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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
SUMMARY OF FINDINGS	4
BACKGROUND	7
OBJECTIVES	8
METHODS	8
RESULTS	11
Figure 1.	12
Figure 2.	16
Figure 3.	17
DISCUSSION	25
AUTHORS' CONCLUSIONS	26
ACKNOWLEDGEMENTS	27
REFERENCES	28
CHARACTERISTICS OF STUDIES	33
ADDITIONAL TABLES	99
CONTRIBUTIONS OF AUTHORS	106
DECLARATIONS OF INTEREST	106
SOURCES OF SUPPORT	106
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	106

[Intervention Review]

Intranasal corticosteroids for non-allergic rhinitis

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ABSTRACT

Background

Non-allergic rhinitis is defined as dysfunction and non-infectious inflammation of the nasal mucosa that is caused by provoking agents other than allergens or microbes. It is common, with an estimated prevalence of around 10% to 20%. Patients experience symptoms of nasal obstruction, anterior rhinorrhoea/post-nasal drip and sneezing. Several subgroups of non-allergic rhinitis can be distinguished, depending on the trigger responsible for symptoms; these include occupation, cigarette smoke, hormones, medication, food and age. On a cellular molecular level different disease mechanisms can also be identified. People with non-allergic rhinitis often lack an effective treatment as a result of poor understanding and lack of recognition of the underlying disease mechanism. Intranasal corticosteroids are one of the most common types of medication prescribed in patients with rhinitis or rhinosinusitis symptoms, including those with non-allergic rhinitis. However, it is unclear whether intranasal corticosteroids are truly effective in these patients.

Objectives

To assess the effects of intranasal corticosteroids in the management of non-allergic rhinitis.

Search methods

The Cochrane ENT Information Specialist searched the Cochrane ENT Register; Cochrane Central Register of Controlled Trials (CENTRAL 2019, Issue 7); PubMed; Ovid Embase; CINAHL; Web of Science; ClinicalTrials.gov; ICTRP and additional sources for published and unpublished trials. The date of the search was 1 July 2019.

Selection criteria

Randomised controlled trials (RCTs) comparing intranasal corticosteroids, delivered by any means and in any volume, with (a) placebo/no intervention or (b) other active treatments in adults and children (aged ≥ 12 years).

Data collection and analysis

We used the standard methodological procedures expected by Cochrane. The primary outcomes were patient-reported disease severity and a significant adverse effect - epistaxis. Secondary outcomes were (disease-specific) health-related quality of life, objective measurements of airflow and other adverse events. We used GRADE to assess the certainty of the evidence for each outcome.

Main results

We included 34 studies (4452 participants); however, only 13 studies provided data for our main comparison, intranasal corticosteroids versus placebo. The participants were mainly defined as patients with perennial rhinitis symptoms and negative allergy tests. No distinction between different pheno- and endotypes could be made, although a few studies only included a specific phenotype such as pregnancy rhinitis, vasomotor rhinitis, rhinitis medicamentosa or senile rhinitis. Most studies were conducted in a secondary or tertiary healthcare setting. No studies reported outcomes beyond three months follow-up. Intranasal corticosteroid dosage in the review ranged from 50 µg to 2000 µg daily.

Intranasal corticosteroids versus placebo

Thirteen studies (2045 participants) provided data for this comparison. These studies used different scoring systems for patient-reported disease severity, so we pooled the data in each analysis using the standardised mean difference (SMD). Intranasal corticosteroid treatment may improve patient-reported disease severity as measured by total nasal symptom score compared with placebo at up to four weeks (SMD -0.74, 95% confidence interval (CI) -1.15 to -0.33; 4 studies; 131 participants; $I^2 = 22\%$) (low-certainty evidence). However, between four weeks and three months the evidence is very uncertain (SMD -0.24, 95% CI -0.67 to 0.20; 3 studies; 85 participants; $I^2 = 0\%$) (very low-certainty evidence). Intranasal corticosteroid treatment may slightly improve patient-reported disease severity as measured by total nasal symptom score change from baseline when compared with placebo at up to four weeks (SMD -0.15, 95% CI -0.25 to -0.05; 4 studies; 1465 participants; $I^2 = 35\%$) (low-certainty evidence).

All four studies evaluating the risk of epistaxis showed that there is probably a higher risk in the intranasal corticosteroids group (65 per 1000) compared to placebo (31 per 1000) (risk ratio (RR) 2.10, 95% CI 1.24 to 3.57; 4 studies; 1174 participants; $I^2 = 0\%$) (moderate-certainty evidence). The absolute risk difference (RD) was 0.04 with a number needed to treat for an additional harmful outcome (NNTH) of 25 (95% CI 16.7 to 100).

Only one study reported numerical data for quality of life. It did report a higher quality of life score in the intranasal corticosteroids group (152.3 versus 145.6; SF-12v2 range 0 to 800); however, this disappeared at longer-term follow-up (148.4 versus 145.6) (low-certainty evidence).

Only two studies provided data for the outcome objective measurements of airflow. These data could not be pooled because they used different methods of outcome measurement. Neither found a significant difference between the intranasal corticosteroids and placebo group (rhinomanometry SMD -0.46, 95% CI -1.06 to 0.14; 44 participants; peak expiratory flow rate SMD 0.78, 95% CI -0.47 to 2.03; 11 participants) (very low-certainty evidence).

Intranasal corticosteroids probably resulted in little or no difference in the risk of other adverse events compared to placebo (RR 0.99, 95% CI 0.87 to 1.12; 3 studies; 1130 participants; $I^2 = 0\%$) (moderate-certainty evidence).

Intranasal corticosteroids versus other treatments

Only one or a few studies assessed each of the other comparisons (intranasal corticosteroids versus saline irrigation, intranasal antihistamine, capsaicin, cromoglycate sodium, ipratropium bromide, intranasal corticosteroids combined with intranasal antihistamine, intranasal corticosteroids combined with intranasal antihistamine and intranasal corticosteroids with saline compared to saline alone). It is therefore uncertain whether there are differences between intranasal corticosteroids and other active treatments for any of the outcomes reported.

Authors' conclusions

Overall, the certainty of the evidence for most outcomes in this review was low or very low. It is unclear whether intranasal corticosteroids reduce patient-reported disease severity in non-allergic rhinitis patients compared with placebo when measured at up to three months. However, intranasal corticosteroids probably have a higher risk of the adverse effect epistaxis. There are very few studies comparing intranasal corticosteroids to other treatment modalities making it difficult to draw conclusions.

PLAIN LANGUAGE SUMMARY

Intranasal corticosteroids for non-allergic rhinitis

Review question

We wanted to find out whether intranasal corticosteroids (steroids applied into the nose) are effective for the treatment of rhinitis that is not caused by allergy.

Background

Non-allergic rhinitis is a chronic disease of the nose, which is not caused by infection or allergies. People with non-allergic rhinitis experience symptoms that affect their quality of life, such as nasal obstruction, runny nose and sneezing. Non-allergic rhinitis patients can

be divided into different subgroups who have different underlying causes for their disease. The underlying causes of non-allergic rhinitis are not fully understood, therefore treatment is often unsuccessful in these patients.

Topical (intranasal) corticosteroids are used with the aim of reducing inflammation. They are the most commonly prescribed drug in other chronic diseases of the nose and sinuses, such as allergic rhinitis and chronic rhinosinusitis. Intranasal corticosteroid treatment can be delivered with sprays or drops and for different time periods.

Study characteristics

We included 34 randomised controlled trials (RCTs) with a total of 4452 participants in this review. Most of the studies were relatively small, although the largest study had 983 patients in total. All of the patients were either adults or adolescents (aged between 12 and 18 years old) with non-allergic rhinitis. The studies looked at a range of types, doses and methods of administration (e.g. spray, drops) of intranasal corticosteroids. Nine studies were sponsored by the pharmaceutical industry or had commercial sponsors. One study was funded by the government. In several studies, the pharmaceutical industry or commercial sponsor may have provided medications, but the funding role was unclear. Funding was not reported in eight studies.

Key results

Intranasal corticosteroids compared with placebo

It is uncertain whether intranasal corticosteroids reduce patient-reported disease severity in non-allergic rhinitis patients compared with placebo when measured at up to three months. They may improve patient-reported disease severity compared with placebo at up to four weeks, however this evidence is of low certainty. Treatment with intranasal corticosteroids probably increases the risk of epistaxis (nosebleed) but there is no difference in the risk of other adverse effects. It is not possible to tell from this review whether there is a difference between the different concentrations, delivery methods or treatment plans of intranasal corticosteroids. There are no good-quality studies assessing changes in quality of life with intranasal corticosteroids.

Intranasal corticosteroids compared with other treatments

There is not enough evidence to know whether intranasal corticosteroid treatment is better, worse or the same as using other treatment strategies such as saline irrigation, intranasal antihistamines, capsaicin or ipratropium bromide for non-allergic rhinitis.

Certainty of the evidence

Overall, the evidence for intranasal corticosteroids compared with placebo for most outcomes was either low-certainty (our confidence in the effect estimate is low) or very low-certainty (our confidence in the effect estimate is very low). This was because most studies were very small and used different methods to measure the same outcome. This evidence is up to date to July 2019.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Intranasal corticosteroids compared to placebo for non-allergic rhinitis

Intranasal corticosteroids compared to placebo for non-allergic rhinitis

Patient or population: adults and children > 12 with non-allergic rhinitis

Setting: secondary/tertiary health care

Intervention: intranasal corticosteroids

Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	N° of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with intranasal corticosteroids				
Disease severity as measured by patient-reported symptom score (total nasal symptom score)	Follow-up ≤ 4 weeks	—	SMD 0.74 lower (1.15 lower to 0.33 lower)	131 (4 RCTs)	⊕⊕⊕⊖ low ¹	Intranasal corticosteroids may improve patient-reported disease severity at a follow-up of up to 4 weeks compared to placebo. The mean difference in disease severity score was 0.74 standard deviations lower (1.15 lower to 0.33 lower) with intranasal corticosteroids compared to placebo. This represents a medium effect size (Cohen 1988).
	Follow-up > 4 weeks	—	SMD 0.24 lower (0.67 lower to 0.20 higher)	85 (3 RCTs)	⊕⊕⊕⊖ very low ²	It is uncertain whether intranasal corticosteroids improve patient-reported disease severity with a follow-up of more than 4 weeks compared to placebo, because the certainty of the evidence is very low.
	Change from baseline	—	SMD 0.15	1465 (4 RCTs)	⊕⊕⊕⊖ low ³	Intranasal corticosteroids may slightly improve patient-reported disease severity change from baseline with

	Follow-up ≤ 4 weeks	lower (0.25 lower to 0.05 lower)				a follow-up of up to 4 weeks compared to placebo. The SMD of 0.15 represents a small effect size. There are two large studies (Jacobs 2009 ; Webb 2002). Jacobs 2009 reports with a high degree of certainty a small improvement in favour of intranasal corticosteroids. Webb 2002 reports a less certain clinically relevant improvement in favour of intranasal corticosteroids. Jacobs 2009 has an adjusted SD value (presented SD are most likely SEM).
Significant adverse event: epistaxis	Study population		RR 2.10 (1.24 to 3.57)	1174 (4 RCTs)	⊕⊕⊕⊖ moderate ⁴	There is probably a higher risk of epistaxis with intranasal steroids compared to placebo.
Follow-up: 2 weeks to 33 days	(31 per 1000	65 per 1000 (39 to 111)				
Disease-specific health-related quality of life	Just one study reported quality of life (Lin 2017). Quality of life was better in the intranasal corticosteroids group versus the placebo group, however while this difference was significant at a follow-up of 1 month (152.3 versus 145.6) it was barely noticeable at a follow-up of 3 months (148.4 versus 145.6).		49 (1 RCT)	⊕⊕⊕⊖ low ⁵	There is not enough information (1 study) to conclude whether there is a difference.	
Short Form 12 (SF-12v2) (range 0 to 800)						
Follow-up: 1 month to 3 months						
Objective measurement of airflow: peak flow rate (expiratory)	Just two studies reported objective measurement of airflow (Malm 1981 ; Spector 1980). However, they used different outcome measurements to measure outflow: rhinomanometry and expiratory peak flow rate (PEFR). Neither found a significant difference between groups: rhinomanometry (Malm 1981) SMD -0.46, 95% CI -1.06 to 0.14; 44 participants; PEFR (Spector 1980) SMD 0.78, 95% CI -0.47 to 2.03; 11 participants.		55 (2 RCTs)	⊕⊕⊕⊖ very low ⁶	There is not enough information (2 studies with different methods of measurement) to conclude whether there is a difference.	
Follow-up: 2 weeks to 4 weeks						
Other adverse events	Study population		RR 0.99 (0.87 to 1.12)	1130 (3 RCTs)	⊕⊕⊕⊖ moderate ⁷	Intranasal corticosteroids probably result in little or no difference in the risk of other adverse events compared to placebo.
Follow-up: 1 month to 6 weeks	454 per 1000	450 per 1000				

(395
to
509)

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RCT:** randomised controlled trial; **RR:** risk ratio; **SD:** standard deviation; **SEM:** standard error of the mean; **SMD:** standardised mean difference

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

¹Due to the small sample size we downgraded once for imprecision and once due to the risk of publication bias. The I^2 value in this pooled analysis was 22% so there was no reason to downgrade for heterogeneity.

²We downgraded twice for serious imprecision due to the small sample size and because the confidence interval includes both meaningful benefit and harm. We downgraded once for risk of publication bias due to the small sample size.

³We downgraded twice for serious inconsistency because the I^2 value was 96% when the original SD values presented in the [Jacobs 2009](#) study were used and in that case the confidence interval for [Jacobs 2009](#) does not overlap with the other studies. [Jacobs 2009](#) has an unlikely SD value, which does not match the mean, n and P values. It is likely that the originally SD value presented should actually be a standard error of the mean (SEM), therefore we re-calculated the SD values.

⁴We downgraded once due to study limitations (risk of bias) because there were unclear blinding domains, which could have influenced the significant adverse events (epistaxis) outcome. The I^2 value in this pooled analysis is 0% so there is no reason to downgrade for heterogeneity. We judged that there were no other reasons to downgrade.

⁵Due to the small sample size we downgraded once for imprecision and once due to the risk of publication bias.

⁶We downgraded once for inconsistency (when the two studies are combined the I^2 value is 67%). The two studies used different methods for measuring objective airflow, which contributed to the heterogeneity. Due to the small sample size we downgraded once for imprecision and once due to the risk of publication bias.

⁷We downgraded once due to study limitations (risk of bias) as there were unclear blinding domains, which could have influenced the adverse events outcome. The I^2 value in the pooled analysis is 0% so there is no reason to downgrade for heterogeneity. We judged that there were no other reasons to downgrade.

BACKGROUND

Description of the condition

Chronic rhinitis (allergic and non-allergic) affects up to 30% to 40% of the general population (Bousquet 2008). Non-allergic rhinitis is diagnosed when anatomic, infectious and allergic aetiologies are excluded and symptoms have been present for more than 12 weeks. The symptoms include nasal congestion, clear rhinorrhoea, sneezing and, less frequently, nasal itching. It is common, with an estimated prevalence of around 10% to 20% (Bachert 2008). Most epidemiological studies report that 25% to 50% of chronic rhinitis patients can be categorised as having non-allergic rhinitis (Fokkens 2002), with a worldwide estimated prevalence of 200 to 400 million people (Bousquet 2008a). Most studies agree on a female predominance (Knudsen 2009; Molgaard 2007). A recent study has shown that quality of life is significantly impaired in people with non-allergic rhinitis and this impairment is equal to that in people with allergic rhinitis (Segboer 2018). Around 60% of non-allergic rhinitis patients develop non-allergic asthma (Hellings 2017).

Within non-allergic rhinitis several phenotypes can be differentiated: environmental (occupational, smoking), hormonal (e.g. pregnancy), gustatory, age (rhinitis of the elderly), medication-induced and inflammatory (non-allergic rhinitis with eosinophilia syndrome (NARES) or local allergic rhinitis) (Hellings 2017; Papadopoulos 2015). In local allergic rhinitis, patients have the clinical characteristics of allergic rhinitis and an allergen sensitisation but no systemic signs of atopy. NARES patients have high numbers of eosinophils in their nasal mucosa and can have micro-polyposis, hyposmia and signs of bronchial hyper-responsiveness in a limited way, comparable to patients with chronic rhinosinusitis. The prevalence rates of these different phenotypes are unknown.

Environmental (occupational (chemical) and smoking) rhinitis can be clearly linked to an affecting agent. In close to 60% of cases, occupational rhinitis can be associated with occupational asthma (Ameille 2013). Smoking is considered a specific irritant of the nasal mucosa, which can cause non-allergic rhinitis (van Rijswijk 2005). Hormonal rhinitis can occur during the menstrual cycle and puberty, due to hypothyroidism or acromegaly, as well as during pregnancy, where it resolves postpartum. Gustatory rhinitis is accompanied by oversecretion of nasal mucus in response to irritating gustatory agents, usually spicy foods (Waibel 2008). Rhinitis of the elderly (senile rhinitis) is encountered in the older generation and characterised by the presence of constant rhinorrhoea and a lack of other nasal complaints.

In the case of medication-induced rhinitis (rhinitis medicamentosa), several medications have been implicated (Varghese 2010). The most common is the misuse of topical sympathomimetics (e.g. oxy- or xylometazoline) for more than 10 days, resulting in dysregulation of the adrenergic receptors in the nasal mucosa and a relative increase of the parasympathetic drive, leading to significant rhinorrhoea and nasal obstruction. These symptoms cause the patients to continue using topical adrenergics, perpetuating a vicious cycle. Treatment is usually focused on cessation of the affecting agent, as well as support with intranasal corticosteroids.

In terms of the pathophysiological mechanisms, neurogenic, inflammatory and idiopathic endotypes can be distinguished. Two phenotypes clearly belong to the inflammatory endotype: local allergic rhinitis and non-allergic rhinitis with eosinophilia syndrome (NARES). Within the neurogenic endotype, neurogenic dysbalance (for example, senile rhinitis) and neurogenic inflammation (for example, idiopathic rhinitis) can be differentiated.

Local allergic rhinitis is diagnosed when skin prick and serum specific IgE testing are negative, however a nasal allergen provocation test is positive (Rondon 2012a). A recent report attributed over a quarter of chronic rhinitis patients to local allergic rhinitis (Rondon 2012b). NARES is considered in the presence of rhinitis symptoms, no evidence of allergy and more than 20% eosinophilia on nasal smears (Ellis 2007). Its pathophysiology is poorly understood, but is thought to involve a local, self-perpetuating nasal inflammation with eosinophilia (Groger 2012). Idiopathic rhinitis has for a long time remained a diagnosis of exclusion, when the other causes of rhinitis have been ruled out (Burns 2012). Its suggested pathophysiology includes chronic inflammation of an antigenic or neurogenic nature (van Rijswijk 2005).

In explaining non-allergic rhinitis to patients, doctors have often referred to the concept of nasal hyperreactivity. For that reason, non-allergic rhinitis - or idiopathic rhinitis - was also called vasomotor rhinitis in the past. However, recent literature shows us that nasal hyperreactivity is a common symptom in both allergic and non-allergic rhinitis. The terminology of vasomotor rhinitis is therefore no longer used.

Treatment of non-allergic rhinitis includes trigger avoidance, topical and systemic medications, and surgery. When rhinitis is caused by a known aetiological factor, such as smoking or chemical exposure, the mainstay of treatment is trigger avoidance.

Several medications are widely utilised in the treatment of non-allergic rhinitis, including oral and topical nasal antihistamines, intranasal and (rarely) systemic corticosteroids, and anticholinergics (ipratropium bromide). Other medical options include capsaicin, intranasal injection of botulinum toxin type A, intranasal saline rinse, local and systemic sympathomimetics and cromolyn sodium. The exact mechanisms of effect of these therapies in non-allergic rhinitis remain largely unknown.

Some medications are particularly useful in specific types of non-allergic rhinitis. Specifically, ipratropium bromide is mostly used in the treatment of rhinitis of the elderly, due to its alleviation of the main symptom, rhinorrhoea (van Rijswijk 2005). Intranasal antihistamines are usually prescribed when sneezing is the main symptom (Schroer 2012). Capsaicin (8-methyl-N-vanillyl-6-nonenamide), the active component of chili peppers, appears to have a therapeutic effect in idiopathic rhinitis, based on several randomised controlled trials (Ciabatti 2009; van Rijswijk 2003).

Surgical reduction can be considered to treat inferior turbinate hypertrophy, when it contributes to nasal obstruction and mucosal hypersecretion in chronic rhinitis (Garzaro 2012). Vidian neurectomy, causing denervation of the autonomic supply of the nasal mucosa, can reduce the symptoms of rhinorrhoea and nasal obstruction (Robinson 2006).

Description of the intervention

Topical (local) intranasal corticosteroids are administered as nasal sprays or drops. Intranasal corticosteroids act locally on the nasal mucosa, eliciting anti-inflammatory and immunosuppressant effects, while mostly avoiding the systemic side effects of corticosteroids (Bruni 2009; Emin 2011; Mizrachi 2012).

Currently available intranasal corticosteroid preparations include the earlier generation medications beclomethasone dipropionate, triamcinolone acetonide, flunisolide and budesonide, and the newer preparations fluticasone propionate, fluticasone furoate and mometasone furoate. They differ in their local potency, lipid solubility, bioavailability, and local and systemic side effects.

The local side effects of intranasal corticosteroids include epistaxis (5% to 10%), nasal irritation (5% to 10%, including dryness, burning and stinging), headache, nasal septal perforation (< 1%), candida infection of the nose and pharynx, and impaired wound healing after recent nasal surgery or trauma (Merck 2012).

How the intervention might work

Corticosteroids have immunosuppressant and anti-inflammatory effects, modifying and reducing inflammation through suppression of the synthesis of pro-inflammatory cytokines and pro-inflammatory enzymes, inhibiting lymphocyte proliferation and chemotaxis (Mygind 2001).

The local pharmacology of intranasal corticosteroids is connected with absorption characteristics (lipid solubility), topical potency (receptor-binding ability) and systemic bioavailability (Benninger 2003). The delivery mechanism (sprays versus drops) can also influence local drug concentration and its subsequent metabolism.

In allergic rhinitis, optimal therapeutic efficacy can be achieved after daily use of intranasal corticosteroids for two weeks (Bousquet 2008). However, it is unknown when optimal therapeutic efficacy in non-allergic rhinitis can be achieved.

Intranasal corticosteroids are likely to work better for the inflammatory endotypes of non-allergic rhinitis, i.e. NARES and local allergic rhinitis (Mygind 2001).

Why it is important to do this review

Establishing the clinical effectiveness of intranasal corticosteroids in non-allergic rhinitis could have important clinical implications. Several well-conducted randomised controlled trials have evaluated intranasal corticosteroids for non-allergic rhinitis. Most of these studies have small numbers of participants and variations in the included non-allergic rhinitis phenotypes, as well as variations in the dosages and schedule of intranasal corticosteroid administration. However, there are no reported meta-analyses on this topic.

This review aims to assess the evidence for the use of intranasal corticosteroids in non-allergic rhinitis, to define the responsive subgroups and, specifically, to establish the most advantageous dosing and scheduling regimens.

OBJECTIVES

To assess the effects of intranasal corticosteroids in the management of non-allergic rhinitis.

METHODS

Criteria for considering studies for this review

Types of studies

We **included** studies with the following design characteristics:

- randomised controlled trials (RCTs), including cluster-randomised and cross-over trials (cross-over trials were only to be included if the data from the first phase were available); and
- patients were followed up for at least two weeks.

We **excluded** studies with the following design characteristics:

- randomised patients by side of nose (within-patient controlled) because it is difficult to ensure that the effects of any interventions considered can be localised; or
- peri-operative studies.

Types of participants

Adults and children ≥ 12 years with all phenotypes of non-allergic rhinitis. We consider patients 12 years of age and above to have the same phenotype as adults. We included studies in which participants with perennial rhinitis were enrolled when it was possible to extract data for those participants with non-allergic rhinitis.

We excluded studies that included a majority of patients with:

- allergic rhinitis;
- infectious rhinitis;
- acute or chronic rhinosinusitis;
- auto-immune rhinitis;
- rhinitis related to anatomical abnormalities.

Types of interventions

Intervention

We included all intranasal corticosteroids in nasal spray and nasal drops form, at any dose and frequency, and for any duration.

First-generation intranasal corticosteroids:

- Beclomethasone dipropionate
- Triamcinolone acetonide
- Flunisolide
- Budesonide

Second-generation intranasal corticosteroids:

- Fluticasone furoate
- Fluticasone propionate
- Mometasone furoate
- Betamethasone sodium phosphate
- Ciclesonide

If other interventions (for example, decongestants) were used, these must have been used equally in all treatment arms.

Comparisons

The comparators were placebo or no intervention or other active treatments.

The main comparison pair was:

- intranasal corticosteroids versus placebo.

Other possible comparison pairs included:

- intranasal corticosteroids versus saline irrigation;
- intranasal corticosteroids versus intranasal antihistamine;
- intranasal corticosteroids versus capsaicin;
- intranasal corticosteroids versus sodium cromoglycate;
- intranasal corticosteroids versus ipratropium.

Types of outcome measures

Primary outcomes

- Disease severity as measured by patient-reported symptom score (such as a total nasal symptom score (TNSS) or visual analogue scale (VAS)).
- Significant adverse event: epistaxis.

Secondary outcomes

- Disease-specific health-related quality of life (using disease-specific health-related quality of life questionnaires scores such as the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) and the Mini Rhinoconjunctivitis Quality of Life Questionnaire (mini-RQLQ)).
- Inspiratory peak flow levels, rhinomanometry or other objective measurements of airflow.
- Other adverse events: for example, local irritation/discomfort.

Outcomes were measured at follow-up time points of ≤ 4 weeks and > 4 weeks.

Search methods for identification of studies

The Cochrane ENT Information Specialist conducted systematic searches for randomised controlled trials and controlled clinical trials. There were no language, publication year or publication status restrictions. The date of the search was 1 July 2019.

Electronic searches

The Information Specialist searched:

- the Cochrane ENT Register (searched via the Cochrane Register of Studies 1 July 2019);
- the Cochrane Central Register of Controlled Trials (CENTRAL 2019, Issue 7) (searched via the Cochrane Register of Studies 1 July 2019);
- PubMed (1946 to 1 July 2019);
- Ovid EMBASE (1974 to 1 July 2019);
- EBSCO CINAHL (1982 to 1 July 2019);
- Ovid CAB Abstracts (1910 to 1 July 2019);
- LILACS (Latin American and Caribbean Health Science Information database), lilacs.bvsalud.org (searched 1 July 2019);
- Web of Science (1945 to 1 July 2019);

- ClinicalTrials.gov (searched via the Cochrane Register of Studies and clinicaltrials.gov 1 July 2019);
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP), www.who.int/ictpr (searched 1 July 2019).

The Information Specialist modelled subject strategies for databases on the search strategy designed for CENTRAL. Where appropriate, they were combined with subject strategy adaptations of the highly sensitive search strategy designed by Cochrane for identifying randomised controlled trials and controlled clinical trials (as described in the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0, Box 6.4.b. ([Handbook 2011](#))). Search strategies for major databases including CENTRAL are provided in Appendix 1.

Searching other resources

We scanned the reference lists of identified publications for additional trials and contacted trial authors where necessary. In addition, the Information Specialist searched PubMed to retrieve existing systematic reviews relevant to this systematic review, so that we could scan their reference lists for additional trials. The Information Specialist also ran non-systematic searches of Google Scholar to retrieve grey literature and other sources of potential trials.

We did not perform a separate search for adverse effects of intranasal steroids. We considered adverse effects described in the included studies only.

Data collection and analysis

Selection of studies

We merged the identified studies using the [Covidence](#) online reference management software. We removed any duplicate records of the same report.

Two authors (AG and CS, a rhinology fellow and a junior otorhinolaryngology trainee, respectively) independently examined the titles and abstracts of the studies and removed obviously irrelevant reports. We then retrieved the full texts of potentially relevant articles. We linked multiple reports of the same study together. The same two authors independently examined the full-text reports for compliance of the studies with the eligibility criteria. We contacted the study authors, where appropriate, to clarify study eligibility. The two authors then independently made final decisions on study inclusion. Any disagreements on study inclusion were resolved by discussion. If necessary, disagreement was resolved by arbitration of a third author (KS). We noted the primary reason for exclusion.

Data extraction and management

Two authors (AG and CS) independently extracted the data with a predetermined data collection form (Appendix 2). We piloted the form on a small number of studies to identify any discrepancies in coding. If there were multiple reports of the same study, each author collected data separately from each report and then we collated this into a single study report. Disagreements were again resolved by discussion, with arbitration by a third author (KS) if necessary.

For dichotomous outcomes, we extracted the numbers in each of the two outcome categories in each of the intervention groups, or odds ratio, or risk accompanied by measures of uncertainty (e.g. standard error, 95% confidence interval or an exact P value). For continuous outcomes, we extracted the mean value of the outcome measurements in each intervention group, respective standard deviation and number of participants. If the data were presented in another format, we made appropriate calculations and/or transformations according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2011). We extracted ordinal outcomes and outcomes presented as counts in the form reported in the original studies.

Assessment of risk of bias in included studies

AG and CS undertook assessment of the risk of bias of the included studies independently, with the following taken into consideration, as guided by the *Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2011):

- sequence generation;
- allocation concealment;
- blinding;
- incomplete outcome data;
- selective outcome reporting; and
- other sources of bias.

We used the Cochrane 'Risk of bias' tool in RevMan 5 (RevMan 2014), which involved describing each of these domains as reported in the trial and then assigning a judgement about the adequacy of each entry: 'low', 'high' or 'unclear' risk of bias.

Measures of treatment effect

We calculated a weighted treatment effect across studies using RevMan 5 (RevMan 2014). For dichotomous outcomes, we calculated risk ratios (RR) after appropriate conversions. For continuous outcomes, we calculated a mean difference (MD) or a standardised mean difference (SMD) as appropriate. We analysed longer ordinal scales (e.g. visual analogue scale (VAS) scores) as continuous data, using MD or SMD. As suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2011), we used standard rules of thumb in the interpretation of SMD effect sizes (SMD, or Cohen's effect size of < 0.41 = small, 0.40 to 0.70 = moderate, > 0.70 = large effect size) (Cohen 1988). We analysed short ordinal scales as dichotomous data (using RR), combining adjacent scores together whenever it was possible to find an appropriate cut-off point. We treated more frequent count data as continuous. We expressed pooled treatment effects with their 95% confidence intervals (95% CI) for all types of data.

Unit of analysis issues

We determined appropriate units of analysis from the included studies and presented them in the results. We analysed cluster-randomised trials based on the level of allocation, i.e. clusters of patients. Cross-over trials were only included if the data from the first phase were available.

Dealing with missing data

We recorded all missing data on the data collection form and reported this in the 'Risk of bias' tables. Whenever possible, we

contacted the original investigators to request missing data and information for our risk of bias assessments.

Imputing total symptom scores

We planned to adopt the strategy outlined by Chong et al to deal with missing total disease severity outcomes (Chong 2016). Where a paper did not present information for the total disease severity in terms of patient-reported symptom scores but did present data for the results of individual symptoms, we used the symptoms rhinorrhoea, blockage and sneezing to calculate a total symptom score. Where mean final values or changes from baseline were presented in the paper for the individual symptoms we summed these to calculate a 'total symptom score'. We calculated standard deviations for the total symptom score as if the symptoms were independent, random variables that were normally distributed. We acknowledge that there is likely to be a degree of correlation between the individual symptoms, however we used this process because the magnitude of correlation between the individual symptoms is not currently well understood (no evidence found). If the correlation is high, the summation of variables as discrete variables is likely to give a conservative estimate of the total variance of the summed final score. If the correlation is low, this method of calculation will underestimate the standard deviation of the total score. However, the average patient-reported symptom scores have a correlation coefficient of about 0.5; if this is also applicable to non-allergic rhinitis, the method used should have minimal impact (Balk 2012). As this method of calculation does not take into account weighting of different symptoms (no evidence found), we downgraded all the disease severity outcomes for lack of use of validated scales whenever this occurred.

Assessment of heterogeneity

To assess the heterogeneity of effect size across pooled studies, we calculated the I^2 statistic in RevMan 5. We did not plan to perform a meta-analysis if heterogeneity was considered substantial (50% to 90%) or considerable (75% to 100%).

Assessment of reporting biases

We had planned to use a funnel plot to detect reporting biases if there were at least 10 studies included in the meta-analysis and to analyse the visual asymmetry of the plot. However, none of our meta-analyses included more than 10 studies.

Data synthesis

We used RevMan 5 to perform a meta-analysis using the random-effects model if we did not consider the heterogeneity of the included studies to be substantial or considerable. We performed a meta-analysis of studies that were sufficiently homogenous in terms of participants, treatments and outcome measures. When a meta-analysis could not be performed due to the level of heterogeneity, we provided a narrative analysis. We analysed the data on an intention-to-treat basis using the generic inverse variance method. We made comparisons for all available outcomes between intranasal corticosteroids and no therapy, intranasal corticosteroids and placebo, intranasal corticosteroids and other topical or systemic medications, intranasal corticosteroids and two or more of the above therapies in combination, and between different intranasal corticosteroids regimens (dose, frequency or duration comparisons, if available).

Subgroup analysis and investigation of heterogeneity

We performed subgroup analysis to compare the effects of intranasal corticosteroids:

- different types of intranasal corticosteroids (type A versus type B).

The following subgroup analyses were planned but not conducted due to insufficient data.

- different types of non-allergic rhinitis (e.g. rhinitis medicamentosa, pregnancy rhinitis);
- different doses of intranasal corticosteroids (dose A versus dose B, e.g. 200 µg versus 400 µg/day budesonide);
- different regimens of intranasal corticosteroids (regimen A versus regimen B, e.g. once a day versus twice a day);
- different delivery devices for intranasal corticosteroids (device A versus device B).

Sensitivity analysis

We carried out sensitivity analyses on the basis of the methodological diversity of the included studies. We considered the following factors when repeating the analysis:

- risk of bias: excluding studies with high risk of bias (defined as four out of seven domains deemed to have high risk).

GRADE and 'Summary of findings' table

Two authors (CS, AG) independently used the GRADE approach to rate the overall certainty of evidence for each outcome using the GDT tool (<https://gradepro.org/>). The certainty of evidence reflects the extent to which we are confident that an estimate of effect is correct and we applied this in the interpretation of results. There are four possible ratings: 'high', 'moderate', 'low' and 'very low'. A rating of 'high' certainty evidence implies that we are confident in

our estimate of effect and that further research is very unlikely to change our confidence in the estimate of effect. A rating of 'very low' certainty implies that any estimate of effect obtained is very uncertain.

The GRADE approach rates evidence from RCTs that do not have serious limitations as high certainty. However, several factors can lead to the downgrading of the evidence to moderate, low or very low. The degree of downgrading is determined by the seriousness of these factors:

- study limitations (risk of bias);
- inconsistency;
- indirectness of evidence;
- imprecision;
- publication bias.

The 'Summary of findings' table presents only the outcomes for the main comparison, intranasal corticosteroids versus placebo.

RESULTS

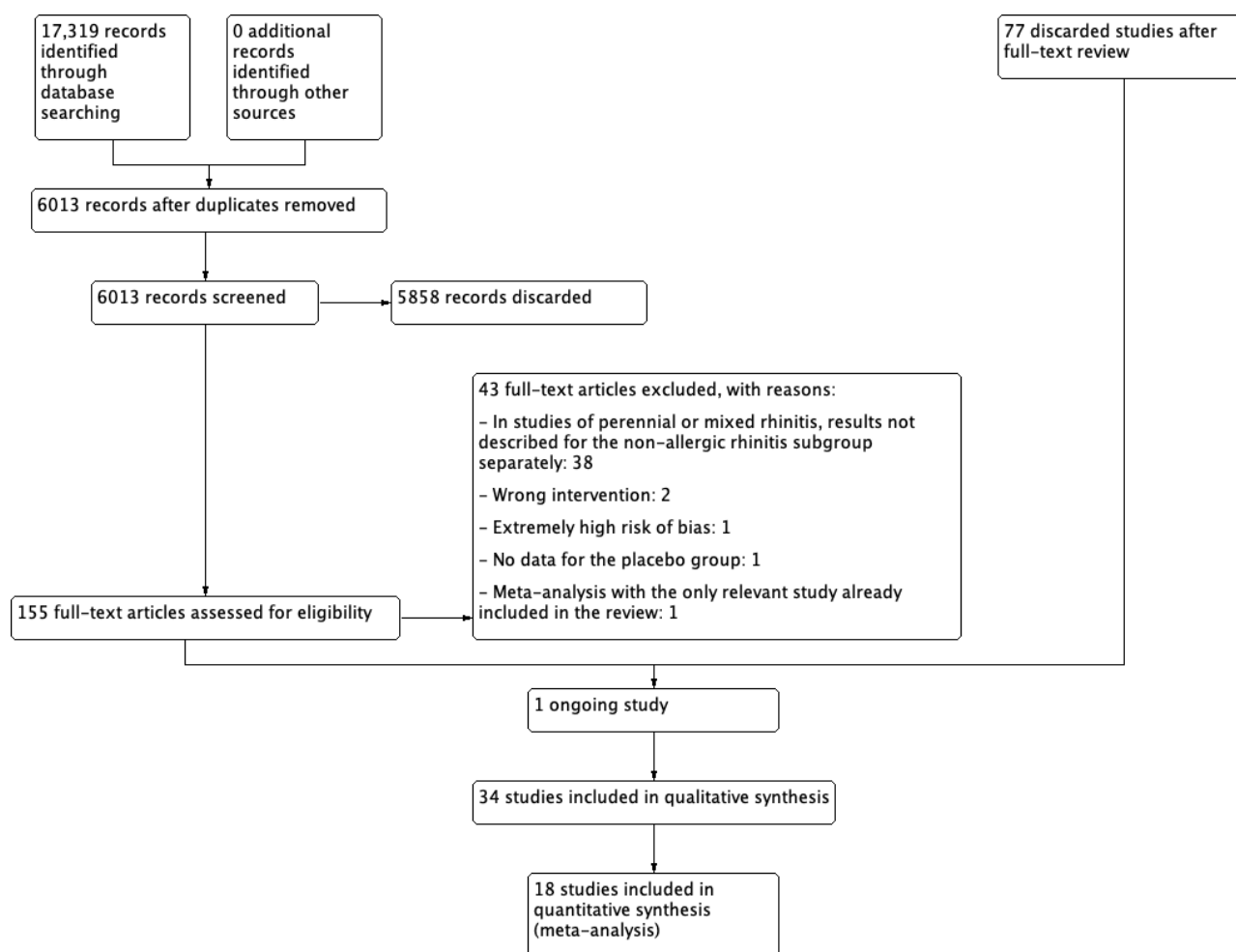
Description of studies

See [Characteristics of included studies](#); [Characteristics of excluded studies](#).

Results of the search

The results of the search are presented in the study flow diagram in [Figure 1](#). The search retrieved 17,319 references. We identified no further references by screening the reference lists of studies. We screened and excluded duplicates and obviously irrelevant studies, leaving 6013 studies. After screening of the titles and abstracts of these references, we discarded 5858 studies, leaving 155 references to assess for eligibility. We assessed the full texts of these 155 references. We discarded 77 of these references after full-text review.

Figure 1. Process for sifting search results and selecting studies for inclusion.



We formally excluded 43 studies with reasons recorded in the review (see [Excluded studies](#)). The most common reason for exclusion was the lack of separate reporting of the non-allergic rhinitis subpopulation in studies that initially enrolled patients with perennial rhinitis or mixed rhinitis.

We identified one ongoing study ([NCT04002349](#)). This study is a randomised, open-label clinical trial comparing both nasal saline, intranasal corticosteroid, intranasal antihistamine and combination therapy in non-allergic rhinitis patients. The expected completion date of the study is 31 March 2020. See [Characteristics of ongoing studies](#). No studies are awaiting assessment.

We included 34 studies in the systematic review. Out of these, we were able to include data from 18 studies in our analyses.

Included studies

We included 34 studies in this review ([Arikan 2006](#); [Balle 1982](#); [Behncke 2006](#); [Boechat 2019](#); [Blom 1997](#); [Day 1990](#); [Ellegård 2001](#); [Guo 2015](#); [Hallén 1997](#); [Havas 2002](#); [Hillas 1980](#); [Incaudo 1980](#); [Jacobs 2009](#); [Jessen 1990](#); [Kalpaklioglu 2010](#); [Lin 2017](#); [Löfkvist 1976](#); [Lundblad 2001](#); [Malm 1976](#); [Malm 1981](#); [Meltzer 1994](#); [Miller 1969](#); [O'Reilly 1991](#); [Scadding 1995](#); [Schulz 1978](#); [Singh 2017](#); [Song 2018](#); [Spector 1980](#); [Tantilipikorn 2010](#); [Tarlo 1977](#); [Turkeltaub 1982](#);

[Varricchio 2011](#); [Warland 1982](#); [Webb 2002](#)). See [Characteristics of included studies](#).

Design

Most of the included studies were randomised ([Arikan 2006](#); [Balle 1982](#); [Behncke 2006](#); [Blom 1997](#); [Boechat 2019](#); [Day 1990](#); [Ellegård 2001](#); [Guo 2015](#); [Hallén 1997](#); [Hillas 1980](#); [Jacobs 2009](#); [Jessen 1990](#); [Kalpaklioglu 2010](#); [Lin 2017](#); [Lundblad 2001](#); [Malm 1981](#); [Meltzer 1994](#); [Scadding 1995](#); [Schulz 1978](#); [Singh 2017](#); [Song 2018](#); [Spector 1980](#); [Tantilipikorn 2010](#); [Tarlo 1977](#); [Turkeltaub 1982](#); [Varricchio 2011](#); [Warland 1982](#); [Webb 2002](#)). Two studies were quasi-randomised ([Havas 2002](#); [Miller 1969](#)). Randomisation was unclear in four studies ([Incaudo 1980](#); [Löfkvist 1976](#); [Malm 1976](#); [O'Reilly 1991](#)).

The majority of the studies used a parallel-group design ([Arikan 2006](#); [Behncke 2006](#); [Blom 1997](#); [Boechat 2019](#); [Day 1990](#); [Ellegård 2001](#); [Guo 2015](#); [Hallén 1997](#); [Havas 2002](#); [Incaudo 1980](#); [Jacobs 2009](#); [Kalpaklioglu 2010](#); [Lin 2017](#); [Lundblad 2001](#); [Meltzer 1994](#); [Scadding 1995](#); [Schulz 1978](#); [Singh 2017](#); [Song 2018](#); [Spector 1980](#); [Tantilipikorn 2010](#); [Turkeltaub 1982](#); [Varricchio 2011](#); [Webb 2002](#)). Ten studies had cross-over design ([Balle 1982](#); [Hillas 1980](#); [Jessen 1990](#); [Löfkvist 1976](#); [Malm 1976](#); [Malm 1981](#); [Miller 1969](#); [O'Reilly 1991](#); [Tarlo 1977](#); [Warland 1982](#)).

Funding sources were reported in 11 studies, of which 10 were industry-sponsored (Ellegård 2001; Hallén 1997; Hillas 1980; Jacobs 2009; Lin 2017; Lundblad 2001; Singh 2017; Spector 1980; Tantilipikorn 2010; Webb 2002), and one was government-sponsored (Song 2018). In another five studies, the industry provided drugs for the study, but no grant support (Balle 1982; Day 1990; Havas 2002; Löfkvist 1976; Malm 1976). In five studies, the industry was involved and may have provided medication, but the funding role was unclear (Incaudo 1980; Malm 1981; Scadding 1995; Schulz 1978; Turkeltaub 1982). Finally, funding was not reported in 12 studies (Arikan 2006; Behncke 2006; Blom 1997; Guo 2015; Jessen 1990; Kalpaklioglu 2010; Meltzer 1994; Miller 1969; O'Reilly 1991; Tarlo 1977; Varricchio 2011; Warland 1982). For the other studies it was unclear whether there was any funding.

Conflicts of interest were not clearly reported. In 10 studies, at least one of the authors was an employee of a pharmaceutical company (Day 1990; Ellegård 2001; Incaudo 1980; Jacobs 2009; Malm 1981; Scadding 1995; Schulz 1978; Tantilipikorn 2010; Turkeltaub 1982; Webb 2002). Other conflicts of interest were not reported.

Sample size

Samples sizes ranged from 15 (Balle 1982) to 983 (Webb 2002).

Setting

Most studies took place in secondary or tertiary referral hospital outpatient clinic departments. The countries involved were Australia, Belgium, Brazil, Canada, China, the Czech Republic, Denmark, Finland, France, Germany, Iceland, Ireland, Italy, the Netherlands, New Zealand, Norway, Romania, Thailand, Turkey, Sweden, Switzerland, the UK and the USA.

Participants

There were 4452 patients reported in 34 included studies. The exact number of randomised patients is difficult to assess, given that many studies included both allergic and non-allergic rhinitis patients and the total number randomised was reported only for the combined population.

Overall, there were more females than males. In 17 studies where information was available 60% were female (Blom 1997; Ellegård 2001; Hallén 1997; Havas 2002; Incaudo 1980; Jacobs 2009; Jessen 1990; Lin 2017; Lundblad 2001; Löfkvist 1976; Malm 1976; Malm 1981; Miller 1969; Singh 2017; Spector 1980; Tantilipikorn 2010; Varricchio 2011). In the study Song 2018 the proportion male/female was comparable. In the other studies, the exact proportions were not reported, or were reported for a combined allergic and non-allergic rhinitis population; in most cases there were more females. Interestingly, Incaudo 1980 was comprised only of male patients. Conversely, Ellegård 2001 was a study of pregnancy rhinitis in females. Behncke 2006 studied rhinitis symptoms in geriatric patients.

Several studies reported mean patient age, which was between 29 and 49 years. Age range also varied by study, for example Boechat 2019 included elderly patients. The overall range was from 9 years (Miller 1969) to 87 years (Boechat 2019). Most patients were between 18 and 70 years of age.

Description of non-allergic rhinitis in included patients

The majority of studies used a conventional description of rhinitis, by which patients with chronic perennial rhinitis had negative allergy testing. This included the description of non-allergic rhinitis as vasomotor rhinitis (Arikan 2006; Löfkvist 1976; Malm 1976; Miller 1969; Song 2018; Warland 1982) and non-allergic, non-infectious perennial rhinitis (NANIPER) (Blom 1997). Only a few studies focused on specific subtypes of non-allergic rhinitis: Hallén 1997 studied rhinitis medicamentosa, Jacobs 2009 investigated a weather and temperature-sensitive subtype of vasomotor rhinitis, while Tantilipikorn 2010 focused on the irritant subtype due to air pollution, wind/temperature triggers and strong odours. Boechat 2019 focused on senile rhinitis patients (≥ 60 years), with both allergic and non-allergic rhinitis. Webb 2002 subdivided the overall non-allergic rhinitis population into NARES and non-NARES subtypes. Finally, Ellegård 2001 specifically studied pregnancy rhinitis. Interestingly, the majority of studies purposefully excluded pregnant women from their populations. All patients had perennial symptoms. In most studies severity was rated as moderate or severe.

Interventions

Comparisons

Twenty-five studies compared intranasal corticosteroids with placebo (Arikan 2006; Balle 1982; Blom 1997; Day 1990; Ellegård 2001; Hallén 1997; Incaudo 1980; Jacobs 2009; Lin 2017; Lundblad 2001; Löfkvist 1976; Malm 1976; Malm 1981; Meltzer 1994; Miller 1969; O'Reilly 1991; Scadding 1995; Schulz 1978; Spector 1980; Tantilipikorn 2010; Tarlo 1977; Turkeltaub 1982; Varricchio 2011; Warland 1982; Webb 2002). In all but one of these studies, placebo was described as the inactive vehicle of the intervention medication, or its ingredients were not described. In Varricchio 2011, isotonic saline solution was used as placebo.

Among these, three studies also compared different doses of intranasal corticosteroids in a multiple-arm study (Blom 1997; Scadding 1995; Webb 2002), one study compared different regimens of intranasal corticosteroids (Blom 1997), and one study compared two different types of intranasal corticosteroids (Scadding 1995).

Two studies compared azelastine combined with an intranasal corticosteroid to an intranasal corticosteroid alone (Guo 2015; Song 2018). One study compared azelastine combined with fluticasone propionate to placebo (Singh 2017). Another study compared intranasal corticosteroids with capsaicin (Havas 2002).

One study compared intranasal corticosteroids with ipratropium (Jessen 1990). Three studies compared intranasal corticosteroids with intranasal antihistamine (Behncke 2006; Kalpaklioglu 2010; Song 2018). One study compared intranasal corticosteroids versus saline, versus no treatment and versus intranasal corticosteroids combined with saline (Lin 2017). Another study compared intranasal corticosteroids with sodium cromoglycate (Hillas 1980). One study compared intranasal corticosteroids with azelastine (Kalpaklioglu 2010). Finally, one study compared intranasal corticosteroids with saline to saline alone (Boechat 2019).

Types of steroids

Fluticasone propionate was the most commonly used intranasal corticosteroid and was the main intervention in 10 studies (Arikan

2006; Behncke 2006; Blom 1997; Ellegård 2001; Guo 2015; Hallén 1997; Meltzer 1994; Scadding 1995; Singh 2017; Webb 2002). It was used in total daily doses (calculated as a sum of total dose for both nostrils) of 200 µg (Arikan 2006; Blom 1997; Ellegård 2001; Hallén 1997; Scadding 1995; Singh 2017; Webb 2002) or 400 µg daily (Blom 1997; Scadding 1995; Webb 2002). Singh 2017 and Guo 2015 used a combination of fluticasone propionate and azelastine. The length of treatment varied from two weeks to three months. Arikan 2006 used treatment for three months; Blom 1997, Blom 1997 and Ellegård 2001 for eight weeks; Guo 2015 for six weeks; Hallén 1997 and Singh 2017 for two weeks; Scadding 1995 for 12 weeks; and Webb 2002 for four weeks.

Beclomethasone dipropionate was used in seven studies (Jessen 1990; Hillas 1980; Löfkvist 1976; Malm 1976; O'Reilly 1991; Scadding 1995; Tarlo 1977). Daily doses varied from 200 µg to 800 µg per day. Hillas 1980 used 400 µg daily for four weeks. Jessen 1990 used 400 µg daily for two weeks. Löfkvist 1976 used 300 µg daily for four weeks. Malm 1976 used daily doses of 200 µg, 400 µg and 800 µg for two weeks. O'Reilly 1991 used 600 µg per day for 12 weeks. Finally, Scadding 1995 used 200 µg and 400 µg daily for 12 weeks.

Flunisolide nasal spray was used in six studies (Incaudo 1980; Schulz 1978; Spector 1980; Turkeltaub 1982; Varricchio 2011; Warland 1982). The daily doses ranged from 200 µg to 2 mg per day. Incaudo 1980 used 200 µg per day for six weeks. Schulz 1978 used 300 µg for six weeks. Spector 1980 used 400 µg daily for four weeks. Turkeltaub 1982 used 300 µg daily for 12 weeks. Varricchio 2011 used 2 mg daily for eight weeks, which appears to be at least a five times higher dose compared to the other four studies.

Budesonide was used in five studies (Balle 1982; Day 1990; Havas 2002; Malm 1981; Song 2018). The daily doses ranged from 200 µg to 800 µg daily. Balle 1982 used 200 µg and 500 µg daily for two weeks. Day 1990 used 400 µg daily for four weeks. Havas 2002 used a total daily dose of 512 µg for two weeks. Finally, Malm 1981 used 50 µg, 200 µg and 800 µg daily for two weeks.

Fluticasone furoate was used in two studies (Jacobs 2009; Tantilipikorn 2010). Both studies used 100 µg once daily for four weeks.

Triamcinolone acetonide was used in Kalpaklioglu 2010. A total daily dose of 220 µg was used for two weeks.

Mometasone furoate was used in Lundblad 2001 and Boechat 2019. Lundblad 2001 used a total daily dose of 200 µg for six weeks. Boechat 2019 used a total daily dose of 200 µg for two weeks.

Finally, dexamethasone nasal spray was used in Miller 1969. A total daily dose of 672 µg or 1008 µg was used (patients used two to three times per day) for one month.

Steroid dosage

Different doses of the same intranasal corticosteroids were used in six studies in addition to the placebo comparison (Balle 1982; Blom 1997; Malm 1976; Malm 1981; Scadding 1995; Webb 2002). Balle 1982 used budesonide at daily doses of 200 µg and 400 µg in a cross-over study design. Blom 1997 (parallel-group study) used fluticasone propionate respectively 200 µg once daily and twice daily in different regimens: a) fluticasone propionate 200 µg once daily and placebo once daily for eight weeks; b) fluticasone propionate 200 µg once daily and placebo once daily for four weeks

followed by fluticasone propionate 200 µg twice daily for four weeks; and c) fluticasone propionate 200 µg twice daily for eight weeks. Malm 1976 used 200 µg, 400 µg and 800 µg daily doses of beclomethasone dipropionate in a cross-over study design. Malm 1981, in comparison to the previous study, used budesonide at daily doses of 50 µg, 200 µg or 800 µg, also in a cross-over study design. Webb 2002 (parallel-group study) used fluticasone propionate respectively at 200 µg and 400 µg daily dosage. Finally, Scadding 1995 used both different doses of fluticasone and another intranasal corticosteroid - beclomethasone. Specifically, they used fluticasone propionate 200 µg once daily, 200 µg twice daily and beclomethasone dipropionate 200 µg twice daily for 12 weeks.

Rescue medication

Some studies allowed for rescue medications to be used concurrently in all study groups (Day 1990; Havas 2002; Lundblad 2001; Malm 1981; Spector 1980).

Outcomes

Primary outcomes

Disease severity as measured by patient-reported symptom score

Thirty-four studies reported a patient-reported disease severity score ranging from one symptom to a total nasal symptom score or an overall disease severity score. These scores differed greatly in the method of reporting, ranging from a mean of symptoms to individual scales for up to 10 symptoms. The summary scores were also all constructed differently. A summary of the scales is shown in Table 1.

The individual symptom scores varied and included nasal obstruction, nasal congestion, rhinorrhoea, post-nasal drip, sneezing, itchy nose, facial pain, anosmia, itchy eyes, watery or red eyes, headache, cough, mucus production and sore or itchy throat. These were most commonly measured on a scale ranging from 0 to 3 to 0 to 6, or a visual analogue scale (VAS) ranging from 0 to 5 to 0 to 100.

We used the symptoms rhinorrhoea (secretion), congestion (obstruction) and sneezing to calculate a total nasal symptom score in cases where only individual symptom scores were reported.

The majority of studies reported an overall symptom score (Balle 1982; Blom 1997; Boechat 2019; Day 1990; Guo 2015; Havas 2002; Incaudo 1980; Jacobs 2009; Kalpaklioglu 2010; Löfkvist 1976; O'Reilly 1991; Scadding 1995; Schulz 1978; Song 2018; Tantilipikorn 2010; Turkeltaub 1982; Varricchio 2011; Webb 2002). Most studies combined individual symptom scores into a sum score of total nasal symptom score (Blom 1997; Day 1990; Havas 2002; Jacobs 2009; Löfkvist 1976; O'Reilly 1991; Schulz 1978; Tantilipikorn 2010; Turkeltaub 1982; Varricchio 2011; Webb 2002). Balle 1982 used a mean of individual symptom scores. Blom 1997 measured intensity of nasal symptoms on a VAS from 0 to 10. Boechat 2019 and Song 2018 measured a combined nasal symptom score on a VAS from 0 to 10. Incaudo 1980 assessed overall severity of rhinitis on a scale of 1 to 4. Kalpaklioglu 2010 evaluated a total nasal symptom score on a scale of 0 to 4. Finally, Scadding 1995 reported overall assessment of symptoms by patients on a scale of 0 to 3, and at clinic visits on a VAS of 0 to 10.

Significant adverse events: epistaxis

Eight studies reported on the significant adverse event 'epistaxis' (Arikan 2006; Incaudo 1980; Jacobs 2009; Lin 2017; Lundblad 2001; Malm 1981; Scadding 1995; Tantilipikorn 2010). In almost all studies this adverse event was reported as the number of cases of epistaxis at the end of follow-up, either actively asked for by the investigator and/or spontaneously reported by the patient or recorded daily in a diary or on a question form (Jacobs 2009). Scadding 1995 only mentioned "generally minor adverse events" and reported no explicit numbers.

The risk of epistaxis was reported in five studies included in the meta-analysis (Incaudo 1980; Jacobs 2009; Lundblad 2001; Malm 1981; Tantilipikorn 2010).

Secondary outcomes

Disease-specific health-related quality of life

Six studies measured quality of life (Behncke 2006; Boechat 2019; Kalpaklioglu 2010; Lin 2017; Lundblad 2001; Song 2018). Behncke 2006 used the Rhinitis Quality of Life Questionnaire (RQLQ) (but reported no numerical data on the non-allergic rhinitis group separately). Boechat 2019 used the SNOT-22. Kalpaklioglu 2010 used the mini-Rhinitis Quality of Life Questionnaire (mini-RQLQ) (but reported no numerical data on the non-allergic rhinitis group separately). Lin 2017 used the SF-12v2 and Lundblad 2001 did not report on how quality of life was measured. Song 2018 used the SF12-v2 to measure quality of life. Boechat 2019 and Song 2018 were included in our analyses.

Inspiratory peak flow levels, rhinomanometry or other objective measurements of airflow

Ten studies objectively measured nasal airflow (Boechat 2019; Ellegård 2001; Hallén 1997; Jessen 1990; Kalpaklioglu 2010; Malm 1981; O'Reilly 1991; Singh 2017; Spector 1980; Tarlo 1977). Boechat 2019 measured peak nasal inspiratory flow (PNIF) (L/min). Ellegård 2001 measured a blockage index ((PEF-nPEF)/PEF) and acoustic rhinometry. Hallén 1997 measured rhinostereometry, acoustic rhinometry (MCA2 area) and PNIF (L/min). Jessen 1990 measured rhinomanometry during inclusion of patients but it was not used to objectively measure airflow after treatment. Kalpaklioglu 2010 measured nPIFR (nasal peak inspiratory flow rate). Malm 1981 measured rhinomanometry (in degrees). O'Reilly 1991 measured rhinomanometry using the Brom's method. Singh 2017 used the minimal cross-sectional area (MCA) before and after cold dry air (CDA) provocation. Spector 1980 used the nasal peak expiratory flow rate (PEFRn), the mouth peak expiratory flow rate (PEFRm) and the blockage index. Tarlo 1977 measured nasal airway resistance used the method of Taylor and Shivalkar.

Only three studies provided numerical data for objective airway measurements for non-allergic rhinitis patients that we could use in our analysis (Boechat 2019; Malm 1981; Spector 1980). The other studies assessed another comparison than intranasal corticosteroids versus placebo or reported no numerical data for the non-allergic rhinitis subgroup.

Other adverse events: local irritation, discomfort

Nineteen studies included 'adverse events' (besides epistaxis) as an outcome (Arikan 2006; Day 1990; Incaudo 1980; Jacobs 2009; Jessen 1990; Kalpaklioglu 2010; Lin 2017; Lundblad 2001; Malm 1976; Malm 1981; Miller 1969; O'Reilly 1991; Scadding 1995; Song

2018; Spector 1980; Tantilipikorn 2010; Tarlo 1977; Turkeltaub 1982; Varricchio 2011). In almost all studies these adverse events were reported as the number of cases of adverse events at the end of follow-up, either actively asked for by the investigator and/or spontaneously or recorded daily by the patient in a diary or on a question form (Day 1990; Jacobs 2009). Of these studies four were included in the meta-analysis (Jacobs 2009; Lundblad 2001; Song 2018; Tantilipikorn 2010). The studies that were not included in the meta-analysis either did not report data on non-allergic rhinitis patients separately, did not report numerical data or were excluded from the meta-analysis for other reasons (for example, too low or too high an intranasal corticosteroid dosage or unclear dosage subgroup).

Excluded studies

In total we excluded 43 studies (see [Characteristics of excluded studies](#)).

Astafieva 2012 compared two types of intranasal corticosteroids, brand versus generic, which was not a comparison included in our protocol and therefore we excluded this study.

Celiker 2011 compared intranasal corticosteroids with radiofrequency ablation of the inferior turbinate for nasal obstruction. It was excluded because the comparison intranasal corticosteroids versus radiofrequency ablation was not defined in our protocol.

We excluded studies with high risks of bias such as Synnerstad 1996. Besides obvious high risks of bias for allocation concealment, blinding of participants and personnel, and blinding of outcome assessors, the study had minor issues with incomplete outcome data, and some with selective outcome reporting (individual nasal symptoms measured but not thoroughly reported, total nasal symptoms reported but not included in methods). This study was supported by a grant from Astra Draco AB, Lund, Sweden, and the second author worked for the company. The company provided budesonide (Rhinocort). The study suggested that budesonide was better than beclomethasone. There are significant grounds to suspect high risk of bias. Based on these observations, we decided to exclude this study.

The Small 1982 study (comparing beclomethasone with placebo in non-allergic rhinitis patients) did not provide the results for the placebo group and was therefore excluded.

We also excluded 38 studies that were performed in patients with perennial rhinitis and did not present results for the non-allergic rhinitis subgroup separately (Adamopoulos 1995; Arbesman 1983; Balle 1982b; Basran 1995; Berger 2012; Bernstein 1997; Blair 1977; Bunnag 1992; Chatterjee 1974; Dieges 1978; Dockhorn 1999; Gibson 1974; Hansen 1974; Harding 1976; Hartley 1985; Haye 1993; Jones 1979; Joubert 1983; Juniper 1993; Kakumanu 2003; Kivisaari 1998; Kohan 1989; Lahdensuo 1977; Lau 1990; Lebowitz 1993; Malmberg 1988; McAllen 1969; McAllen 1980; Negreiros 1975; Price 2013; Rusnak 1981; Scadding 1991; Shaw 1979; Svendsen 1989; Sy 1979; Turner Warwick 1980; Webb 1977; Weckx 2001; Wight 1992). We contacted the authors of the studies in an attempt to obtain these results, without success.

One excluded study was a meta-analysis with the only relevant study already included in our review (Zucker 2019).

Besides the 43 excluded studies, two other studies did not present results for the non-allergic rhinitis subgroup separately but also did not have any authors listed. These studies were considered 'discarded'.

Risk of bias in included studies

We included 34 studies in this review. Our judgements about risk of bias are presented as a 'Risk of bias' graph in percentage form for all included studies combined (Figure 2). The risk of bias in individual studies is shown in a 'Risk of bias' summary (Figure 3).

Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

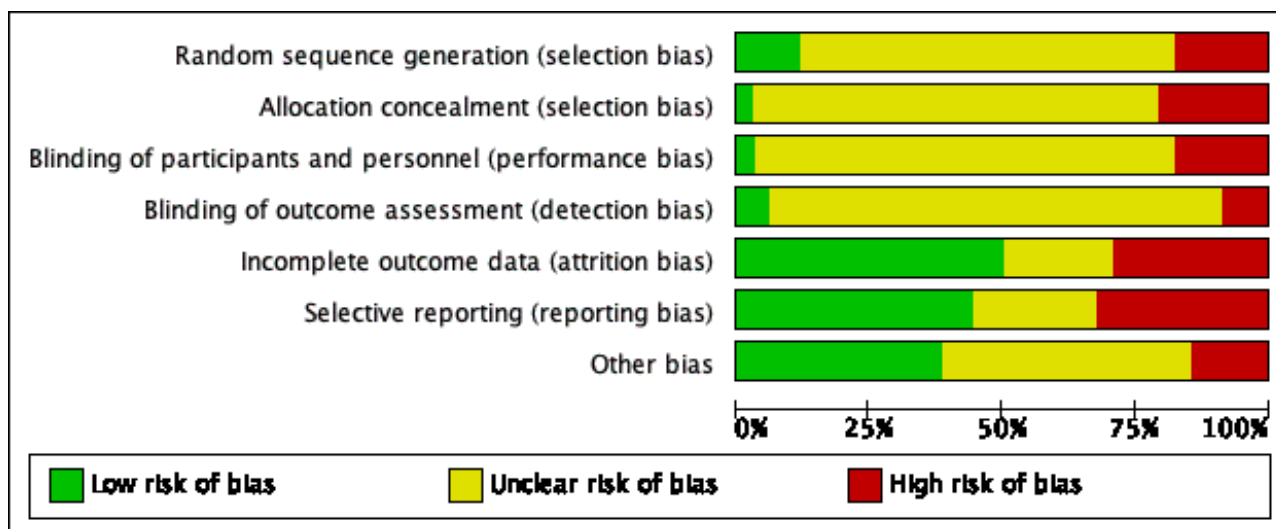


Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Arikan 2006	?	?	+	+	+	+	?
Balle 1982	?	?	?	?	+	?	?
Behncke 2006	?	?	?	?	-	-	?
Blom 1997	?	?	?	?	+	-	+
Boechar 2019	+	?	-	?	+	+	+
Day 1990	+	?	?	?	+	+	?
Ellegård 2001	?	?	?	?	?	-	+
Guo 2015	?	?	?	?	+	-	+
Hallén 1997	?	?	?	?	?	+	?
Havas 2002	-	-	-	?	+	+	+
Hillas 1980	?	?	?	?	?	?	+
Incaudo 1980	-	-	?	?	+	+	-
Jacobs 2009	?	?	?	?	?	+	?
Jessen 1990	?	?	?	?	-	?	-
Kalpakkiloglu 2010	?	?	?	?	+	+	+
Lin 2017	+	-	-	-	?	?	+
Löfkvist 1976	-	-	?	?	?	?	?
Lundblad 2001	?	?	?	?	+	-	?
Malm 1976	-	-	?	?	+	-	-

Figure 3. (Continued)

Lindegren 2001	?	?	?	?	+	-	?
Malm 1976	-	-	?	?	+	-	-
Malm 1981	?	?	?	?	-	+	?
Meltzer 1994	?	?	?	?	-	-	?
Miller 1969	-	+	?	?	+	+	?
O'Reilly 1991	-	-	?	?	-	-	+
Scadding 1995	?	?	?	?	-	?	?
Schulz 1978	?	?	?	+	?	?	+
Singh 2017	?	?	-	-	+	-	?
Song 2018	+	?	-	-	+	+	+
Spector 1980	?	?	?	?	-	+	-
Tantilipikorn 2010	?	?	?	?	+	+	+
Tarlo 1977	?	?	?	?	-	-	?
Turkeltaub 1982	?	?	?	?	-	+	?
Varricchio 2011	?	-	-	?	+	+	+
Warland 1982	?	?	?	?	-	-	?
Webb 2002	?	?	?	?	+	?	-

Allocation

Most studies described a random component in the sequence generation process but with no more information, so we judged them to have an unclear risk of bias. The exceptions are [Havas 2002](#) and [Miller 1969](#), which had a high risk of bias due to pseudo-randomisation and quasi-randomisation. [Incaudo 1980](#), [Löfkqvist 1976](#), [Malm 1976](#) and [O'Reilly 1991](#) also have a high risk of bias because they did not describe randomisation at all although the study type is very suggestive of a randomised trial. [Boechat 2019](#) (randomisation by a computer-generated code), [Day 1990](#) (balanced and stratified randomisation), [Lin 2017](#) (computer software) and [Song 2018](#) (number table method) have a low risk of selection bias.

Allocation concealment was unclear in most studies, with the exception of [Havas 2002](#), which had a high risk of bias (pseudo-randomisation), [Lin 2017](#) (had a non-random component: day/order of admission) and [Varricchio 2011](#) (allocation was not concealed, single-blinded study). In addition, [Incaudo 1980](#), [Löfkqvist 1976](#), [Malm 1976](#) and [O'Reilly 1991](#) also had a high risk of bias as they did not describe randomisation at all although the study type is very suggestive of a randomised trial. [Miller 1969](#) had a low risk of bias for allocation concealment as the authors described allocation concealment in detail (i.e. "over-printed on a tear-off portion of the label which was attached to the case report form").

Blinding

Most studies reported blinding of patients and physicians but did not give more information on the blinding process so had an unclear risk of bias. [Arikan 2006](#) had a low risk of bias as one of the main outcomes (CT scoring) was at low risk because of blinding of the radiologist. [Boechat 2019](#), [Havas 2002](#), [Lin 2017](#), [Singh 2017](#), [Song 2018](#) and [Varricchio 2011](#) had high risk of bias for blinding either because of no reporting of blinding and different treatment strategies per group making blinding complicated, pseudo-randomisation, no randomisation or single-blinding of the study.

Incomplete outcome data

Nineteen studies had a low risk of attrition bias because data for all included participants were reported. In 10 studies, the risk of attrition bias was high due to incomplete outcome data reporting or violation of the intention-to-treat protocol ([Behncke 2006](#); [Jessen 1990](#); [Malm 1981](#); [Meltzer 1994](#); [O'Reilly 1991](#); [Scadding 1995](#); [Spector 1980](#); [Tarlo 1977](#); [Turkeltaub 1982](#); [Warland 1982](#)). In eight studies, the risk of attrition bias was unclear because only a very small amount of data was not reported and this had an unclear (and most likely low) effect on clinical outcome ([Ellegård 2001](#); [Hallén 1997](#); [Hillas 1980](#); [Jacobs 2009](#); [Löfkqvist 1976](#); [Schulz 1978](#); [Singh 2017](#); [Webb 2002](#)).

Selective reporting

Fifteen studies had a low risk of selective reporting bias because all of the outcomes described in the methods section could be found in the results. We were not able to find a study protocol for any of the included studies.

In eight studies the risk of reporting bias was unclear due to incomplete presentation of all outcomes (Balle 1982; Hillas 1980; Jessen 1990; Lin 2017; Löfkvist 1976; Scadding 1995; Schulz 1978; Webb 2002). In the remaining 12 studies the risk of selective reporting bias was high due to major lack of reporting of significant outcomes, which could influence the conclusions (Behncke 2006; Blom 1997; Ellegård 2001; Guo 2015; Lundblad 2001; Malm 1976; Meltzer 1994; O'Reilly 1991; Singh 2017; Tarlo 1977; Warland 1982).

Other potential sources of bias

The risk of other bias was high in four studies (Incaudo 1980; Jessen 1990; Malm 1976; Spector 1980). Incaudo 1980 included only male patients. In Jessen 1990, it was unclear if blinding was compromised for patients to report medication safety. In addition, the scale up to "3 or 4 for severe symptoms" is vague. Finally, it was not clear which groups the patients (5 of 24) co-treated with xylometazoline belonged to. In Malm 1976, the cross-over study design had no washout period, leaving it possible for there to be a carry-over effect. In Spector 1980, women of childbearing potential were excluded, making the study biased.

Several studies received funding from a pharmaceutical company without clarifying their role. Another extra bias in some studies resulted from limited ways of reporting data, for example without mean and standard deviation. Only 15 studies had a low risk of other potential sources of bias (Boechat 2019; Blom 1997; Ellegård 2001; Guo 2015; Havas 2002; Hillas 1980; Jacobs 2009; Kalpaklioglu 2010; Lin 2017; O'Reilly 1991; Schulz 1978; Song 2018; Tantilipikorn 2010; Varricchio 2011).

Effects of interventions

See: [Summary of findings for the main comparison](#) Intranasal corticosteroids compared to placebo for non-allergic rhinitis

See [Summary of findings for the main comparison](#) for the main comparison: 'Intranasal corticosteroids versus placebo'.

Intranasal corticosteroids versus placebo

Thirteen studies (2045 participants) comparing intranasal corticosteroid treatment with placebo provided data that could be used in our analyses (Arikan 2006; Balle 1982; Blom 1997; Day 1990; Incaudo 1980; Jacobs 2009; Lundblad 2001; Malm 1976; Malm 1981; Spector 1980; Tantilipikorn 2010; Turkeltaub 1982; Webb 2002). Twelve included studies could not be used in the analyses (Ellegård 2001; Hallén 1997; Lin 2017; Löfkvist 1976; Meltzer 1994; Miller 1969; O'Reilly 1991; Scadding 1995; Schulz 1978; Tarlo 1977; Varricchio 2011; Warland 1982).

Different types of intranasal corticosteroids were used (budesonide, beclomethasone, flunisolide, fluticasone propionate, fluticasone furoate, dexamethasone, mometasone furoate).

Among the studies treatment dosage varied from 50 µg to 2000 µg daily. Most of the studies that compared different dosages of intranasal corticosteroids used a cross-over study design, with the

exception of Blom 1997 and Webb 2002, which used a parallel-group study design. In the cross-over studies the same patients were treated with different dosages of intranasal corticosteroids, with a short (one-week) or no washout, complicating a clear comparison between these dosage subgroups (Balle 1982; Malm 1976; Malm 1981). Only Balle 1982 showed a dosage effect for two nasal symptom score outcomes. Malm 1976 and Malm 1981 showed no significant difference between the dosage subgroups. The two parallel-group studies both concluded that there were no statistically significant differences among the different intranasal corticosteroid dosage subgroups (Blom 1997; Webb 2002). In the parallel-group studies different dosage subgroups contained different patients but were compared with the same control group. To prevent counting the same patients or controls more than once, we decided to include one intranasal corticosteroids dosage in the meta-analysis. The most common intranasal corticosteroid dosage was 200 µg. A test for subgroup differences showed no significant difference ('no dosage effect') between 200 µg and 400 µg. We therefore included studies in the meta-analysis with an intranasal corticosteroid dosage range of 200 µg to 400 µg.

Treatment vehicles varied and included spray, aerosol, nebuliser, pressured canister and atomised bottle. Frequency of usage varied from once daily to four times daily.

Disease severity, as measured by patient-reported total nasal symptom score

Eleven studies presented data for disease severity using a number of different scales that could be used in meta-analysis (Balle 1982; Blom 1997; Day 1990; Incaudo 1980; Jacobs 2009; Malm 1976; Malm 1981; Spector 1980; Tantilipikorn 2010; Turkeltaub 1982; Webb 2002). Table 1 shows the different scales used. Some studies provided us with a total nasal symptom score (TNSS). In studies that did not provide a total nasal symptom score, we calculated this score based on individual rhinitis symptom scores, i.e. rhinorrhoea (secretion), congestion (obstruction) and sneezing. Due to the differences in the scales used, we used a standardised mean difference (SMD) in the analysis.

Outcomes were measured at up to four weeks follow-up in four studies and at more than four weeks (six weeks to three months) follow-up in three studies. Outcomes were also measured as change from baseline in another four studies.

Up to four weeks follow-up

We were able to pool data from four studies that reported a patient-reported total nasal symptom score (or individual scores that could be calculated into a total nasal symptom score) with a follow-up of up to four weeks (Balle 1982; Malm 1976; Malm 1981; Spector 1980). These studies showed that patients treated with intranasal corticosteroids had lower total nasal symptom scores compared to placebo (SMD -0.74, 95% confidence interval (CI) -1.15 to -0.33; 4 studies; 131 participants; $I^2 = 22\%$) (Analysis 1.1) (low-certainty evidence). This represents a medium effect size (Cohen 1988). Spector 1980 was the only study that did not report an improvement of total nasal symptom score with intranasal corticosteroids.

The heterogeneity in this analysis is mainly the result of Spector 1980. Removing this study reduces the heterogeneity to 0%.

There were not enough data to carry out our planned subgroup analyses to assess the differences between different dosages (see above), types, vehicles or frequencies of intranasal corticosteroid treatment.

More than four weeks follow-up (six weeks to three months)

Three studies reported a patient-reported total nasal symptom score with a follow-up of more than four weeks (Blom 1997; Incaudo 1980; Turkeltaub 1982). The follow-up period varied between six weeks and three months.

These studies showed that patients treated with intranasal corticosteroids had no difference in nasal symptom scores compared to placebo but the evidence is very uncertain (SMD -0.24, 95% CI -0.67 to 0.20; 3 studies; 85 participants; $I^2 = 0\%$) (Analysis 1.2) (very low-certainty evidence).

Blom 1997 studied four different treatment regimens with different intranasal corticosteroid dosages. The authors concluded that there were no statistically significant differences among the four treatment regimens in the investigators' assessments of symptoms and rhinoscopy at clinic visits.

There were not enough data to carry out our planned subgroup analyses to assess the differences between different dosages (see above), types, vehicles or frequencies of intranasal corticosteroid treatment.

Change from baseline, up to four weeks follow-up

Four studies reported on the change from baseline of a patient-reported total nasal symptom score, with a follow-up of up to four weeks (Day 1990; Jacobs 2009; Tantilipikorn 2010; Webb 2002).

These studies showed that patients treated with intranasal corticosteroids had a significant difference in total nasal symptom scores compared to placebo (SMD -0.15 95% CI -0.25 to -0.05; $P = 0.004$; 4 studies; 1465 participants; $I^2 = 35\%$) (Analysis 1.3) (low-certainty evidence). This represents a small effect size.

These results use adjusted data from Jacobs 2009 that are different from the original results presented and published by the study authors. The Jacobs 2009 study reports a very unlikely standard deviation (SD) value that does not match with the presented means, n and P values. Using the data presented in Jacobs 2009 resulted in very high heterogeneity ($I^2 = 96\%$). The data would make more sense if the presented SD values were actually standard error of the mean (SEM), which we confirmed by a re-analysis. We were not able to obtain a response from the study authors to our questions about the data. Jacobs 2009 is one of the larger studies and is also one of the most well-known and frequently cited. We therefore decided to retain the study in the meta-analysis. Using the formula $SD = SEM * \sqrt{n}$ we calculated the adjusted SD values assuming the SD values presented in the study were actually SEM. We used these adjusted SD values in Analysis 1.3.

Webb 2002 studied two daily dosages (200 µg and 400 µg) in a parallel-group study, with nearly the same effect on total nasal symptom score change from baseline. Only the highest dosage (400 µg) from Webb 2002 was included in the meta-analysis.

Webb 2002 also reports an improvement in favour of intranasal corticosteroids, however this is less certain than in Jacobs 2009. The amount of improvement is more clinically relevant than in Jacobs

2009, i.e. around a 10% improvement in total nasal symptom score. In general, the data from Webb 2002 seem to be far more reliable than the data from Jacobs 2009.

Webb 2002 studied different daily dosages (200 µg and 400 µg) and concluded that there were no statistically significant differences.

There were not enough data to carry out our planned subgroup analyses to assess the differences between different dosages (see above), types, vehicles or frequencies of intranasal corticosteroids treatment.

For the outcome total nasal symptom score change from baseline there were no studies reporting a follow-up of more than four weeks.

Twelve studies that did report nasal symptom score(s) could not be included in the meta-analysis (Arikan 2006; Meltzer 1994; Miller 1969; Lin 2017; Lundblad 2001; Löfkvist 1976; O'Reilly 1991; Scadding 1995; Schulz 1978; Tarlo 1977; Varricchio 2011; Warland 1982). Arikan 2006 and Lundblad 2001 are, however, included in the meta-analysis for other outcomes (adverse events). Miller 1969 and Varricchio 2011 are not included in the total nasal symptom score(s) meta-analysis because they used an intranasal corticosteroid dosage higher than 200 µg to 400 µg daily. See Table 2 for a summary of the results from these 12 studies for nasal symptom score(s).

Significant adverse events: epistaxis

The risk of epistaxis was reported in four studies included in the meta-analysis, two with a follow-up of up to four weeks (Malm 1981; Tantilipikorn 2010) and two with a follow-up of more than four weeks (Jacobs 2009; Lundblad 2001). Malm 1981 studied different dosages of intranasal corticosteroids in a cross-over study design. The daily dosage of 200 µg was included in the meta-analysis (see reasons above).

We decided to combine the four studies and not to separate them into up to four weeks and more than four weeks follow-up. All studies showed a significantly higher risk of epistaxis in the intranasal corticosteroids group compared to placebo (risk ratio (RR) 2.10, 95% CI 1.24 to 3.57; 1174 participants; 4 studies; $I^2 = 0\%$) (moderate-certainty evidence). The absolute risk difference for epistaxis was 0.04 (Analysis 1.4), with a number needed to treat for an additional harmful outcome (NNTH) of 25 (95% CI 16.7 to 100).

Three of the studies included in the meta-analysis that reported on the risk of epistaxis showed no significant difference between intranasal corticosteroids and placebo (Jacobs 2009; Malm 1981; Tantilipikorn 2010). For these studies the NNT, NNTB (number needed to treat for an additional beneficial outcome) and NNTH are as follows: Tantilipikorn 2010 had a NNT of 25, with NNTB 10 and NNTH 50. Jacobs 2009 had a NNT of 50, with NNTB 20 and NNTH 100. Malm 1981 had a NNT of 10, with NNTB 6.25 and NNTH 14.29. Finally, Lundblad 2001 did show a significant difference with a NNT of 14.29 (95% CI 7.69 to 100).

Three studies reported on epistaxis but were not included in the meta-analysis because the study did not report numerical data for the non-allergic rhinitis subgroup (Scadding 1995), due to lack of quality of the study (Lin 2017), or because no events were observed in either group (Arikan 2006). Scadding 1995 reported "generally minor" adverse events in the intranasal corticosteroids group and

Lin 2017 reported two cases of epistaxis in a total group of 22 patients treated with budesonide versus no cases of epistaxis in the placebo group. Arian 2006 reported no epistaxis in either the intervention group or the control group.

Disease-specific health-related quality of life

No studies except Lin 2017 reported numerical data on (health-related) quality of life for non-allergic rhinitis patients. Lin 2017 used the Short Form 12 (SF-12v2) questionnaire to measure quality of life (scale range 0 to 800). This study was not included in the analysis because of lack of quality of the study data (see reasons above). Lin 2017 reported a higher quality of life in the intranasal corticosteroids group versus the placebo group after one month (152.3 versus 145.6); however, while this difference was clear at one-month follow-up it was barely noticeable at three months follow-up (148.4 versus 145.6) (low-certainty evidence).

Lundblad 2001 reported no numerical data on quality of life but did report narratively that there was no significant difference in quality of life between the intranasal corticosteroids group and the placebo group.

Inspiratory peak flow levels, rhinomanometry or other objective measurements of airflow

Only two studies provided data for objective airway measurements that we could use in our analyses (Malm 1981; Spector 1980), one using peak flow expiratory rate (Spector 1980) and one using rhinomanometry (Malm 1981). The study using peak flow expiratory rate did not find a significant difference for flunisolide over placebo (SMD 0.78, 95% CI -0.47 to 2.03; 11 participants) (Analysis 1.5). For rhinomanometry there was also no significant difference (SMD -0.46, 95% CI -1.06 to 0.14; 44 participants) (Analysis 1.6) (Malm 1981). This evidence is of very low certainty.

Ellegård 2001 was not included in the meta-analysis as it compared intranasal corticosteroids versus placebo in a single separate subgroup of non-allergic rhinitis patients, i.e. participants with pregnancy rhinitis. Ellegård 2001 reported a blockage index ((PEF-nPEF)/PEF) to objectify airflow after treatment. The mean blockage index after eight weeks of treatment in the fluticasone group was 0.39 (SD 0.16) and the mean blockage index in the placebo group was 0.41 (SD 0.15), therefore there was no significant difference between the intranasal corticosteroids and placebo groups.

Hallén 1997 was not included in the meta-analysis as it compared intranasal corticosteroids versus placebo in a single separate subgroup of non-allergic rhinitis patients, i.e. participants with rhinitis medicamentosa. Hallén 1997 reported both acoustic rhinometry and PNIF after 13 days of treatment. The mean acoustic rhinometry outcome in the intranasal corticosteroids group was 0.28 cm² (SD 0.19) and the mean acoustic rhinometry outcome in the placebo group was 0.03 cm² (SD 0.17) (SMD -1.34, 95% CI -0.35 to -2.33). The mean PNIF outcome in the intranasal corticosteroids group was 121.2 L/min (SD 69.0) and the mean PNIF outcome in the placebo group was 128.7 L/min (SD 40.4) (SMD -0.13, 95% CI -0.75 to 1.00), i.e. there was no significant difference.

O'Reilly 1991 was not included in the meta-analysis because it only reported P values and there was too wide a variation between baseline and placebo values.

Tarlo 1977 was not included in the meta-analysis because it reported no numerical data for the non-allergic rhinitis subgroup.

Jessen 1990 used rhinomanometry during the inclusion of patients but it was not used to objectively measure airflow after treatment and could therefore not be used in the meta-analysis.

Kalpakioglu 2010 was included in the meta-analysis for the comparison of intranasal corticosteroids versus ipratropium bromide.

The objective airflow measurements of Singh 2017 could not be included as they were related to cold dry air exposure.

Other adverse events

The outcome 'other adverse events' was defined as adverse events other than epistaxis, for example pharyngitis, nasal dryness/crusting and headache.

Three studies included in the meta-analysis reported on 'other adverse events' besides epistaxis (Jacobs 2009; Lundblad 2001; Tantilipikorn 2010). We decided to combine the three studies and not to make a separation into up to four weeks and more than four weeks follow-up. Intranasal corticosteroids probably result in little or no difference in the risk of other adverse events compared to placebo (RR 0.99, 95% CI 0.87 to 1.12; 3 studies; 1130 participants; I² = 0%) (Analysis 1.7) (moderate-certainty evidence).

Lin 2017 was not included in the meta-analysis due to lack of quality of the study data (see above). Miller 1969 was not included in the meta-analysis as it used a dosage of dexamethasone of 672 µg to 1008 µg per day and only studies with an intranasal corticosteroid dosage of 200 µg to 400 µg were included in the meta-analysis (see above). Malm 1981 was not included in the meta-analysis as it was unclear in which intranasal corticosteroid dosage subgroup the other adverse events occurred. Other studies describing 'other adverse events' as an outcome in their 'Materials and methods' sections did not report actual numbers/data in the 'Results' section or did not report for the non-allergic rhinitis group separately and were therefore not included in the review.

Lin 2017 was not included in the meta-analysis but reported seven cases of other adverse events in a total group of 22 patients treated with budesonide versus no other adverse events in the placebo group.

Miller 1969 described two (non-epistaxis) adverse events in the intranasal corticosteroids group and two adverse events in the placebo group.

Malm 1981 reported four 'other adverse events' in the intranasal corticosteroids group versus none in the placebo group.

Varricchio 2011 reported no clinically relevant adverse events in either the treatment or control group.

Subgroups/phenotypes

Within the comparison of intranasal corticosteroids versus placebo there were not enough data to perform a subgroup analysis for different subgroups/phenotypes of non-allergic rhinitis. Ellegård 2001 evaluated intranasal corticosteroids in pregnancy rhinitis patients (see also under 'Objective measurement of airflow'). Overall, the study did not find a beneficial effect of intranasal

corticosteroids over placebo. [Hallén 1997](#) evaluated intranasal corticosteroids in rhinitis medicamentosa patients (see also 'Objective measurement of airflow'). They concluded that the symptom scores for nasal stuffiness showed a marked reduction during the treatment period in both groups, but there was a faster onset of symptom reduction after treatment with fluticasone propionate.

Intranasal corticosteroids versus saline

One four-armed study compared intranasal budesonide nasal spray 256 µg once daily and nasal saline irrigation 100 mL of 3% saline per nostril combined with intranasal budesonide nasal spray 256 µg once daily to nasal saline alone and no treatment ([Lin 2017](#)). This study was not included in the meta-analysis due to lack of quality of the study data (see above).

Disease severity, as measured by patient-reported total nasal symptom score

This study reported a total nasal symptom score using a visual analogue scale (VAS) (unclear scale per individual symptom and uncLEAR total range of symptoms).

There was a significant difference between budesonide (from VAS 5.91 to VAS 5.68 after three months) and saline (from VAS 5.96 to VAS 4.80 after three months) in favour of saline (t-test, $P < 0.05$).

Significant adverse events: epistaxis

The risk of epistaxis was higher in the intranasal corticosteroids group (two participants with epistaxis) compared to the saline group (no participants with epistaxis).

Disease-specific health-related quality of life

The quality of life measurement (SF-12v2: range 0 to 800) also showed a significant effect (t-test, $P < 0.05$) in favour of saline (SF-12v2 increase from 146 at baseline to 151.30 after three months) compared to budesonide (SF-12v2 increase from 146 to 148.40).

Inspiratory peak flow levels, rhinomanometry or other objective measurements of airflow

The study did not report objective measurements of nasal airflow.

Other adverse events

There were seven other adverse events in the budesonide treatment group (pharyngitis and nasal dryness/crusting) and no other adverse events in the saline group.

Intranasal corticosteroids versus intranasal antihistamine

Three studies reported on intranasal corticosteroids versus an intranasal antihistamine ([Behncke 2006](#); [Kalpaklioglu 2010](#); [Song 2018](#)). [Kalpaklioglu 2010](#) and [Song 2018](#) were included in the meta-analysis. [Kalpaklioglu 2010](#) compared triamcinolone acetonide nasal spray 220 µg once daily to azelastine hydrochloride and [Song 2018](#) compared budesonide 200 µg two times per day to azelastine 200 µg two times per day.

Disease severity, as measured by patient-reported total nasal symptom score

In [Song 2018](#), there was a non-significant difference in combined nasal symptom VAS score in favour of budesonide nasal spray

(mean difference (MD) -0.25, 95% CI -0.69 to 0.19; 80 participants) (Analysis 2.1).

In [Kalpaklioglu 2010](#), there was a non-significant difference in total nasal symptom score mean change from baseline in favour of triamcinolone acetonide nasal spray (MD -0.50, 95% CI -1.92 to 0.92; 63 participants) (Analysis 2.2). The study reports a significant improvement in sneezing with triamcinolone in patients with non-allergic rhinitis ($P < 0.01$), as well as conjunctivitis.

Significant adverse events: epistaxis

Epistaxis was not evaluated.

Disease-specific health-related quality of life

[Kalpaklioglu 2010](#) assessed quality of life with the mini-Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) but these results were not reported for non-allergic rhinitis participants separately.

[Song 2018](#) assessed quality of life with the SF12-v2 questionnaire (a higher score indicates better quality of life). There was a non-significant difference in favour of azelastine in quality of life (MD -1.30, 95% CI -3.60 to 1.00; 80 participants) (Analysis 2.3).

Inspiratory peak flow levels, rhinomanometry or other objective measurements of airflow

[Kalpaklioglu 2010](#) also reported on the inspiratory peak flow rate (change from baseline) and showed a small, non-significant difference in favour of triamcinolone acetonide (MD -6.17, 95% CI -15.25 to 2.91; 63 participants) (Analysis 2.4).

Other adverse events

[Song 2018](#) reported a higher risk of 'other adverse events' (such as dryness of the nasal mucosa) in the budesonide group compared to azelastine (RR 2.00, 95% CI 0.19 to 21.18; 80 participants) (Analysis 2.5).

[Behncke 2006](#) was not included in the meta-analysis because it reported no numerical data for non-allergic rhinitis participants separately. This study does conclude that there is no difference in effectiveness between intranasal corticosteroids and intranasal antihistamines. The authors conclude that azelastine nasal spray and fluticasone nasal spray improve RQLQ scores and rhinitis symptom scores in geriatric patients with either allergic or non-allergic rhinitis.

Intranasal corticosteroids versus capsaicin

One study provided data for this comparison. [Havas 2002](#) compared budesonide nasal spray applied twice daily (256 µg daily dosage) to capsaicin 2.616 µg once weekly.

Disease severity, as measured by patient-reported total nasal symptom score

There was a large significant difference in mean total nasal score in favour of capsaicin (MD 1.60, 95% CI 0.03 to 3.16; 40 participants) (Analysis 3.1). A total nasal symptom score was calculated as the mean sum of rhinorrhoea, congestion and sneezing (VAS 0 to 5 for each symptom, per side; range 0 to 30).

Significant adverse events: epistaxis

Epistaxis was not evaluated.

Disease-specific health-related quality of life

Quality of life was not evaluated.

Inspiratory peak flow levels, rhinomanometry or other objective measurements of airflow

Objective measurements of airflow were not evaluated.

Other adverse events

Other adverse events were not evaluated.

Intranasal corticosteroids versus sodium cromoglycate

One study provided data for this comparison (Hillas 1980). This study compared sodium cromoglycate 2% six times daily to beclomethasone dipropionate 400 µg daily. It reported no numerical data for the non-allergic rhinitis group separately and was therefore not included in the meta-analysis.

Disease severity, as measured by patient-reported total nasal symptom score

Intranasal corticosteroids relieved symptoms in 76.9% of patients versus 50% of patients treated with sodium cromoglycate, a significant difference. The total symptom score (mean of a total of seven symptoms that were scored on a range from 0 to 3) at the end of treatment was 4.12 in participants treated with sodium cromoglycate and 2.37 in participants treated with intranasal corticosteroids, a significant difference.

Significant adverse events: epistaxis

The study reported that occasionally (no numerical data) patients using intranasal corticosteroids had blood spotting while blowing their noses. This was not reported in the group treated with sodium cromoglycate.

Disease-specific health-related quality of life

Quality of life was not evaluated.

Inspiratory peak flow levels, rhinomanometry or other objective measurements of airflow

Objective measurements of airflow were not evaluated.

Other adverse events

No numerical data on other adverse events were reported, however some patients experienced sneezing after using intranasal corticosteroids. No significant adverse events were reported for cromoglycate sodium.

Intranasal corticosteroids versus ipratropium bromide

One study provided data for this comparison (Jessen 1990). This cross-over study compared beclomethasone aerosol, twice daily (total daily dose 400 µg) with ipratropium bromide 160 µg.

Disease severity, as measured by patient-reported total nasal symptom score

There was no significant difference between the treatments in total nasal symptom score (MD -1.50, 95% CI -12.24 to 9.24; 48 participants) (Analysis 4.1).

Significant adverse events: epistaxis

Epistaxis was not evaluated.

Disease-specific health-related quality of life

Quality of life was not evaluated.

Inspiratory peak flow levels, rhinomanometry or other objective measurements of airflow

The study used rhinomanometry during the inclusion of patients but it was not used to objectively measure airflow after treatment.

Other adverse events

No other adverse events were evaluated.

Intranasal corticosteroids versus intranasal corticosteroids combined with intranasal antihistamine

Three studies provided data for this comparison (Guo 2015; Singh 2017; Song 2018).

Guo 2015 compared fluticasone dipropionate nasal spray in an unknown dosage of two sprays in each nostril once daily with fluticasone dipropionate nasal spray 100 µg combined with azelastine in an unknown dosage in each nostril twice daily.

Singh 2017 reported no numerical data and was therefore not included in the meta-analysis.

Song 2018 compared budesonide nasal spray 200 µg two times per day with budesonide nasal spray 200 µg two times per day combined with azelastine nasal spray 200 µg two times per day.

Disease severity, as measured by patient-reported total nasal symptom score

There was a significant difference between intranasal corticosteroids alone and intranasal corticosteroids combined with intranasal antihistamine for nasal symptom score (SMD 0.75, 95% CI 0.48 to 1.02; 2 studies; 242 participants) (Analysis 5.1).

Guo 2015 reported a small but significant difference in total nasal symptom score (unclear scale and range) in favour of fluticasone dipropionate nasal spray combined with azelastine after six weeks of treatment (SMD 0.37, 95% CI 0.06 to 0.68; 162 participants).

Song 2018 also reported a significant difference in total symptom VAS score (range 0 to 10) in favour of budesonide nasal spray combined with azelastine after eight weeks of treatment (SMD 0.75, 95% CI 0.48 to 1.02; 80 participants).

Significant adverse events: epistaxis

Guo 2015 and Song 2018 did not report any cases of epistaxis in either treatment group.

Disease-specific health-related quality of life

In Guo 2015, quality of life was not evaluated.

Song 2018 did evaluate quality of life by means of the SF12-v2 questionnaire (a higher score indicating a better quality of life). It showed a significantly higher quality of life in the group treated with budesonide combined with azelastine nasal spray compared to budesonide nasal spray alone (MD -7.20, 95% CI -9.77 to -4.63; 80 participants) (Analysis 5.2).

Inspiratory peak flow levels, rhinomanometry or other objective measurements of airflow

In Guo 2015 and Song 2018 objective measurements of airflow were not evaluated.

Other adverse events

Two studies included in the meta-analysis reported on 'other adverse events' (Guo 2015; Song 2018). Both studies showed a nearly significant higher rate of other adverse events in the combined intranasal corticosteroid and intranasal antihistamine group (RR 0.26, 95% CI 0.07 to 1.01; 2 studies; 242 participants; $I^2 = 15\%$) (Analysis 5.3).

Guo 2015 reported more adverse events (five reporting fatigue and bitter taste) in the fluticasone dipropionate with azelastine group than in the fluticasone dipropionate alone group (no adverse events) (RR 0.09, 95% CI 0.00 to 1.54; 162 participants) (Analysis 5.3).

Song 2018 also reported more adverse events (dryness of nasal mucosa, dry throat discomfort, bitter taste, slight erosion of nasal mucosa) in the budesonide with azelastine group than in the budesonide alone group (RR 0.50, 95% CI 0.10 to 2.58; 80 participants) (Analysis 5.3).

Singh 2017 compared intranasal corticosteroids combined with azelastine to placebo instead of intranasal corticosteroids. It could not be included in the meta-analysis because the total nasal symptom score was not reported numerically. Total nasal symptom score and objective measurement of airflow were both related to cold dry air provocation. The study did report that there were no statistically significant differences between the two treatments.

Intranasal corticosteroids versus intranasal corticosteroids combined with saline irrigation

One study provided data for this comparison (Lin 2017). This study was not included in the meta-analysis due to lack of quality of the study data (see above). It compared nasal saline irrigation (100 mL of 3% saline per nostril twice a day) with intranasal budesonide nasal spray 256 µg once daily (two sprays per nostril per day, 64 µg per spray) to intranasal budesonide alone.

Disease severity, as measured by patient-reported total nasal symptom score

There was a significant difference between combination therapy (from VAS 6.18 to VAS 4.48 after three months) and budesonide (from VAS 5.91 to VAS 5.68 after three months) in favour of combination therapy (t-test, $P < 0.05$).

Significant adverse events: epistaxis

The combination therapy group had one patient with epistaxis, while the budesonide group had two patients with epistaxis.

Disease-specific health-related quality of life

The quality of life measurement (SF-12v2) also showed a significant effect in favour of combination therapy (increase from 146 at baseline to 152.9 after three months) over budesonide (increase from 146 to 148.40) (t-test, $P < 0.05$).

Inspiratory peak flow levels, rhinomanometry or other objective measurements of airflow

The study did not report on objective measurements of nasal airflow.

Other adverse events

The combined therapy group had eight participants with other adverse events (pharyngitis, nasal dryness/crusting), while the budesonide group had seven participants with other adverse events.

Intranasal corticosteroids with saline spray versus saline spray alone

One study provided data for this comparison (Boechat 2019). It compared mometasone furoate 200 µg daily with isotonic saline spray to isotonic saline spray alone.

Disease severity, as measured by patient-reported total nasal symptom score

There was a non-significant difference between intranasal corticosteroid spray combined with isotonic saline spray (VAS score 4.1 (SD 2.4)) and isotonic saline spray alone (VAS score 5.4 (SD 2.1)) after two weeks (MD -1.30, 95% CI -2.97 to 0.37; 28 participants) (Analysis 6.1).

The pre-treatment VAS score for intranasal corticosteroid spray combined with isotonic saline spray was 5.2 (SD 2.0) and for nasal spray alone was 5.3 (SD 2.5). Although the combined treatment showed better symptom improvement compared to saline alone the reduction was non-significant ($P = 0.056$).

Significant adverse events: epistaxis

The study reported no adverse events.

Disease-specific health-related quality of life

The quality of life measurement (SNOT-22 questionnaire with a lower score indicating a better quality of life) showed no significant difference between intranasal corticosteroid spray combined with isotonic saline spray (24.3 (SD 16.5)) and isotonic nasal spray alone (32.3 (SD 15.2)) after two weeks (MD -8.0, 95% CI -19.75 to 3.75; 28 participants) (Analysis 6.2). Pre-treatment quality of life (SNOT-22) for intranasal corticosteroid spray combined with isotonic saline spray was 30.0 (SD 15.2) and for nasal spray alone was 38.1 (SD 19.9). The reduction was non-significant ($P = 0.095$).

Inspiratory peak flow levels, rhinomanometry or other objective measurements of airflow

The peak nasal inspiratory flow (PNIF) measurements showed no significant difference between intranasal corticosteroid spray combined with isotonic saline spray (72.9 L/min (SD 25.5)) and isotonic nasal spray alone (82.1 L/min (SD 39.8)) after two weeks (MD -9.20, 95% CI -33.96 to 15.56; 28 participants) (Analysis 6.3). Pre-treatment PNIF for intranasal corticosteroid spray combined with

isotonic saline spray was 77.1 (SD 25.8) and for nasal spray alone was 90.7 (SD 38.5). The reduction was non-significant ($P = 0.688$).

Other adverse events

The study reported no adverse events.

DISCUSSION

Summary of main results

See [Summary of findings for the main comparison](#).

We included 34 studies with a total of 4452 participants in this review, reporting on our main comparison (intranasal corticosteroids versus placebo) and eight further comparisons: intranasal corticosteroids versus saline, versus intranasal antihistamine, versus capsaicin, versus cromoglycate sodium, versus ipratropium bromide, versus intranasal corticosteroids and intranasal antihistamine, versus intranasal corticosteroids with saline and intranasal corticosteroids with saline versus saline alone. We were able to analyse data from 18 studies for the eight different comparisons.

Intranasal corticosteroids versus placebo

We were only able to identify a significant number of studies (25) for the main comparison, intranasal corticosteroids versus placebo; 13 of these studies could be included in the meta-analysis. However, the evidence was limited by the fact that most studies had only small numbers of patients and there was a high degree of variance in their results. The two largest studies did show a significant improvement in symptom scores ([Jacobs 2009](#); [Webb 2002](#)). However, the study data in [Jacobs 2009](#) are unlikely to be credible. The study presented very unlikely standard deviation (SD) values, which did not match the presented mean, n and P values, resulting in very high heterogeneity of the data for the outcome 'Total nasal symptom score, change from baseline'. Most likely the standard deviation (SD) values should have been standard error of the mean (SEM) values, as we confirmed by re-analysis. When we used the adjusted SD values (assuming the SD values presented were actually SEM), the improvement in symptom score in [Jacobs 2009](#) was no longer significant.

There may be an improvement in patient-reported disease severity as measured by a total nasal symptom score (TNSS) with intranasal steroids but we are uncertain because we assessed the certainty of the evidence as low to very low due to high imprecision and risk of publication bias due to small patient numbers. There were too few data to draw conclusions on any differences according to type of intranasal corticosteroids, dosage, vehicle used, frequency of usage or duration of treatment.

There is probably a higher risk of epistaxis with intranasal corticosteroids compared to placebo (moderate-certainty evidence).

One study assessed quality of life ([Lin 2017](#)). This study showed that quality of life was better in the intranasal corticosteroids group compared to the placebo group. However, while this difference was significant at one-month follow-up it was barely noticeable at three-month follow-up. [Lin 2017](#) was not included in the meta-analysis because of lack of quality of the study data. Firstly, the study presents unexpected data with disappearance of benefit of intranasal corticosteroids with longer follow-up. Secondly,

including the study in the meta-analysis resulted in a high level of heterogeneity. Finally, the SD values that are presented in the study do not match with presented means, n and P values. The data make more sense if the SD values presented are actually standard error of the mean (SEM), which we again confirmed by a re-analysis.

As only two studies evaluated objective measurements of airflow and the data could not be pooled due to the different methods used, we cannot draw conclusions on this outcome. Neither study found a difference between intranasal corticosteroids and placebo.

Intranasal corticosteroids probably result in little or no difference in the risk of other adverse events compared to placebo (moderate-certainty evidence).

Other comparisons

For the following comparisons it is uncertain whether there are differences between intranasal corticosteroids and the comparator group for any of the outcomes because only one study assessed each comparison and in each case the certainty of the evidence was very low: intranasal corticosteroids versus saline irrigation; intranasal corticosteroids versus intranasal antihistamine; intranasal corticosteroids versus capsaicin; intranasal corticosteroids versus cromoglycate sodium; intranasal corticosteroids versus ipratropium bromide; intranasal corticosteroids versus intranasal corticosteroids combined with intranasal antihistamines; intranasal corticosteroids versus intranasal corticosteroids combined with saline irrigation; and intranasal corticosteroids with intranasal isotonic nasal spray versus isotonic nasal spray alone.

Three studies compared an intranasal corticosteroid with an intranasal corticosteroid combined with an intranasal antihistamine. Two studies reported a significant difference in favour of intranasal corticosteroids combined with an intranasal antihistamine versus intranasal corticosteroids alone ([Guo 2015](#); [Song 2018](#)). The difference in favour of the combined treatment strategy in these two studies was significant. The third study reported no statistically significant differences between the two treatments ([Singh 2017](#)).

Overall completeness and applicability of evidence

The types and dosages of intranasal corticosteroids used in the studies were in keeping with manufacturers' recommendations and are applicable to the population being studied. The phenotype/endotype population of patients with non-allergic rhinitis studied most likely varied among studies. As discussed in the [Background](#), one would expect the inflammatory non-allergic rhinitis endotypes (local allergic rhinitis/non-allergic rhinitis with eosinophilia syndrome (NARES)) to benefit more from intranasal corticosteroids than the neurogenic or idiopathic endotypes.

Quality of life, which is one of the most important outcomes for patients, was only included in three studies as an outcome measure ([Boechat 2019](#); [Lin 2017](#); [Song 2018](#)). There is too little information, therefore, to establish whether intranasal steroids have an impact on patients' quality of life.

Quality of the evidence

The certainty of the evidence (GRADE assessment) for our primary outcome, disease severity as measured by patient-reported

symptom score (total nasal symptom score) was in general low because most studies had small participant numbers resulting in high imprecision and high risk of publication bias. One of the only two studies with a large number of participants was [Jacobs 2009](#). Unfortunately this study presented unlikely standard deviation values that were most likely to be standard error of the mean values.

It is likely that the variety of different intranasal corticosteroid treatment strategies (type of intranasal corticosteroids, dosage, method of delivery), the differences in included non-allergic rhinitis pheno- and endotypes and the differences in the ways of measuring disease severity scores that were used contributed to the heterogeneity in the study results. There was great variety in the methods used to measure symptom severity scores and many scales were not validated. Not all studies defined non-allergic rhinitis endotypes, for example presence or absence of inflammatory cells such as eosinophils (NARES), which complicated subgroup analyses based on pheno- and endotypes. A higher proportion of inflammatory cells (eosinophils) might improve the chances of treatment effectiveness.

This low certainty of evidence is in contrast to the epistaxis adverse event outcome, where we can be more certain that there is probably an increased risk in the intranasal corticosteroids group compared to placebo (moderate-certainty evidence).

For quality of life and objective measurements of airflow there was not enough information to draw conclusions (low-certainty evidence).

There was moderate-certainty evidence (large number of patients, low heterogeneity) that intranasal corticosteroids probably result in little or no difference in the risk of other adverse events compared to placebo.

Potential biases in the review process

The primary outcome total nasal symptom score consisted of different nasal symptoms in different studies, measured on different measurement scales. When only individual nasal symptom scores were reported but no total nasal symptom score, we calculated a total nasal symptom scores for rhinorrhoea (secretion), nasal obstruction (blockage) and sneezing: the most common symptoms used to calculate a total nasal symptom score in the other included studies ([Table 1](#)). We decided not to include itching, as a previous study by our research group has shown that ocular itch plays a less dominant role in non-allergic rhinitis compared to allergic rhinitis ([Segboer 2018](#)). However, given that itching was included in the total nasal symptom score of a few other studies, this may have resulted in a potential bias.

In some cases, the studies did not report enough information for us to analyse the results further. Therefore for some studies we manually measured pixels from graphs to calculate mean values and imputed standard deviations based on the P values reported.

Some studies did include both allergic and non-allergic rhinitis participants but did not provide (enough) separate data for non-allergic rhinitis participants to calculate a mean and standard deviation (SD).

In the meta-analysis we included only studies with an intranasal corticosteroid dosage range of 200 µg to 400 µg. The reason for this was to prevent double counting of the same patients or controls

(see [Differences between protocol and review](#)). This leads to a potential bias in the review as the meta-analysis is limited to certain dosages. However, only one study was excluded from the meta-analysis because of this dosage limitation ([Varricchio 2011](#)).

Among studies the daily dosage of intranasal corticosteroids varied from 50 µg to 2000 µg. Most of the studies that compared different dosages of intranasal corticosteroids used a cross-over study design with the exception of [Blom 1997](#) and [Webb 2002](#), which used a parallel-group study design. In the cross-over studies the same participants were treated with different dosages of intranasal corticosteroids, with a short (one-week) or no washout, complicating a clear comparison between these dosage subgroups ([Balle 1982](#); [Malm 1976](#); [Malm 1981](#)). Only [Balle 1982](#) showed a dosage effect for two nasal symptom score outcomes. [Malm 1976](#) and [Malm 1981](#) showed no significant difference between the dosage subgroups. The two parallel-group studies both concluded that there were no statistically significant differences between the different intranasal corticosteroid dosage subgroups ([Blom 1997](#); [Webb 2002](#)). In the parallel-group studies the different dosage subgroups contained different participants but were compared with the same control group. To prevent counting the same patients or controls more than once, we decided to include one intranasal corticosteroid dosage in the meta-analysis. The most common intranasal corticosteroids dosage was 200 µg. A test for subgroup differences showed no significant difference (no 'dosage effect') between 200 µg and 400 µg of intranasal corticosteroids. We therefore included studies in the meta-analysis with an intranasal corticosteroid dosage range of 200 µg to 400 µg.

Agreements and disagreements with other studies or reviews

There are no previous published Cochrane Reviews on intranasal corticosteroids in non-allergic rhinitis. There are, however, some position papers on non-allergic rhinitis, such as [Hellings 2017](#). This paper states that the inflammatory group of non-allergic rhinitis patients (occupational and drug-induced rhinitis) may benefit from anti-inflammatory treatment such as nasal/oral corticosteroids. However, they conclude that most randomised controlled trials evaluating local corticosteroids in non-allergic rhinitis patients have shown a lack of efficacy. The PRACTALL report suggests that intranasal corticosteroids could be effective in two phenotypes of non-allergic rhinitis, i.e. NARES and possibly rhinitis medicamentosa, but it does not mention effectiveness for other pheno- or endotypes of non-allergic rhinitis ([Papadopoulos 2015](#)).

AUTHORS' CONCLUSIONS

Implications for practice

For people with non-allergic rhinitis and clinicians

Overall, the certainty of the evidence for most outcomes in this review was low or very low. It is unclear whether intranasal corticosteroids reduce patient-reported disease severity in non-allergic rhinitis patients compared with placebo when measured at up to three months. However, intranasal corticosteroids probably have a higher risk of the adverse effect epistaxis. There is a lack of evidence comparing intranasal corticosteroids with other pharmacological treatments. It is unclear which is the best intranasal corticosteroid to use with respect to type, concentration, vehicle and how often to use it.

For those funding health care

When measured at up to three months, it is unclear whether intranasal corticosteroids reduce patient-reported disease severity in non-allergic rhinitis patients compared with placebo. However, they probably have a higher risk of adverse effects such as epistaxis. Further research is needed: this could include large randomised controlled trials comparing the effects of intranasal corticosteroids in different pheno- and endotypes of non-allergic rhinitis and comparing different types, concentrations, vehicles or frequencies of administration.

Implications for research

Evidence

As of July 2019, we have identified 34 studies that investigated the use of intranasal corticosteroids in non-allergic rhinitis. The studies were generally small, included different pheno- and endotypes of non-allergic rhinitis, and used different outcome measurements for patient-reported disease severity at up to four weeks. The evidence identified indicates that there may be benefits in terms of patient-reported disease severity when compared with placebo but the range of unvalidated instruments used, along with heterogeneity in the study characteristics, made it difficult to draw definite conclusions.

The reported evidence for adverse effects was of moderate certainty, i.e. there seems to be a small but significant increased risk of epistaxis with intranasal corticosteroid treatment.

More research on the use of intranasal corticosteroids in non-allergic rhinitis in the form of large randomised controlled trials is important. The following aspects should be considered when designing trials:

Population

- The different pheno- and endotypes of non-allergic rhinitis should be recognised and trials should use stratified randomisation within these subgroups or focus on one or other of the phenotypes. Care should be taken to adequately identify the inflammatory endotypes (local allergic rhinitis and non-allergic rhinitis with eosinophilia syndrome (NARES)).
- Trials should be adequately powered and imbalances in prognostic factors (for example, inflammatory or non-inflammatory endotypes) must be accounted for in the statistical analysis.
- Study participants should be diagnosed with non-allergic rhinitis using appropriate diagnostic methods including clinical symptoms characteristic of (different pheno- and endotypes of) non-allergic rhinitis with negative allergen sensitisation skin

prick test (SPT) and/or blood testing for allergen-specific IgE in serum (such as ImmunoCAP or radioallergosorbent test (RAST)) and proper rhinoscopy/nasal endoscopy.

Intervention and comparison

- A trial of intranasal corticosteroids compared with placebo could be considered in patients with non-allergic rhinitis in primary care.
- Investigators should consider the type, concentration, vehicle and frequency of administration of intranasal corticosteroids used.
- Investigators should consider comparing intranasal corticosteroids to other types of treatment such as saline, intranasal antihistamines, capsaicin and ipratropium bromide.

Outcomes

- Studies should focus on outcomes that are important to patients with non-allergic rhinitis (symptom scores, quality of life) and use validated instruments to measure these, in particular using standard, validated, patient-reported disease severity scores and disease-specific health-related quality of life scores (e.g. the (mini) Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ)).
- The duration of the trial needs to be carefully considered. The current evidence only includes trials that had up to a three-month treatment duration. A duration of follow-up of 12 months is more likely to be meaningful given the chronicity of the condition.
- Trials and other high-quality studies should use consistent outcomes and adhere to reporting guidelines, so that results can be compared across future trials. The development of a standardised set of outcomes, or core outcome set, for non-allergic rhinitis, agreed by researchers, clinicians and patients, would facilitate this process.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Arikan 2006

Methods	Double-blind, parallel-group, randomised, placebo-controlled trial with 3 months duration of treatment
Participants	Setting: Otorhinolaryngology - Head and Neck Surgery and Chest Disease Departments, Faculty of Medicine, Kirikkale University, Turkey Sample size: Number randomised: 35 patients (20 in intervention, 15 in control) Number completed: 35 patients Participant (baseline) characteristics: Age: not reported Gender: not reported * No significant age or sex differences Symptom duration: 1 to 8 years Severity: N/A

Arikan 2006 (Continued)

Inclusion criteria: vasomotor rhinitis patients with bilateral inferior turbinate hypertrophy suffering from chronic nasal obstruction, whose allergic skin prick test and nasal cytologic examination for eosinophils were negative

Exclusion criteria: previous sinonasal surgery, acute rhinosinusitis, nasal polyps, clinically significant structural abnormalities, a history of hypersensitivity to corticosteroids or food allergy, a need for regular use of inhaled or systemic glucocorticosteroids for asthma and any systemic renal, endocrine, cardiovascular, gastrointestinal or hematological diseases or neuropsychiatric disorders, pregnant and lactating women; allergic rhinitis (presence of three out of four of the following symptoms: nasal obstruction, clear rhinorrhoea, repeated sneezing and itching of the nose for 1 year; and allergic status as confirmed by radioallergosorbent tests and a skin prick test using a range of common allergens)

Interventions	Intervention group: fluticasone propionate (n = 20) - Dose: 50 µg, 1 puff each nostril (daily dose of 200 µg) - Frequency: twice daily (morning and evening) - Duration: 3 months - Vehicle: pressurised aerosol spray Comparator group: placebo (vehicle) (n = 15) Use of additional interventions: none
Outcomes	1. Nasal obstruction - VAS (0 to 10; 0 is better) - Measured prior to trial and after 1, 2 and 3 months of double-blind treatment - Reported as before and after treatment - No numerical data provided 2. Adverse effects
Funding sources	None
Declarations of interest	None declared
Notes	Summary data not reported to allow inclusion in meta-analysis: - Outcomes reported as median, min, max and P value, so cannot derive mean and SD to include in meta-analysis - Study reports significantly greater relief of nasal obstruction with fluticasone propionate versus placebo, however summary data were not provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random component in the sequence generation process: "patients with vasomotor rhinitis were randomly assigned to receive a 3-month course of either an FP aqueous nasal spray or a matching intranasal placebo spray". The random sequence generation is not further explained.
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study: "Clinical evaluation was performed prior to the trial and after 1, 2 and 3 months of double-blind treatment."

Arikan 2006 (Continued)

"Fifteen patients in the control group were treated with placebo FP, which was administered in the same fashion as the active treatment."

Blinding is not further described in detail.

Both treatments consisted of nasal spray making adequate blinding possible. The outcomes consisted of a symptom-related questionnaire (outcome 1) completed by patients. The CT assessment of turbinate size (outcome 2) was done by a blinded radiologist. The symptom scores could have been influenced by inadequate blinding (blinding not further described) of the patients. The CT assessment is unlikely to have high risk of bias.

Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The radiologist was blinded regarding the study medication."
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants that were randomised were reported in the 'Results' section
Selective reporting (reporting bias)	Low risk	All outcomes that were pre-defined in 'Materials and methods' were reported in the 'Results' section
Other bias	Unclear risk	Data not reported in means and SDs, but rather median, mean, max and P values

Balle 1982

Methods	Double-blind, cross-over, randomised, placebo-controlled trial of 5 weeks total: unclear run-in, 2 weeks treatment, 1 week washout, 2 weeks treatment
Participants	Setting: Departments of Otorhinolaryngology and Lung Medicine, Aalborg hospital in Aalborg, Denmark Sample size: • Number randomised: 36 perennial rhinitis, 15 non-allergic rhinitis patients • Number completed: 36 perennial rhinitis, 15 non-allergic rhinitis patients Participant (baseline) characteristics: • Age: adults (specific age not described) • Gender: not described • Symptom duration: not described • Severity: not described Inclusion criteria: patients with perennial rhinitis, with at least 2 of the 3 symptoms: nasal obstruction, rhinorrhoea, sneezing. Non-allergic rhinitis group was defined by negative cutaneous allergy or RAST testing. Exclusion criteria: diabetes, pregnancy, asthma, bronchitis
Interventions	Intervention group: budesonide 200 µg daily (n = 15) • Dose: cross-over trial with 2 dosages of budesonide (200 µg and 400 µg daily) • Frequency: unclear • Duration: 2 weeks • Vehicle: not described

Balle 1982 (Continued)

Comparator group: placebo (n = 15)

Use of additional interventions: none

Outcomes	Total nasal symptom score (mean score of obstruction, rhinorrhoea and sneezing) - Scale unclear, low indicates fewer symptoms - Presented as mean and SEM Individual symptom scores - Measured, but not reported for non-allergic rhinitis subgroup only
Funding sources	The role of the pharmaceutical company, AB Draco, besides providing the medication for the study, is not clarified
Declarations of interest	None declared
Notes	Cross-over trial with 2 dosages of budesonide (200 µg and 400 µg) versus placebo. Dosage of 400 µg daily included in the meta-analysis. Single author reports this RCT. Non-allergic rhinitis data (15 patients with non-allergic rhinitis) available only for total nasal symptom score. Unclear scale.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Patients were randomly assigned: 'Material and methods': "They were randomly assigned to treatment with placebo, budesonide 200 µg or budesonide 400 µg." The random sequence generation is not further explained.
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	'Abstract': "double-blind cross-over study" and in 'Materials and methods': "36 consecutive patients ... completed a double-blind cross-over trial." Both treatments consisted of nasal spray making adequate blinding possible. Outcomes were patient symptom scores by the patient and rhinoscopy by the investigator; these could have been influenced by inadequate blinding.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	All 36 patients included as described in 'Materials and methods' are reported in the 'Results' section
Selective reporting (reporting bias)	Unclear risk	Individual symptom scores not described for non-allergic rhinitis subgroup separately
Other bias	Unclear risk	Single author reports a RCT

Behncke 2006

Methods	Open-label, parallel-group randomised controlled trial with a 6-week study period
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Behncke 2006 (Continued)

Participants	Setting: Otorhinolaryngology, Cleveland Clinic Florida, Weston, FL Sample size: • Number randomised: 15 non-allergic rhinitis patients (negative SPT), 3 allergic rhinitis • Number completed: 15 non-allergic rhinitis patients Participant (baseline) characteristics: • Age: unclear • Gender: unclear • Symptom duration: 6-week study period • Severity: moderate-to-severe rhinitis Inclusion criteria: 18 patients 65 years and older with a history of moderate-to-severe rhinitis Exclusion criteria: unclear
Interventions	Intervention group: intranasal corticosteroids: fluticasone 2 sprays per nostril daily (200 µg) (n = unclear) Comparator group: intranasal antihistamine: azelastine: azelastine nasal spray 2 sprays per nostril twice daily (1.1 mg) (n = unclear) Use of additional interventions: none
Outcomes	The primary outcome variable was quality of life as assessed by the Rhinitis Quality of Life Questionnaire (RQLQ). Patients completed the RQLQ at baseline and at week 3 and week 6. Patients also recorded symptoms and side effects each day in a diary. There is a stated significant improvement of symptom score from baseline, however no definition/scale/range or numerical data for this symptom score.
Funding sources	None
Declarations of interest	None declared
Notes	Study in geriatric patients No numerical data for non-allergic rhinitis subgroup Conclusion: • No difference in effectiveness between intranasal corticosteroids and intranasal antihistamine. • Azelastine nasal spray and fluticasone nasal spray improved RQLQ scores and rhinitis symptom scores in geriatric patients with either allergic or non-allergic rhinitis.
Risk of bias	
Bias	Authors' judgement Support for judgement
Random sequence generation (selection bias)	Unclear risk Randomised: "Eligible patients were randomized to treatment with either azelastine nasal spray 2 sprays per nostril bid (1.1 mg) or fluticasone 2 sprays per nostril qd (200 µg) for a 6-week study period". The random sequence generation is not further explained.
Allocation concealment (selection bias)	Unclear risk No information

Behncke 2006 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information
Incomplete outcome data (attrition bias) All outcomes	High risk	No numerical data on allergic or non-allergic rhinitis subgroup
Selective reporting (reporting bias)	High risk	No numerical data on allergic or non-allergic rhinitis subgroup
Other bias	Unclear risk	No information

Blom 1997

Methods	Double-blind, multi-centre, parallel-group, randomised, placebo-controlled trial of 6 weeks total: 2 weeks run-in period, 8 weeks treatment
Participants	Setting: outpatient Ear, Nose, and Throat Departments of the Leyenburg Hospital in the Hague and the Dijkzigt University Hospital in Rotterdam, the Netherlands Sample size: • Number randomised: 65 • Number completed: 65 Participant (baseline) characteristics: • Age: mean age 34 years (range 17 to 62 years) • Gender: 32 male, 33 female • Symptom duration: over 1 year • Severity: not described Inclusion criteria: patients with NANIPER, with a history of nasal complaints such as nasal obstruction, sneezing, and rhinorrhoea for a period of over 1 year; negative skin prick testing and Phadiatop. Periods of nasal discharge, sneezing and congestion for an average of at least 1 hour per day for at least 5 days during a period of 14 days Exclusion criteria: allergic rhinitis, nasal or paranasal sinus infection, anatomic disorders affecting nasal function (e.g. septal deviation, septal perforation, synechia or bullous medial concha), pregnancy or lactation, systemic disorders, and/or the use of medication affecting nasal function; nasal polyps; use of systemic or inhaled corticosteroids, inhaled sodium cromoglycate or nedocromil sodium or astemizole within the previous; inability of the patient to stop taking medication affecting nasal function; a serious and/or unstable disease; nasal surgery within the previous 6 weeks; abnormal laboratory results or abnormal findings at physical examination
Interventions	Parallel-group study; 4 different treatment regimens: a. Fluticasone propionate 200 µg once daily and placebo once daily for 8 weeks b. Fluticasone propionate 200 µg once daily and placebo once daily for 4 weeks after which patients will be treated for 4 weeks longer with FP 200 µg twice daily and placebo twice daily

Blom 1997 (Continued)

c. Fluticasone propionate 200 µg twice daily and placebo twice daily for 8 weeks

d. Placebo twice daily for 8 weeks

Included in meta-analysis: fluticasone propionate (200 µg) twice daily for 8 weeks (n = 15)

- Dose: a total daily dose of 400 µg for 8 weeks
- Frequency: twice daily
- Duration: 8 weeks
- Vehicle: aqueous nasal spray

Comparator group: placebo twice daily for 8 weeks (n = 16)

- Frequency: twice daily
- Duration: 8 weeks

Use of additional interventions: none

Outcomes	Individual symptoms: • Blockage • Sneezing • Rhinorrhoea • Measured by daily record chart used to measure symptoms. Investigators scored it on a scale (see below). Presented as increase in percentage of symptom-free days. • Only mean data provided, but not SD Individual symptom scores • Coughing • Mucus production • Eye irritation • Likely measured the same way as other individual symptoms • No data reported Investigator scored individual symptoms • Nasal blockage • Sneezing • Rhinorrhoea • Post-nasal drip • Measured on a scale of 0 to 3 (3 means worse) • No data reported Total nasal score (sum score of blockage, sneezing and rhinorrhoea) • Likely measured as sum score of 3 symptoms, and presented as mean sum score for 1 week • A more reliable VAS measure use in this meta-analysis instead Total symptom scores - intensity of nasal symptoms • Measured on a VAS scale (0 to 10) • Time points: 2 weeks pre-treatment, 4 weeks after first batch of treatment, 8 weeks after treatment
Funding sources	None
Declarations of interest	None declared

Blom 1997 (Continued)

Notes

There are 2 measures of total nasal symptoms in this study that provide numerical data. One is the mean sum score of blockage, sneezing and rhinorrhoea. The other one is intensity of nasal symptoms on a VAS. The latter is a more established measurement, so we included this one in the meta-analysis.

Total symptom scores are measured at 4 weeks and at 8 weeks after treatment. Symptom score measurement after 8 weeks of treatment is included in the meta-analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised study: eligible patients were randomised into 1 of 4 different treatment regimens: placebo administered twice daily for 8 weeks, FPANS (200 µg) once daily and placebo once daily for 8 weeks, FPANS (200 µg) once daily and placebo once daily for 4 weeks followed by FPANS (200 µg) twice daily for 4 weeks, and FPANS (200 µg) twice daily for 8 weeks. The random sequence generation is not further explained.
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"A single-investigator, multicenter, double-blind, placebo controlled study was done." No further details regarding blinding. Both treatments consisted of nasal spray making adequate blinding possible. Outcomes: patient symptom scores by the patient and biopsy/cytology by the investigator (single-investigator); these outcomes could be influenced by inadequate blinding.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients included as described in 'Materials and methods' are reported in the 'Results' section
Selective reporting (reporting bias)	High risk	Outcomes not reported numerically or in figures: coughing, mucus production, eye irritation, terfenadine tablets used, rhinoscopy
Other bias	Low risk	Not described

Boechat 2019

Methods	A randomised, open-label, active comparator trial, with 2 weeks treatment
Participants	Setting: outpatient allergy clinic at hospital, Universitario Antonio Pedro/Universidade Federal Fluminense in the Metropolitan Region of Rio de Janeiro, Brazil Sample size: Number randomised: 40 (20 to each treatment group, per treatment group 14 non-allergic rhinitis patients, 28 non-allergic rhinitis patients in total) Number completed: 40 (28 non-allergic rhinitis patients in total) Participant (baseline) characteristics:

Boechat 2019 (Continued)

- **Age:** described for allergic and non-allergic rhinitis subgroups together: varies between 60 and 87 years old (mean 71 years)
- **Gender:** described for allergic and non-allergic rhinitis subgroups together: 31 (75%) female participants
- **Symptom duration:** not described
- **Severity:** not explicitly described, however at least 2 chronic symptoms of rhinitis, congestion, rhinorrhoea, itching of the nose or sneezing. Pre-treatment patients had combined nasal symptom scores of 5.0 to 5.8 on a 0 to 10 scale.

Inclusion criteria: at least 2 chronic symptoms of rhinitis, congestion, rhinorrhoea, itching of the nose or sneezing

Exclusion criteria: primary or secondary immunodeficiency, mechanical obstruction of upper airways and respiratory infection in the last 2 weeks

Interventions

Intervention group: intranasal steroid (mometasone furoate) + saline (n = 14)

- Dose: 200 µg
- Frequency: once a day
- Duration: 2 weeks
- Vehicle: nasal spray

Comparator group: isotonic nasal saline spray (n = 14), 4 times a day

Use of additional interventions: no

Outcomes

Individual symptoms:

- **Blocked nose**
- **Itchy nose**
- **Runny nose**
- **Sneezing**
- Measured on a scale of 0 to 3 daily
- Mean change in symptom score from end of treatment to baseline reported
- Data available for non-allergic rhinitis subgroup

Combined symptom score

- Combined nasal symptoms intensity score rated by a 10-point visual analogue scale (VAS) at 2 weeks, with 0 indicating no symptoms and 10 the worst possible discomfort
- Measured pre-treatment and 2 weeks after treatment
- Data available for non-allergic rhinitis subgroup

Peak nasal inspiratory flow

- 3 satisfactory maximal inspirations were obtained and the highest of the 3 results was taken as the PNIF
- Measured pre-treatment and 2 weeks after treatment
- Measured in L/min

Quality of life

- SNOT-22 (sinonasal outcome test) questionnaire of quality of life. SNOT-22 is the only questionnaire of quality of life in nasal chronic problem that is validated in Brazilian Portuguese. This consists of 22 questions scored between 0 and 5, with higher scores meaning greater problems. Data available for non-allergic rhinitis subgroup.
- Measured pre-treatment and 2 weeks after treatment

Adverse events

Boechat 2019 (Continued)

- No adverse events (evaluated type of adverse events not described)

Funding sources	Unclear/none reported
Declarations of interest	None declared
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The randomisation scheme was generated using a computer-generated code
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding of participants and personnel is not described. However, one patient group received 2 different nasal sprays while the other patient group received only one type of nasal spray, making blinding complicated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of the person who evaluated the objective outcome (PNIF) is not described, nor the blinding of the patients (subjective outcomes VAS and SNOT-22). However, one patient group received two different nasal sprays while the other patient group received only one type of nasal spray, making blinding complicated at least for the participants
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised patients completed the study
Selective reporting (reporting bias)	Low risk	All described outcomes of all included patients can be found in 'Results'
Other bias	Low risk	The authors declare no funding

Day 1990

Methods	Double-blind, parallel-group, randomised, placebo-controlled trial of 6 weeks total: 2 weeks baseline, 4 weeks treatment
Participants	Setting: Kingston General Hospital, Ontario, Canada Sample size: • Number randomised: 107 patients enrolled including children and adults, of which 100 received treatment, and 99 were reported; out of these, there were 23 patients with non-allergic rhinitis (10 treated with budesonide and 13 with placebo) • Number completed: 99 Participant (baseline) characteristics: • Age: described for allergic and non-allergic rhinitis subgroups together: range 22 to 65 years (mean 41.9 years in budesonide, and 45.9 years in placebo groups) • Gender: not described separately for allergic and non-allergic rhinitis subgroups

Day 1990 (Continued)

- **Symptom duration:** at least 2 years
- **Severity:** not described
- Conclusion cannot be reached specifically about the non-allergic rhinitis subgroup

Inclusion criteria: perennial rhinitis over a period of at least 2 years, and currently not receiving therapy for rhinitis. Skin prick testing done either within the last 6 months, or at baseline. In this review, only patients with non-allergic rhinitis are included.

Exclusion criteria: pregnancy, tuberculosis, respiratory infection, additional nasal disease, asthma requiring treatment with corticosteroids. In addition, all other rhinitis medications were discontinued besides terfenadine. Immunotherapy was allowed as long as antigens relative to that time of year were not involved.

Interventions	Intervention group: budesonide (n = 10) • Dose: a total daily dosage of 400 µg • Frequency: 2 puffs per nostril each morning and each evening • Duration: 4 weeks • Vehicle: pressured canisters mounted in a nasal applicator Comparator group: placebo (n = 13) Use of additional interventions: terfenadine as rescue medication if symptoms became intolerable
Outcomes	Individual symptoms: • Blocked nose • Itchy nose • Runny nose • Sneezing • Measured on a scale of 0 to 3 daily • Mean change in symptom score from end of treatment to baseline reported • Data available for non-allergic rhinitis subgroup Combined symptom score • Measured and reported as above • Data available for non-allergic rhinitis subgroup Global evaluation of efficacy • Measured by patient • At final clinic visit • Scale 0 (aggravated) to 4 (total control) • Data not available for non-allergic rhinitis subgroup Adverse events • Data not available for non-allergic rhinitis subgroup
Funding sources	None declared
Declarations of interest	None declared
Notes	—
Risk of bias	
Bias	Authors' judgement Support for judgement

Day 1990 (Continued)

Random sequence generation (selection bias)	Low risk	Randomisation was stratified according to age (6 to 11 years, 12 to 18 years, above 18 years) and in the oldest group also according to atopy. Authors report balanced randomisation.
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind, randomised, parallel-group design study. However, blinding is not described in further detail. Both treatments consisted of nasal spray making adequate blinding possible. Subjective nasal scores could have been influenced by inadequate blinding of patients.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blind, randomised, parallel-group design study. However, blinding is not described in further detail.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Out of 107 randomised patients, 7 discontinued the study before use of any medication and 1 in the placebo group failed to follow-up. The authors do not describe what they did with the data of the patient who failed to return for follow-up. Given it was 1 patient only out of a remaining 100, it is reasonable to consider the effect to be small. Hence, we considered this low risk for incomplete outcome data.
Selective reporting (reporting bias)	Low risk	All described outcomes can be found in the results, though not all outcomes could be used for this review as it focuses on non-allergic rhinitis
Other bias	Unclear risk	The role of the pharmaceutical company AB Draco is not clarified

Ellegård 2001

Methods	Double-blind, parallel-group, randomised, placebo-controlled trial with 1-week run-in, 8 weeks treatment, 16 weeks follow-up, total 24 weeks
Participants	Setting: 28 maternity centres in the southern part of the County of Bohuslän (Bohuslandstinget) and in the city of Göteborg, Sweden Sample size: • Number randomised: 60 patients randomised; 26 (of 31) reported in fluticasone group and 27 (of 29) reported in placebo group • Number completed: 53 Participant (baseline) characteristics: • Age: 18 to 39 years • Gender: all females (given pregnancy rhinitis) • Symptom duration: at least 10 days • Severity: at least moderate, given requirement to demand treatment • Overall no difference with respect to age, number of children, weeks of nasal congestion, gestational week and number of cigarette smokers Inclusion criteria: Pregnancy rhinitis: pregnant women 18 to 39 years of age with a treatment demanding nasal congestion for at least 10 days, without other signs of respiratory tract infection.

Ellegård 2001 (Continued)

Exclusion criteria: 1) corticosteroid treatment during the present pregnancy, or a contra-indication for corticosteroids; 2) sodium cromoglycate 1 month before entry; 3) medication with known influence on nasal mucosa, apart from local decongestants, that were allowed for continuous use up to 6 weeks before entry; 4) serious or unstable concurrent disease; 5) anatomical abnormalities affecting nasal breathing, nasal surgery during the present pregnancy or chronic nasal symptoms before pregnancy; 6) purulent respiratory infection within 1 month before entry; and 7) more than 1 fetus.

Interventions	Intervention group: fluticasone propionate (n = 31 randomised, 26 reported) - Dose: 50 µg per actuation - Frequency: 2 actuations to each nostril in the morning (200 µg daily dosage) - Duration: 8 weeks treatment - Vehicle: nasal spray Comparator group: placebo (vehicle of the active spray) (n = 29 randomised, 27 reported) Use of additional interventions: none
Outcomes	Nasal congestion - Measured on a scale of 0 to 4; 0 = better - Reported for 8 weeks of treatment and 16 weeks of post-treatment follow-up - In our analysis, we used data at the end of 8 weeks of treatment Blockage index (BI) - Measured as $BI = (PEF - nPEF) / PEF$ - Reported for 8 weeks of treatment and 16 weeks of post-treatment follow-up - In our analysis, we used data at the end of 8 weeks of treatment Acoustic rhinometry - Reported as 3 separate parameters: volume (cm³), MCA (cm²), dip 2 (cm²), however SDs could not be recalculated
Funding sources	Göteborg Medical Society and GlaxoWellcome
Declarations of interest	None declared
Notes	This is the only study of intranasal corticosteroids in pregnancy rhinitis. Even though it was industry sponsored, it found no effect of the studied medication. Outcomes not included here due to lack of summary data or clinical: acoustic rhinometry (full summary data not reported), anterior rhinoscopic assessment of nasal secretions.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised study: "The investigation was designed as a single-centre, placebo controlled, randomized, double-blind study with parallel groups." Random sequence generation is not further described.
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind study: "may be due to the fact that we made a blind, placebo-controlled study". "The investigation was designed as a single-centre, placebo controlled, randomized, double-blind study with parallel groups."

Ellegård 2001 (Continued)

However, blinding is not described in further detail.

Both treatments consisted of nasal spray making adequate blinding possible.

Subjective nasal scores could have been influenced by inadequate blinding of patients. For a small amount also reporting of nasal secretions and nasal crusts could have been influenced by inadequate blinding of investigators. Assessment of nPEF and PEF are less likely to be influenced by inadequate blinding.

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described, see above. Blinding of outcome assessment: patients are said to be blinded, but this is not further described. Blinding of the investigator is not further described, it is said to be "double blinded".
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not all results listed in 'Methods' are fully reported, however most clinically important results are presented
Selective reporting (reporting bias)	High risk	5 patients withdrawn from treatment group, 2 from placebo group
Other bias	Low risk	Even though this was an industry-sponsored trial, it did not show a beneficial effect of the studied medication.

Guo 2015

Methods	Parallel-group randomised controlled trial with 6 weeks duration of treatment
Participants	Setting: Eye Otolaryngology Department, Eye Otolaryngology Hospital Affiliated to Fudan University, China Sample size: Number randomised: 162 Number completed: 154 Participant (baseline) characteristics: Age: AZENS + FPNS (44.91 ± 6.77 years); FPNS only (42.43 ± 8.24 years) Gender: N/A, no difference stated in paper Symptom duration: AZENS + FPNS (2.70 ± 1.42 years); FPNS only (3.01 ± 1.41 years) Severity: AZENS + FPNS (nasal symptom score: 2.48 ± 0.40); FPNS only (nasal symptom score: 2.50 ± 0.37) - Overall no difference for age, symptom duration and nasal symptom score Inclusion criteria: - Patients between 30 to 60 years of age - Symptoms present for at least 9 months per year, with a history of at least 1 year - Primary symptom of nasal congestion; may be accompanied by sticky or clear rhinorrhoea or sneezing - The symptom of nasal mucosal hyperaemia and congestion is mainly caused by inferior turbinate enlargement - The nasal symptom score ≥ 2, and the patients have strong willingness to improve the nasal symptom and have confidence in drug treatment Exclusion criteria:

Guo 2015 (Continued)

- Nasal symptoms caused by allergy, typical symptoms of allergic rhinitis, in patients once suffered from asthma or eczema, and allergen testing is positive
- Another cause of rhinitis (e.g. infectious or rhinitis medicamentosa)
- Anatomic abnormalities (e.g. deviated nasal septum or spur)
- Acute or chronic sinusitis, nasal polyps or the other space-occupying nasal lesions
- Use of nasal corticosteroids, decongestants, antihistamines or cold medicine within one month
- History of nasal surgery

Interventions

Intervention groups: fluticasone propionate nasal spray (FPNS): same as in comparator group below; dosage unclear (n = 82 randomised, 78 treated, 5 lost to follow-up)

- Dose: no information provided
- Frequency: FPNS - 2 sprays each nostril, once a day
- Duration: 6 weeks
- Vehicle: nasal spray

Comparator group: azelastine nasal spray (AZENS) combined with FPNS (n = 79 randomised, 76 received treatment as allocated, 3 lost to follow-up)

- Dose: no information provided
- Frequency: AZENS - 2 sprays in each nostril, twice a day; FPNS - 2 sprays each nostril, once a day
- Duration: 6 weeks
- Vehicle: nasal spray

Use of additional interventions: none

Outcomes
1. Total nasal symptom scores (no breakdown)

- Measured pre-intervention, at 2 weeks and at 6 weeks (in the meta-analysis reported at 6 weeks)

2. Satisfaction score

- Binary outcome
- Comprising a composite of ease of medication use, adverse outcomes, cost, treatment efficacy

Funding sources

None

Declarations of interest

None declared

Notes

- Funding source not provided
- Total nasal symptom scores are measured at 2 weeks and at 6 weeks. Results at 6 weeks are reported in the meta-analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised controlled trial; however, there was not sufficient information on sequence generation
Allocation concealment (selection bias)	Unclear risk	There was no information about allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	As the primary outcomes of nasal symptom scores and adverse events are both self-reported outcome measures, and the article had no information on blinding, there was not sufficient information to make a judgement

Guo 2015 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	As the primary outcomes of nasal symptom scores and adverse events are both self-reported outcome measures, and the article had no information on blinding, there was not sufficient information to make a judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	8 of 161 patients lost to follow-up, likely not significant
Selective reporting (reporting bias)	High risk	No protocol provided and all the reported outcomes were not prespecified in the methods section of the article. Total nasal symptom score calculation is not specified.
Other bias	Low risk	No other sources of bias were found in this study

Hallén 1997

Methods	Double-blind, parallel-group, randomised, placebo-controlled trial with 14 days duration of treatment
Participants	Setting: outpatient department of the ENT clinic at Sodersjukhuset, Stockholm, Sweden Sample size: • Number randomised: 20 patients randomised; 10 per treatment group, 19 patients reported • Number completed: 20 (results for 1 patient were excluded because of a concurrent common cold during study period) Participant (baseline) characteristics: • Age: mean age 33 years • Gender: 12 female and 8 male • Symptom duration: 2 years of topical decongestant use • Severity: not described Inclusion criteria: patients with rhinitis medicamentosa, defined as overuse of topical decongestants for at least 2 years, using their spray 1 to 15 times a day. 5 patients with documented allergies were NOT excluded. Exclusion criteria: anatomic problems on rhinoscopy (not identified in any patient)
Interventions	Intervention group: fluticasone propionate (n = 10 randomised, 9 or 10 reported (1 patient excluded without identification of group)) • Dose: 50 µg per spray (200 µg per day total) • Frequency: 2 sprays into each nostril in the morning • Duration: 2 weeks treatment • Vehicle: aqueous nasal spray Comparator group: placebo (vehicle of the active spray) (n = 10 randomised, 9 or 10 reported (1 patient excluded without identification of group)) Use of additional interventions: none
Outcomes	1. Nasal congestion • Measured on a VAS, 0 to 100 • Reported for all days, 0 to 14 days 2. Rhinostereometry

Hallén 1997 (Continued)

- Measure of nasal mucosal swelling: changes in the position of the mucosal surface of the medial side of the head of the inferior concha are registered in the plane of focus along the mm scale

3. Acoustic rhinometry (MCA 2 area)

- Measured in cm²

4. PNIF

- Measured in L/min

Funding sources	GlaxoWellcome
Declarations of interest	None declared
Notes	• 5 patients with documented allergies were NOT excluded. • No difference between AM (Fig 4) and PM (Fig 5) data, AM data included. • 1 patient's results not reported, but it is not indicated which group they belonged to, so most likely both groups had 10 patients. • The study was financially supported by Glaxo Wellcome AB, Molndal, Sweden.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"A parallel randomized, double-blind study". Random sequence generation was not further described.
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"Double-blind study", however blinding was not further described. Both treatments consisted of nasal spray making adequate blinding possible. Outcome 1 (nasal airflow) as measured by rhinostereometry, acoustic rhinometry and the peak inspiratory flow meter, are unlikely to be influenced by inadequate blinding. Outcome 2 (symptom scoring) is more likely to be influenced by inadequate blinding.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described although it says it is a double-blind study
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The results from 1 patient were excluded because of a concurrent common cold during the study period.
Selective reporting (reporting bias)	Low risk	All outcomes described in 'Methods' are fully reported in 'Results'
Other bias	Unclear risk	The study was financially supported by Glaxo Wellcome AB, Molndal, Sweden

Havas 2002

Methods	Double-blind, parallel-group, quasi-randomised (on odds and even basis) controlled trial; 31 days total (3 days prior to treatment and 4 weeks of treatment)
Participants	Setting: Department of Otolaryngology - Head and Neck Surgery, Prince of Wales Hospital, Sydney, Australia Sample size: • Number randomised: 40 • Number completed: 40 Participant (baseline) characteristics: • Age: * Budesonide group: males 40.3 years; females 37.0 years * Capsaicin group: males 41.5 years; females 41.0 years • Gender: 20 males, 20 females • Symptom duration: perennial • Severity: not reported • No significant difference for main examined symptoms (based on figures) Inclusion criteria: patients with perennial non-allergic rhinitis (IgE < 100 and RAST negative) examined by the senior author. Nasal endoscopy used to confirm rhinitis. Exclusion criteria: any relevant antecedent history of rhinosinusitis or antecedent nasal or sinus surgery. Presence on nasoendoscopy of nasal septal deviation, nasal polyposis, rhinosinusitis and/or neoplasm. Smokers.
Interventions	Intervention group: budesonide (n = 20) • Dose: 64 µg/dose), 2 puffs of the spray in each nostril, after administration of lignocaine/phenylephrine (co-phenylcaine) before the 1st treatment • Frequency: each AM and PM • Duration: 2 weeks • Vehicle: nasal spray Comparator group: capsaicin (n = 20) • Dose: 70 µL, delivering 0.654 µg of capsaicin (capsaicin 71%, dihydrocapsaicin 20.94% and nordihydrocapsaicin 4.94%), 2 puffs into each nostril. Co-phenylcaine spray 10 minutes prior to capsaicin first treatment. • Frequency: once weekly self-administration of 2 puffs of capsaicin in each nostril weekly • Duration: 4 weeks • Vehicle: nasal spray Use of additional interventions: co-phenylcaine spray before both budesonide and capsaicin
Outcomes	Individual symptom scores (headache, post-nasal drip, rhinorrhoea, nasal blockage, sore throat, sneezing) • Assessed on a VAS (0 to 5; 0 = no symptoms), separately for each side, 3 days prior to treatment and during last 3 days of treatment Aggregate total relief • Decrease of symptom scores after treatment: sum of relief scores for all 6 symptoms Responders (improved versus worse or unchanged)
Funding sources	None

Havas 2002 (Continued)

Declarations of interest	None declared	
Notes	Calculated a total nasal symptom score from means rhinorrhoea, blockage and sneezing and calculated a pooled SD.	
	Disclosures: no financial interest with company supplying capsaicin	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Pseudo-randomisation: "they were pseudo-randomized in two groups based on odds and evens basis".
Allocation concealment (selection bias)	High risk	Sequence generation was on an odds and evens basis
Blinding of participants and personnel (performance bias) All outcomes	High risk	High risk due to pseudo-randomisation
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcomes described in 'Methods' are reported in 'Results'
Selective reporting (reporting bias)	Low risk	No selective outcome reporting identified
Other bias	Low risk	No other sources of bias identified

Hillas 1980

Methods	Double-blind, cross-over, randomised controlled trial with 4-week treatments, washout not described. Cross-over, in 4 sequences: 1) sodium cromoglycate/placebo/beclomethasone dipropionate/placebo; 2) beclomethasone dipropionate/placebo/sodium cromoglycate/placebo; 3) placebo/sodium cromoglycate/placebo/beclomethasone dipropionate; and 4) placebo/beclomethasone dipropionate/placebo/sodium cromoglycate)	
Participants	Setting: Department of Medicine, University of Auckland School of Medicine, Auckland, and Auckland Hospital Board, Auckland, New Zealand Sample size: Number randomised: 58 patients randomised, 52 patients analysed, of which 21 were non-allergic rhinitis patients Number completed: 52 Participant (baseline) characteristics: Age: 13 to 58 years (mean age 29 years) for allergic and non-allergic rhinitis groups Gender: females: 29; males: 23 for allergic and non-allergic rhinitis groups Symptom duration: 1 to 45 years (mean 11 years)	

Hillas 1980 (Continued)

- **Severity:** severe

Inclusion criteria: only patients with severe chronic perennial rhinitis, usually without asthma, were admitted to the trial. Almost all patients had been treated previously either surgically or with drugs, or both. Patients who received no relief from the sprays and were severely debilitated by their symptoms were permitted to use antihistamine tablets, but were requested to record the number taken each day. Nasal infections, including those not clinically obvious but detected by the presence of increased numbers of neutrophils in nasal smears, were treated with a short course of antibiotics before the trial.

Exclusion criteria: large polyps, mechanical obstruction, severe nasal infections, aspirin sensitivity, steroid dependence, use of continuous medication excepting oral contraceptives, pregnant women and children under the age of 12

Interventions

Intervention group: sodium cromoglycate/Comparator group: beclomethasone dipropionate

Beclomethasone dipropionate (n = 21)

- Dose: 50 µg/puff; 1 puff into each nostril
- Frequency: 4 times per day (total daily dosage of 400 µg)
- Duration: 4 weeks
- Vehicle: aerosol

Beclomethasone dipropionate placebo (n = 21)

- Dose: placebo
- Frequency: 4 times per day
- Duration: 4 weeks
- Vehicle: aerosol

Sodium cromoglycate (n = 21)

- Dose: 2%
- Frequency: 6 times per day
- Duration: 4 weeks
- Vehicle: spray

Sodium cromoglycate placebo (n = 21)

- Dose: placebo
- Frequency: 6 times per day
- Duration: 4 weeks
- Vehicle: spray

Use of additional interventions: none

Outcomes

Total nasal symptom score

- Measured as a composite score of individual symptom scores of sneezing, rhinorrhoea, nasal pruritis, blocked nose, itchy eyes, watery eyes and red eyes
- Measured on a scale of 0 to 3, where 0 = nil, 1 = mild, 2 = moderate and 3 = severe
- Reported as a mean of 4-week treatment period
- Data not available for non-allergic rhinitis group separately

Individual symptom scores

- Measured as above
- Data not available for non-allergic rhinitis group separately

Symptomatic relief (responders)

Hillas 1980 (Continued)

- Patients were asked whether the drug relieved their symptoms partially or completely

Funding sources	Medical Research Council of New Zealand, Fisons (Australia) Ltd, Essex Laboratories, Australia and Schering Corporation
Declarations of interest	None declared
Notes	Only data on responders versus no responders for non-allergic rhinitis subgroup. Washout period not described, potential spillover of treatment effect. Industry-sponsored trial by 2 companies providing 2 different drugs. The study shows no preference for one of the drugs, and therefore likely industry involvement was unbiased. Conclusion: Beclomethasone dipropionate was significantly more effective in relieving symptoms than sodium cromoglycate (76.9% and 50% of the patients improved respectively, $P < 0.001$). Both drugs were more active than placebos but while beclomethasone dipropionate was very clearly more effective ($P < 0.0005$), sodium cromoglycate was only marginally better than its placebo ($P < 0.05$). Beclomethasone dipropionate was selected by 56% of the patients as the best agent for continuing therapy.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Patients were assigned randomly to the cross-over sequence: "Patients were assigned randomly to one of the above sequences." However, random sequence generation is not further described.
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind trial, however blinding not further described. Both treatments consisted of nasal spray making adequate blinding possible. Outcomes were improvement, symptom scores and drug preference. These could have been influenced by inadequate blinding.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear, see above
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	58 allergic rhinitis and non-allergic rhinitis patients were selected for the study and 52 were reported
Selective reporting (reporting bias)	Unclear risk	Not all outcomes are reported for the non-allergic rhinitis subgroup separately
Other bias	Low risk	Industry-sponsored trial for both studied drugs, however it is unlikely that one company would have been favoured against the another.

Incaudo 1980

Methods	Double-blind, parallel-group, controlled trial with 2 weeks baseline, 6 weeks of treatment. Randomisation was not described.
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Intranasal corticosteroids for non-allergic rhinitis (Review)

Incaudo 1980 (Continued)

Participants	Setting: Allergy Clinic, Departments of Pediatrics and Internal Medicine and Clinical Investigation Center, Naval Regional Medical Center, and the Akgy Department. Kaiser-Permanente Medical Center. San Diego, and Syntex Corporation, Palo Alto Sample size: Number randomised: 56 patients; some analyses reported for 52 patients with skin prick testing results; out of these, there were a total of 22 patient with non-allergic rhinitis Number completed: 56 (of the 52 patients with skin prick test testing, all were reported in 'Results') Participant (baseline) characteristics: Age: 19 to 62 (mean age 34.7) Gender: all male Symptom duration: at least 2 years Severity: overall moderate severity: the patients chosen had symptoms severe enough to require medication on the majority of days during the 3 months prior to the study - Overall no difference with respect to age, duration of symptoms or concomitant medication use. Nasal congestion ($P = 0.029$) and a past history of complicating nasal disorders were more frequent in the flunisolide group. Conclusion cannot be reached specifically about the non-allergic rhinitis subgroup. Inclusion criteria: perennial rhinitis consisting primarily of nasal stuffiness, rhinorrhoea or sneezing for a duration of at least 2 years. Non-allergic rhinitis patients could be isolated from this study based on negative skin prick testing Exclusion criteria: nasal polyps
Interventions	Intervention group: flunisolide ($n = 11$) - Dose: 0.025% flunisolide in aqueous propylene glycol/polyethylene glycol. On average, 200 µg/day of flunisolide daily. - Frequency: 2 sprays in each nostril twice daily - Duration: 2 weeks baseline, 6 weeks treatment - Vehicle: coarse droplet spray via a pump-activated, non-Freon-propelled device Comparator group: placebo(vehicle of the active spray) ($n = 11$) Use of additional interventions: usual symptomatic medication in both groups during baseline and double-blind periods of the study
Outcomes	Individual symptoms: sneezing, stuffy nose, runny nose, nose blowing, post-nasal drip, measured on a scale of 1 to 4 - Only P values reported: no difference between flunisolide and placebo in non-allergic rhinitis subgroup - Data available for non-allergic rhinitis subgroup Overall severity of rhinitis - Recalculated from Figure 1 of the article - Scale 1 (absent) to 4 (severe) Disease control - Data reported as P values for allergic and non-allergic groups, or cumulatively for both groups. Missing summary data cannot be imputed. Adverse events - Data available for non-allergic rhinitis subgroup Significant benefit from flunisolide

Incaudo 1980 (Continued)

- Compares only those patients in the flunisolide group, therefore comparisons cannot be made with placebo

Funding sources	None
Declarations of interest	None declared
Notes	Individual symptoms: sneezing, stuffy nose, runny nose, nose blowing, post-nasal drip. For all individual symptoms, only P values are presented in Table III. All P values are negative for non-allergic rhinitis group, but actual data cannot be calculated from this table. Study of perennial rhinitis including both allergic and non-allergic rhinitis patients, but only males. Co-intervention in the form of usual symptomatic medication was allowed to be used by patients. Company involvement unclear - manufacturer? Ethics approval not cited.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	"Thereafter, the patients were issued in a double blind fashion either the active drug or the vehicle control in identical plastic bottles." "After the study procedures were completed, the code was broken."
Allocation concealment (selection bias)	High risk	Randomisation not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding is not further described. Both treatments consisted of nasal spray in identical bottles making adequate blinding possible. Outcomes were symptom scores/severity of rhinitis symptoms and immunological studies. The first outcome is likely to be influenced by inadequate blinding, the second outcome is unlikely to be influenced by inadequate blinding.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described, see above. Mainly symptom scores assessed by patients could be influenced by inadequate (unclear, not enough information) blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Of 52 patients who had skin testing, all 52 are reported
Selective reporting (reporting bias)	Low risk	All clinically relevant outcomes reported, although not all can be used for assessment of non-allergic rhinitis only.
Other bias	High risk	The role of the pharmaceutical company Syntex is not clarified. Also, only males were included in this study.

Jacobs 2009

Methods	Double-blind, parallel-group, randomised, placebo-controlled trial with 7- to 14-day screening; 4-week treatment; follow-up phone call 3 to 5 days after
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Jacobs 2009 (Continued)

Participants

Setting: 106 investigative centres in 6 countries (United States, Canada, Czech Republic, Germany, Norway and Romania)

Sample size:

- **Number randomised:** 699
- **Number completed:** 660

Participant (baseline) characteristics:

- **Age:**
 - * 12 to 18 years - 33 (5%)
 - * 18 to 65 years - 589 (84%)
 - * 65 to 75 years - 59 (8%)
 - * 75 years - 18 (3%)
- **Gender:** female 479 (69%), male 220 (31%)
- **Symptom duration:** symptomatic on the average of the last 8 recordings of rTNSS
- **Severity:** at least moderate (4.5 out of 9 on the average of the last 8 recordings of rTNSS and 2 out of 3 for average reflective congestion symptom)
- Pooled patient demographics and baseline characteristics were similar between the active and placebo groups

Inclusion criteria: vasomotor rhinitis (VMR) eligibility requirements included a confirmed 2-year clinical history of perennial VMR, negative skin prick tests and no history of responses to seasonal or perennial allergens, a positive response to histamine skin testing, a normal sinus radiograph (to rule out infectious sinusitis), and negative nasal cytology for eosinophils, defined as the absence of eosinophils in nasal smears. In addition, a diagnosis of the VMR w/t (weather/temperature) subtype was required, which required confirmation of disease fluctuation with weather conditions by selection of weather/temperature change as the predominant trigger for worsened rhinitis on the Vasomotor Rhinitis Questionnaire.

Exclusion criteria: participants with rhinitis principally caused by airborne irritant triggers (VMRir), allergic rhinitis, infectious disease or non-allergic rhinitis with eosinophilic syndrome were excluded; and participants were required to meet minimum symptom criteria and show persistence of their symptoms. Participants were excluded if they had evidence of significant concurrent disease, a clinically significant abnormal ECG, severe physical obstruction or septal perforation of the nose, moderate-to-severe asthma, rhinitis medicamentosa, upper respiratory tract infection, ocular disease (glaucoma, cataracts, or herpes simplex), nasal or oropharyngeal candidiasis, history of adrenal insufficiency or shingles, or a risk of developing chickenpox or measles during the study. Participants could not use tobacco products. Pregnant women or those planning to become pregnant were excluded.

Interventions

Intervention group: fluticasone furoate (n = 353)

- Dose: 110 µg
- Frequency: once daily
- Duration: 4 weeks
- Vehicle: nasal spray

Comparator group: placebo (vehicle of the active spray) (n = 346)

Use of additional interventions: none

Outcomes

1. Change in daily reflective total nasal symptom score (rTNSS)

- Participants rated congestion, rhinorrhoea, and post-nasal drip twice daily on diary cards using a 4-point categorical scale ranging from 0 (symptom not present) to 3 (symptom hard to tolerate; interferes with daily activities or sleeping)
- Recorded as reflective symptom ratings (severity over the last 12 hours) and instantaneous symptom ratings (severity at the moment of the assessment)
- TNSS is the sum of the 3 symptom scores

Jacobs 2009 (Continued)

- Measured over treatment period (week 1 to 4)

2. Change in morning instantaneous TNSS

- Measured as above
- We chose to not report, as severity over 12 hours would be more relevant than instantaneous symptoms

3. Change in individual symptom scores for congestion, rhinorrhoea and post-nasal drip

- Recorded as above

4. Overall response to therapy

- For the entire treatment period
- 7-point categorical scale (significantly improved, moderately improved, mildly improved, no change, mildly worse, moderately worse, significantly worse)
- We converted the first 3 orders of the scale into 'responders' and the last 4 into 'non-responders' achieving a dichotomous outcome

5. Adverse events

- Reported for headache, nasopharyngitis, epistaxis, pharyngo-laryngeal pain, diarrhoea, sinus headache, nausea, back pain, dysphonia and vomiting
- We decided to include any adverse events in the meta-analysis
- Individual results were not significantly different

Funding sources	GlaxoSmithKline
Declarations of interest	None declared
Notes	Study sponsored by GlaxoSmithKline. Weather and temperature-sensitive vasomotor rhinitis. One of the biggest and most well known (frequently cited) studies. 5% belongs to age 12 to 18 years. Outcomes - TNSS, individual symptoms, overall response and adverse events. No significant difference between allergic and non-allergic rhinitis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised study: "To evaluate the efficacy and safety of fluticasone furoate nasal spray in subjects with VMRW/t, two global, multicenter, randomized, double-blind, placebo-controlled studies were conducted". "Subjects were stratified at randomization by country to account for possible country-specific medical practice differences and effects on study outcome." Random sequence generation is not further described.
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	Unclear risk	"Double-blind study" but blinding is not further described. Both treatments consisted of nasal spray making adequate blinding possible.

Jacobs 2009 (Continued)

All outcomes		Outcomes were symptom scores and adverse events. These could have been influenced by inadequate blinding.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described, see above
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Data available for 95% of patients
Selective reporting (reporting bias)	Low risk	All outcomes described in 'Methods' are fully reported in 'Results'
Other bias	Unclear risk	Company-sponsored study, but results do not support the use of the medication. The Jacobs 2009 study reports a very unlikely standard deviation (SD) value that does not match with the presented means, n and P values. The data would make more sense if the standard deviation (SD) presented values were actually standard error of the mean (SEM), which was confirmed by a re-analysis.

Jessen 1990

Methods	Double-blind, double-dummy, cross-over, randomised controlled trial with 2 weeks treatment, 2 weeks washout, 2 weeks treatment; 3 weeks follow-up after treatment
Participants	Setting: Department of Otolaryngology, University of Lund, Sweden Sample size: • Number randomised: 31 patients randomised, 24 patients reported • Number completed: 24 Participant (baseline) characteristics: • Age: 20 to 77 years (mean age 49 years) • Gender: 14 female, 10 male • Symptom duration: 0.5 to 30 years (mean 5.4 years) • Severity: at least moderate degree Inclusion criteria: patients with the diagnosis of cholinergic non-allergic rhinitis, with excessive nasal secretion for 0.5 to 30 years, and negative skin prick test Exclusion criteria: asthma or nasal polyps; pregnancy; negative response to ipratropium testing; negative skin prick testing; upper airway infection or use of other relevant medication 2 weeks before the trial
Interventions	Intervention group: beclomethasone (n = 24) • Dose: 400 µg per day • Frequency: 2 puffs in the morning and evening to each nostril • Duration: 2 weeks treatment, 2 weeks washout, 2 weeks treatment with comparator • Vehicle: aerosol Comparator group: ipratropium (n = 24)

Jessen 1990 (Continued)

- Dose: 160 µg

Co-treatment:

- 5 out of 24 patients were treated with 0.1% xylometazoline due to high nasal airway resistance on rhinomanometry. It is unclear which group these patients belonged to.

Use of additional interventions: none

Outcomes	1. Rhinomanometry 2. Secretions • Measured by patient on a scale of 0 for no symptoms to "3 or 4 for severe symptoms" • Reported as cumulative score for 2 weeks 3. Sneezing • As above 4. Blockage • As above 5. Number of tissues used 6. Adverse events - no data
Funding sources	None
Declarations of interest	None declared
Notes	Scale somewhat ambiguous ("0 for no symptoms to "3 or 4 for severe symptoms"). Symptom data presented for the period of 2 weeks. Given scale is up to 3-4, and given numbers presented are in range of 6.1 to 19.8, we assume that these are cumulative scores for 2 weeks (sum of scores). Five of 24 patients had co-treatment with 0.1% xylometazoline. It is unclear which group these patients belonged to. Rhinomanometry data was not reported. Patients report preference for drug; unclear how can they prefer if they are blinded.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Double blind double dummy randomized cross-over design". Random sequence generation not described.
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"Double-blind study"; however, blinding not described in further detail. Both treatments consisted of nasal spray making adequate blinding possible. Outcomes were symptom scores and preference of treatment that could be influenced by inadequate blinding. Assessment of eosinophilia in nasal smears is a little bit less likely to be influenced by inadequate blinding.

Jessen 1990 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described. See above.
Incomplete outcome data (attrition bias) All outcomes	High risk	31 patients randomised, but only 24 patients included: 5 excluded due to no benefit from ipratropium and 2 found the trial regime too time-consuming. This violates the intention-to-treat protocol.
Selective reporting (reporting bias)	Unclear risk	Most clinically relevant outcomes fully reported, however reported as means for each outcome.
Other bias	High risk	The study comments on patient preference for medication and it is unclear how patients could comment unless blinding was compromised. Scale somewhat ambiguous (0 for no symptoms to "3 or 4 for severe symptoms"). Five of 24 patients had co-treatment with 0.1% xylometazoline. It is unclear which group these patients belonged to.

Kalpaklioglu 2010

Methods	Single-blind, parallel-group, randomised controlled trial with 2 weeks duration of treatment
Participants	Setting: tertiary care university hospital in Turkey Sample size: • Number randomised: 63 patients with non-allergic rhinitis, additional 69 patients with allergic rhinitis, not considered in this analysis • Number completed: 63 Participant (baseline) characteristics: • Age: not reported separately for non-allergic rhinitis group • Gender: more female in the triamcinolone acetone nasal spray group for both allergic and non-allergic rhinitis combined, however unclear if this holds true for non-allergic rhinitis group only. • Symptom duration: not reported • Severity: at least moderate, given requirement to demand treatment • Overall no difference with respect to age, education, BMI, duration of rhinitis, nasal operation, sinusitis. As noted above, there were more females in the triamcinolone acetone nasal spray group for both allergic and non-allergic rhinitis combined, however unclear if this holds true for non-allergic rhinitis group only. Inclusion criteria: history of at least 2 of the following symptoms: nasal itching, sneezing, rhinorrhoea and/or nasal congestion, as described by the Allergic Rhinitis and Its Impact on Asthma guidelines. Allergic rhinitis was defined as nasal symptoms accompanied by SPT positivity with clinical relevance, whereas non-allergic rhinitis was defined as nasal symptoms with negative SPTs. Exclusion criteria: patients with nasal polyposis, infectious or occupational rhinitis, major structural nasal abnormalities, current sinusitis and those who were pregnant or lactating.
Interventions	Intervention group: triamcinolone acetonide (n = 32) • Dose: 2 sprays/nostril (220 µg/day) • Frequency: once daily • Duration: 14 days

Kalpaklioglu 2010 (Continued)

- Vehicle: nasal spray

Comparator group: azelastine hydrochloride 0.1%, 2 sprays/nostril twice daily, 1.1 mg/day (n = 31)

Use of additional interventions: none

Outcomes	1. Total nasal symptom score (TNSS) • Measured on a scale of 0 to 4; 0 = better • Reported for 2 weeks after treatment • Reported as mean change from baseline 2. Individual nasal symptom scores (rhinorrhoea, congestion, itching, sneezing, anosmia, conjunctivitis) • Measured on a scale of 0 to 4; 0 = better • Reported for 2 weeks after treatment • SDs and P values missing for non-allergic rhinitis group • However, text reports significant improvement of sneezing with triamcinolone in patients with non-allergic rhinitis ($P < 0.01$), as well as of conjunctivitis (summary data not provided) 3. Peak nasal inspiratory flow (nasal peak inspiratory flow rate, nPIFR, in this study) • The best of the 3 measurements was used for data analysis 4. Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) • Not reported for non-allergic rhinitis subgroup separately 5. Mini-Rhinitis Quality of Life Questionnaire (mini-RQLQ) • Not reported for non-allergic rhinitis subgroup separately 6. Epworth Sleepiness Scale (ESS) • Not reported for non-allergic rhinitis subgroup separately 7. Adverse events • Not reported for non-allergic rhinitis subgroup separately
Funding sources	None
Declarations of interest	None declared
Notes	Individual nasal symptom scores (rhinorrhoea, congestion, itching, sneezing, anosmia, conjunctivitis): SDs and P values missing for non-allergic rhinitis group. However, text reports significant improvement of sneezing with triamcinolone in patients with non-allergic rhinitis ($P < 0.01$), as well as of conjunctivitis (summary data not provided). Non-allergic rhinitis group not reported separately for: SF-36, mini-RQLQ and adverse events

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised study: "randomized parallel-group trial", but random sequence generation not further described.
Allocation concealment (selection bias)	Unclear risk	Not described

Kalpaklioglu 2010 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Single-blind study, but likely participants blinded; not described in detail, however. Symptom scores can be influenced in case of inadequate blinding, assessment of nasal lavage is less likely to have high risk of bias.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Single-blind study and likely assessors not blinded; not described in detail, however. See above.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients reported
Selective reporting (reporting bias)	Low risk	Most outcomes reported, however individual symptom SDs not reported.
Other bias	Low risk	No other risks of bias can be distinguished.

Lin 2017

Methods	Parallel-group randomised controlled trial with 3 months duration
Participants	Setting: single-centre, university hospital in China Sample size: Number randomised: 101 patients non-allergic rhinitis (VMR) patients were randomised, Group A control 24, Group B budesonide 25, Group C saline 25, Group D combination 27. Receiving treatment: Group A 20, Group B 22, Group C 23, Group D 25 Number completed: 90 Participant (baseline) characteristics: Age: (mean/SD) Group A: 40.8 ± 2.7; Group B: 41.2 ± 2.7; Group C: 43.9 ± 1.9; Group D: 43.6 ± 2.2 Gender: Group A: 13/11; Group B: 13/12; Group C: 14/11; Group D: 13/14 (male/female respectively) Symptom duration: not reported Severity: VAS (mean/SD): Group A: 6.00 ± 0.18; Group B: 5.91 ± 0.21; Group C: 5.96 ± 0.17; Group D: 6.18 ± 0.17 - Balanced in gender, age, VAS and SF-12v2 Inclusion criteria: Patient living in Shanghai; age: 18 to 75 years; patients who present with symptoms and body signs of VMR; allergen skin prick test negative; allergen-specific serum IgE negative (< 0.35 kU/L); blood eosinophil percentage < 5%; percentage of eosinophil in nasal secretion smears < 5% Exclusion criteria: allergic rhinitis; acute/chronic inflammation of the respiratory tract; a history of nose surgery; a history of systemic use of corticosteroids in the past 4 weeks; symptomatic deviation of nasal septum; cancer; patients with contraindication of corticosteroid use; patients with contraindication of hypertonic saline use; patients who participated in other clinical trials in the past 3 months; pregnant women
Interventions	Intervention group: Group B (intranasal budesonide) (n = 25)

Lin 2017 (Continued)

- Dose (per spray and per day if available): 2 sprays per nostril per day (64 µg per spray) = 256 µg/day
- Frequency: every morning
- Duration: 3 months (outcomes measured at 1 month, 2 months and 3 months)
- Vehicle: nasal spray

Group D (nasal irrigation + intranasal budesonide) (n = 27)

- Dose (per spray and per day if available): nasal irrigation: 100 mL of 3% saline per nostril; intranasal budesonide: same as Group B
- Frequency: nasal irrigation : twice a day; intranasal budesonide: same as Group B
- Duration: outcomes are measured at 1 month and 3 months follow-up
- Vehicle: nasal irrigation: syringe; intranasal budesonide: nasal spray

Comparator group:

Group A (no treatment) (n = 20)

Group C (saline irrigation using 3% saline) (n = 25)

Use of additional interventions: none

Outcomes	Primary outcomes: • Total nasal symptom scores in VAS • Significant adverse event epistaxis: number is reported Secondary outcomes: • Quality of life is reported in SF-12v2 • Other adverse events (pharyngitis, nasal dryness/crusting): numbers are reported
Funding sources	National Natural Science Foundation of China
Declarations of interest	None declared
Notes	Only vasomotor rhinitis patients. Unexpected data with disappearance of benefit of intranasal corticosteroids with longer follow-up. Results measured after 1 month, 2 months and after 3 months follow-up. Funded by National Natural Science Foundation of China.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation: "random sequence generated by software"
Allocation concealment (selection bias)	High risk	P448 (in Chinese): "The allocation was performed using random sequence generation software. 1~120 random sequence was generated and assigned to each patient according to their order of admission. Patients assigned to Number 1~30, 31~60, 61~90, 91~120 were respectively allocated to Group A, B, C, and D." There is non-random component: day/order of admission.
Blinding of participants and personnel (performance bias)	High risk	Allocation concealment has a high risk of bias.

Intranasal corticosteroids for non-allergic rhinitis (Review)

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Lin 2017 (Continued)

All outcomes

Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of participants and personnel was not reported in this paper. However, considering that the outcomes were primarily patient-reported, blinding could not be achieved.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The dropout of participants was 11/101 = 10.89%.
Selective reporting (reporting bias)	Unclear risk	It is unknown whether there was selective reporting because the protocol for this trial is not available.
Other bias	Low risk	No other risks of bias can be distinguished.

Lundblad 2001

Methods	Double-blind, parallel-group, randomised, placebo-controlled trial with 2 weeks screening, 6 weeks of treatment, 3 weeks follow-up after treatment	
Participants	Setting: Department of Otorhinolaryngology, 16 sites (7 in Sweden, 3 in Denmark, 3 in Finland and 3 in Norway) Sample size: • Number randomised: 329 • Number completed: 329 Participant (baseline) characteristics: • Age: 18 to 82 years (mean 42.8 years) • Gender: 167 males, 162 females • Symptom duration: mean duration of 9 years • Severity: at least moderate degree Inclusion criteria: patients with unspecific rhinitis symptoms of at least moderate degree for at least 4 days per week during the month before entering the study; a negative skin prick test to a standard test panel; a score of ≥ 2 for rhinorrhoea or congestion and at least a moderate score during the month prior to the trial for at least 1 hour daily and for at least 4 days per week. Exclusion criteria: intolerance to aspirin or NSAIDs; significant septal deviations or other structural deformities, nasal polyps; use of prohibited medications (topical nasal, ocular or oral decongestants, nasal saline, short- or long-acting antihistamines (for 24 to 72 hours); nasal atropine or ipratropium bromide, ketotifen, azelastine and intranasal or ocular corticosteroids (for 1 to 2 weeks); investigational drugs, high potency dermatological corticosteroids group III–IV (Nordic classification), inhaled, oral, intravenous, rectal or intramuscular corticosteroids (for 1 to 3 months).	
Interventions	Intervention group: mometasone furoate (n = 167) • Dose: 200 µg • Frequency: once daily • Duration: 6 weeks • Vehicle: spray Comparator group: placebo (constituents not described) (n = 162)	

Lundblad 2001 (Continued)

Use of additional interventions: as a rescue medication Clarityn (loratadine) 10 mg was dispensed by the physician at baseline and, if needed, at visits 3 and 4.

Outcomes	1. Subjective improvement ("subject's overall evaluation of improvement") - Reported as a dichotomous outcome (improved versus not improved) - Based on TNSS assessed via 4 symptoms: rhinorrhoea, nasal stuffiness/congestion, nasal itching and sneezing, measured on a scale of 0 to 3 - Possible scores from 0 to 12 - Improvement defined as a reduction of at least 1 point in the overall symptom score - Assessed during treatment 2. Objective improvement ("investigator's overall evaluation of improvement") - Measured and reported as above - Unclear how specifically subjective improvement was distinguished from investigator's assessment of improvement 3. Therapeutic response - Reported as a scale of improvement, reported subjectively - Scale 1 to 5: 1 complete relief (virtually no symptoms present); 2 marked relief (symptoms greatly improved and, although present, scarcely troublesome); 3 moderate relief; 4 slight relief; 5 treatment failure - Here, we have combined "complete relief", "marked relief" and "moderate relief" into "responder" and "slight relief" and "treatment failure" into "non-responder" 4. Relapse - no numerical data reported, only P values 5. Quality of life - no numerical data reported 6. Adverse outcomes - Reported as number of events - Individual numerical data reported for URTI, headaches, epistaxis, sore throat	
Funding sources	Schering-Plough AB, Sweden	
Declarations of interest	None declared	
Notes	TNSS converted into "improvement" versus "failure" analysis, with sometimes unclear methods of distinguishing between different outcome measures derived from same original TNSS data. Good data on adverse events, not on quality of life. Study supported by Schering-Plough AB, Sweden.	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"... a Nordic, multicenter, randomized, double-blind, placebo-controlled study" Random sequence generation is not described.
Allocation concealment (selection bias)	Unclear risk	Not described

Lundblad 2001 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind study, however blinding is not further described. Improvement and quality of life assessment can be influenced by inadequate blinding, as well as report of adverse events.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described, see above
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analysis data available (all patients described in 'Materials and methods' are reported in 'Results'), even though per protocol data also reported
Selective reporting (reporting bias)	High risk	Several sets of collected data not reported: quality of life, relapse and vitals data not reported numerically
Other bias	Unclear risk	Initially, total nasal symptom scores were collected, however data were reported as subjective and objective relief scores, leading to interpretation about original TNSS. Study supported by Schering-Plough AB, Sweden.

Löfkvist 1976

Methods	Double-blind, cross-over, placebo-controlled trial with 4 weeks treatment, 1 week washout, 4 weeks placebo or in reverse order. Randomisation is unclear.
Participants	Setting: university hospital in Lund, Sweden Sample size: • Number randomised: 39 • Number completed: 39 Participant (baseline) characteristics: • Age: 19 to 66 years (mean 39 years) • Gender: 19 males, 20 females • Symptom duration: half of the patients had had symptoms for more than 10 years • Severity: not reported Inclusion criteria: patients with a history of vasomotor rhinitis for many years, who had perennial symptoms in the form of obstruction, nasal drip, sneezing and nasal itching in varying degrees, and had negative allergy testing. Exclusion criteria: nasal polyposis, obvious septum deviation, bronchial asthma, pregnancy, or influenza-like disease.
Interventions	Intervention group: beclomethasone dipropionate (n = 19) • Dose: 50 µg (300 µg daily dose) • Frequency: 3 times per day • Duration: 4 weeks • Vehicle: spray Comparator group: placebo (constituents not described) (n = 20)

Löfkvist 1976 (Continued)

Use of additional interventions: none

Outcomes	1. Total nasal symptom score • Reported as a mean values and SD, in Figure 1 of the publication • Time points - day 1, weeks 1 to 9 • Assessed via 4 symptoms nasal catarrh, blockage, nasal itching and sneezing, each measured on a scale of 0 to 3 • Possible scores from 0 to 12 2. Individual nasal symptom scores • For nasal catarrh, blockage, nasal itching and sneezing, each measured on a scale of 0 to 3 • Reported as a mean values and SD, in Figure 1 of the publication • Time points - day 1, weeks 1 to 9 3. Patient's subjective evaluation of therapeutic effect • Patients rated improvement after beclomethasone or placebo periods • Originally reported as "free of trouble", "improved", "unchanged" or "worsened" • We converted this into "responder", to include "free of trouble", "improved" and "non-responder", to include "unchanged" or "worsened"
Funding sources	Glaxo Lakemedel AB, Sweden; Alfred Osterlund's Stiftelse, Malmo, Sweden
Declarations of interest	None declared
Notes	Patients rated improvement after beclomethasone or placebo periods. Originally reported as "free of trouble", "improved", "unchanged" or "worsened", converted into "responder", to include "free of trouble", "improved", and "non-responder", to include "unchanged" or "worsened".
Risk of bias	
Bias	Authors' judgement Support for judgement
Random sequence generation (selection bias)	High risk Randomisation not described
Allocation concealment (selection bias)	High risk Randomisation not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk Double-blind study, not further described. Nasal sprays were in identical packages so blinding could have been possible. Symptom scores could have been influenced by inadequate blinding, cortisol levels not likely.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk See above
Incomplete outcome data (attrition bias) All outcomes	Unclear risk One patient withdrew due to influenza-simulating disease during beclomethasone treatment. It is unclear what happened with this patient's data. Plasma cortisol levels reported for 19 patients only.

Löfkvist 1976 (Continued)

Selective reporting (reporting bias)	Unclear risk	Medical examination results not reported numerically, however given this is not an important outcome, we judged the risk of bias as unclear.
Other bias	Unclear risk	Cross-over design with no clear signs of randomisation.

Malm 1976

Methods	Double-blind, cross-over, placebo-controlled trial with 1 week prior to treatment, 2 weeks treatments x 4, given in 4 different sequences. No washout period. Data only from 2nd week is used to minimise spill-over effect. Randomisation not described.
Participants	Setting: ENT Department, General Hospital, Malmo, Sweden Sample size: • Number randomised: 21 • Number completed: 21 Participant (baseline) characteristics: • Age: average 36 years (18 to 61 years) • Gender: 12 female, 9 male • Symptom duration: at least 1 year • Severity: not reported Inclusion criteria: vasomotor rhinitis, as defined by symptoms of nasal blockage, watery secretion and sneezing, and no relevant allergens found on history, skin prick testing and provocation testing Exclusion criteria: not described
Interventions	Intervention group: beclomethasone dipropionate (n = 21) • Doses: (50 µg per puff) 200 µg daily, 400 µg daily, 800 µg daily (cross-over study design) • Frequency: twice daily (200 µg) or 4 times daily (400 µg, 800 µg) • Duration: 2 weeks • Vehicle: Becotide aerosol used for asthma, with a special adaptor Comparator group: placebo (constituents not described) (n = 21) Use of additional interventions: not described
Outcomes	1. Individual symptom scores for nasal obstruction, rhinorrhoea, sneezing, eye irritation • All symptoms ranked on a scale of 0 to 3 • Data obtained from figure 2. Adverse effects - transient irritation, sneezing, streaks off blood. No data to perform analysis. No patient stopped study medication.
Funding sources	Glaxo Lakemedel
Declarations of interest	None declared
Notes	• Cross-over trial. Only overall summary data available for each intervention. • Randomisation unclear.

Malm 1976 (Continued)

- Beclomethasone dipropionate 200 µg, 400 µg and 800 µg daily versus placebo. 2-week treatments each, no washout period. Patients assigned to 4 treatment sequences to go through all interventions in different orders.
- Dosage of 400 µg daily included in meta-analysis.
- Not clarified how many patients per treatment sequence.
- Calculated a total nasal symptom score from means rhinorrhoea, blockage and sneezing and calculated a pooled SD.
- Remarkable decrease in symptom scores from baseline in [Malm 1976](#) (60% decrease from baseline) and [Malm 1981](#) (75% decrease from baseline) studies.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Randomisation not described
Allocation concealment (selection bias)	High risk	Randomisation not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind study, not further described. Nasal sprays were in identical packages so blinding could have been possible. Symptom scores could have been influenced by inadequate blinding, cortisol levels not likely.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described, so see above
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients completed the study
Selective reporting (reporting bias)	High risk	Summary data for each intervention group per treatment sequence not available
Other bias	High risk	Cross-over design with no washout period

Malm 1981

Methods	Double-blind, cross-over, randomised controlled trial with 2 weeks run-in period; 2 weeks treatment; 1 week washout; 2 weeks treatment; 1 week washout; 2 weeks treatment; 1 week washout; 2 weeks treatment
Participants	Setting: university hospital in Lund, Sweden Sample size: • Number randomised: 23 patients randomised • Number completed: 22 Participant (baseline) characteristics: • Age: 20 to 68 years (mean: 42 years) • Gender: 5 males, 17 females

Malm 1981 (Continued)

- **Symptom duration:** at least 1 year
- **Severity:** not reported

Inclusion criteria: patients with perennial non-allergic rhinitis with 2 or more of the symptoms of nasal obstruction, nasal secretion, sneezing attacks for at least 1 year, and negative skin prick test.

Exclusion criteria: bronchial asthma or nasal polyposis

Interventions	Intervention groups: budesonide (n = 22) • Doses: 50 µg daily, 200 µg daily and 800 µg per day (cross-over study design) • Frequency: 1 puff in each nostril, twice a day (morning and evening) • Duration: 2 weeks • Vehicle: pressurised aerosol Comparator group: placebo (constituents not described) (n = 22) Use of additional interventions: phenylpropanolamine as rescue medication was allowed
Outcomes	1. Nasal obstruction • Measured by patient • Scale of 0 to 3 (0 is good) • Reported as mean ± SEM of at least 3 days of the patient's symptom score in each treatment period 2. Nasal secretion • As above 3. Sneezing • Measured by patient • Scale of 0 to 3 (0 is good: no sneezing = 0; 1 to 5 sneezes = 1 point; 6 to 15 = 2 points; more than 15 sneezes = 3 points) • Reported as above 4. Nasal airway resistance • Measured via rhinomanometry: nasal resistance parameter v2 • Measured once at the end of the first week of the run-in period and then on the day after each treatment period • Reported in degrees, 0 to 360 theoretically, wider angles correspond to higher levels of resistance, low score is good 5. Treatment side effects
Funding sources	AB Draco, a subsidiary of AB Astra
Declarations of interest	None declared
Notes	• This is a cross-over trial. • Budesonide 50 µg, 200 µg and 800 µg daily versus placebo. 2-week run-in, 2-week treatment each, 1-week washout period. • Dosage 200 µg daily included in the meta-analysis. • 22 patients, however: 3 patients with no nasal obstruction and 1 patient with no sneezing attacks during the trial were excluded. Another patient from the originally randomised patients was excluded for social reasons. • Outcomes: nasal obstruction, nasal secretion, sneezing; patient-reported, scale of 0 to 3, reported as mean ± SEM of at least 3 days of the patient's symptom score in each treatment period.

Malm 1981 (Continued)

- Calculated a total nasal symptom score from means for rhinorrhoea, blockage and sneezing and calculated a pooled SD.
- Remarkable decrease in symptom scores from baseline in [Malm 1976](#) (60% decrease from baseline) and [Malm 1981](#) (75% decrease from baseline) studies.
- Involvement of AB Draco, a subsidiary of AB Astra, a pharmaceutical company, is unclear.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: not described, but reports "preparations were given in randomized order"
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Study reported as "double-blind", blinding not further described.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	See above. As nasal sprays were compared, adequate blinding could have been achieved. For outcomes: rhinomanometry, nasal secretion/smears and cortisol are less likely to be influenced by inadequate blinding than symptom scoring.
Incomplete outcome data (attrition bias) All outcomes	High risk	22 patients were included for randomisation in a cross-over study design. 3 patients with no nasal obstruction and 1 patient with no sneezing attacks during the trial were excluded. Another patient from the originally randomised patients was excluded for social reasons. This has a risk of attrition bias.
Selective reporting (reporting bias)	Low risk	All described outcomes can be found in the results
Other bias	Unclear risk	Involvement of AB Draco, a subsidiary of AB Astra, a pharmaceutical company, is unclear.

Meltzer 1994

Methods	Double-blind, multi-centre, parallel-group, randomised, placebo-controlled trial with 4 weeks duration of treatment
Participants	Setting: Allergy and Asthma Research Centre, part of multi-centre trial Sample size: • Number randomised: 286 non-allergic rhinitis patients • Number completed: 286 non-allergic rhinitis patients Participant (baseline) characteristics: • Age: not reported • Gender: not reported • Symptom duration: at least 4 of 7 days prior to receiving study drug

Meltzer 1994 (Continued)

- **Severity:** nasal symptom scores of > 150 of 400 possible points for sneezing, rhinorrhoea, nasal obstruction and post-nasal drip and, on those 4 days the severity of at least 1 of the 4 symptoms must have been at least 50 of 100 points

Inclusion criteria: 1) history of non-allergic rhinitis; 2) total serum immunoglobulin E (IgE) level < 250 IU-ml; 3) negative SPT; 4) normal sinus radiograph

Exclusion criteria: not defined, see inclusion criteria

Interventions	Intervention group: FPANS (fluticasone propionate) 100 µg or 200 µg twice daily Comparator group: placebo Use of additional interventions: none
Outcomes	Reduction of nasal symptom scores, particularly obstruction, overall assessment of response to therapy: unclear definition, scale/range of nasal symptom scores
Funding sources	None declared
Declarations of interest	None declared
Notes	No numerical data for non-allergic rhinitis group separately, only note that FPANS in non-allergic rhinitis reduces total symptoms, improves individual symptoms, mainly obstruction, and achieves significant overall improvement

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Placebo-controlled, double-blind randomised trial but randomisation not further described
Allocation concealment (selection bias)	Unclear risk	Placebo-controlled, double-blind randomised trial but randomisation not further described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding not described in detail
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding not described in detail
Incomplete outcome data (attrition bias) All outcomes	High risk	No numerical data on non-allergic rhinitis subgroup
Selective reporting (reporting bias)	High risk	No numerical data on non-allergic rhinitis subgroup
Other bias	Unclear risk	No data available

Miller 1969

Methods	Double-blind, cross-over, quasi-randomised (serial assignment into 2 groups) controlled trial with 2 months total: 1 month on one treatment, then another month on another. No washout period described.
Participants	Setting: unclear, likely private office, USA Sample size: • Number randomised: 90 patients randomised, 88 reported • Number completed: 88 Participant (baseline) characteristics: • Age: nearly all were adults, except 4 boys (9 to 14 years of age), 1 girl of 17 years of age. Most patients were between 31 and 60 years of age • Gender: 61 female, 27 male • Symptom duration: not reported • Severity: not reported Inclusion criteria: vasomotor rhinitis, as defined by physical examination (reactive non-allergic nasal membranes), skin testing where appropriate and absence of allergic history Exclusion criteria: pregnancy, active tuberculosis, ocular herpes simplex, acute or chronic infection, or other contraindication to adrenocortical hormone therapy, use of medication for vasomotor rhinitis from 1 week before the trial until the end of the trial
Interventions	Intervention groups: dexamethasone (n = 88) • Doses: 0.084 mg of dexamethasone per spray, 2 sprays in each nostril (672 µg to 1008 µg of dexamethasone per day) • Frequency: 2 to 3 times per day • Duration: 1 month (no washout period) • Vehicle: aerosol container Comparator group: placebo (inactive ingredients) (n = 88) Use of additional interventions: none
Outcomes	1. Response to therapy • Measured on a scale: 100% = excellent; 75% to 99% = good; 50% to 74% = fair; < 50% = poor • Measured at 1 month after treatment • Data could be used for numerical analysis 2. Nasal obstruction • Measured by patient at 2 and 4 weeks after treatment • Scale 0 to 3, 0 is good • Reported as mean; SD recalculated based on P value 3. Discharge • Same as above • Data not included given P value not presented 4. Post-nasal drip • Same as above • Data not included 5. Sneezing

Miller 1969 (Continued)

- Same as above
- Data not available

6. Anosmia

- Same as above
- Data not available

7. Side effects

- Headache: data available

Funding sources	None
Declarations of interest	None declared
Notes	No washout period in cross-over study. Vasomotor rhinitis patients. Only 1 patient had polyps, so decided that contamination was not an issue. 5 patients were below 18 years of age, but given that the majority appeared to be over 12 we decided to include all patients. Reported means for secretion, obstruction and post-nasal drip, however we were not able to calculate a SD for secretion and post-nasal drip as the P value was not reported, only the mean. So we can calculate a TNSS of obstruction, secretion and post-nasal drip, but we cannot calculate a pooled SD, making this outcome useless.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quasi-randomised (serial assignment into 2 groups): "The patients were divided into two groups, in serial assignment, to a list of numbers which designated the kind of medication to be given"
Allocation concealment (selection bias)	Low risk	Allocation concealed: "... were concealed by being over-printed on a tear-off portion of the label which was attached to the case report form"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"Double-blind study" but blinding not further described.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Double-blind study" but blinding not further described. Symptom scoring could have been influenced by inadequate blinding, same as symptoms by investigation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 patients from 90 were excluded: 1 due to not being able to identify group belonging, second due to loss to follow-up. We think this exclusion has a low chance of affecting overall outcomes.
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Unclear risk	SDs not reported, but could be recalculated using P values No washout period

O'Reilly 1991

Methods	Double-blind, cross-over, controlled trial with 24 weeks total: 12 weeks on one treatment, then another 12 weeks on another. No washout period described. Randomisation not described.
Participants	Setting: general ENT clinics at Whitechapel and Halton, UK Sample size: • Number randomised: 23 patients randomised • Number completed: 16 reported (5 withdrew in placebo phase, 2 in treatment phase because symptoms became intolerable) Participant (baseline) characteristics: • Age: not described • Gender: not described • Symptom duration: not described • Severity: not reported Inclusion criteria: patients with perennial rhinitis, defined as the presence of nasal obstruction, paroxysmal sneezing and seromucinous rhinorrhoea. Patients who had no positive skin prick test result to one or more allergens were classified as non-allergic. Exclusion criteria: patients with a personal or family history of atopy, positive skin prick test to any of the common inhaled allergens, nasal polyps, nasal sepsis, a deviated septum or abnormal sinus X-rays.
Interventions	Intervention groups: beclomethasone dipropionate (n = 23) • Doses: 600 µg per day (4 puffs) • Frequency: 3 times per day • Duration: 12 weeks (no washout period) • Vehicle: not described Comparator group: placebo (not described) (n = 23) Use of additional interventions: none
Outcomes	1. Nasal obstruction • Measured on a scale of 0 to 5 • Reported as P values only 2. Anterior rhinorrhoea • As above 3. Posterior rhinorrhoea • As above 4. Sneezing • As above 5. Facial pain • As above 6. Total nasal symptom score • Composite score for all 5 symptoms

O'Reilly 1991 (Continued)

- Reported only as P values

7. Rhinomanometry

- Using Brom's method with the symptom scoring
- Not reported given too wide a variation between baseline and placebo values

8. Adverse reactions

- Not specified

Funding sources	None
Declarations of interest	None declared
Notes	No washout period 7 out of 23 dropout rate Only P values reported, no means and SDs

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Randomisation not described
Allocation concealment (selection bias)	High risk	Randomisation not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind study, however blinding was not further described. Symptom scoring and patient preference could have been influenced by inadequate blinding.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blind study, however blinding was not further described. Symptom scoring and patient preference could have been influenced by inadequate blinding.
Incomplete outcome data (attrition bias) All outcomes	High risk	Out of 23 recruited patients, 5 withdrew in the placebo stage and 2 in the treatment stage (30.4% missing data)
Selective reporting (reporting bias)	High risk	Summary data not reported per group, and therefore verification of reported P values is impossible.
Other bias	Low risk	No other risks of bias were distinguished

Scadding 1995

Methods	Double-blind, parallel-group, randomised controlled trial with 2-week run-in period, 12 weeks of treatment
Participants	Setting: 36 centres in Western Europe Sample size:

Scadding 1995 (Continued)

- **Number randomised:** 516 patients with allergic and non-allergic rhinitis were randomised (106 withdrawals before randomisation).
- **Number completed:** 371 patients with allergic and non-allergic rhinitis were included in analysis, of which 188 were patients with non-allergic rhinitis reported (50 with fluticasone propionate once daily, 49 with fluticasone propionate twice daily, 43 with beclomethasone, 46 with placebo)

Participant (baseline) characteristics:

- **Age:** not described separately for non-allergic rhinitis group, range 10 to 83
- **Gender:** percentage of females in the overall groups ranged 50% to 57% in different arms
- **Symptom duration:** 5 or more of the 14-day period
- **Severity:** moderate to severe (score of 2 or 3 on a 0 to 3 scale)
- Not described for non-allergic rhinitis group separately, overall homogenous for combined allergic and non-allergic rhinitis

Inclusion criteria: patients aged over 12 years with a history of moderate to severe perennial rhinitis were recruited. Skin prick tests to common inhaled perennial allergens (house dust, house dust mite, cat, dog, moulds) were performed. Patients with negative skin prick test were classified as non-allergic.

Exclusion criteria: allergic rhinitis, invalid or insufficient diary record card data, fewer than 2 symptoms of rhinitis at visit 1, insufficient symptoms in run-in, disallowed concurrent medication, baseline nasal infection and non-compliance.

Interventions

Intervention groups: fluticasone propionate once daily (n = 50)

- Doses: 200 µg per dose
- Frequency: once per day
- Duration: 12 weeks
- Vehicle: aqueous nasal spray

Comparator group: fluticasone propionate twice daily (n = 49)

- As above, but twice a day

Comparator group: beclomethasone dipropionate (n = 43)

- Doses: 200 µg per dose
- Frequency: twice per day
- Duration: 12 weeks
- Vehicle: aqueous nasal spray

Comparator group: placebo (n = 46)

- Frequency of treatment not described
- Otherwise same as above

Use of additional interventions: none

Outcomes

1. Nasal blockage on waking

- Measured by patient on a scale of 0 to 3 on a daily card, 3 is severe

2. Nasal blockage during the rest of the day

- As above

3. Sneezing

- As above

4. Rhinorrhoea

Scadding 1995 (Continued)

- As above

5. Overall assessment of symptoms

- As above

6. Overall assessment of symptoms at clinic visit

- VAS, 0 to 10 cm, 10 = worst symptoms

7. Adverse events

- No numerical data

Funding sources	Glaxo Group Research Ltd
Declarations of interest	None declared
Notes	Data not reported separately for non-allergic rhinitis group, but authors suggest that tests for interaction between rhinitis category and treatment were carried out and no interaction was found. Conclusion: their analysis suggests no differences based on allergic sensitisation.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised trial, however random sequence generation was not described.
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind study, however blinding was not further described. Symptom scoring could have been influenced by this; eosinophilia has less risk of bias.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blind study, however blinding was not further described. See above.
Incomplete outcome data (attrition bias) All outcomes	High risk	Of 516 initially randomised patients with perennial allergic and non-allergic rhinitis, only 371 were reported (attrition of 28.1%).
Selective reporting (reporting bias)	Unclear risk	Outcomes were reported as percentage of symptom-free or no and mild symptom days, instead of the recorded symptom scores. SDs were not reported, but can be recalculated based on mean and P values.
Other bias	Unclear risk	Funding of this multi-centre study is unclear. The pharmaceutical company provided medications. The corresponding author represents a pharmaceutical company.

Schulz 1978

Methods	Double-blind, parallel-group, randomised controlled trial with 2-week baseline, 6 weeks of treatment
Participants	Setting: Division of Clinical Immunology and Allergy, Montreal General Hospital, Montreal, Canada

Intranasal corticosteroids for non-allergic rhinitis (Review)

Schulz 1978 (Continued)

Sample size:

- **Number randomised:** 69 with allergic and non-allergic rhinitis (perennial rhinitis) randomised
- **Number completed:** 60 (9 patients terminated early and excluded from analysis) (32 non-allergic rhinitis)

Participant (baseline) characteristics:

- **Age:** 15 to 71 years
- **Gender:** in the combined allergic and non-allergic rhinitis population: 29 males, 40 females. Distribution for non-allergic rhinitis group not reported
- **Symptom duration:** not reported
- **Severity:** not described for non-allergic rhinitis group separately. In the combined allergic and non-allergic rhinitis population, there were no significant demographic or historical differences between treatment groups. During the 2-week baseline period, however, patients in the flunisolide group reported a greater number of hours with the symptom "stuffy nose" than patients in the placebo group.

Inclusion criteria: perennial rhinitis, seasonal allergic rhinitis, including non-allergic rhinitis

Exclusion criteria: allergic rhinitis

Interventions	Intervention groups: flunisolide (n = 14) • Doses: 25 µg per spray, 2 sprays per nostril, 300 µg per day total for both sides • Frequency: 3 times per day • Duration: 6 weeks • Vehicle: aqueous solution, via metered dose pump spray Comparator group: placebo (n = 18) • Identical vehicle, without the flunisolide • Otherwise same as above Use of additional interventions: none
Outcomes	1. Sneezing • Measured by patient on daily record chart • Duration (in hours) measured 2. Stuffy nose • As above 3. Runny nose • As above 4. Nose blowing • As above 5. Post-nasal drip • As above 6. TNSS • All 5 symptoms combined to determine overall duration of patients' symptoms • Reported as percentage of days during which all 5 of the symptoms lasted 1 hour or less and the percentage of days during which at least 1 of the 5 symptoms lasted 4 hours or more. 7. Overall effect of the test drug

Schulz 1978 (Continued)

- Evaluated by patient at the end of treatment
- Measured as total control, substantial but not complete control, minor but definite control, no benefit and aggravated nasal symptoms
- Only data available for non-allergic rhinitis group

Funding sources	None
Declarations of interest	None declared
Notes	Most outcomes not available for non-allergic rhinitis group separately. Only data for non-allergic rhinitis (Table 2) were overall effect of symptoms (responder data) and this was recalculated into responder and non-responder data.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomized trial", however random sequence generation was not described.
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"Double-blind", however blinding was not further described. Symptom scoring could have been influenced by this; plasma cortisol less likely.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Double-blind", however blinding was not further described. See above.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Of 69 total enrolled patients, only 60 were reported for efficacy. Of these, 32 were patients with non-allergic rhinitis. It is unclear how many of the 9 non-reported patients were in the non-allergic rhinitis subgroup. Adverse effect data were reported for all 69 patients.
Selective reporting (reporting bias)	Unclear risk	All results reported fully for overall group, only responder data reported for non-allergic rhinitis group
Other bias	Low risk	No other risks of bias could be distinguished.

Singh 2017

Methods	Non-blinded, parallel-group, randomised clinical study with 2 weeks duration of treatment
Participants	Setting: the clinical EEC study and collection of biospecimens were conducted at Inflamax Research (Mississauga, ON, Canada) and the biospecimens were analysed at the University of Cincinnati Sample size: • Number randomised: 30 • Number completed: 30 Participant (baseline) characteristics:

Singh 2017 (Continued)

- **Age:** AzeFlu (44.91 ± 6.77 years); placebo (42.43 ± 8.24 years)
- **Gender:** AzeFlu: female: 12, male: 8; placebo: female: 6, male
- **Symptom duration:** unclear
- **Severity:** unclear

Inclusion criteria: NAVMR based on symptoms and triggers; nasal symptoms in response to a panel of non-allergic triggers, including CDA, in a NAVMR questionnaire

Exclusion criteria: positive test skin; mechanical obstruction; infection of the nasal cavity

Interventions	Intervention group: AzeFlu (n = 20) FDA-approved dosing regimen (1 spray in each nostril twice daily) at home for 2 weeks. AzeFlu was supplied in a spray bottle containing a suspension of azelastine hydrochloride (137 µg) and fluticasone propionate (50 µg) per spray (0.137 mL) The inactive ingredients included preservatives (alcohols, benzalkonium) and a chelating agent (EDTA) Comparator group: placebo (n = 10) Placebo contained the same excipients as the AzeFlu preparation without the active drug. During the study period, none of participants used concomitant medications for NAVMR or medications that interact with AzeFlu. Use of additional interventions: none
Outcomes	1. Total nasal symptom scores (after cold dry air provocation), before and after treatment 2. Minimal cross-sectional area (MCA) (before and after cold dry air provocation) before and after treatment
Funding sources	None
Declarations of interest	None declared
Notes	• Outcome measures do not meet the definition as in the protocol, i.e. total nasal symptom score and objective measurement of airflow are both related to cold dry air provocation; despite that: should be reported in systematic review. • There is no statistically significant difference between AzeFlu and placebo for the most important outcome, i.e. TNSS. Numerical data are not reported so cannot be used in meta-analysis but should be reported in systematic review.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised trial. There was insufficient information on sequence generation.
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	As the primary outcomes of nasal symptom scores and adverse events are both self-reported outcomes and the study is not blinded, this has a high risk of bias.
Blinding of outcome assessment (detection bias) All outcomes	High risk	See above

Singh 2017 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	High risk	For the most important outcome TNSS the outcomes are not reported; the authors only state: "The mean change in TNSS for the AzeFlu cohort (vs. placebo cohort) was reduced, but did not reach statistical significance. A similar numerical trend was observed, albeit to a lesser extent, for individual symptom scores of runny nose, post-nasal drip, and nasal congestion."
Other bias	Unclear risk	No other risks of bias could be distinguished

Song 2018

Methods	Unclear blinded, parallel-group, randomised clinical study with 8 weeks treatment
Participants	Setting: Department of Otolaryngology, Head and Neck Surgery, Affiliated Hospital of Guizhou Medical University Guiyang, China Sample size: Number randomised: 120 (40 budesonide, 40 azelastine, 40 budesonide with azelastine) Number completed: 120 Participant (baseline) characteristics: Age: Group A (budesonide and azelastine) 42.4 ± 2.9 years; Group B (budesonide) 41.6 ± 2.7 years; Group C (azelastine) 43.8 ± 1.9 years Gender: general: male (M): 61, female (F): 59; Group A (budesonide and azelastine): M/F: 21/19; Group B (budesonide) : M/F: 18/22; Group C (azelastine) : M/F: 21/18 Symptom duration: not reported Severity: baseline VAS: budesonide (VAS: 6.81 ± 1.61); azelastine (VAS: 6.63 ± 1.85); budesonide with azelastine (VAS: 6.75 ± 1.48) Inclusion criteria: typical symptoms and characteristics of vasomotor rhinitis; negative skin prick test results; serum specific IgE (-); blood eosinophilia % < 5%; nasal secretion eosinophilia % < 5% Exclusion criteria: allergic rhinitis, asthma, eczema, acute or chronic rhinosinusitis, nasal tumour, systemic or any disease that might influence the result of this study, usage of nasal, oral or systemic glucocorticoids, antihistamines, leukotriene receptor inhibitors, various blood decongestant or theophylline in last 3 months; involvement of any other clinical trials; allergy to glucocorticoid or antihistamine drugs; pregnancy or breastfeeding; healthcare workers for the study.
Interventions	Intervention group: budesonide (n = 40) - Dose: 50 g/ puff, 2 puffs per nostril - Frequency: 2 times per day: total dosage 400 µg - Duration: 8 weeks - Vehicle: spray Comparator groups: Azelastine (n = 40) - Dose: 50g/ puff, 2 puffs per nostril - Frequency: 2 times per day: total dosage 400 µg - Duration: 8 weeks

Song 2018 (Continued)

- Vehicle: spray

Budesonide with azelastine (n = 40)

- Dose: 50 µg/puff, 2 puffs per nostril
- Frequency: 2 times per day: total dosage 400 µg
- Duration: 8 weeks
- Vehicle: spray

Use of additional interventions: none

Outcomes	1. Visual analogue scale (VAS): overall VAS score and VAS score for nasal congestion, nasal itching, sneezing, rhinorrhoea 2. Score reduction index (SRI) = ((score before treatment-score after treatment))/(score before treatment) x 100 (%): ≥ 80% = significant effectiveness; 30% to ~80% = effective; ≤ 30% = no effectiveness 3. Quality of life (SF-12v2) 4. Adverse events (in general, not specified)
Funding sources	Science and technology plan of Guizhou province (Guizhou LH (2015) no. 7418)
Declarations of interest	No information provided
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"120 patients with VMR were randomly grouped by number table method"
Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding reported. However, the intervention in the treatment group is distinct from that in the control group, therefore it is likely that the self-reported outcomes have been influenced by lack of blinding.
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding reported, however self-reported outcomes are likely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The number of patients reported in the outcomes was the same as that at baseline.
Selective reporting (reporting bias)	Low risk	All outcomes stated in the 'Methods' were reported in the 'Results'.
Other bias	Low risk	No co-intervention; baseline characteristics were comparable; government funding

Spector 1980

Methods	Double-blind, parallel-group, randomised, placebo-controlled trial with 2-week baseline period and a 4-week treatment
Participants	Setting: hospital and office patients in Denver, Colorado, USA Sample size: • Number randomised: 20 patients randomised, 15 included in analysis • Number completed: 15 Participant (baseline) characteristics: • Age: 15 to 66 years (mean: 35.1 years) • Gender: 10 males, 5 females • Symptom duration: at least 2 years • Severity: severe enough to require the use of medications more than 50% of the time and undesirable side effects from the usual medications (can be judged to be moderate or severe) • Summary data not reported, however recalculation of age, sex ratio, baseline total symptom score, physician evaluation score not different between groups Inclusion criteria: 1) a history of perennial non-allergic rhinitis of at least 2 years duration; 2) symptoms severe enough to require the use of medications more than 50% of the time and undesirable side effects from the usual medications; 3) symptoms stable for at least 3 months prior to the study; 4) age 18 years or older; and 5) no systemic or topical steroids used for at least 6 months prior to the study. Exclusion criteria: patients with nasal polyps who had symptoms of nasal obstruction and women of child-bearing potential.
Interventions	Intervention group: flunisolide (n = 7) • Dose: a solution containing 0.25% flunisolide, approximately 25 µg flunisolide per spray, 2 sprays in each nostril (400 µg daily) • Frequency: 4 times per day • Duration: 4 weeks • Vehicle: plastic atomised bottle Comparator group: placebo (vehicle only) (n = 8) Use of additional interventions: patients were instructed not to change their basic medication programme, which included a decongestant or antihistamine or both.
Outcomes	1. Sneezing • Daily symptom diary • Duration (in hours) measured per day 2. Stuffiness • Same as above 3. Runny nose • Same as above 4. Nose blowing • Same as above 5. Post-nasal drip • Same as above

Spector 1980 (Continued)

6. Adverse effects

- No data provided

TNSS: patient evaluation, sum of 5 symptoms (sneezing, stuffiness, runny nose, nose blowing and post-nasal drip) numerically assessed as absent (1), mild (2), moderate (3) or severe (4)

7. Peak expiratory flow rate, nasal (PEFRn)
8. Peak expiratory flow rate, mouth (PEFRm)
9. Blockage index

- $(\text{PEFRm} - \text{PEFRn}) / \text{PEFRm}$

Funding sources	Study funded in part by Syntex Corporation. The authors' relationship with the funder is unclear.
Declarations of interest	None declared
Notes	Women of childbearing potential excluded. Same study reported in Jones 1979, which however, did not provide numerical data on symptom scores (only Figure 1 in article with no SDs or P values). We have decided to include Spector 1980 and not Jones 1979. A PEFR was not obtained for all patients.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random sequence generation was not further described.
Allocation concealment (selection bias)	Unclear risk	See above.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"Neither the patients nor personnel involved in the study knew the contents of the randomly assigned bottles containing either flunisolide or vehicle." Blinding not further described.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	See above. Patient symptom evaluation and physician evaluation could have been influenced.
Incomplete outcome data (attrition bias) All outcomes	High risk	5 patient dropouts out of a total 20 randomised patients (25%). One explained by non-compliance, the other 4 by lack of sufficient material for nasal biopsies, however their clinical outcomes could ideally have been reported. The most clinically important outcome, TNSS, is fully reported. PEFR (peak expiratory flow rate) was not done/reported for all patients.
Selective reporting (reporting bias)	Low risk	All outcomes are adequately reported.
Other bias	High risk	Funded in part by Syntex Corporation. It is unclear if the authors have a relationship with the funder. Women of childbearing potential excluded.

Tantilipikorn 2010

Methods	Double-blind, parallel-group, randomised, placebo-controlled trial with 2-week screening period, 4 weeks treatment, 3 to 5 days follow-up after treatment
Participants	Setting: multi-centre, 7 centres in Thailand Sample size: • Number randomised: 102 total; fluticasone furoate (FFNS), n = 53, placebo, n = 49 • Number completed: 102 Participant (baseline) characteristics: • Age: 12 to 64 years; FFNS: 37.1 ± 12.78, range 12 to 58; placebo: 35.9 ± 10.89, range 18 to 64 • Gender: female (33), male (20) • Symptom duration: more than 2 years • Severity: average of 4.5 (maximum = 9) for the last 8 reflective TNSS (rTNSS) assessments, an average of 2 (maximum = 3) for the last 8 reflective nasal congestion assessments and an 80% compliance with their diary card entries over the span of their screening period. • Not significant for age, gender, compliance, trigger factors, mean daily rTNSS, percentage of eosinophils in nasal smear. Participants in the FFNS group spent 0.5 to 1.5 hours longer outside compared with participants in the placebo group (unclear significance). Inclusion criteria: participants to identify air pollution as the predominant trigger that made their rhinitis symptoms worse, via completion of an irritant rhinitis trigger questionnaire to select their predominant trigger from 3 types of irritants (air pollution, wind/temperature triggers and strong odours). Inclusion criteria also included a negative skin prick test to local seasonal and perennial allergens, a positive histamine control skin prick test and a normal sinus radiograph (Waters view) to rule out sinusitis. Randomisation criteria at Visit 2 required participants to have an average of ≥ 4.5 (maximum = 9) for the last 8 reflective TNSS assessments, an average of ≥ 2 (maximum = 3) for the last 8 reflective nasal congestion assessments and an 80% compliance with their diary card entries over the span of their screening period. Exclusion criteria: nasal obstruction, septal perforation, recent nasal surgery, nasal infections; medications known to produce allergy symptoms, such as congestion; use of face masks (e.g. used for protection from air pollution), continuous positive airflow pressure, saline nasal sprays and lavages, eye drop, and local, herbal and homeopathic treatments.
Interventions	Intervention group: fluticasone furoate (n = 53) • Dose: 110 µg (110 µg fluticasone furoate equals around 200 µg fluticasone propionate, budesonide or beclomethasone dipropionate) • Frequency: once daily • Duration: 4 weeks • Vehicle: not described • Delivery method: nasal spray Comparator group: placebo (n = 49) Use of additional interventions: none
Outcomes	1. Rhinorrhoea • Measured by patient on paper diary card, in AM and PM • 4-point categorical scale of 0 to 3 (none, mild, moderate, severe) • Measured as instantaneous (i) and over previous 12 hours (reflective) • Instantaneous measured in AM, and reflective in both AM and PM • Measured during screening and treatment periods 2. Nasal congestion

Tantilipikorn 2010 (Continued)

- Same as above

3. Post-nasal drip

- Same as above

4. Eye itching/burning

- Same as above

5. Eye tearing/watering

- Same as above

6. Eye redness

- Same as above

7. rTNSS - reflective total nasal symptom score

- Combined 3 reflective individual nasal symptom scores
- Measured in AM and PM, which were averaged to arrive at the final daily value (daily rTNSS)
- Weekly data averaged

8. rTOSS - reflective total ocular symptom score

- Same as above, to derive daily rTOSS

9. AM iTOSS - morning instantaneous predose TOSS

- Obtained by summing of instantaneous pre-dose morning ocular scores

10. Adverse effects

- Epistaxis and any other adverse events

Funding sources	GlaxoSmithKline
Declarations of interest	None declared
Notes	Some of the study authors were investigators for GlaxoSmithKline, while rest of the authors were its employees. However, the study shows negative outcomes and it is unlikely that the relationship with the company influenced the study results.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised study: "Subjects who fulfilled the randomization criteria were randomly assigned in a 1:1 ratio to receive either FFNS 110 mcg once daily or vehicle placebo nasal spray once daily with the first dose being administered in the clinic following device demonstration. Subjects were stratified into two groups based on nasal cytology: those with eosinophils constituting >5% or <5% of nasal white blood cells." The sequence generation is not described.
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	Unclear risk	Double-blind study, blinding is not further described.

Tantilipikorn 2010 (Continued)

All outcomes

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blind study, blinding is not further described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients reported
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	Some of the study authors were investigators for GlaxoSmithKline, while the rest of the authors were its employees. However, the study shows negative outcomes and it is unlikely that the relationship with the company influenced the study results.

Tarlo 1977

Methods	Double-blind, cross-over, randomised controlled trial with 6 weeks treatment, 6 months follow-up (BDA for 3 weeks and placebo for 3 weeks; the order of administration was randomised)
Participants	Setting: Chest Allergy Clinic of St. Joseph's Hospital in Hamilton Sample size: Number randomised: 26 patients with perennial rhinitis, 9 non-allergic rhinitis Number completed: 26 Participant (baseline) characteristics: Age: ranged from 15 to 61 years (mean 34 years) Gender: 16 male and 10 female Symptom duration: rhinitis had been present for 2 to 20 years (mean 8.6 years) Severity: not reported - In the week prior to the start of the inhalers, the mean daily values for the symptom scores in the 26 patients was 4.5 for nasal congestion, 2.4 for rhinorrhoea, and 1.0 for sneezing (maximum 6 each). Both taste and smell were absent or impaired in 9, and smell alone was absent or impaired in 3. Inclusion criteria: unclear Exclusion criteria: not reported
Interventions	Intervention group: BDA (beclomethasone dipropionate aerosol (BDA), 50 µg 4 times daily sprayed into each nostril) (n = unclear) Comparator group: placebo: Freon propellant, same schedule (n = unclear) Use of additional interventions: none
Outcomes	- Recording of symptoms on dairy cards: the diary card was similar to that used by Norman and colleagues. Daily and nightly sneezing, nasal congestion and rhinorrhoea were each recorded as 0 if absent, 1 if they lasted less than 30 minutes, 2 if between 30 minutes and 2 hours, and 3 if longer than 2 hours. Taste and smell were recorded daily on the same card as normal, impaired or absent. - NAIR (nasal airway resistance) was measured by a modification of the method of Taylor and Shivalkar. A tight-fitting skin diver's mask was applied over the patient's nose and eyes. This was connected to a pneumotachograph for measuring flow and to a pressure transducer for measuring the transnasal pressure between the inside of the mask and a mouthpiece held tightly between the teeth and lips.

Intranasal corticosteroids for non-allergic rhinitis (Review)

Tarlo 1977 (Continued)

Flow and pressure were recorded on the y and x axes, respectively, of an x-y recorder, and NAIR was calculated from the slope of the tangent to the pressure-flow curve at a flow of 0.4 L/set. Before the use of the inhalers was started, NAIR was measured on 2 occasions. It was elevated (> 4 cm H₂O/L/sec) on one occasion in 6 and on both occasions in 10; borderline (3 to 4 cm H₂O/L/sec) on one occasion in 4; normal (< 3 cm H₂O/L/sec) on both occasions in 6.

- Total nasal symptoms: the sum of the nasal symptom scores (sneezing, congestion and rhinorrhoea, as well as the total) was measured during the third week of treatment
- Adverse events (no data for non-allergic rhinitis group separately), in general reported as mild

Funding sources	None
Declarations of interest	None declared
Notes	• Limited numerical data for non-allergic rhinitis group separately. • Polyps were present in 8 and asthma in 6 patients. 16 patients showed some evidence of increased IgE production. 9 patients had no signs of allergy and perennial rhinitis. Conclusions: • After 6 months 6/9 were successfully treated with intranasal corticosteroids and 3/9 were unsuccessfully treated with intranasal corticosteroids. • General conclusion: results in those in whom a possible allergic component could be identified were not different from those of the whole group.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised but random sequence generation not further described.
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinded but blinding not further described.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinded but blinding not further described. Symptom scoring could have been influenced.
Incomplete outcome data (attrition bias) All outcomes	High risk	Limited numerical data for non-allergic rhinitis group separately
Selective reporting (reporting bias)	High risk	Limited numerical data for non-allergic rhinitis group separately
Other bias	Unclear risk	8 patients had polyposis

Turkeltaub 1982

Methods	Double-blind, parallel-group, randomised, placebo-controlled trial with 2 weeks pre-treatment, 12 weeks of treatment
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Turkeltaub 1982 (Continued)

Participants	Setting: hospital clinic, USA Sample size: • Number randomised: unclear number of patients randomised to non-allergic rhinitis only group; 75 patients with perennial rhinitis randomised. Data reported for 33 patients in the non-allergic rhinitis only group. • Number completed: 33 non-allergic rhinitis (unclear how many non-allergic rhinitis patients randomised, 75 perennial rhinitis patients randomised) Participant (baseline) characteristics: • Age: not described • Gender: not described • Symptom duration: not described • Severity: "having year-round nasal symptoms severe enough to require medication", presumably moderate to severe • Reported as not different in terms of age, sex, duration and severity of nasal symptoms, or prior history of chronic sinusitis, polyposis and nasal surgery Inclusion criteria: patients with seasonal or perennial rhinitis: having year-round nasal symptoms severe enough to require medication, or who had a history of being treatment failures and using a variety of over-the-counter and prescription medication were selected for study. Specifically, non-allergic rhinitis patients were those who tested negatively to ragweed, rye grass, Bermuda, <i>Alternaria sp.</i>, house dust, cat and dog. Exclusion criteria: sinusitis, underlying nasal pathology resulting in fixed occlusion of a nostril, or patients receiving medication for another indication, which might suppress symptoms of perennial or seasonal rhinitis
Interventions	Intervention group: flunisolide (n = 20 after exclusions) • Dose: 25 µg per spray per nostril (300 µg daily) • Frequency: 3 times per day • Duration: 12 weeks • Vehicle: 20% propylene/15% polyethylene glycol Comparator group: placebo (20% propylene/15% polyethylene glycol vehicle) (n = 13 after exclusions) Use of additional interventions: none
Outcomes	1. Total symptom score • Sum score of symptoms scores for sneezing, runny nose, stuffy nose, eye itch and throat itch, each measured on a 0 to 6 scale. To this was added the number of tablets and nasal sprays required to control nasal symptoms for the preceding 12-hour period. • Possible scores from 0 to 40 2. Adverse effects • Measured for allergic and non-allergic rhinitis groups together • Cannot be recalculated for non-allergic rhinitis only
Funding sources	Syntex Corporation
Declarations of interest	None declared
Notes	Unconventional total nasal symptom score calculation. 15 patients excluded from perennial rhinitis group in efficacy assessment.

Turkeltaub 1982 (Continued)

Involvement of Syntex Corporation (a pharmaceutical company) is unclear.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random allocation for perennial rhinitis patients; random sequence generation was not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Study described as "double-blind", however blinding was not further described.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Study described as "double-blind", however blinding was not further described; symptom scoring could have been influenced.
Incomplete outcome data (attrition bias) All outcomes	High risk	15 patients in perennial rhinitis group (comprised of perennial allergic and non-allergic rhinitis patients) were not included in the analysis of efficacy, even though they were included in the analysis of side effects.
Selective reporting (reporting bias)	Low risk	All described outcomes (in perennial rhinitis group) can be found in the results, even though only symptom scores can be separated for the non-allergic rhinitis group only, and other outcomes are reported cumulatively for both allergic and non-allergic rhinitis perennial rhinitis groups.
Other bias	Unclear risk	Involvement of Syntex Corporation (a pharmaceutical company) is unclear.

Varricchio 2011

Methods	Single-blind (patients not blinded), parallel-group, randomised, placebo-controlled trial with 8 weeks duration of treatment
Participants	Setting: 2 hospitals in Naples, Italy Sample size: • Number randomised: 60 • Number completed: 60 Participant (baseline) characteristics: • Age: 21 to 63 years (mean 42.8 years) • Gender: 39 male, 21 female • Symptom duration: unclear • Severity: unclear • Not significant for age, gender, nasal score, turbinate hypertrophy, nasal cytology Inclusion criteria: patients with diagnosis of non-allergic rhinitis based on history of nasal symptoms (including sneezing, rhinorrhoea and nasal obstruction typically dependent on exposure to triggers such as odours, irritants, weather changes), presence of inflammatory cells on nasal smear, and negative SPT according to validated criteria.

Varricchio 2011 (Continued)

Exclusion criteria: acute or chronic upper respiratory infections, anatomic nasal defects, documented sensitisation (skin prick testing done to confirm), using intranasal or oral corticosteroids, nasal or oral decongestants, anti-leukotrienes, and intranasal or oral antihistamines during the previous 4 weeks, or had a history of chronic epistaxis, immunodeficiency, or hypersensitivity to flunisolide

Interventions	Intervention group: flunisolide (n = 30) • Dose: 0.5 mg/ml, 2 mL (1 mg) at each application, twice a day (total 2 mg per day) = 2000 µg/day • Frequency: twice a day • Duration: 8 weeks • Vehicle: Rinowash nebuliser Comparator group: placebo (isotonic saline solution) (n = 30) Use of additional interventions: none	
Outcomes	1. Total symptom score: • 4 items (nasal itching, sneezing, rhinorrhoea and nasal obstruction) assessed on a scale of 0 to 3 • Possible scores from 0 to 12 • Lower score indicates better outcome • Assessed on day 1 and 8 weeks 2. Adverse events • Unclear how assessed (only narrative results reported)	
Funding sources	None	
Declarations of interest	None declared	
Notes	Comparisons made both between groups, as well as change of baseline. Very high dose of flunisolide - 2 mg per day. Other studies used 200 µg to 400 µg per day.	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomly assigned; random sequence generation was not described.
Allocation concealment (selection bias)	High risk	Allocation was not concealed from patients; single-blinded study.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Single-blind study: patients were not blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessing physicians were blinded, patients not; no more details on blinding of physicians. Symptom scoring by patients.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients enrolled in the study completed the 8-week trial.

Varricchio 2011 (Continued)

Selective reporting (re-reporting bias)	Low risk	All data reported.
Other bias	Low risk	No others potential biases could be distinguished.

Warland 1982

Methods	Double-blind, cross-over, randomised, placebo-controlled trial with 4 weeks per treatment, 2-week interval between 2 treatment periods
Participants	Setting: University of Bergen, Norway Sample size: • Number randomised: 34 patients suffering from perennial rhinitis, 22 allergic rhinitis patients, 12 vasomotor rhinitis patients • Number completed: 12 vasomotor rhinitis patients reported Participant (baseline) characteristics: • Age: mean 32.5 (range 16 to 76) • Gender: 14 males, 20 females • Symptom duration: mean 5.9 years • Severity: 1 slight, 24 moderate, 9 severe Inclusion criteria: unclear Exclusion criteria: patients who were pregnant, who were suffering from nasal obstruction due to nasal polyps, or who were taking corticosteroids were excluded from the trial
Interventions	Intervention groups: flunisolide nasal solution: 200 µg per day (n = unclear) Comparator group: placebo (n = unclear) Use of additional interventions: none
Outcomes	Daily record of overall severity of symptoms on a scale from 0 to 3 Sneezing, runny nose, nose blowing and post-nasal drip per individual nasal symptom on a scale from 0 to 4. Condition of nasal mucosa and quantity and aspect of nasal secretions. Conclusion: a statistically significant difference in favour of flunisolide nasal solution Vasomotor rhinitis: total effect: 0/12, substantial effect: 3/13, minor effect: 3/12
Funding sources	None
Declarations of interest	None declared
Notes	Flunisolide nasal solution seems to be effective in both allergic rhinitis as vasomotor rhinitis, although it seems to be more effective in an allergic state. Limited separate data for non-allergic rhinitis subgroup versus allergic rhinitis subgroup. No numerical data for non-allergic rhinitis subgroup for one of the outcomes from our protocol.

Warland 1982 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised study; unclear random sequence generation
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind, no more details on blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blind, no more details on blinding; scoring of symptoms could be influenced
Incomplete outcome data (attrition bias) All outcomes	High risk	Limited numerical data for vasomotor rhinitis patients only
Selective reporting (reporting bias)	High risk	Limited numerical data for vasomotor rhinitis patients only
Other bias	Unclear risk	No other risks of bias could be distinguished

Webb 2002

Methods	Double-blind, double-dummy, parallel-group, randomised, placebo-controlled trial with 7 days screening, 28 days treatment
Participants	Setting: clinic patients, Allergy and Asthma Research Associates, USA. Reported as integrated data from 2 multi-centre trials and 1 single-centre trial Sample size: • Number randomised: 983 • Number completed: 651 Participant (baseline) characteristics: • Age: range 12 to 83 years; mean 41 to 43 years • Gender: % males 34% to 39% in 3 treatment groups • Symptom duration: more than 1 year • Severity: as above • Ethnicity: 93% to 96% Caucasian • No differences between groups for age, gender, ethnicity, duration of symptoms, % NARES and baseline TNSS (overall, in NARES and in non-NARES) Inclusion criteria: perennial non-allergic rhinitis, negative skin tests to all geographically relevant allergens. Symptom severity 150 on TNSS on at least 4 of 7 days immediately preceding randomisation Exclusion criteria: other rhinitis medications (e.g. antihistamines)
Interventions	Parallel-group study:

Intranasal corticosteroids for non-allergic rhinitis (Review)

Webb 2002 (Continued)

a. Fluticasone propionate 200 µg daily

b. Fluticasone propionate 400 µg daily

Included in meta-analysis:

Fluticasone propionate 400 µg daily (n = 325)

- Doses: 400 µg daily
- Frequency: twice daily
- Duration: 28 days
- Vehicle: aqueous solution
- Device: aqueous nasal spray

Comparator group: placebo (n = 326)

- Vehicle without active ingredient
- Otherwise same as above

Use of additional interventions: none

Outcomes	1. Nasal obstruction • Diary card each evening • Time points: baseline, 2 and 4 weeks • VAS, 0 to 100 mm 2. Post-nasal drip • As above 3. Rhinorrhoea • As above 4. TNSS • Sum of individual scores • 2 studies used 3 symptoms (nasal obstruction, post-nasal drip, and rhinorrhoea) - 0 to 300 score for TNSS • Third study used 4 symptoms (nasal obstruction, post-nasal drip, rhinorrhoea and sneezing) - 0 to 400 score for TNSS • Only patients with a combined score of 150 on the first 2 studies and 200 of the third study were randomised. • For this combined report, only 3 symptoms were used to calculate TNSS (nasal obstruction, post-nasal drip and rhinorrhoea) • Possible scores are 0 to 300
Funding sources	SmithKline Beecham Corporation doing business as GlaxoSmithKline
Declarations of interest	None declared
Notes	Integrated data from 2 multi-centre trials and 1 single-centre trial: report of 3 individual studies pulled together (done by pharmaceutical company). Included the same outcome separately for NARES and non-NARES groups: only mean value of TNSS change from baseline presented, without SD or P value, so cannot include in meta-analysis. Sponsored by a grant from SmithKline Beecham Corporation doing business as GlaxoSmithKline.

Risk of bias

Webb 2002 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised, double-blind trial. Random sequence generation was not described.
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding was not described in further detail
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	See above. Symptom scoring could have been influenced.
Incomplete outcome data (attrition bias) All outcomes	Low risk	"In all, 95% of patients completed the protocol-specified 28 days of treatment, with 2% of any treatment group being withdrawn for lack of efficacy." This percentage is low enough that it likely did not affect the results in a major way.
Selective reporting (reporting bias)	Unclear risk	Individual symptom scores measured but only TNSS reported.
Other bias	High risk	Individual symptom scores measured, but only TNSS reported and 4 employees of the company are authors.

AZENS: azelastine nasal spray
 BDA: beclomethasone dipropionate aerosol
 BMI: body mass index
 ECG: electrocardiogram
 FDA: (US) Food and Drug Administration
 FFNS: fluticasone furoate nasal spray
 FP: fluticasone propionate
 FPANS: fluticasone propionate aqueous nasal spray
 FPNS: fluticasone propionate nasal spray
 MCA: minimal cross-sectional area
 N/A: not available
 NANIPER: non-allergic, non-infectious perennial rhinitis
 NARES: non-allergic rhinitis with eosinophilia syndrome
 NAVMR: non-allergic vasomotor rhinitis
 NSAID: non-steroidal anti-inflammatory drug
 PEF: peak expiratory flow
 PEFR: peak expiratory flow rate
 PNIF: peak nasal inspiratory flow
 RAST: radioallergosorbent
 RCT: randomised controlled trial
 RQLQ: Rhinoconjunctivitis Quality of Life Questionnaire
 rTNSS: reflective total nasal symptom score
 rTOSS: reflective total ocular symptom score
 SD: standard deviation
 SEM: standard error of the mean
 SNOT-22: Sinonasal Outcomes Test 22
 SPT: skin prick test
 TNSS: reflective total nasal symptom score
 TOSS: total ocular symptom score
 URTI: upper respiratory tract infection

Intranasal corticosteroids for non-allergic rhinitis (Review)

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VAS: visual analogue scale

VMR: vasomotor rhinitis

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

Study	Reason for exclusion
Adamopoulos 1995	Neither numerical nor narrative data available for non-allergic rhinitis subgroup
Arbesman 1983	Neither numerical nor narrative data available for non-allergic rhinitis subgroup
Astafieva 2012	COMPARISON: this study compared 2 types of intranasal corticosteroids, brand versus generic. This was not included in our protocol.
Balle 1982b	Neither numerical nor narrative data available for non-allergic rhinitis subgroup
Berger 2012	Neither numerical nor narrative data available for non-allergic rhinitis subgroup
Bernstein 1997	Neither numerical nor narrative data available for non-allergic rhinitis subgroup
Blair 1977	Neither numerical nor narrative data available for non-allergic rhinitis subgroup
Bunnag 1992	Neither numerical nor narrative data available for non-allergic rhinitis subgroup
Celiker 2011	COMPARISON: this study compared intranasal corticosteroids with radiofrequency ablation. This comparison was not included in our protocol.
Chatterjee 1974	Neither numerical nor narrative data available for non-allergic rhinitis subgroup
Dieges 1978	Neither numerical nor narrative data available for non-allergic rhinitis subgroup
Dockhorn 1999	Neither numerical nor narrative data available for non-allergic rhinitis subgroup
Gibson 1974	Neither numerical nor narrative data available for non-allergic rhinitis subgroup
Hansen 1974	Neither numerical nor narrative data available for non-allergic rhinitis subgroup
Harding 1976	Neither numerical nor narrative data available for non-allergic rhinitis subgroup
Hartley 1985	Neither numerical nor narrative data available for non-allergic rhinitis subgroup
Haye 1993	Neither numerical nor narrative data available for non-allergic rhinitis subgroup
Jones 1979	Neither numerical nor narrative data available for non-allergic rhinitis subgroup
Joubert 1983	Neither numerical nor narrative data available for non-allergic rhinitis subgroup
Juniper 1993	Neither numerical nor narrative data available for non-allergic rhinitis subgroup
Kakumanu 2003	Neither numerical nor narrative data available for non-allergic rhinitis subgroup
Kivisaari 1998	Neither numerical nor narrative data available for non-allergic rhinitis subgroup
Kohan 1989	Neither numerical nor narrative data available for non-allergic rhinitis subgroup
Lahdensuo 1977	Neither numerical nor narrative data available for non-allergic rhinitis subgroup

Study	Reason for exclusion
Lau 1990	Neither numerical nor narrative data available for non-allergic rhinitis subgroup
Lebowitz 1993	Neither numerical nor narrative data available for non-allergic rhinitis subgroup
Malmberg 1988	Neither numerical nor narrative data available for non-allergic rhinitis subgroup
McAllen 1969	Neither numerical nor narrative data available for non-allergic rhinitis subgroup
McAllen 1980	Neither numerical nor narrative data available for non-allergic rhinitis subgroup
Negreiros 1975	Neither numerical nor narrative data available for non-allergic rhinitis subgroup
Price 2013	The authors were contacted, but suggested "the subpopulation studied with NAR is too small from which to draw any meaningful conclusions"
Rusnak 1981	Neither numerical nor narrative data available for non-allergic rhinitis subgroup
Scadding 1991	Neither numerical nor narrative data available for non-allergic rhinitis subgroup
Shaw 1979	Neither numerical nor narrative data available for non-allergic rhinitis subgroup
Small 1982	No data were provided in the results for the placebo group
Svendsen 1989	Neither numerical nor narrative data available for non-allergic rhinitis subgroup
Sy 1979	Neither numerical nor narrative data available for non-allergic rhinitis subgroup
Synnerstad 1996	This was a parallel-group, open-label (non-blinded) randomised study of budesonide versus beclomethasone dipropionate nasal sprays. In addition to obvious high risk of bias for allocation concealment, blinding of participants and personnel, and blinding of outcome assessors, the study had issues with incomplete outcome data, and some issues with selective outcome reporting (individual nasal symptoms measured but not thoroughly reported, total nasal symptoms reported but not included in methods). This study was supported by a grant from Astra Draco AB, Lund, Sweden, and the second author worked for the company. The company provided budesonide (Rhinocort). The study suggested that budesonide was better than beclomethasone. There are significant grounds to suspect high risk of bias. Based on these observations combined with incomplete and selective outcome data reporting little to no valuable numerical or descriptive outcome data, we decided to exclude this study.
Turner Warwick 1980	Neither numerical nor narrative data available for non-allergic rhinitis subgroup
Webb 1977	Neither numerical nor narrative data available for non-allergic rhinitis subgroup
Weckx 2001	Neither numerical nor narrative data available for non-allergic rhinitis subgroup
Wight 1992	Neither numerical nor narrative data available for non-allergic rhinitis subgroup
Zucker 2019	Meta-analysis with the only relevant study already included in our review

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

NCT04002349

Trial name or title	'Study of medication for nonallergic rhinitis (NAR) based on cluster analysis'
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Intranasal corticosteroids for non-allergic rhinitis (Review)

NCT04002349 (Continued)

Methods	Randomised, parallel-group clinical trial
Participants	Non-allergic rhinitis patients
Interventions	Placebo (0.9% natural saline spray), budesonide nasal spray (Rhinocort), levocabastine nasal spray, combined treatment
Outcomes	Unclear
Starting date	1 July 2019
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Notes	Estimated study completion date: 31 March 2020

ADDITIONAL TABLES

Table 1. Summary of patient-reported disease severity scores

Study ID	Symptoms measured	Score for each symptom	Summation (total range)	Notes
Arikan 2006	Nasal obstruction	Measured on a VAS: 0 to 10, 0 is better	Completed prior to trial and at 1, 2 and 3 months (range 0 to 10); as only one symptom no summation needed	No summary data reported to allow inclusion in the meta-analysis for this outcome
Balle 1982	1. Obstruction 2. Rhinorrhoea 3. Sneezing	Scale unclear, low indicates fewer symptoms	Total scores (for the last 7 days of a 2-week treatment period) represented the means of scores for the 3 symptoms (range unclear)	Unclear scale for individual symptoms
Blom 1997	A. Total nasal score (sum score of blockage, sneezing and rhinorrhoea) 1. Blockage 2. Sneezing 3. Rhinorrhoea B. Overall intensity of total nasal symptoms Does not consist of individual symptoms	A. Measured on a scale of 0 to 3 (3 means worse) B. Measured on a VAS: 0 to 10 (0 is better)	A. Presented as mean sum score of 3 symptoms for 1 week (range 0 to 3) B. Measured at 2 weeks pre-treatment, 4 weeks after first batch of treatment, 8 weeks after treatment (range 0 to 10); overall intensity, therefore no summation of symptoms	We used B as a total nasal symptom score because a VAS is a more established measurement
Boechat 2019	Combined nasal symptom score (after emailing author):	Measured on a VAS scale of 0 to 10 (10 is worse)	Measured pre-intervention and at 2 weeks	—

Table 1. Summary of patient-reported disease severity scores (Continued)

	1. Nasal blockage 2. Sneezing 3. Nasal itching 4. Rhinorrhoea			
Behncke 2006	Total nasal symptom score, unclear definition	Unclear	Unclear	—
Day 1990	1. Blocked nose 2. Itchy nose 3. Runny nose 4. Sneezing	Measured on a scale of 0 to 3 (0 is better)	Mean change in total combined symptom score (range 0 to 3) from end of treatment to baseline (week 4 versus week 0)	—
Ellegård 2001	Congestion	Measured on a scale of 0 to 4 (0 is better)	Reported after 8 weeks of treatment and 16 weeks of post-treatment follow-up (range 0 to 4); as only one symptom no summation needed	We evaluated the data at the end of 8 weeks of treatment as this was the most common method of measurement among other studies
Guo 2015	Total nasal symptom score; no breakdown in individual symptoms	Scale unclear	Measured pre-intervention and at 2 weeks; range and summation unclear	—
Hallén 1997	Nasal congestion	Measured on a VAS of 0 to 100 (0 is better)	Reported for all days, 0 to 14 days, in the morning and in the evening (range 0 to 100); as only one symptom no summation needed	No differences between morning and evening data. Reported morning data at day 13.
Havas 2002	1. Rhinorrhoea 2. Nasal blockage 3. Sneezing 4. Headache 5. Post-nasal drip 6. Sore throat	Measured on a VAS of 0 to 5 (0 = no symptoms), separately for each side	Sum of mean values of rhinorrhoea, nasal blockage and sneezing (range 0 to 30); measurement at end of treatment	We did not use the reported aggregate relief score, but instead calculated a total nasal symptom score out of rhinorrhoea, nasal blockage and sneezing (mean values and SDs per symptom were provided)
Hillas 1980	Total nasal symptom score 1. Sneezing 2. Rhinorrhoea 3. Nasal pruritis 4. Blocked nose 5. Itchy eyes 6. Watery eyes 7. Red eyes	Both measured on a scale of 0 to 3 (0 = nil, 1 = mild, 2 = moderate and 3 = severe)	Total nasal symptom score: reported as a mean of 4-week treatment period	No separate data reported for non-allergic rhinitis, only responder/non-responder data

Table 1. Summary of patient-reported disease severity scores *(Continued)*

Individual symptom scores				
Incaudo 1980	Overall severity of rhinitis	Measured daily on a scale of 1 to 4 (0 is better)	Reported mean at end of week 2, 4, 6 and 8 (range 0 to 4)	We did not use the reported individual rhinitis symptoms to calculate a total nasal symptom score, as only P values were reported
Jacobs 2009	1. Congestion 2. Rhinorrhoea 3. Post-nasal drip	Measured twice daily on diary cards using a 4-point categorical scale ranging from 0 (symptom not present) to 3 (symptom hard to tolerate; interferes with daily activities or sleeping)	TNSS is sum of the 3 symptom scores (range 0 to 9). Change in TNSS (range 0 to 9) from end of treatment (week 4) to baseline.	We used daily reflective TNSS and not morning instantaneous TNSS
Jessen 1990	1. Nasal secretion 2. Sneezing 3. Nasal blockage	All 3 symptoms were measured daily on a scale of 0 to 3/4 (0 is better)	Reported as sum score of 2-week treatment period (range 0 to 126/168)	Unclear whether maximum scale was 3 or 4
Kalpakioglu 2010	1. Rhinorrhoea 2. Congestion 3. Itching 4. Sneezing 5. Anosmia 6. Conjunctivitis	Scale of 0 to 4 (0 is better)	Most likely - although not explicitly cited - sum of all individual symptoms. Reported for 2 weeks after treatment. Reported as mean change from baseline.	—
Lin 2017	1. Nasal obstruction 2. Nasal itch 3. Rhinorrhoea 4. Sneezing	Unclear scale	Unclear total range of symptoms	—
Lundblad 2001	1. Rhinorrhoea 2. Nasal stuffiness/congestion 3. Nasal itching 4. Sneezing	Measured on a scale of 0 to 3 (0 is better)	Range 0 to 12; reported most likely as sum at the end of treatment	Converted into dichotomous outcome: improved versus unimproved. Improvement defined as a reduction of at least 1 point in the overall symptom score. No numerical data on original TNSS, so not included in meta-analysis for this outcome
Löfkvist 1976	1. Nasal catarrh 2. Blockage 3. Nasal itching 4. Sneezing	Measured on a scale of 0 to 3 (0 is better)	Range 0 to 12	No numerical data on original TNSS, therefore not included in meta-analysis. There are data on 'non-responder/improvement/responder'

Table 1. Summary of patient-reported disease severity scores (Continued)

Malm 1976	1. Nasal obstruction 2. Rhinorrhoea 3. Sneezing 4. Eye irritation	Measured on a scale of 0 to 3 (0 is better)	TNSS not reported, but calculated for meta-analysis: sum of mean values of nasal obstruction, rhinorrhoea and sneezing (range 0 to 9); measurement at end of treatment)	We calculated a total nasal symptom score out of rhinorrhoea, nasal blockage and sneezing (mean values and SDs per symptom were provided) for the dosages 200 µg, 400 µg and 800 µg
Malm 1981	1. Nasal obstruction 2. Nasal secretion 3. Sneezing	Measured on a scale of 0 to 3 (0 is better) Reported as mean ± SEM of at last 3 days of the patients symptom score in each treatment period for nasal obstruction and secretion. For sneezing: scale of 0 to 3 (0 is good: no sneezing = 0; 1 to 5 sneezes = 1 point; 6 to 15 = 2 points; more than 15 sneezes = 3 points)	TNSS not reported, but calculated for meta-analysis: sum of mean values of nasal obstruction, rhinorrhoea and sneezing (range 0 to 9)	We calculated a total nasal symptom score out of rhinorrhoea, nasal blockage and sneezing (mean values and SDs per symptom were provided) for the dosages 50 µg, 200 µg and 800 µg
Meltzer 1994	Nasal symptom score, unclear definition	Unclear	Unclear	Unclear
Miller 1969	1. Nasal obstruction 2. Discharge 3. Post-nasal drip 4. Sneezing	Measured by patient at 2 and 4 weeks after treatment on a scale of 0 to 3 (0 is better)	Not reported	We were unable to calculate a SD for rhinorrhoea (secretion) and post-nasal drip as the P values for these symptoms were not reported, therefore not included in meta-analysis for this outcome
O'Reilly 1991	1. Nasal obstruction 2. Anterior rhinorrhoea 3. Posterior rhinorrhoea 4. Sneezing 5. Facial pain	Measured on a scale of 0 to 5 (0 is better)	Composite score for all 5 symptoms, range 0 to 25	Only P values reported, therefore not included in meta-analysis for this outcome
Scadding 1995	A. 1. Nasal blockage on waking 2. Nasal blockage during the rest of the day 3. Sneezing 4. Rhinorrhoea B. 1. Overall assessment of symptoms by patient 2. Overall assessment of symptoms at clinic visit	A. Measured by patient on a scale of 0 to 3 on a daily card (0 is better) B. 1. Measured by patient on a scale of 0 to 3 on a daily card (0 is better) 2. VAS, 0 to 10 cm (10 = worst symptoms)	A. Range 0 to 12 B.1. Range 0 to 3 B.2. Range 0 to 10	No data reported for non-allergic rhinitis subgroup separately, therefore not included in meta-analysis. The study states that there were no differences between allergic and non-allergic rhinitis patients

Table 1. Summary of patient-reported disease severity scores (Continued)

Schulz 1978	1. Sneezing 2. Stuffy nose 3. Runny nose 4. Nose blowing 5. Post-nasal drip	Duration in hours per symptom measured	All 5 symptoms combined to determine overall duration of patients' symptoms. Reported as percentage of days during which all 5 of the symptoms lasted 1 hour or less and the percentage of days during which at least one of the 5 symptoms lasted 4 hours or more	No data reported for non-allergic rhinitis subgroup separately for this outcome, therefore not included in meta-analysis. There are data on 'responder/non-responder'.
Singh 2017	—	—	—	Not included in meta-analysis as TNSS data are reported in relationship to cold dry air provocation
Song 2018	A. Overall VAS B. Individual symptom VAS: 1. Congestion 2. Sneezing 3. Itching 4. Rhinorrhoea	Measured on a VAS: 0 to 10, 0 is better	Range (0 to 10), measurement at week 8	—
Spector 1980	1. Sneezing 2. Stuffiness 3. Runny nose 4. Nose blowing 5. Post-nasal drip	Patient evaluation, sum of 5 symptoms numerically assessed as absent (1), mild (2), moderate (3), or severe (4); range 1 to 4	Range (5 to 20), measurement at week 4	—
Tan-tilipikorn 2010	1. Rhinorrhoea 2. Nasal congestion 3. Post-nasal drip 4. Eye itching/burning 5. Eye tearing/watering 6. Eye redness	4-point categorical scale of 0 to 3 (none, mild, moderate, severe), measured by patient on paper diary card, in AM and PM, as instantaneous (i) and over previous 12 hours (reflective). Instantaneous score measured in AM, and reflective in both AM and PM - measured during screening and treatment periods	Combined 3 reflective individual nasal symptom scores (range 0 to 9) Measured in AM and PM, which were averaged to arrive at the final daily value (daily rTNSS)	Compared data from week 4 to baseline to arrive at change from baseline TNSS. We included the reflective TNSS (rTNSS) in the meta-analysis, not the instantaneous TNSS (iTNSS).
Tarlo 1977	Individual rhinitis symptoms: 1. Daily and nightly sneezing 2. Nasal congestion 3. Rhinorrhoea	0 if absent, 1 if they lasted less than 30 minutes, 2 if between 30 minutes and 2 hours, and 3 if longer than 2 hours	Total nasal symptoms: the sum of the nasal symptom scores (sneezing, congestion, and rhinorrhoea, as well as the total)	No separate data for non-allergic rhinitis subgroups

Table 1. Summary of patient-reported disease severity scores (Continued)

Total nasal symptoms				
Turkeltaub 1982	1. Sneezing 2. Runny nose 3. Stuffy nose 4. Eye itch 5. Throat itch	Measured on 0 to 6 scale (0 is better)	Sum score of symptoms scores for sneezing, runny nose, stuffy nose, eye itching and throat itching measured post-treatment, each measured on 0 to 6 scale (range 0 to 30). To this was added the number of tablets and nasal sprays required to control nasal symptoms for the preceding 12-hour period; possible scores range from 0 to 40	Unusual method of measurement of TNSS
Varricchio 2011	1. Nasal itching 2. Sneezing 3. Rhinorrhoea 4. Nasal obstruction	Measured on 0 to 3 scale (0 is better)	Range 0 to 12; assessed on day 1 and at 8 weeks	Reported TNSS as continuous data and change from baseline. We have included the first approach
Warland 1982	Overall severity of symptoms Individual rhinitis symptoms: 1. Sneezing 2. Runny nose 3. Nose blowing 4. Post-nasal drip	Overall severity of symptoms: scale from 0 to 3 Individual nasal symptoms: scale from 0 to 4	—	—
Webb 2002	1. Nasal obstruction 2. Post-nasal drip 3. Rhinorrhoea	Measured on a VAS, 0 to 100 (0 is better)	Range 0 to 300, measured at both 2 weeks and 4 weeks	TNSS reported as change from baseline. Combination of 3 studies

TNSS: total nasal symptom score

iTNSS: instantaneous total nasal symptom score

rTNSS: reflective total nasal symptom score

SD: standard deviation

Table 2. Nasal symptom scores: studies not included in meta-analysis

Study	Findings
Arikan 2006	Concluded that treatment with fluticasone propionate provided significantly greater relief from the symptom of nasal obstruction compared with placebo over the entire 3-month treatment period. Patients' subjective assessments of nasal obstruction after medical treatment correlated with the results of objective testing.
Lin 2017	This study was not included in the meta-analysis because of lack of quality of the study data. Firstly, the study presents unexpected data, with disappearance of the benefit of intranasal corticosteroids with longer follow-up. Secondly, including the study in the meta-analysis resulted in a high level of heterogeneity. The SD values that are presented in the study do not match with the pre-

Table 2. Nasal symptom scores: studies not included in meta-analysis (Continued)

	sented means, n and P values. The data make more sense if the as-presented SD values should actually be standard error of the mean (SEM), which was confirmed by a re-analysis. As the authors did not reply to our question regarding the above, we decided to not include this study in the meta-analysis. The study did show a beneficial effect of intranasal corticosteroids over placebo, however this effect disappeared with longer follow-up.
Meltzer 1994	This study was not included in the meta-analysis for this outcome as it did not report numerical data for the non-allergic rhinitis subgroup. They did conclude that fluticasone propionate reduces total symptoms, improves individual symptoms (mainly obstruction) and achieves a significant overall improvement in non-allergic rhinitis compared to placebo.
Miller 1969	Reported a statistically significant difference in symptoms in favour of intranasal corticosteroids (it did not report P values for rhinorrhoea and post-nasal drip so we were not able to calculate a SD).
Lundblad 2001	Reported no numerical data on original TNSS, so it could not be included in the meta-analysis for this outcome. It did report data that could be translated into proportions of 'responders/non-responders'. The study did not find significant differences between intranasal corticosteroids and placebo. The study converted TNSS into a dichotomous outcome: improved versus unimproved. Improvement was defined as a reduction of at least 1 point in the overall symptom score. No numerical data on original TNSS was provided, therefore this study was not included in the meta-analysis for this outcome.
Löfkvist 1976	This study was not included in the meta-analysis as no data on TNSS were reported. The study did report data on 'responders/non-responders' with 29/39 responders in the intranasal corticosteroids group and 12/39 responders in the placebo group, favouring intranasal corticosteroids with an odds ratio (OR) of 0.44 (95% confidence interval (CI) 0.24 to 0.64).
O'Reilly 1991	This study was not included in the meta-analysis as only P values were reported. Patients reported subjective symptom scores on a scale of 0 to 5 for nasal obstruction, anterior rhinorrhoea, posterior rhinorrhoea, sneezing and facial pain. When the composite scores for all 5 symptoms were compared, there was a significant difference between beclomethasone dipropionate and baseline ($P = 0.01$) and beclomethasone dipropionate and placebo ($P = 0.02$) in favour of beclomethasone dipropionate.
Scadding 1995	This study on 2 types of intranasal corticosteroids versus placebo in perennial rhinitis patients (allergic and non-allergic rhinitis) reported a number of individual rhinitis symptoms and an overall assessment of symptoms, but no separate data on non-allergic rhinitis patients were presented. However, the study does state that there were no differences between allergic and non-allergic rhinitis. This study reported a significant improvement with intranasal corticosteroids versus placebo in perennial allergic rhinitis, with fluticasone propionate aqueous nasal spray (200 µg) as effective as beclomethasone dipropionate µg twice daily.
Schulz 1978	This study was not included in the meta-analysis as no data on TNSS were reported. The study did report data on responders/non-responders with 6 of 14 responders in the intranasal corticosteroids group and 8 of 18 responders in the placebo group with an OR of 0.02 (95% CI 0.33 to 0.36), therefore not a significant difference.
Tarlo 1977	This study was not included in the meta-analysis for this outcome as it did not report enough numerical data for the non-allergic rhinitis subgroup. They concluded that after 6 months 6 of 9 non-allergic rhinitis patients were successfully treated with intranasal corticosteroids and 3 of 9 non-allergic rhinitis patients were unsuccessfully treated with intranasal corticosteroids. They concluded that their results (in favour of intranasal corticosteroids over placebo) in those in whom a possible allergic component could be identified were not different from those of the whole group.
Varricchio 2011	This study was not included in the meta-analysis because we decided to only include studies with an intranasal corticosteroid dosage of 200 µg to 400 µg. This study uses an intranasal corticosteroid dosage of 2000 µg. The study did report a significant improvement in nasal symptoms in non-allergic rhinitis after an 8-week treatment period with intranasal flunisolide.

Table 2. Nasal symptom scores: studies not included in meta-analysis *(Continued)*

Warland 1982

This study was not included in the meta-analysis for this outcome because it did not report numerical data for the non-allergic rhinitis subgroup. They concluded that flunisolide nasal solution seems to be effective in both allergic rhinitis and vasomotor rhinitis patients, although it seems to be more effective in an allergic state.

SD: standard deviation

TNSS: total nasal symptom score

CONTRIBUTIONS OF AUTHORS

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WJF, AG, CS and LR were responsible for drafting the review, selecting the studies, data extraction and analysis, and drafting the final manuscript. WJF conceived the idea and participated in drafting the review and the final manuscript. KA participated in data extraction and analysis and drafting the final manuscript. SC, JK and SA participated in reviewing the review manuscript and giving expert opinions. KS participated in selecting the studies, data extraction and analysis, and reviewing the review manuscript.

DECLARATIONS OF INTEREST

Christine Segboer: none known.

Artur Gevorgyan: Artur Gevorgyan has received speaker fees in 2017 from Takeda Canada, Abbott, Meda Pharmaceuticals and Mylan. Meda and Mylan are related to Dymista nasal spray. Takeda is related to Omnisar.

Klementina Avdeeva: none known.

Supinda Chusakul: none known.

Jesada Kanjanaumporn: none known.

Songklot Aeumjaturapat: none known.

Laurens Reeskamp: none known.

Wytske Fokkens: WJ Fokkens has received private sector support for research and/or clinical trials related to the treatment of allergic and non-allergic rhinitis from Chordate (2018/19), as well as public sector research support from the EU, and for studies not related to allergic and non-allergic rhinitis from GSK (2017-19), Sanofi (2016-19) and Novartis (2018-19). WJ Fokkens has also received a speaker fee from Sanofi (2018-19).

Kornkiat Snidvongs: none known.

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Internal sources

- No sources of support supplied

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the protocol the outcome 'other adverse events' was defined as local irritation/discomfort. While performing the review it became clear that widening the definition of 'other adverse events' to all other adverse events besides epistaxis (for example, pharyngitis, nasal dryness/crusting and headache) would result in more information.

Although we did not plan to perform a meta-analysis if heterogeneity was considered substantial (50% to 90%) or considerable (75% to 100%), we made one exception. We carried out pooling in the presence of very high heterogeneity in the case of the comparison 'Total nasal symptom score (change from baseline)' as result of the study [Jacobs 2009](#). The problems with [Jacobs 2009](#) that are responsible for

the high heterogeneity are described in detail above. This study is, however, one of the largest of the studies on this topic and very well known. For that reason we decided to retain it in the meta-analysis.

We calculated a total nasal symptom score (sum of mean symptom scores) and pooled SD ($\text{SQRT}(\text{SD}_a^2 + \text{SD}_b^2 + \text{SD}_c^2)$) from the individual symptoms of 'rhinorrhoea/secretions', 'congestion/obstruction' and 'sneezing' when studies only provided us with individual symptom scores. When assessing the individual symptoms that were used to calculate a total nasal symptom score in the other included studies (Table 1), these three symptoms were the most common. One could consider also including 'itch' (Hellings 2017); however, previous studies have shown that ocular itch plays a less dominant role in non-allergic rhinitis patients compared to allergic rhinitis patients (Segboer 2018). In addition, Malm 1976 would have been the only study for which we could also have included 'itch' to calculate a total nasal symptom score. Miller 1969 was the only study that also reported 'post-nasal drip' as an extra symptom that we could have included in a calculated total nasal symptom score; however, as we were not able to calculate a pooled standard deviation from this study, we were not able to calculate a total nasal symptom score from rhinorrhoea, congestion and post-nasal drip, which would otherwise have been justifiable.

Among studies treatment daily dosage varied from 50 µg to 2000 µg. Most of the studies that compared different dosages of intranasal corticosteroids used a cross-over study design with the exception of Blom 1997 and Webb 2002, which used a parallel-group study design. In the cross-over studies the same participants were treated with different dosages of intranasal corticosteroids, with short (one-week) or no washout, complicating a clear comparison between these dosage subgroups (Balle 1982; Malm 1976; Malm 1981). Only Balle 1982 showed a dosage effect for two nasal symptom score outcomes. Malm 1976 and Malm 1981 showed no significant difference between the dosage subgroups. The two parallel-group studies both concluded that there were no statistically significant differences between the different intranasal corticosteroid dosage subgroups (Blom 1997; Webb 2002). In the parallel-group studies the different dosage subgroups contained different participants but were compared with the same control group. To prevent counting the same participants or controls more than once, we decided to include one intranasal corticosteroid dosage in the meta-analysis. The most common intranasal corticosteroid dosage was 200 µg. A test for subgroup differences showed no significant difference ('no dosage effect') between 200 µg and 400 µg of intranasal corticosteroids. We therefore included studies in the meta-analysis with an intranasal corticosteroid dosage range of 200 µg to 400 µg.

In the protocol, under electronic searches we planned to search KoreaMed, PakMedinet, IndMed and ISRCTN. However, the Cochrane ENT Information Specialist has deemed that these sources are not worth searching for the majority of reviews. These searches were not performed and were therefore not reported in the Search methods for identification of studies section.