaiting classification' section. One study (Albernaz 2007) was in Portuguese and did not match our inclusion criteria following translation. Only one study matched our inclusion criteria; the remaining studies were excluded and the reasons for their exclusion were noted in the 'Characteristics of excluded studies' table.

Included studies

Although a large number of studies were retrieved from our comprehensive search of the literature, we only identified one trial (Can 2006) eligible for inclusion in our review.

Excluded studies

Seven studies identified in the searches were abstracts to conference proceedings and provided limited information on study design or the age of the participants (Chao 2003; Di Lorenzo 2004; Filipovic 2001; Kamenov 2003; Ozcan 2002; Schenkel 1997; Stricker 1998). One of the conference abstracts stated that it included children but lacked further details on the study design and results (Cox 1997). Eleven studies included adults and either did not include children or did not report separate data for children (Anolik 2008; Barnes 2006; Benincasa 1994; Berger 1999; D'Ambrosio 1998; Drouin 1995; Juniper 1989; Lee 2003; Pinar 2008; Ratner 1998; Snyman 2004). One study (Albernaz 2007) did not match our inclusion criteria and Kessel 2008 had a control group with healthy children.

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In Gupta 1999 the comparison was topical nasal steroids against each other and Paunovic 2007 compared combination therapy with placebo.

Three of the retrieved articles were reviews or meta-analyses that did not include any potentially relevant studies (Andy 2002; Berger 2005; Waddell 2003).

Risk of bias in included studies

The one included study (Can 2006) was judged as having a high risk of bias. Full details are shown in the 'Risk of bias' table ('Characteristics of included studies').

Allocation

The patients were randomised into two groups based on their file protocol numbers: odd numbers for group I and even numbers for group II. The generation of the allocation sequence was therefore judged as inadequate ('No') and the allocation was not concealed ('No').

Blinding

There were no attempts to blind the patients or trialists. One of the groups received nasal spray along with syrup and the other one only received a nasal spray. Patients and trialists were therefore not blinded to the intervention and this criterion was also judged as 'Unclear'.

Incomplete outcome data

The authors did not report whether any of the patients were lost to follow up or withdrew. This criterion was therefore judged as 'Unclear'.

Selective reporting

We did not have access to the protocol for this trial, therefore this criterion was also judged as 'Unclear'.

Other potential sources of bias

There was no indication of further potential sources of bias in the reported trial. The trialists did not report whether they had any conflict of interest and also did not report their source of funding for the trial.

Effects of interventions

Primary outcomes

1) Improvement of global symptoms recorded in validated daily or weekly diaries and any scores from validated visual analogue scales

For the subjective assessment of allergic rhinitis and conjunctivitis symptoms a four-point scale (0 to 3) for both daytime (completed in the evening) and night-time (completed on awakening) was used, but the report was unclear as to whether the scale had been validated. We reported and assessed the score using the *checklist for describing and assessing patient reported outcomes in clinical trials* (Table 1) (Patrick 2008).

Data obtained from symptoms scores are usually non-normally distributed (skewed) and therefore in many studies (Calderon 2007), including this one, data are reported as median values. In the absence of mean values for symptom scores, we were unable to further evaluate and report the data for this outcome.

2) Adverse events

The authors did not include adverse events as an outcome in their trial and did not report any adverse events. This does not necessarily mean that the patients did not experience any adverse events.

Secondary outcomes

1) Nasal assessment scores of inspiratory peak flow levels

The trial authors assessed nasal peak inspiratory flow (NPIF) both at home or during the visits. At each visit, a portable inspiratory flowmeter (In check; Clement Clarke Int. Ltd., Harlow, UK) was used three times and the highest value was recorded. The authors report the data as median and not mean values and we were unable to obtain the means from the information provided in the paper.

2) Rhinomanometry or other objective measurement of nasal airflow

No data reported.

3) Assessment of allergen sensitivity in either the eye or nose

No data reported.

4) Measurement of serum IgE antibodies

No data reported.

5) Quality of life

We sought any outcomes where quality of life instruments had been utilised to measure any of the following domains: performance at school, absenteeism, social behaviour, emotional well-being and social relationships, however no such data were reported.

DISCUSSION

Summary of main results

Despite our comprehensive search, we were unable to find any well-conducted randomised controlled trials with adequately reported data which investigated the effectiveness or efficacy of combination therapy of topical nasal steroids with antihistamines versus topical nasal steroids alone in children. A substantial number of the potentially eligible studies were conference abstracts which provided limited information on study design and in general did not report the age of the participants. We retrieved studies which had recruited and included adults with children but we were unable to include them in this review as the children were usually a small proportion of the total number of participants and in most cases the data were not reported separately.

The lack of evidence to support decisions on the clinical care of children is an important issue and needs to be addressed with well-designed clinical trials. A study in Europe observed that over half of the pharmacological interventions used in hospitalised children were off-label drugs, which is a recognised cause for concern and raises questions about both the effectiveness and safety of these interventions in children (Klassen 2008).

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Overall completeness and applicability of evidence

Despite the importance of the topic, there is a lack of evidence to address this review question. There was one quasi-randomised study comparing the use of intranasal glucocorticosteroids alone in comparison with intranasal glucocorticosteroids and antihistamines. This study did not find any additional benefit from the add-on use of antihistamines (Can 2006), however flawed study design and limited data make it impossible to draw conclusions based on these results. The limited evidence on the effectiveness of antihistamine add-on therapy and the potential for more adverse events in children should be carefully taken into consideration by practitioners.

The evidence on the safety and effectiveness of monotherapy with topical nasal steroids in children with allergic rhinitis is also unfortunately limited and sparse. A Cochrane Review provided some weak and unreliable evidence for the effectiveness of topical nasal steroids (Beconase® and flunisolide) in the treatment of intermittent and persistent allergic rhinitis in children (Al Sayyad 2007). The Center for Evidence Based Policy in US undertook a systematic review evaluating nasal corticosteroids and looked at direct and indirect comparisons of nasal corticosteroids with a control group in children with allergic rhinitis. This review found a positive effect for some topical nasal steroids (e.g. beclomethasone, fluticasone and mometasone) in reducing rhinitis symptoms. The latter review also concluded that topical nasal steroids are associated with adverse events, for example nasal irritation, epistaxis/blood tinged nasal secretions and headache). In addition to this there were concerns about the potential association of beclomethasone with lower growth in the height of children over 12 months compared to placebo. Only one small trial was available which evaluated the effect of topical nasal steroids in children under five years of age. Despite reports of respiratory tract infection and skin trauma in the treatment group (mometasone), no firm conclusions can be drawn at this time as to the association between treatment and effect (Selover 2008). Notwithstanding the potential differences in the effectiveness of the treatment between children and adults, none of the randomised controlled trials (RCTs) undertook an analysis exploring this heterogeneity. An empirical study looking at 319 RCTs in major medical journals found that the majority of RCTs frequently ignore or incorrectly analyse the potential heterogeneity in the subgroups (Gabler 2009). Future studies including children from both sexes and different ethnic and socioeconomic groups can provide better evidence to guide clinical practice. In addition to this, trialists who include both children and adults in their trials need to consider the possibility of using statistical techniques to explore the heterogeneity of treatment effects in different age groups and preferably report the data separately.

We identified a number of conference abstracts which were potentially relevant to this review but these mostly lacked sufficient information to enable judgements to be made about study design and the ages of participants. This makes it difficult to judge the relevance and eligibility of these studies for inclusion in this review. Moreover, in a number of these conference abstracts the authors did not provide sufficient contact details to allow us to reach them and request further trial information. Adequate reporting of contact details can help systematic reviewers to contact trialists for detailed information about the methods and results of their trial. In future updates of this review, we will try to identify alternative ways to contact trialists of conference abstracts which are not published as full papers elsewhere. Unfortunately, only half of the randomised trials of health interventions initially represented in the form of abstracts are subsequently published as full reports. It is therefore essential that sufficient details are reported in the abstracts so that review authors can also consider these trials and assess their methodological quality (Hopewell 2005; Hopewell 2006; Scherer 1994).

In future updates of this review we will try further to contact the authors of identified trials which included a number of children and adolescents (< 18 years old) and, if possible, acquire separate data for children to allow a comparison between combination therapy and monotherapy. If we are unsuccessful in obtaining these data, we will explore the possibility of expanding the inclusion criteria of this review to include trials comparing combination therapy with placebo. If appropriate, we will carry out an indirect comparison using these trials.

AUTHORS' CONCLUSIONS

Implications for practice

In view of the lack of evidence on the benefit or lack of benefit of adding antihistamines to topical nasal steroids for children with intermittent or persistent allergic rhinitis, it is important that clinicians are mindful of whether the additional costs and adverse effects of antihistamines are justifiable.

Implications for research

There is an urgent need for well-designed randomised controlled trials (parallel, cross-over, N-of-1 trials) to address the safety and effectiveness of antihistamine add-on therapy in children with allergic rhinitis who use topical nasal steroids. The trials should be reported according to the Consolidated Standards of Reporting Trials (CONSORT) statement (http://www.consort-statement.org) or the extensions of the CONSORT statement. Trials need to have an adequate sample size and follow-up period. If a cross-over design is used, the trialists should ensure that there is a sufficiently long enough wash-out period between intervention and placebo. If cross-over trials include children with seasonal allergic rhinitis, trialists should be mindful about the variations in pollen seasons as this might further complicate the interpretation of data due to environmental co-factors (Akerlund 2005). We have also provided a research recommendation based on the EPICOT format (Table 2) (Brown 2006).

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Can 2006

Methods	Randomised controlled trial conducted between March and July 2002 in Ege University Faculty of Medicine, Division of Pediatric Allergy and Respiratory Diseases in Turkey. The study included 7 visits.
Participants	24 patients (randomly selected from a pool of 78 patients) with moderate to severe seasonal allergic rhinitis sensitive to pollen who were followed up for at least 2 years Age (mean): 12.17 ± 2.26 years with a range of 9 to 18 years old (16 boys, 8 girls). All of the patients were only sensitive to 5 types of grass pollen (*Dactylis glomerata, Anxhoxantum odoratum*, *Loium prenne*, *Phleum pratense and Poa pratensis*) in the prick test. Patients with mild allergic rhinitis on local/sys-

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Can 2006 *(Continued)*

	temic glucocorticosteroids or H1-antihistamines patients with remarkable nose deformities or with an upper airway infection in the last month were excluded from the study.
Interventions	Group 1 received oral H1-antihistamine (loratadine syrup, 10 mg/10 mL) for children < 12 years old and loratadine, 10 mg o.d. for patients > 12 years old and intranasal glucocorticosteroid (mometasone furoate aqueous nasal spray, 100 µg, 1 puff/day) Group 2 received intranasal glucocorticosteroid alone (mometasone furoate aqueous nasal spray, 100 µg, 1 puff/day)
Outcomes	*Subjective parameters:* *Daily rhinitis diary card* to record allergic rhinitis and conjunctivitis symptoms on a 4-point scale (0 to 3) for both daytime (completed in the evening) and night-time (completed on awakening) *Objective parameters:* Nasal peak inspiratory flow Nasal smear Nasal biopsy
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	High risk	Quote (on page 249 of the article) "...the patients were randomised into two groups. Our randomisation method is based on the file's protocol numbers, odd numbers for group I and even numbers for group II". Comment: quasi-randomised
Allocation concealment?	High risk	There were no attempts to conceal the allocation of patients to the 2 groups
Blinding? All outcomes	High risk	There were no attempts to blind the patients
Incomplete outcome data addressed? All outcomes	Unclear risk	The authors did not report whether there was any loss to follow up
Free of selective reporting?	Unclear risk	The protocol for the study was not available
Free of other bias?	Low risk	No indication for further concern

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

Study	Reason for exclusion
Albernaz 2007	Allocation: Randomised Participants:

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Study	Reason for exclusion
	Adults
Anolik 2008	Allocation: Randomised Participants: Adults and adolescents (age: ≥ 12) and did not report separate data for children
Barnes 2006	Allocation: Randomised Participants: The participants were between 16 and 75 years
Benincasa 1994	Allocation: Randomised Participants: This study included patients between 12 and 80 years old and did not provide separate data for children
Berger 1999	Allocation: Randomised Participants: The participants were between 12 and 80 years and did not match our inclusion criteria
Chao 2003	This is a conference abstract. The abstract does not provide details of the methodology or age of the participants and we were unable to contact the authors to request further details.
Cox 1997	This is a conference abstract. The abstract claims it to be a randomised controlled trial performed in children but did not provide details on the methods of the study or outcomes.
D'Ambrosio 1998	Allocation: Randomised Participants: This trial included participants who were 16 to 39 years and separate data for children were not available
Di Lorenzo 2004	This is a conference abstract. The abstract does not provide details of the methodology or age of the participants and we were unable to contact the authors to request further details.
Drouin 1995	Allocation: Randomised Participants: This study includes adults not children
Filipovic 2001	This is a conference abstract. The abstract does not provide details of the methodology or age of the participants and we were unable to contact the authors to request further details.
Gupta 1999	Allocation: Randomised Participants: The age range of the male patients was between 10 and 64 years and the female patients between 12 and 58 years Interventions:

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Study	Reason for exclusion
	Comparing different nasal steroid sprays
Juniper 1989	Allocation: Randomised Participants: The participants were over 18 years and did not match our inclusion criteria
Kamenov 2003	This is a conference abstract. The abstract does not provide details of the methodology or age of the participants and we were unable to contact the authors and request further details.
Kessel 2008	Allocation: Not clear Participants: The control group were healthy children
Lee 2003	Allocation: Randomised Participants: The study includes patients between 7 and 56 years
Ozcan 2002	This is a conference abstract. The abstract does not provide details of the methodology or age of the participants and we were unable to contact the authors to request further details.
Paunovic 2007	Allocation: Randomised Participants: Not clear Intervention: The trial compared combination therapy with placebo
Pinar 2008	Allocation: Not randomised
Ratner 1998	Allocation: Randomised Participants: The study includes patients between 13 and 80 years and did not provide separate data for children
Schenkel 1997	This is a conference abstract. The abstract does not provide details of the methodology or age of the participants and we were unable to contact the authors to request further details.
Snyman 2004	Allocation: Randomised Participants: The study included patients over 12 years (adults plus adolescents)
Stricker 1998	This is a conference abstract. The abstract does not provide details of the methodology or age of the participants and we were unable to contact the authors to request further details.

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Characteristics of studies awaiting assessment *[ordered by study ID]*

Brooks 1996

Methods	Randomised controlled trials. The authors report that they randomly allocated the patients into 3 groups but do not define the method of randomisation.
Participants	60 individuals enrolled and completed the study and were allocated to 3 groups, each with 20 people. The age of participants was unclear. We therefore categorised the study as awaiting assessment until we are able to get more information
Interventions	Group 1: loratadine (Claritin, Schering Plough) (LOR) once a day, plus a placebo spray twice a day Group 2: beclomethasone (Vancenase AQ, Schering-Plough) (BEC) 2 sprays (about 84 mcg) each side of the nose twice a day, plus placebo LOR Group 3: BEC twice a day plus LOR once daily During the treatment comparison, subjects took no other treatment that might affect their hay fever
Outcomes	1) Symptom severity diaries recorded the level of discomfort perceived by the subjects for each of the 5 classes of seasonal allergic rhinitis symptoms 2) Subjective global assessment by the patient
Notes	The authors did not report the age of participants and we were unable to evaluate whether it could be included or not

Brooks 1997

Methods	Controlled clinical trial; unclear whether randomised or not
Participants	Not described in the abstract
Interventions	Low-dose systemic corticoid (methylprednisolone, MP), standard dose antihistamine (terfenadine, TF) or a combination
Outcomes	Nasal airway resistance (NAR), sneeze count and weight of blown nasal secretions
Notes	We were unable to obtain the full text

Kotwani 2001

Methods	—
Participants	—
Interventions	—
Outcomes	—
Notes	We were unable to obtain the full text

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ADDITIONAL TABLES

Table 1. Checklist for describing and assessing patient-reported outcomes (PROs) in clinical trials (daily rhinitis diary card)

What were PROs measuring? (a. What concepts were the PROs used in the study measuring? b. What rationale (if any) for selection of concepts or constructs did the authors provide? c. Were patients involved in the selection of outcomes measured by the PROs?)	*Daily rhinitis diary card* to record allergic rhinitis and conjunctivitis symptoms with a 4-point scale (0 to 3) for both daytime (completed in the evening) and night-time (completed on awakening)
Omissions (Were there any important aspects of health (e.g. symptoms, function, perceptions) or quality of life (e.g. overall evaluation, satisfaction with life) that were omitted in this study from the perspectives of the patient, clinician, significant others, payers, or other administrators and decision makers?)	The score has a very limited focus and only evaluated allergic rhinitis and conjunctivitis symptoms. It does not evaluate functional impairments, quality of life or the impact of the disease on parents' and carers' quality of life.
If randomised trials and other studies measured PROs, what were the instruments? (Measurement strategies) (a. Did investigators use instruments that yield a single indicator or index number, a profile, or a battery of instruments? b. If investigators measure PROs, did they use specific or generic measures, or both? c. Who exactly completed the instruments?)	The symptom score yields an overall score representing the severity of the symptoms in the patient
Did the instruments work in the way they were supposed to work? (Validity) (a. Had the instruments used been validated previously (provide reference)? Was evidence of prior validation for use in this population presented? b. Were the instruments re-validated in this study?)	There was no indication that the measurement tool was validated previously or in this study
Did the instruments work in the way they were supposed to work? (Ability to measure change) (Are the PROs able to detect change in patient status, even if those changes are small?)	There were changes reported in the symptom score
Can you make the magnitude of effect (if any) understandable to readers? (Can you provide an estimate of the difference in patients achieving a threshold of function or improvement, and the associated number needed to treat (NNT))	It is possible but as the trialists only reported medians we were unable to report it in this review

Table 17.6.a from Patrick D, Guyatt GH, Acquadro C. Chapter 17: Patient-reported outcomes. In: Higgins JPT, Green S (editors), *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.0.1 (updated September 2008). The Cochrane Collaboration, 2008. Available from www.cochrane-handbook.org. This table is based on Chapter 7 of Patrick and Erickson, a Users' Guide to the Medical Literature, CDC guidance for evaluation of community preventive services, and criteria used by the Medical Outcomes Trust (Guyatt 1997; Lohr 2002; Patrick 1993; Zaza 2000).

Table 2. Research recommendations based on a gap in the evidence on antihistamines as an adjunct to topical nasal steroids for intermittent and persistent allergic rhinitis in children

Core elements	Issues to consider	Status of research for this review
Evidence (**E**)	What is the current state of evidence	A systematic review with one small and high risk of bias RCT
Population (**P**)	Diagnosis, disease stage, comorbidity, risk factor, sex, age,	Children under the age of 18 with a history of allergic rhinitis, with or without allergic conjunctivitis or asthma, in whom topical nasal steroids are being used. The diagnosis will have been confirmed by the clinical history or the allergen will have been identified and the sensitivity proven by positive skin prick test or high circulating levels of allergen-spe-

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Table 2. Research recommendations based on a gap in the evidence on antihistamines as an adjunct to topical nasal steroids for intermittent and persistent allergic rhinitis in children *(Continued)*

	ethnic group, specific inclusion or exclusion criteria, clinical setting	cific IgE antibody, detected by radioallergosorbent test (RAST). Children with different age groups, ethnicity or sex should be preferably reported separately. Variations in pollen seasons and environmental co-factors should be also taken into consideration
Intervention (**I**)	Type, frequency, dose, duration, prognostic factor	All participants will receive topical nasal steroids (any topical nasal steroid preparation prescribed for allergic rhinitis, at any dosage, over any period of time) and the active interventions studied: oral or topical antihistamine preparations at any dosage over any time period
Comparison (**C**)	Type, frequency, dose, duration, prognostic factor	The control group will receive topical nasal steroids with type, dosage and over a period of time similar to the intervention group plus placebo (looking, smelling and tasting similar to the antihistamine)
Outcome (**O**)	Which clinical or patient related outcomes will the researcher need to measure, improve, influence or accomplish? Which methods of measurement should be used?	**Primary outcomes:** 1. *Improvement of global symptoms.* Recorded in validated daily or weekly diaries and any scores from validated visual analogue scales. Individual symptom scores may include any appropriate measures of nasal obstruction, runny nose, sneezing, itching and eye symptoms. Depending on the age of the child, parent-rated rhinitis symptom scores will be acceptable but all scores must be confirmed and investigator rated. 2. *Adverse events.* Any specific adverse effects, systemic or local, and any clinically diagnosed hypersensitivity or other adverse reactions to the topical nasal steroid medications. **Secondary outcomes:** • Nasal assessment scores of inspiratory peak flow levels • Rhinomanometry or other objective measurement of nasal airflow • Assessment of allergen sensitivity in either the eye or nose • Measurement of serum IgE antibody • In addition we will consider any outcomes which have utilised quality of life instruments to measure any of the following domains; performance at school, absenteeism, social behaviour, emotional well-being and social relationships We would recommend that the trialists use validated disease specific quality of life instruments for children and their parents, e.g. Paediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ) or Parents Questionnaire: the effects of Rhinopharyngitis and/or otitis of the child upon family life (PAR-ENT-QoL)
Time Stamp (**T**)	Date of literature search or recommendation	September 2009
Study Type	What is the most appropriate study design to address the proposed question?	Randomised controlled trial (parallel, cross-over, N-of-1 trial) *Methods:* concealment clear *Blindness:* preferably patients and their parents, therapist, trialists, outcomes assessors blind, data analysts (at least patient and their parents and the outcome assessor should be blinded) *Setting:* primary care or outpatient care with follow up If a cross-over design is used, the trialists should ensure that there is a sufficiently long wash-out period between intervention and placebo. If in the cross-over trials children with seasonal allergic rhinitis are included, trialists should be careful about the variations

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Table 2. Research recommendations based on a gap in the evidence on antihistamines as an adjunct to topical nasal steroids for intermittent and persistent allergic rhinitis in children *(Continued)*

	in pollen seasons as it might further complicate the interpretation of data due to environmental co-factors.

APPENDICES

Appendix 1. Search strategies

CENTRAL	PubMed	EMBASE (Ovid)	CINAHL (EBSCO)
#1 MeSH descriptor Steroids explode all trees #2 MeSH descriptor Anti-Inflammatory Agents explode all trees #3 MeSH descriptor Anti-Inflammatory Agents, Non-Steroidal explode all trees #4 (#2 AND #3) #5 ((#2 OR #4) AND NOT #3) #6 MeSH descriptor Glucocorticoids explode all trees #7 (steroid* OR corticosteroid* OR glucocorticoid* OR corticoid* OR beclomethason* OR beclamet* OR beclocort* OR becolmetasone* OR becotide* OR beconase* OR vancenase OR betamethason* OR betametasone* OR betadexamethasone* OR flubenisolone* OR celesto* OR hydrocortison* OR cortisol* OR dexamethason* OR dexametason* OR hexadecadrol* OR decadron* OR dexacort* OR dexasone* OR hexadrol* OR methylfluorprednisolone* OR millicorten* OR oradexon* OR budesonid* OR horacort* OR pulmicort* OR rhinocort* OR flunisolid* OR nasalide* OR nasarel* OR rhinalar* OR fluticason* OR flonase* OR flounce* OR flixonase* OR mometason* OR nasonex* OR triamcinolon* OR nasacort* OR tri NEXT nasal* OR aristocort* OR volon*) #8 (#1 OR #6 OR #7) #9 MeSH descriptor Histamine H1 Antagonists explode all trees #10 (antihistam* OR (anti NEXT histam*) OR (histamine* NEAR antagonist*) OR acrivastine* OR antazoline* OR azelastine* OR astemizole* OR azatadine* OR brompheniramine* OR buclizine* OR carbinoxamine* OR cetirizine* OR chlorpheniramine* OR chlorphenamine*	#1 "Steroids"[Mesh] #2 "Anti-Inflammatory Agents"[Mesh] #3 "Anti-Inflammatory Agents, Non-Steroidal"[Mesh] #4 #2 AND #3 #5 (#2 OR #4) NOT #3 #6 "Glucocorticoids"[Mesh] #7 (steroid* [tiab] OR corticosteroid* [tiab] OR glucocorticoid* [tiab] OR corticoid* [tiab] OR beclomethason* [tiab] OR beclamet* [tiab] OR beclocort* [tiab] OR becolmetasone* [tiab] OR becotide* [tiab] OR beconase* [tiab] OR vancenase [tiab] OR betamethason* [tiab] OR betametasone* [tiab] OR betadexamethasone* [tiab] OR flubenisolone* [tiab] OR celesto* [tiab] OR hydrocortison* [tiab] OR cortisol* [tiab] OR dexamethason* [tiab] OR dexametason* [tiab] OR hexadecadrol* [tiab] OR decadron* [tiab] OR dexacort* [tiab] OR dexasone* [tiab] OR hexadrol* [tiab] OR methylfluorprednisolone* [tiab] OR millicorten* [tiab] OR oradexon* [tiab] OR budesonid* [tiab] OR horacort* [tiab] OR pulmicort* [tiab] OR rhinocort* [tiab] OR flunisolid* [tiab] OR nasalide* [tiab] OR nasarel* [tiab] OR rhinalar* [tiab] OR fluticason* [tiab] OR flonase* [tiab] OR flounce* [tiab] OR flixonase* [tiab] OR mometason* [tiab] OR nasonex* [tiab] OR triamcinolon* [tiab] OR nasacort* [tiab] OR "tri nasal" [tiab] OR aristocort* [tiab] OR volon* [tiab]) #8 #1 OR #5 OR #6 OR #7 #9 "Histamine Antagonists"[Mesh] #10 (antihistam* [tiab] OR "anti histam*" [tiab] OR (histamine* [tiab] and antagonist* [tiab]) OR acrivastine* [tiab] OR antazoline* [tiab] OR azelastine* [tiab] OR astemizole* [tiab] OR azatadine* [tiab] OR brompheniramine* [tiab] OR buclizine* [tiab] OR carbinoxamine* [tiab] OR cetirizine* [tiab] OR chlorpheniramine* [tiab] OR chlorphenamine* [tiab] OR clemastine* [tiab] OR cyproheptadine* [tiab] OR cinnar-	1 exp Corticosteroid/ 2 exp Antiinflammatory Agent/ 3 exp Nonsteroid Antiinflammatory Agent/ 4 3 and 2 5 (2 or 4) not 3 6 (steroid* or corticosteroid* or glucocorticoid* or corticoid* or beclomethason* or beclamet* or beclocort* or becolmetasone* or becotide* or beconase* or vancenase or betamethason* or betametasone* or betadexamethasone* or flubenisolone* or celesto* or hydrocortison* or cortisol* or dexamethason* or dexametason* or hexadecadrol* or decadron* or dexacort* or dexasone* or hexadrol* or methylfluorprednisolone* or millicorten* or oradexon* or budesonid* or horacort* or pulmicort* or rhinocort* or flunisolid* or nasalide* or nasarel* or rhinalar* or fluticason* or flonase* or flounce* or flixonase* or mometason* or nasonex* or triamcinolon* or nasacort* or (tri adj nasal*) or aristocort* or volon*).tw. 7 6 or 1 or 5 8 exp Antihistaminic Agent/ 9 (antihistam* or (anti adj histam*) or (histamine* adj3 antagonist*) or acrivastine* or anta-	S1 (MH "Steroids +") S2 (MH "Anti-inflammatory Agents, Steroidal +") S3 (MH "Anti-inflammatory Agents, Non-Steroidal+" S4 S2 AND S3 S5 (S2 OR S4) NOT S3 S6 (MH "Glucocorticoids+") S7 TX (steroid* OR corticosteroid* OR glucocorticoid* OR corticoid* OR beclomethason* OR beclamet* OR beclocort* OR becolmetasone* OR becotide* OR beconase* OR vancenase OR betamethason* OR betametasone* OR betadexamethasone* OR flubenisolone* OR celesto* OR hydrocortison* OR cortisol* OR dexamethason* OR dexametason* OR hexadecadrol* OR decadron* OR dexacort* OR dexasone* OR hexadrol* OR methylfluorprednisolone* OR millicorten* OR oradexon* OR budesonid*

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OR clemastine* OR cyproheptadine* OR cinnarizine* OR cyclizine* OR doxylamine OR desloratadine* OR dexbrompheniramine* OR dexchlorpheniramine* OR dimetapp*OR dimenhydrinate* OR dimethindene* OR diphenhydramine* OR diphenylpyraline* OR drixoral* OR ebastine* OR fexofenadine* OR flunarizine* OR hydroxyzine* OR ketotifen* OR levocetirizine* OR levocabastine* OR loratadine* OR meclizine* OR meclozine* OR methapyrilene* OR methdilazine* OR mequitazine* OR mizolastine* OR oxatomide* OR pheniramine* OR promethazine* OR pyrilamine* OR mepyramine* OR phenyltoloxamine* OR trimeprazine* OR alimemazine* OR triprolidine* OR tritoqualine* OR ripelennamine* OR terfenadine* OR dimotane* OR zirtek* OR clarityn* OR eoclarityn* OR telfast* OR xyzal* OR mistamine* OR mizollen* OR limemazine* OR vallergan* OR optimine* OR piriton* OR piriteze* OR tavegil* OR periactin* OR phenergan* OR xaldatin* OR claramax* OR clarinex* OR actidil* OR myidil* OR allegro* OR telfast* OR antihistam* OR anti NEXT histam*)
#11 (#9 OR #10)
#12 (#8 AND #11)
#13 MeSH descriptor Rhinitis explode all trees
#14 (rhinitis OR hayfever OR (hay NEXT fever) OR pollinosis OR pollenosis OR pollonosis)
#15 ((nose:ti OR nasal:ti) AND allerg*:ti)
#16 allerg*:ti AND (cat*:ti OR dander:ti OR mite*:ti OR dog*:ti OR ragweed:ti OR pollen:ti OR grass*:ti OR cedar:ti OR alder:ti OR willow:ti OR birch:ti OR mugwort:ti OR tree*:ti OR weed*:ti OR perennial*:ti OR season*:ti OR spring:ti OR summer:ti OR respiratory:ti)
#17 (#13 OR #14 OR #15 OR #16)
#18 (#12 AND #17)

izine* [tiab] OR cyclizine* [tiab] OR doxylamine [tiab] OR desloratadine* [tiab] OR dexbrompheniramine* [tiab] OR dexchlorpheniramine* [tiab] OR dimetapp* [tiab] OR dimenhydrinate* [tiab] OR dimethindene* [tiab] OR diphenhydramine* [tiab] OR diphenylpyraline* [tiab] OR drixoral* [tiab] OR ebastine* [tiab] OR fexofenadine* [tiab] OR flunarizine* [tiab] OR hydroxyzine* [tiab] OR ketotifen* [tiab] OR levocetirizine* [tiab] OR levocabastine* [tiab] OR loratadine* [tiab] OR meclizine* [tiab] OR meclozine* [tiab] OR methapyrilene* [tiab] OR methdilazine* [tiab] OR mequitazine* [tiab] OR mizolastine* [tiab] OR oxatomide* [tiab] OR pheniramine* [tiab] OR promethazine* [tiab] OR pyrilamine* [tiab] OR mepyramine* [tiab] OR phenyltoloxamine* [tiab] OR trimeprazine* [tiab] OR alimemazine* [tiab] OR triprolidine* [tiab] OR tritoqualine* [tiab] OR ripelennamine* [tiab] OR terfenadine* [tiab] OR dimotane* [tiab] OR zirtek* [tiab] OR clarityn* [tiab] OR eoclarityn* [tiab] OR telfast* [tiab] OR xyzal* [tiab] OR mistamine* [tiab] OR mizollen* [tiab] OR limemazine* [tiab] OR vallergan* [tiab] OR optimine* [tiab] OR piriton* [tiab] OR piriteze* [tiab] OR tavegil* [tiab] OR periactin* [tiab] OR phenergan* [tiab] OR xaldatin* [tiab] OR claramax* [tiab] OR clarinex* [tiab] OR actidil* [tiab] OR myidil* [tiab] OR allegro* [tiab] OR telfast* [tiab])
#11 #9 OR #10
#12 #8 AND #11
#13 "Rhinitis"[Mesh]
#14 (rhinitis [tiab] OR hayfever [tiab] OR "hay fever" [tiab] OR pollinosis [tiab] OR pollenosis [tiab] OR pollonosis [tiab])
#15 (nose [ti] OR nasal [ti]) AND allerg* [ti])
#16 allerg* [ti] AND (cat* [ti] OR dander [ti] OR mite* [ti] OR dog* [ti] OR ragweed [ti] OR pollen [ti] OR grass* [ti] OR cedar [ti] OR alder [ti] OR willow [ti] OR birch [ti] OR mugwort [ti] OR tree* [ti] OR weed* [ti] OR perennial* [ti] OR season* [ti] OR spring [ti] OR summer [ti] OR respiratory[ti])
#17 #13 OR #14 OR #15 OR #16
#18 #12 AND #17

zoline* or azelastine* or astemizole* or azatadine* or brompheniramine* or buclizine* or carbinoxamine* or cetirizine* or chlorpheniramine* or chlorphenamine* or clemastine* or cyproheptadine* or cinnarizine* or cyclizine* or doxylamine or desloratadine* or dexbrompheniramine* or dexchlorpheniramine* or dimetapp*OR dimenhydrinate* or dimethindene* or diphenhydramine* or diphenylpyraline* or drixoral* or ebastine* or fexofenadine* or flunarizine* or hydroxyzine* or ketotifen* or levocetirizine* or levocabastine* or loratadine* or meclizine* or meclozine* or methapyrilene* or methdilazine* or mequitazine* or mizolastine* or oxatomide* or pheniramine* or promethazine* or pyrilamine* or mepyramine* or phenyltoloxamine* or trimeprazine* or alimemazine* or triprolidine* or tritoqualine* or ripelennamine* or terfenadine* or dimotane* or zirtek* or clarityn* or eoclarityn* or telfast* or xyzal* or mistamine* or mizollen* or limemazine* or vallergan*OR optimine* or piriton* or piriteze* or tavegil* or periactin* or phenergan* or xaldatin* or claramax* or clarinex* or actidil* or myidil* or allegro* or telfast* or antihistam* or (anti adj histam*)).tw.
10 8 or 9
11 7 and 10
12 exp Rhinitis/
13 (rhinitis or hayfever or hay NEXT fever or pollinosis or pollenosis or pollonosis).tw.
14 ((nose or nasal) and allerg*).ti.

OR horacort* OR pulmicort* OR rhinocort*)
S8 (MH "Histamine Antagonists+")
S9 TX (antihistam* OR (anti NEXT histam*) OR (histamine* adj antagonist*) OR acrivastine* OR antazoline* OR azelastine* OR astemizole* OR azatadine* OR brompheniramine* OR buclizine* OR carbinoxamine* OR cetirizine* OR chlorpheniramine* OR chlorphenamine* OR clemastine* OR cyproheptadine* OR cinnarizine* OR cyclizine* OR doxylamine OR desloratadine* OR dexbrompheniramine* OR dexchlorpheniramine* OR dimetapp*OR dimenhydrinate* OR dimethindene* OR diphenhydramine* OR diphenylpyraline* OR drixoral*)
S10 S1 OR S5 OR S6 OR S7
S11 S8 OR S9
S12 S10 AND S11
S13 (MH "Rhinitis+")
S14 TX (rhinitis OR hayfever OR (hay NEXT fever) OR pollinosis OR pollenosis OR pollonosis)
S15 TI ((nose OR nasal) AND allerg*)
S16 TI (allerg* AND (cat* OR dander OR mite* OR dog* OR ragweed OR pollen OR

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(Continued)

		15 (allerg* and (cat* or dander* or mite* or dog* or ragweed or pollen or grass* or cedar or alder or willow or birch or mugwort or tree* or weed* or perennial* or season* or spring or summer or respiratory)).ti. 16 13 or 12 or 15 or 14 17 11 and 16

BIOSIS Previews	CAB Abstracts	Web of Science
1 (steroid* or corticosteroid* or glucocorticoid* or corticoid* or beclomethason* or beclamet* or beclocort* or becolmetasone* or becotide* or beconase* or vancenase or betamethason* or betametasone* or betadexamethasone* or flubenisolone* or celesto* or hydrocortison* or cortisol* or dexamethason* or dexametason* or hexadecadrol* or decadron* or dexacort* or dexasone* or hexadrol* or methylfluorprednisolone* or millicorten* or oradexon* or budesonid* or horacort* or pulmicort* or rhinocort* or flunisolid* or nasalide* or nasarel* or rhinalar* or fluticason* or flonase* or flounce* or flixonase* or mometason* or nasonex* or triamcinolon* or nasacort* or (tri adj nasal*) or aristocort* or volon*).tw. 2 (antihistam* or (anti adj histam*) or (histamine* adj3 antagonist*) or acrivastine* or antazoline* or azelastine* or astemizole* or azatadine* or brompheniramine* or buclizine* or carbinoxamine* or cetirizine* or chlorpheniramine* or chlorphenamine* or clemastine* or cyproheptadine* or cinnarizine* or cyclizine* or doxylamine or desloratadine* or dexbrompheniramine* or dexchlorpheniramine* or dimetapp*OR dimenhydrinate* or dimethindene* or diphenhydramine* or diphenylpyraline* or drixoral* or ebastine* or fexofenadine* or flunarizine* or hydroxyzine* or ketotifen* or levocetirizine* or levocabastine* or loratadine* or meclizine* or meclozine* or methapyrilene* or methdilazine* or mequitazine* or mizolastine* or oxatomide* or pheniramine* or	1 exp Corticosteroid/ 2 exp Antiinflammatory Agent/ 3 (steroid* or corticosteroid* or glucocorticoid* or corticoid* or beclomethason* or beclamet* or beclocort* or becolmetasone* or becotide* or beconase* or vancenase or betamethason* or betametasone* or betadexamethasone* or flubenisolone* or celesto* or hydrocortison* or cortisol* or dexamethason* or dexametason* or hexadecadrol* or decadron* or dexacort* or dexasone* or hexadrol* or methylfluorprednisolone* or millicorten* or oradexon* or budesonid* or horacort* or pulmicort* or rhinocort* or flunisolid* or nasalide* or nasarel* or rhinalar* or fluticason* or flonase* or flounce* or flixonase* or mometason* or nasonex* or triamcinolon* or nasacort* or (tri adj nasal*) or aristocort* or volon*).tw. 4 (antihistam* or (anti adj histam*) or (histamine* adj3 antagonist*) or acrivastine* or antazoline* or azelastine* or astemizole* or azatadine* or brompheniramine* or buclizine* or carbinoxamine* or cetirizine* or chlorpheniramine* or chlorphenamine* or clemastine* or cyproheptadine* or cinnarizine* or cyclizine* or doxylamine or desloratadine* or dexbrompheniramine* or dexchlorpheniramine* or dimetapp*OR dimenhydrinate* or dimethindene* or diphenhydramine* or diphenylpyraline* or drixoral* or ebastine* or fexofenadine* or flunarizine* or hydroxyzine* or ketotifen* or levocetirizine* or levocabastine* or loratadine* or meclizine* or meclozine* or methapyrilene* or methdilazine* or mequitazine* or mizolastine* or oxatomide* or pheniramine* or promethazine* or pyrilamine* or mepyramine* or phenyltoloxamine* or trimeprazine* or alimemazine* or triprolidine* or tritoqualine* or ripelennamine* or terfenadine* or dimotane* or zirtek* or clarityn* or eoclarityn* or telfast* or xyzal*	# 1 TS=(steroid* OR corticosteroid* OR glucocorticoid* OR corticoid* OR beclomethason* OR beclamet* OR beclocort* OR becolmetasone* OR becotide* OR beconase* OR vancenase OR betamethason* OR betametasone* OR betadexamethasone* OR flubenisolone* OR celesto* OR hydrocortison* OR cortisol* OR dexamethason* OR dexametason* OR hexadecadrol* OR decadron* OR dexacort* OR dexasone* OR hexadrol* OR methylfluorprednisolone* OR millicorten* OR oradexon* OR budesonid* OR horacort* OR pulmicort* OR rhinocort* OR flunisolid* OR nasalide* OR nasarel* OR rhinalar* OR fluticason* OR flonase* OR flounce* OR flixonase* OR mometason* OR nasonex* OR triamcinolon* OR nasacort* OR tri adj nasal* OR aristocort* OR volon*) # 2 TS=(antihistam* OR (anti NEXT histam*) OR (histamine* NEAR antagonist*) OR acrivastine* OR antazoline* OR azelastine* OR astemizole* OR azatadine* OR brompheniramine* OR buclizine* OR carbinoxamine* OR cetirizine* OR chlorpheniramine* OR chlorphenamine* OR clemastine* OR cyproheptadine* OR cinnarizine* OR cyclizine* OR doxylamine OR desloratadine* OR dexbrompheniramine* OR dexchlorpheniramine* OR dimetapp*OR dimenhydrinate* OR dimethindene*) # 3 TS= (diphenhydramine* OR diphenylpyraline* OR drixoral* OR ebastine* OR fexofenadine* OR flunarizine* OR hydroxyzine* OR ketotifen* OR levocetirizine* OR levocabastine* OR loratadine* OR meclizine* OR meclozine* OR methapyrilene* OR methdilazine* OR mequitazine* OR mizolastine* OR oxatomide* OR pheniramine* OR promethazine* OR pyrilamine* OR mepyramine* OR phenyltoloxamine* OR trimeprazine* OR alimemazine* OR triprolidine* OR tritoqualine* OR ripelennamine* OR terfenadine* OR dimotane* OR zirtek* OR clarityn* OR eoclarityn*) # 4 TS=(telfast* OR xyzal* OR mistamine* OR mizollen* OR limemazine* OR vallergan*OR optimine* OR piriton* OR piriteze* OR tavegil*

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promethazine* or pyrilamine* or mepyramine* or phenyltoloxamine* or trimeprazine* or alimemazine* or triprolidine* or tritoqualine* or ripelennamine* or terfenadine* or dimotane* or zirtek* or claritin* or eoclarityn* or telfast* or xyzal* or mistamine* or mizollen* or limemazine* or vallergan*OR optimine* or piriton* or piriteze* or tavegil* or periactin* or phenergan* or xaldatin* or claramax* or clarinex* or actidil* or myidil* or allegro* or telfast* or antihistam* or (anti adj histam*)).tw.
3 (rhinitis or hayfever or hay NEXT fever or pollinosis or pollenosis or pollonosis).tw.
4 ((nose or nasal) and allerg*).ti.
5 (allerg* and (cat* or dander* or mite* or dog* or ragweed or pollen or grass* or cedar or alder or willow or birch or mugwort or tree* or weed* or perennial* or season* or spring or summer or respiratory)).ti.
6 1 and 2
7 4 or 3 or 5
8 6 and 7
or mistamine* or mizollen* or limemazine* or vallergan*OR optimine* or piriton* or piriteze* or tavegil* or periactin* or phenergan* or xaldatin* or claramax* or clarinex* or actidil* or myidil* or allegro* or telfast* or antihistam* or (anti adj histam*)).tw.
5 exp Rhinitis/
6 (rhinitis or hayfever or hay NEXT fever or pollinosis or pollenosis or pollonosis).tw.
7 ((nose or nasal) and allerg*).ti.
8 (allerg* and (cat* or dander* or mite* or dog* or ragweed or pollen or grass* or cedar or alder or willow or birch or mugwort or tree* or weed* or perennial* or season* or spring or summer or respiratory)).ti.
9 6 or 5 or 8 or 7
10 exp antihistaminics/
11 4 or 10
12 1 or 3 or 2
13 11 and 12
14 13 and 9
OR periactin* OR phenergan* OR xaldatin* OR claramax* OR clarinex* OR actidil* OR myidil* OR allegro* OR telfast* OR antihistam* OR anti adj histam*)
5 #4 OR #3 OR #2
6 #5 AND #1
7 TS=(rhinitis OR hayfever OR (hay NEXT fever) OR pollinosis OR pollenosis OR pollonosis)
8 TS=((nose OR nasal) AND allerg*)
9 TI= (allerg* AND (cat* OR dander OR mite* OR dog* OR ragweed OR pollen OR grass* OR cedar OR alder OR willow OR birch OR mugwort OR tree* OR weed* OR perennial* OR season* OR spring OR summer OR respiratory))
10 #9 OR #8 OR #7
11 #10 AND #6

CONTRIBUTIONS OF AUTHORS

MN is the guarantor for the review.

MN and ZF have:

- co-ordinated the review;
- screened the search results;
- appraised the quality of papers;
- abstracted data from papers.

MN was responsible for:

- data management for the review;
- obtaining and screening data on unpublished studies;
- entering data into RevMan;
- analysis of data;
- interpretation of data.

MN organised retrieval of papers, writing to authors of papers for additional information and providing additional data about papers.

MN/ZF/HA and WM contributed in writing the protocol and review.

DECLARATIONS OF INTEREST

There are no financial conflicts of interest and the authors declare that they do not have any associations with any parties who may have vested interests in the results of this review.

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External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The review has a more focused question than the protocol and includes studies comparing the administration of topical nasal steroids along with antihistamines to topical nasal steroids only.

Adverse events have been added as a primary outcome.

To avoid loss of useful data the following has been deleted: "Data obtained from any validated visual analogue scales and any categorical outcomes will be transformed into dichotomous data prior to analysis".

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Intranasal; Administration, Oral; Adrenal Cortex Hormones [*administration & dosage]; Histamine Antagonists [*administration & dosage]; Randomized Controlled Trials as Topic; Rhinitis, Allergic, Perennial [*drug therapy]; Rhinitis, Allergic, Seasonal [*drug therapy]

MeSH check words

Child; Humans

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