

Capsaicin for non-allergic rhinitis (Review)

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Capsaicin for non-allergic rhinitis

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ABSTRACT

Background

There are many forms of rhinitis. Patients are diagnosed with non-allergic rhinitis when anatomic, infectious and allergic aetiologies have been excluded. The symptoms, including nasal congestion, blockage or obstruction, clear rhinorrhoea, sneezing and, less frequently, nasal itching, can range from mild to debilitating. It affects between 25% and 50% of patients with rhinitis. Several medications are widely used in the treatment of non-allergic rhinitis, including oral and topical nasal antihistamines, intranasal and (rarely) systemic corticosteroids, and anticholinergics. Capsaicin, the active component of chili peppers, delivered intranasally, is considered a treatment option for non-allergic rhinitis.

Objectives

To assess the effectiveness of capsaicin in the management of non-allergic rhinitis compared with no therapy, placebo or other topical or systemic medications, or two or more of the above therapies in combination, or different capsaicin regimens.

Search methods

We searched the Cochrane Ear, Nose and Throat Disorders Group Trials Register; the Cochrane Central Register of Controlled Trials (CENTRAL 2015, Issue 5); PubMed; EMBASE; CINAHL; Web of Science; Cambridge Scientific Abstracts; ICTRP and additional sources for published and unpublished trials. The date of the search was 24 June 2015.

Selection criteria

Randomised controlled trials in adult patients with non-allergic rhinitis comparing intranasal capsaicin with no therapy, placebo or other topical or systemic medications, or their combinations.

Data collection and analysis

We used the standard methodological procedures expected by The Cochrane Collaboration.

Main results

We included four studies (five publications) involving 302 participants with idiopathic non-allergic rhinitis. All the included studies described patients with moderately severe, idiopathic non-allergic rhinitis who were between the ages of 16 and 65. Studies had follow-up periods ranging from four to 38 weeks. The overall risk of bias in the studies was either high or unclear (two studies had overall high risk of bias, while two others had low to unclear risk of bias). Using the GRADE system we assessed the evidence as being of low to moderate quality. A meta-analysis was not possible, given lack of similarity of the reported outcomes.

Two studies compared capsaicin with placebo. One study reported that capsaicin resulted in an improvement of overall nasal symptoms (a primary outcome) measured on a visual analogue scale (VAS) of 0 to 10. There was a mean difference (MD) of -3.34 (95% confidence interval (CI) -5.24 to -1.44), MD -3.73 (95% CI -5.45 to -2.01) and MD -3.52 (95% CI -5.55 to -1.48) at two, 12 and 36 weeks post-treatment, respectively. Another study reported that, compared to placebo, capsaicin (at 4 µg/puff) was more likely to produce overall symptom resolution (reduction in nasal blockage, sneezing/itching/coughing and nasal secretion measured with a daily record chart) at four weeks post-treatment (a primary outcome). The risk ratio (RR) was 3.17 (95% CI 1.38 to 7.29).

One study compared capsaicin to budesonide (an intranasal corticosteroid). This study found that patients treated with capsaicin had a better overall symptom score compared to those treated with budesonide (MD 2.50, 95% CI 1.06 to 3.94, VAS of 0 to 10). However, there were no differences in the individual symptom scores for headache, postnasal drip, rhinorrhoea, nasal blockage, sneezing and sore throat assessed during the last three days of a four-week treatment.

One study compared two different regimens of capsaicin administration: five treatments in one day versus five treatments given every two to three days during two weeks. Using daily record charts, the study reported significant improvement of individual symptom scores for rhinorrhoea in patients treated five times per day, however numerical data were not presented. There were no improvements in the other outcomes: rhinorrhoea, nasal obstruction, sneezing and overall nasal symptoms, measured on a VAS.

Finally, one of these studies also compared three doses of capsaicin (to placebo). Patients treated with a 1 µg versus 4 µg per puff dose of capsaicin had a worse daily record chart overall symptom score resolution (RR 0.63, 95% CI 0.34 to 1.16).

Only one study attempted to measure adverse effects (a primary outcome), however due to methodological issues with the assessment we are unable to draw any conclusions.

We sought to include other secondary outcomes (e.g. quality of life measures, treatment dropouts, endoscopic scores, turbinate or mucosal size, cost of therapy), but none of these were measured or reported in the included studies.

Authors' conclusions

Capsaicin may be an option in the treatment of idiopathic non-allergic rhinitis. It is given in the form of brief treatments, usually during the same day. It appears to have beneficial effects on overall nasal symptoms up to 36 weeks after treatment, based on a few, small studies (low-quality evidence). Well-conducted randomised controlled trials are required to further advance our understanding of the effectiveness of capsaicin in non-allergic rhinitis, especially in patients with non-allergic rhinitis of different types and severity, and using different methods of capsaicin application.

PLAIN LANGUAGE SUMMARY

Capsaicin for non-allergic rhinitis

Review question

Is capsaicin applied into the nose (intranasal) effective in the management of non-allergic rhinitis compared with no therapy, placebo or other topical or systemic medications?

Background

Rhinitis means inflammation of the nose. It affects 30% to 40% of the general population. There are many forms of rhinitis: rhinosinusitis (or simply sinusitis), allergic rhinitis and non-allergic rhinitis. Non-allergic rhinitis is diagnosed in patients who have negative tests for allergies and also do not have sinusitis. The symptoms include congestion of the nose, a blocked or obstructed sensation in the nose that causes difficulty breathing, clear nasal discharge (runny nose), sneezing and nasal itching. There are several subtypes of non-allergic rhinitis: occupational (from exposure to chemicals), smoking, gustatory (related to eating food or drinking fluid), hormonal

(from changes in hormone levels in the body), pregnancy, senile or elderly (mostly affecting the older population), medication-induced (for example, from overuse of decongestant nasal sprays) and local allergic (local allergy in the nose, while skin or blood allergy tests are negative). The most common subtype of non-allergic rhinitis is 'idiopathic' or 'vasomotor' rhinitis, which results from imbalance of the neural (nerve) system that manages the function of the nose. The mechanisms of many of these subtypes remain unknown. Non-allergic rhinitis affects about 25% to 50% of patients with rhinitis and is therefore very common.

Capsaicin is the active ingredient of chili peppers. It has medicinal properties and is used elsewhere in medicine, for example for neuralgias (nerve pain) and psoriasis (a skin disease). The side effects of using capsaicin in the nose include irritation, burning, sneezing and coughing, however there are no known long-term side effects of capsaicin use. Capsaicin is given in the form of brief treatments, usually during the same day. It works by down-regulating transient receptor potential vanilloid (TRPV) receptor expression on C-sensory fibres. TRPV represents special ion channels involved in the sensations of pain, cold, hotness, tastes, pressure and vision. C fibres help to conduct some of these sensations. There is ongoing research into the effects of capsaicin on these mechanisms and its clinical uses.

Study characteristics

We included four studies involving 302 patients with idiopathic non-allergic rhinitis. All the included studies described patients with moderately severe idiopathic non-allergic rhinitis, who were between the ages of 16 and 65. The studies had a follow-up ranging from four to 38 weeks after treatment.

Key results

Individually, the studies reported that the overall function of the nose in patients with non-allergic rhinitis improved when treated with capsaicin compared to placebo. Capsaicin also seems to work better than another common type of nasal medication, budesonide (a steroid). The best knowledge that we have on capsaicin treatment supports giving it five times in one day, and to use doses of at least 4 micrograms in each puff. We could not combine the results together. The included studies did not have sufficient information to allow us to draw a conclusion about side effects. We also wanted to include other outcomes (e.g. quality of life measures, treatment dropouts, endoscopic scores, turbinate or mucosal size, cost of therapy), but none of these were measured or reported in the included studies.

Quality of the evidence

Overall, we judged the quality of the evidence to be of low to moderate quality. The evidence is up to date to June 2015.

Conclusions

Given that many other options do not work well in non-allergic rhinitis, capsaicin is a reasonable option to try under physician supervision.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Capsaicin compared to placebo for non-allergic rhinitis						
Patient or population: non-allergic rhinitis Settings: tertiary university hospital Intervention: capsaicin Comparison: placebo						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Capsaicin				
Overall nasal symptom score 36 weeks post-treatment	The mean overall nasal symptom score 36 weeks post-treatment was 6.778	The mean overall nasal symptom score 36 weeks post-treatment in the intervention group was 3.52 lower (5.55 lower to 1.48 lower)	-	24 (1 RCT)	⊕⊕⊕○ moderate ^{1,2}	A lower score indicates better overall nasal symptoms
Daily record chart symptom resolution 4 weeks post-treatment (capsaicin 4 µg/puff versus placebo)	Study population		RR 3.17 (1.38 to 7.29)	104 (1 RCT)	⊕⊕○○ low ³	The bigger the number per 1000, the more patients would have resolution of their symptoms
	115 per 1000	366 per 1000 (159 to 841)				
	Moderate					
	115 per 1000	366 per 1000 (159 to 841)				
Treatment-related adverse events	Not reported	Not reported	-	-	-	-

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹Small sample size (40 patients total).

²Single study.

³Pseudo-randomisation was performed on an odds and evens basis.

BACKGROUND

Description of the condition

Non-allergic rhinitis is a term that includes rhinitis of several aetiologies. Patients are diagnosed with non-allergic rhinitis when anatomic, infectious and allergic aetiologies have been excluded. The symptoms include nasal congestion, blockage or obstruction, clear rhinorrhoea, sneezing and, less frequently, nasal itching. These symptoms can be intermittent or persistent and can range from mild to debilitating (Schroer 2012). Although studies on quality of life in non-allergic rhinitis are scarce, extrapolation of knowledge from studies in allergic rhinitis, as well as unpublished data in non-allergic rhinitis, testify to the significant impact of non-allergic rhinitis symptoms on patients' quality of life (Bousquet 2008; Gelardi 2008; Meltzer 1999).

Non-allergic rhinitis and allergic rhinitis have similar symptoms. Allergic rhinitis is excluded by negative findings of allergy history, skin prick testing and measurement of serum-specific IgE antibodies. The Allergic Rhinitis and its Impact on Asthma (ARIA) initiative, in collaboration with the World Health Organization, has developed guidelines for the diagnosis and treatment of allergic rhinitis (Bousquet 2008).

Non-allergic rhinitis also needs to be differentiated from acute and chronic rhinosinusitis with or without nasal polyps (CRSwNP and CRSsNP, respectively), an inflammation of the nose and paranasal sinuses due to infectious or inflammatory aetiology. Chronic rhinosinusitis is characterised by nasal obstruction, congestion or blockage, anterior or posterior rhinorrhoea, facial pressure or pain, and reduction or loss of smell. Several guidelines for the diagnosis and management of acute and chronic rhinosinusitis have been developed, including the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS 2012), the clinical practice guideline on adult sinusitis by the American Academy of Otolaryngology - Head and Neck Surgery (Rosenfeld 2007), and the Canadian clinical practice guidelines for acute and chronic rhinosinusitis (Desrosiers 2011).

Chronic rhinitis (allergic and non-allergic) affects up to 30% to 40% of the general population (Bousquet 2008). Most epidemiological studies report that 25% to 50% of rhinitis patients can be categorised as having non-allergic rhinitis (Fokkens 2002). Most studies agree on a female predominance of non-allergic rhinitis (Knudsen 2009; Molgaard 2007).

Non-allergic rhinitis can be subclassified based on different aetiologies: occupational (chemical), smoking, gustatory, hormonal, senile (rhinitis of the elderly), atrophic, medication-induced (including rhinitis medicamentosa), local allergic rhinitis, non-allergic rhinitis with eosinophilia syndrome (NARES) and idiopathic (vasomotor or non-allergic, non-infectious perennial allergic rhinitis (NANIPER)). However, the pathophysiology of non-allergic rhinitis remains largely unknown (Van Gerven 2012).

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). Gustatory rhinitis is accompanied by oversecretion of nasal mucus in response to irritating gustatory agents, usually spicy foods (Georgalas 2012). Hormonal rhinitis can occur during the menstrual cycle and puberty, due to hypothyroidism or acromegaly, as well as during pregnancy, where it resolves postpartum. Rhinitis of the elderly (senile rhinitis) is encountered in the older generation and characterised by the presence of constant rhinorrhoea and lack of other nasal complaints.

In the case of 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 5 to 10 days, resulting in dysregulation of the adrenergic receptors in the nasal mucosa and in a relative increase of the parasympathetic drive, leading to significant rhinorrhoea and nasal obstruction. These symptoms cause 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 or, rarely, oral corticosteroids.

Local allergic rhinitis is diagnosed when skin prick and serum-specific IgE testing are negative, however a nasal allergen provocation test is positive (Rondon 2012). A recent report attributed over a quarter of chronic rhinitis patients to local allergic rhinitis (Rondon 2012a). NARES is considered in the presence of rhinitis symptoms, no evidence of allergy and the presence of 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). Idiopathic rhinitis has been referred to as vasomotor rhinitis, NANIPER, non-infectious, non-allergic rhinitis (NINAR) and intrinsic rhinopathy. It is diagnosed based on the patient's complaints and exclusion of other types of rhinitis. Some patients in this group predominantly have congestion, whereas others may have unexplained rhinorrhoea as the main symptom. The latter group has been previously called vasomotor rhinitis. Nasal hyperreactivity is a common and characteristic feature of patients with chronic rhinitis, and can be elicited by cold dry air provocation (van Rijswijk 2005). Several mechanisms have been proposed to explain idiopathic rhinitis, including chronic inflammation, imbalance of parasympathetic and sympathetic neural systems, and activation of the non-adrenergic, non-cholinergic or peptidergic systems with involvement of C sensory fibres.

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 the 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 of non-allergic rhinitis (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 studies. This therapy is usually tried after failed treatment with intranasal corticosteroids (van Rijswijk 2005).

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

Capsaicin (8-methyl-N-vanillyl-6-nonenamide) is the active component of chili peppers, plants of the genus *Capsicum*. Along with other related compounds, it belongs to a group of chemicals identified as capsaicinoids. Capsaicin produces a burning sensation when a tissue comes into contact with it. This occurs via binding to transient receptor potential vanilloid 1 (TRPV1) receptor, an ion-channel type receptor, which can be stimulated by heat and physical abrasion. Binding of capsaicin to it results in a similar burning sensation. As a topical medication, capsaicin has been used for neuralgias and psoriasis. Several similar compounds are currently being tested in clinical trials.

Intranasal capsaicin is currently considered one of the treatment options for non-allergic rhinitis. Capsaicin is also one of the active ingredients (along with eucalyptus oil) in Sinus Buster, an over-the-counter nasal spray available in the United States (Bernstein 2011). The dose and frequency of intranasal capsaicin application have varied significantly in studies. Doses of capsaicin have ranged from 0.1 to 100 mg per application, given through one or several actuations of the spray depending on the capsaicin preparation in a particular study (Blom 1997/1998; Ciabatti 2009; van Rijswijk 2003). The regimen of capsaicin treatment has also ranged widely from five times during the same day, to three times per day for three days, to once daily for five days, or once every two to three

days for seven treatments. The local pharmacology of capsaicin in the nose is poorly understood. It is metabolised in the liver. The side effects of intranasal capsaicin application include irritation, burning, sneezing and coughing. There are no known long-term side effects of capsaicin use.

Intranasal capsaicin is currently available in many countries, including Austria, Belgium, Germany, Mexico, The Netherlands, Sweden, UK and USA.

How the intervention might work

Capsaicin affects the unmyelinated peptidergic sensory C fibres of the nasal mucosa, which are highly sensitive to it (Stjarne 1989). It is hypothesised that repeated high doses of capsaicin lead to degeneration of these nerve fibres. Unmyelinated sensory C fibres play a role in neurogenic reflex mechanisms in the nasal mucosa, both local and central. Stimulation of these sensory fibres by non-specific stimuli can lead to a local reflex in the nasal mucosa with a release of neuropeptides (C-peptide, CGRP, VIP). At the same time, capsaicin does not affect the number of inflammatory cells in the nasal mucosa long-term (Blom 1997/1998). The same study also did not show a difference in neuronal tissue density as expressed by synaptophysin or neurofilament staining.

Although these mechanisms are not considered definitive, several studies have demonstrated a significant improvement of nasal symptoms after topical administration of capsaicin (Lacroix 1991; van Rijswijk 2003).

Interestingly, intranasal capsaicin has also been studied in allergic rhinitis. However, a Cochrane review on capsaicin in allergic rhinitis in adults did not find an evidence of intranasal capsaicin effect (Cheng 2006).

Why it is important to do this review

Establishing the clinical efficacy of capsaicin in non-allergic rhinitis could have important clinical implications. Only a few randomised controlled trials have evaluated the effectiveness of capsaicin in non-allergic rhinitis. Most of these studies have small numbers of participants, as well as variations in the dosing and schedule of capsaicin administration. There are no reported meta-analyses on this topic.

This review aims to assess the evidence for the use capsaicin in non-allergic rhinitis and specifically to establish the most advantageous dosing and scheduling regimens.

OBJECTIVES

To assess the effectiveness of capsaicin in the management of non-allergic rhinitis compared with no therapy, placebo or other topical

or systemic medications, or two or more of the above therapies in combination, or different capsaicin regimens.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised and quasi-randomised controlled trials (RCTs), including cluster-randomised and cross-over trials, irrespective of publication status, date of publication or language.

Types of participants

Inclusion criteria

Adult patients with all types of non-allergic rhinitis in any setting. The types of non-allergic rhinitis included were idiopathic (vasomotor or non-allergic, non-infectious perennial allergic rhinitis), occupational (chemical), smoking, gustatory, hormonal, senile (rhinitis of the elderly), atrophic, medication-induced (including rhinitis medicamentosa), local allergic rhinitis and non-allergic rhinitis with eosinophilia syndrome (NARES). We defined patients over 16 years of age as adults. We included studies involving only a subset of non-allergic rhinitis patients of interest if these data could be used in the analysis. We included studies of perennial rhinitis, if it was possible to isolate outcomes for patients with non-allergic rhinitis.

Exclusion criteria

Patients with allergic rhinitis (history of allergy, skin prick testing or serum-specific IgE antibodies, or following ARIA guidelines), infectious aetiology, acute or chronic rhinosinusitis (following EPOS 2012, Canadian (Desrosiers 2011) or American (Rosenfeld 2007) guidelines on sinusitis), autoimmune rhinitis (presence of autoimmune markers) or rhinitis related to anatomical abnormalities.

Types of interventions

Intervention

Intranasal capsaicin at any dose, frequency and duration. Studies of capsaicin with a co-intervention were to be included and we planned to use sensitivity analysis to assess the impact of their inclusion.

Comparisons

No therapy, placebo or other topical or systemic medications, or two or more of the above therapies in combination, or different capsaicin regimens (dose, frequency or duration).

Types of outcome measures

We analysed the following outcomes in the review, but they were not used as a basis for including or excluding studies.

Primary outcomes

- Overall symptom score (e.g. global symptom scores, daily record chart score)
- Individual symptom scores (e.g. nasal congestion, rhinorrhoea, sneezing, nasal itching), measured by visual analogue scale (VAS)
- Adverse events

Secondary outcomes

- Quality of life measures (e.g. via appropriate validated questionnaires for rhinitis)
- Treatment failure, dropouts, non-compliance with treatment, or unplanned switch to or addition of another medication
- Objective measurements: nasal peak expiratory flow (NPEF), peak nasal inspiratory flow (PNIF), anterior or posterior rhinomanometry, and acoustic rhinometry
- Additional outcomes
 - Endoscopic score
 - Analysis of nasal secretions
 - Turbinate or mucosal size
 - Analysis of nasal mucosal biopsy
 - Haematological, biochemical and urinary parameters
 - Costs of therapy

We sought any follow-up period, as available in the included studies.

Search methods for identification of studies

The Cochrane Ear, Nose and Throat Disorders Group's Trial Search Co-ordinator 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 24 June 2015.

Electronic searches

The Trial Search Co-ordinator searched:

- the Cochrane Register of Studies (CRS) ENT Disorders Group Trials Register (searched 24 June 2015);

- the Cochrane Central Register of Controlled Trials (CENTRAL 2015, Issue 5);
- PubMed (1946 to 24 June 2015);
- Ovid EMBASE (1974 to 2015 week 25);
- Ovid CAB Abstracts (1910 to 2015 week 24);
- EBSCO CINAHL (1982 to 24 June 2015);
- Ovid AMED (1985 to 24 June 2015);
- LILACS (searched 24 June 2015);
- KoreaMed (searched 24 June 2015);
- IndMed (searched 24 June 2015);
- PakMediNet (searched 24 June 2015);
- Web of Knowledge, Web of Science (1945 to 24 June 2015);
- ClinicalTrials.gov (searched via the CRS 24 June 2015);
- ICTRP (searched 24 June 2015);
- Google Scholar (searched 24 June 2015);
- Google (searched 24 June 2015).

Subject strategies for databases were modelled on the search strategy designed for CENTRAL. Where appropriate, they were combined with subject strategy adaptations of the highly sensitive search strategy designed by The Cochrane Collaboration for identifying randomised controlled trials and controlled clinical trials (as described in the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0, 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 Trial Search Co-ordinator searched PubMed, TRIP-database, *The Cochrane Library* and Google to retrieve existing systematic reviews relevant to this systematic review, so that we could scan their reference lists for additional trials. We searched for conference abstracts using the Cochrane Ear, Nose and Throat Disorders Group Trials Register.

Data collection and analysis

Selection of studies

We merged the identified studies using EndNote X2 reference management software (Thomson Reuters, New York, NY, USA). We removed duplicates 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 to remove 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 studies with the eligibility criteria. We contacted the study authors, where appropriate, to clarify study eligibility. Then, the two authors independently made final decisions on study inclusion. Disagreement on study inclusion was resolved by discussion. If necessary, we planned that disagreement would be resolved by arbitration by a third author (CMvD), but this was not required. 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 multiple reports of the same study existed, each author collected data separately from each report and then collated this into a single study report. We resolved disagreements by discussion. If necessary, we planned that disagreements would be resolved by arbitration by a third author (CMvD), but this was not required.

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, the respective standard deviation and the number of participants. If the data were presented in another format, we made appropriate calculations or transformations (or both) 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 trials 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. VAS scores) as continuous data, using MD or SMD. We planned to analyse short ordinal scales as dichotomous data (using RR), combining adjacent scores together whenever it was possible to find an appropriate cut-off point. For rare count data, we planned to calculate rate ratios based on the original data. We planned to treat more frequent count data as continuous. We planned to convert time-to-event data into hazard ratios. We did not carry out the above-mentioned planned analyses due to lack of data. We had planned to express 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. For cross-over trials without a washout period, we planned to analyse data from the first treatment period. For cross-over trials with a washout period, we used summary results of a paired t-test analysis of participant-specific differences between experimental and control intervention measurements to incorporate into the meta-analysis. If participant-specific differences were not reported, we only provided a narrative report of the cross-over trial.

Dealing with missing data

We recorded all missing data on the data collection form and reported this in the 'Risk of bias' table. Whenever possible, we contacted the original investigators to request missing data. We planned for three scenarios for missing data for primary outcomes, however these were not required. In the first scenario, we would have calculated the results without the missing data. In the second scenario, we would have assumed data for primary outcomes to be missing at random, and we would have carried the last observation forward for the missing value. In the third scenario, we would have assumed data for the primary outcome to be not missing at random, and we would have assumed the missing values to have a poor outcome. For secondary outcomes, we would have calculated the results without the missing data. We would have performed sensitivity analyses to assess for changes in overall results based on the assumptions of these scenarios.

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 perform a meta-analysis if we considered heterogeneity substantial (50% to 90%)

or considerable (75% to 100%) according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2011).

Assessment of reporting biases

We planned to use a funnel plot to detect reporting biases when there were at least 10 studies included in the meta-analysis, and we planned to analyse the visual asymmetry of the plot. This was not required because fewer than four studies were included. If there were small studies identified with larger treatment effects, we had planned to perform a sensitivity analysis excluding these studies. This also was not required.

Data synthesis

We planned to use RevMan 5 to perform a meta-analysis using the random-effects model if we did not consider the heterogeneity of the included studies substantial or considerable. We intended to perform a meta-analysis for 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 and using the generic inverse variance method. We made comparisons for all available outcomes between capsaicin and placebo, capsaicin and other topical or systemic medications, and between different capsaicin regimens (dose, frequency or duration comparisons, if available). We planned but ultimately were unable to make comparisons between capsaicin and no therapy, and capsaicin and two or more of the above therapies in combination, due to lack of data.

Subgroup analysis and investigation of heterogeneity

We intended to perform subgroup analyses to compare the effects of capsaicin:

- in different types of non-allergic rhinitis;
- in different severities of non-allergic rhinitis;
- at different time points after treatment;
- in non-allergic rhinitis diagnosed in primary versus secondary or tertiary care settings;
- in patients who did or did not have surgery prior to treatment;
- comparing delivery forms of capsaicin (spray versus drops);
- comparing different schedules of capsaicin delivery;
- comparing different doses of capsaicin delivery.

Sensitivity analysis

We intended to carry 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);
- excluding industry-sponsored studies;

- excluding studies with significant author financial and other conflict of interest;
- excluding studies with co-intervention administered simultaneously with capsaicin;
- analysis by study design: parallel versus cross-over studies;
- statistical model of analysis (fixed-effect versus random-effects model);
- assumptions about missing data (considering the scenarios outlined above).

GRADE and 'Summary of findings' table

We used the GRADE approach to rate the overall quality of evidence. The quality 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 quality of 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 quality 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 quality. 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 the these factors:

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

We included 'Summary of findings' (SOF) tables, constructed according to the recommendations described in Chapter 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2011).

RESULTS

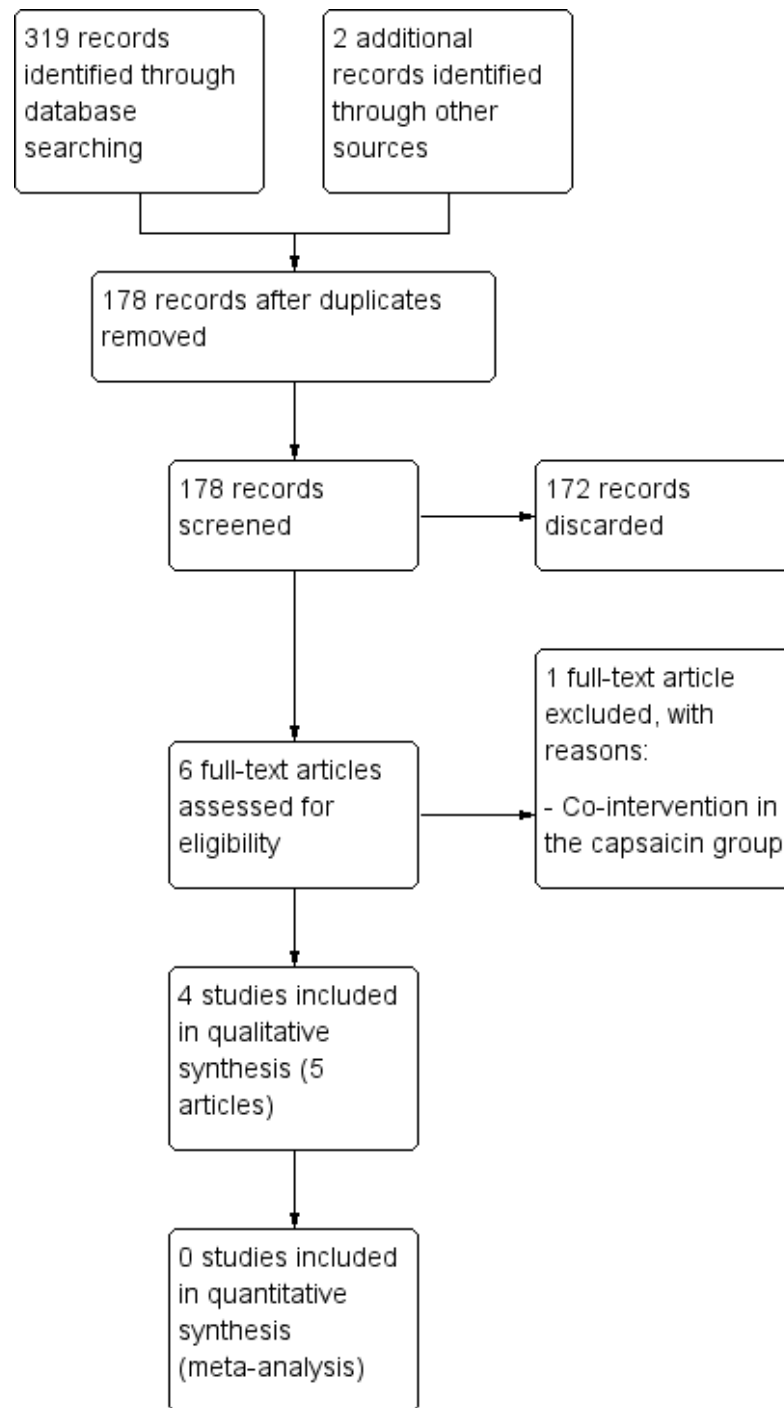
Description of studies

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 319 references. We identified two more records from the references of retrieved studies. We initially screened for duplicates and obviously irrelevant studies and discarded 143 references, leaving 178. After screening the titles and abstracts of these references, we further excluded 172 studies, leaving six references. We assessed the full texts of these references. We excluded one of these references due to the treatment arm being contaminated by co-treatment. We included five references in the systematic review, representing a total of four studies (two references were describing different outcomes of the same study population). We additionally identified one study as ongoing ([NCT02288156](#)) (see [Characteristics of ongoing studies](#)). There are no 'awaiting assessment' studies.

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



Included studies

We included four studies in the review. Of the five references to these studies, two described the same study and patient population with different outcome measures (Blom 1997/1998). Two studies compared capsaicin to placebo (Blom 1997/1998; Ciabatti 2009). One study compared two treatment regimens of capsaicin: five treatments in one day versus five treatments given every two to three days during two weeks (van Rijswijk 2003). The study by Ciabatti, in addition to comparing capsaicin with placebo, also compared three different doses of capsaicin to each other. Finally, the Havas 2002 study compared capsaicin with budesonide.

Design

Blom 1997/1998 and van Rijswijk 2003 were both randomised studies. Ciabatti 2009 and Havas 2002 were quasi-randomised. All four studies used a parallel-group design. None of the studies reported their funding source or any conflicts of interest.

Sample sizes

Sample sizes ranged from 30 (van Rijswijk 2003) to 208 (van Rijswijk 2003).

Setting

Blom 1997/1998 and van Rijswijk 2003 took place in tertiary university hospitals in the Netherlands, Ciabatti 2009 in a similar setting in Italy. The setting for Havas 2002 was a Department of Otolaryngology - Head and Neck Surgery in Australia.

Participants

There were 302 patients in total in the four included studies, of which 165 (54.46%) were males. Patient age was reported in three studies (Blom 1997/1998; Havas 2002; van Rijswijk 2003). In Blom 1997/1998 and van Rijswijk 2003, patient age ranged from 16 to 65 and the mean age was 36 years. The mean age in the Havas 2002 study was 40.3 years for males and 37.0 years for females in the budesonide group, and 41.5 years for males and 41.0 years for females in the capsaicin group. The Ciabatti 2009 study did not report patient age.

Description of non-allergic rhinitis in included patients

All studies included similar patients with a history of nasal complaints such as nasal obstruction, sneezing and rhinorrhoea for a period of more than one year, with symptoms for at least one

hour per day and for at least five days during a period of 14 days preceding the study. The patients were described as having idiopathic rhinitis (Ciabatti 2009; van Rijswijk 2003) and NANIPER (Blom 1997/1998; Havas 2002), the previously used term for idiopathic rhinitis. Specific excluded types of non-allergic rhinitis were smoking, pregnancy, hormonal and rhinitis medicamentosa. All patients had perennial symptoms. Severity could be assessed in two studies as moderate or severe based on symptom scores (Blom 1997/1998; van Rijswijk 2003). We identified no studies that examined patients with other types of non-allergic rhinitis.

Interventions

Capsaicin spray was used in all four included studies. One study used a dose of 15 µg/puff/nostril in the form of seven treatments every two to three days, to a total of 106.9 µg (Blom 1997/1998). The second study used two puffs into each nostril, each containing 0.654 µg of capsaicin (capsaicin 71%, dihydrocapsaicin 20.94% and nordihydrocapsaicin 4.94%), administered once weekly for four weeks, totalling 10.46 µg per treatment (Havas 2002). The third study used a dose of 8.25 µg/puff and compared regimens of five sprays applied in one day (once every hour for five hours) versus application every two to three days for a total of five applications to a total of 82.5 µg per study for both sides (van Rijswijk 2003). The fourth study used 1 µg, 2 µg and 4 µg/puff three times a day for three consecutive days (nine applications), amounting to 72 µg per entire treatment for both sides (Ciabatti 2009).

As a placebo, Blom 1997/1998 used NaCl, van Rijswijk 2003 used the capsaicin solvent and Ciabatti 2009 did not describe the consistency of the placebo used.

In Havas 2002, the comparison group was budesonide aqueous nasal corticosteroid spray, 64 µg per dose, in the form of two puffs of the spray in each nostril in the morning and evening for two weeks.

A co-intervention in the form of xylometazoline hydrochloride and lidocaine-based sprays was used in two studies, Blom 1997/1998 and van Rijswijk 2003, 15 minutes before capsaicin application (in the van Rijswijk 2003 study before the first capsaicin application of the day). In Havas 2002, a co-intervention with lignocaine/phenylephrine (co-phenylcaine) spray was used before the first treatment. No co-interventions were described in Ciabatti 2009.

Outcomes

Primary outcomes

All four studies reported symptoms as an outcome. These were reported as a daily record chart of several nasal symptoms or an

overall nasal symptom score, or individual symptoms scores measured by a VAS. The results were reported either narratively or as a change over time, or resolution of symptoms, or improved versus worse over time.

Ciabatti 2009 measured the side effects of capsaicin application in the form of nasal blockage, itching/sneezing and coughing, though these symptoms also constitute actual symptoms of non-allergic rhinitis, and hence differentiation between them as side effects of capsaicin or as symptoms of non-allergic rhinitis would be difficult. No further information was provided by this study to make such a determination.

None of the other included studies reported adverse events.

Secondary outcomes

Quality of life measures and treatment failure, dropouts, non-compliance with treatment or unplanned switch to or addition of another medication were not reported in any of the included studies.

One study measured the levels of leukotrienes C₄/D₄/E₄, prostaglandin D₂ and tryptase in nasal lavage, blood and urine chemistry, as well as expression of CD1, CD3, CD25, CD68, IgE, MBP, chymase, tryptase, synaptophysin and neurofilament in the epithelium and lamina propria of the inferior turbinate (Blom 1997/1998). One study measured smell, nasal patency and mucosal sensitivity (van Rijswijk 2003).

None of the studies reported nasal peak expiratory flow (NPEF), anterior or posterior rhinomanometry, endoscopic score, turbinate or mucosal size or costs of therapy.

Missing data

We contacted all authors of the included publications with a request to provide summary data (means and standard deviations (SDs)) for the intervention groups for clinically relevant outcomes. The contacted authors were unable to provide the missing data for the included studies.

Follow-up

The study that compared capsaicin with placebo followed patients for 36 weeks post-treatment (Blom 1997/1998). The study that compared two regimens of capsaicin treatment followed patients for 38 weeks (van Rijswijk 2003). The study that compared several doses of capsaicin and capsaicin with placebo followed patients for four weeks before and four weeks after treatment (Ciabatti 2009). Finally, the study comparing capsaicin with budesonide followed the patients for a total of 31 days (three days before and four weeks after treatment) (Havas 2002).

Excluded studies

We excluded only one full-text study (Bernstein 2011). This was a randomised, placebo-controlled, double-blind, parallel study of 21 days total duration (seven days pre-treatment and 14 days during treatment), which compared Sinus Buster (a homeopathic preparation of *Capsicum annuum* and Eucalyptol) with placebo (filtered water). The participants were patients with non-allergic rhinitis and mixed rhinitis between 18 and 60 years of age. The mixed rhinitis patients were defined as having one or more clinically relevant positive skin prick test (wheal $\geq$ 3 mm in diameter with surrounding erythema compared with saline control in conjunction with a positive histamine control) to a panel of aeroallergens that correlated with clinical symptoms and significant upper respiratory symptoms induced by chemical irritants, strong odours, weather or temperature changes. The study did not report outcomes separately for the non-allergic rhinitis and mixed rhinitis cohorts, however the authors provided us with the data for the non-allergic rhinitis cohort only. The main reason for the exclusion of the cohort of purely non-allergic rhinitis patients in this study from the present systematic review was the potential for unaccounted for effects of the co-intervention, Eucalyptol, which was present only in the Sinus Buster and not in the placebo group. In addition, the study used a 'homeopathic' dose of capsaicin.

Risk of bias in included studies

Judgements about risk of bias are presented as a 'Risk of bias' graph in percentage form for all included studies combined (Figure 2). Risk of bias in individual studies is shown in a 'Risk of bias' summary figure (Figure 3).

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

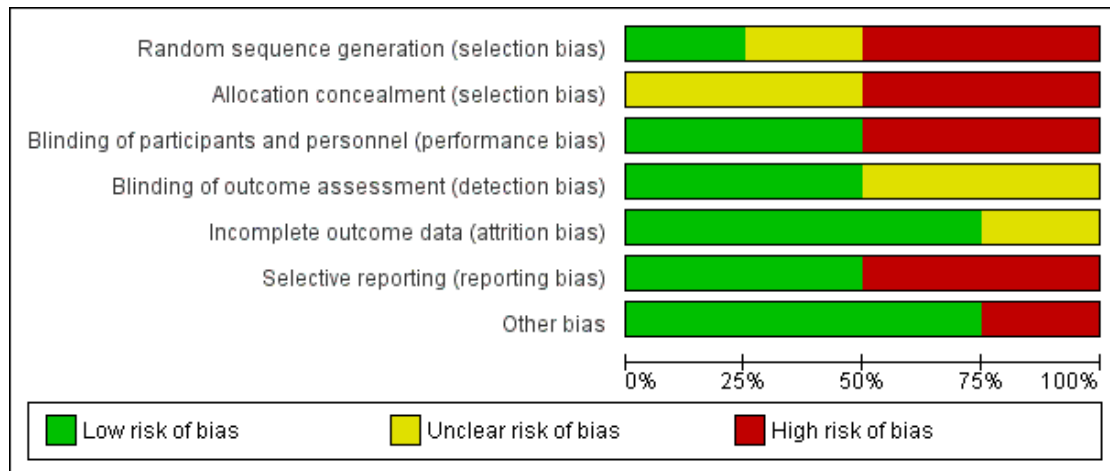


Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

	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
Blom 1997/1998	?	?	+	+	+	-	+
Ciabatti 2009	-	-	-	?	+	-	-
Havas 2002	-	-	-	?	+	+	+
van Rijswijk 2003	+	?	+	+	?	+	+

Allocation

Only one study described random sequence generation and we judged it to have a low risk of selection bias ([van Rijswijk 2003](#)). In this study, computer-generated randomisation was prepared in blocks of eight randomly permuted allocations. Another study did not specify ([Blom 1997/1998](#)), while two others had high risk of bias for random sequence generation ([Ciabatti 2009](#); [Havas 2002](#)). [Havas 2002](#) randomised patients based on an odds and evens basis, while [Ciabatti 2009](#) randomised according to the patients' date of visit. These two techniques are methods of quasi-randomisation, hence opening the opportunity for lack of concealment; we therefore judged them as having high risk of bias. Allocation concealment was not specified by any of the included studies.

Blinding

The studies by [Blom 1997/1998](#) and [van Rijswijk 2003](#) were described as double-blind and hence we assessed their risk of bias for blinding as low. The studies by [Havas 2002](#) and [Ciabatti 2009](#) did not specify the method of blinding and we judged them to have an unclear risk of bias of detection bias (blinding of outcome assessment) and a high risk of performance bias (blinding of participants and personnel).

Incomplete outcome data

We assessed [Blom 1997/1998](#), [Ciabatti 2009](#) and [Havas 2002](#) as having low risk of bias for incomplete outcome data, given all patients were accounted for at the end of the study. One patient in [Blom 1997/1998](#) could not complete capsaicin treatment due to influenza with fever. We judged that this patient's withdrawal before treatment would not affect the results of the study, and hence we judged the risk of bias to be low. In [Havas 2002](#) and [Ciabatti 2009](#), for each outcome all patients were accounted for. In [van Rijswijk 2003](#), there was no specific mention of whether all patients were accounted for at the end of the study, and therefore we considered this as an unclear risk of bias.

Selective reporting

[Blom 1997/1998](#) suffered from selective reporting of outcomes. Specifically, daily record chart data were not fully reported, while VAS data were reported only as a figure ('figure 2' in the article). Levels of leukotrienes, prostaglandins, tryptase, blood and urine chemistry were not reported numerically. [Ciabatti 2009](#) measured, but did not report, daily record chart outcomes measured at four weeks prior to treatment, as a baseline comparison between the groups.

We considered these two studies to have high risk of bias for selective reporting of outcomes.

[Havas 2002](#) and [van Rijswijk 2003](#) reported all measured outcomes and we considered them to have a low risk of bias.

Other potential sources of bias

In [Ciabatti 2009](#), the measured adverse events (nasal blockage, itching/sneezing and coughing) could also be considered symptoms of disease. The study does not clarify when these outcomes were reported by patients. Obviously, if this was immediately after application of the intranasal medications, these symptoms could be considered side effects of capsaicin administration. However, these symptoms, except for coughing, are usual symptoms of non-allergic rhinitis, and reporting them in the days after medication application means that they cannot be differentiated as symptoms of the disease or side effects of the medication. Due to this uncertainty, we deemed this study to have a high risk of bias for other potential sources of bias.

The study by [van Rijswijk 2003](#) was a cluster-randomised trial using computer-generated randomisation in blocks of eight randomly permuted allocations. 'Table 3' of that study shows the baseline characteristics for both treatment regimens of capsaicin (five treatments in one day versus five treatments given every two to three days during two weeks). We did not identify any other issues that could result in bias in this study, and we judged it to be at low risk of other potential sources of bias.

We considered the other two studies to have a low risk of bias for this parameter ([Blom 1997/1998](#); [Havas 2002](#)).

Effects of interventions

See: [Summary of findings for the main comparison Capsaicin compared to placebo for non-allergic rhinitis](#); [Summary of findings 2 Capsaicin compared to budesonide for non-allergic rhinitis](#); [Summary of findings 3 Five capsaicin treatments in one day compared to daily capsaicin treatment for five days for non-allergic rhinitis](#)

We were unable to identify similar data from the included studies for pooling, hence we did not carry out a meta-analysis.

Comparison 1: Capsaicin versus placebo

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

Two studies (in three publications) compared capsaicin with placebo ([Blom 1997/1998](#); [Ciabatti 2009](#)). [Blom 1997/1998](#) accounts for the same study, reporting various outcomes in two publications, with the first one reporting clinically relevant outcomes and the latter reporting molecular outcomes. These two publications used a capsaicin dose of 15.28 µg per puff per nostril, one

puff per treatment, in the form of seven treatments every two to three days. A total of 213.79 µg of capsaicin was applied during the entire treatment to both nasal cavities. The study by [Ciabatti 2009](#) used 1 µg, 2 µg and 4 µg/puff three times a day for three consecutive days (nine applications), to a total of 72 µg for both sides.

Primary outcomes

Overall symptom score

[Blom 1997/1998](#) used a daily record chart to measure symptoms of nasal blockage, clear discharge (runny nose), sneezing, coughing, mucus production and eye irritation. Post-treatment numerical data for each treatment group were not presented, however the authors reported that no significant difference was found for the individual symptoms as well as for the mean sum-score before, during or after therapy.

The same study measured overall nasal symptoms using a visual analogue scale (VAS) from 0 to 10 and reported it in 'figure 2' of their publication. From this figure, we recalculated the mean and standard deviation (SD) for each time point. The respective data and forest plots for post-treatment weeks two, 12 and 36 are presented in Analysis 1.1, Analysis 1.2 and Analysis 1.3. The capsaicin group had a statistically significant improvement at all three post-treatment time points (week two: mean difference (MD) -3.34, 95% confidence interval (CI) -5.24 to -1.44; week 12: MD -3.73, 95% CI -5.45 to -2.01; week 36: MD -3.52, 95% CI -5.55 to -1.48). We considered the quality of this evidence to be moderate for this outcome.

[Ciabatti 2009](#) employed a daily record chart for symptom scores (nasal blockage, sneezing/itching/coughing and nasal secretion). The outcome was persistence of symptoms at four weeks post-treatment in a non-responder analysis. We converted the data instead into a responder analysis. Three different concentrations of capsaicin were compared to placebo. The respective data on symptom resolution are presented in Analysis 1.4, Analysis 1.5 and Analysis 1.6 for the 1 µg, 2 µg and 4 µg dose comparisons with placebo. The 4 µg dose of capsaicin per puff was the only one that had a statistically significant effect over placebo (risk ratio (RR) 3.17, 95% CI 1.38 to 7.29) (Analysis 1.6). We considered the quality of evidence to be low for this outcome.

[Ciabatti 2009](#) was the only study that deliberately compared different doses of capsaicin as well as placebo. Capsaicin doses ranged between 1 µg, 2 µg and 4 µg per puff. These allowed three sets of comparisons: between 1 µg and 2 µg, between 1 µg and 4 µg, and between 2 µg and 4 µg.

Outcomes were measured four weeks after treatment via daily record chart scores for nasal blockage, sneezing/itching/coughing and nasal secretion, and were presented as persistence of symptoms. We converted the data into resolution of symptoms (retaining responder/non-responder analysis). The results are presented

in Analysis 4.1, Analysis 4.2 and Analysis 4.3, and demonstrate statistically significant differences when comparing 4 µg versus 1 µg per puff doses of capsaicin, with the former faring better (RR 0.63, 95% CI 0.34 to 1.16). We considered the quality of evidence to be low for this outcome. Side effects were also measured and these have been addressed above in the capsaicin versus placebo comparison section.

Both [Blom 1997/1998](#) and [Ciabatti 2009](#) employed a daily record chart. However, given the lack of numeral representation of data in [Blom 1997/1998](#), we could not perform a meta-analysis.

Individual symptom scores

[Blom 1997/1998](#) recorded individual symptoms on the daily record chart and reported that no significant difference was found for the individual symptoms, as well as the mean sum-score before, during or after therapy. [Ciabatti 2009](#) reported overall symptoms only in the form of a daily record chart and provided no information regarding individual symptoms.

Treatment-related adverse events as reported in trials

[Ciabatti 2009](#) also compared treatment side effects, which included nasal blockage, itching/sneezing and coughing. However, given these parameters are symptoms of the disease itself, it would be difficult to differentiate whether these symptoms are a result of capsaicin application or the disease, unless it is specified when exactly these symptoms were measured. If they took place immediately after capsaicin application, they could certainly be interpreted as a side effect of capsaicin. Given there was no clarification on this, we omitted these reported side effects from our analysis. [Blom 1997/1998](#) only reported that there were no adverse events, but no real data were presented.

Secondary outcomes

Quality of life measures

Quality of life measures were not reported for this comparison.

Treatment failure, dropouts, non-compliance with treatment, or unplanned switch to or addition of another medication

In [Blom 1997/1998](#), one patient could not complete capsaicin treatment due to influenza with fever. We judged that this patient's withdrawal before treatment would not affect the results of the study, and hence we judged the risk of bias to be low. In [Ciabatti 2009](#), all patients completed the treatment.

Objective measurements

Blom 1997/1998 measured the levels of leukotrienes C₄/D₄/E₄, prostaglandin D₂ and tryptase in the nasal lavage. The authors reported that no significant difference in time trend between the two treatment groups occurred during treatment, however numerical data were not presented.

Blom 1997/1998 also measured the expression of CD1, CD3, CD25, CD68, IgE, MBP (i.e. BMK13 antibody), chymase, tryptase, synaptophysin and neurofilament, and found no statistically significant differences between the groups. Given the lack of clinical relevance of these results, we did not recalculate the numerical data.

Additional outcomes

Additional outcomes were not reported for this comparison.

Comparison 2: Capsaicin versus budesonide

See [Summary of findings 2](#).

In Havas 2002, capsaicin ("full strength capsaicin", two puffs into each nostril, each dose 70 µL, delivering 0.654 µg of capsaicin) was compared with budesonide aqueous nasal corticosteroid spray (64 µg per dose, in the form of two puffs of the spray into each nostril in the morning and evening for two weeks). Treatments were carried out for four weeks, and the outcomes were measured during the last three days of treatment.

Primary outcomes

Overall symptom score

In Havas 2002, aggregate scores were calculated from a combination of individual symptom scores. Aggregate scores during the fourth week of treatment were better in the capsaicin group compared to budesonide (MD -2.46, 95% CI -4.28 to -0.63; VAS 0 to 5) (Analysis 2.1). Aggregate relief scores represented total score change from baseline for all symptoms. Once again, combining the results for both genders per treatment group, the aggregate relief score was overall better with capsaicin versus budesonide (MD 2.50, 95% CI 1.06 to 3.94) (Analysis 2.2). We considered the quality of evidence to be low for this outcome.

Individual symptom scores

In Havas 2002, nasal obstruction was reported using a responder/non-responder approach in the results of the study. There was no significant difference found between the two groups (Analysis 2.3). Individual symptoms were recorded using a 0 to 5 VAS score. All results were presented separately for males and females in the form of means and upper 95% confidence interval (CI) in

figures. We used these figures to calculate the estimated mean and upper 95% CI for males and females separately per each treatment group, then summarised this as cumulative mean and SD for both males and females per treatment group, according to Higgins 2011. There were no differences between budesonide and capsaicin for headache (Analysis 2.4), postnasal drip (Analysis 2.5), rhinorrhoea (Analysis 2.6), nasal blockage (Analysis 2.7), sneezing (Analysis 2.8) or sore throat (Analysis 2.9).

Treatment-related adverse events as reported in trials

Adverse events were not reported for this comparison.

Secondary outcomes

Quality of life measures

Quality of life measures were not reported for this comparison.

Treatment failure, dropouts, non-compliance with treatment, or unplanned switch to or addition of another medication

These outcomes were not reported for this comparison.

Objective measurements

Objective measurements were not reported for this comparison.

Additional outcomes

Additional outcomes were not reported for this comparison.

Comparison 3: Different regimens of capsaicin administration

See [Summary of findings 3](#).

Building on a previous study (Blom 1997/1998), van Rijswijk 2003 compared two treatment regimens of capsaicin: five treatments in one day versus five treatments given every two to three days during two weeks. During provocation, 0.27 ml of a 0.1 mmol/l capsaicin solution was used (a total of 16.49 µg).

Primary outcomes

Overall symptom score

In van Rijswijk 2003, overall nasal symptoms were presented as medians in a figure, without respective measures of variation to allow for calculations of effect size.

Individual symptom scores

Using daily record charts, [van Rijswijk 2003](#) reported significant improvement of rhinorrhoea in patients treated five times per day. There were no improvements in other parameters. However, numerical data were not presented per each measured time point to allow for further analysis.

Rhinorrhoea, nasal obstruction, sneezing and overall nasal symptoms were measured on a VAS. The study noted that a significant improvement was observed in both groups. The difference in the time trend was reported to be significant.

The time trend for decrease of rhinorrhoea symptoms was reported to be non-significant, however treatment with capsaicin five times per day was reported to result in better improvement of rhinorrhoea. For nasal obstruction, the time trend to decrease of symptoms was reported to be significant. The time trend to decrease of sneezing was not significant, and neither was the difference in the absolute VAS levels between the groups. Neither numerical data nor graphs were provided to allow for calculation of effect size per time point.

Treatment-related adverse events as reported in trials

Adverse events were not reported for this comparison.

Secondary outcomes

Quality of life measures

Quality of life measures were not reported for this comparison.

Treatment failure, dropouts, non-compliance with treatment, or unplanned switch to or addition of another medication

There were no dropouts reported for this comparison.

Objective measurements

In [van Rijswijk 2003](#), the mean University of Pennsylvania Smell Identification Test (UPSIT) scores were not different at the beginning of the study. At 12 weeks post-treatment, the UPSIT score continued to be no different between the groups (Analysis 3.1). We considered the quality of evidence to be moderate for this outcome.

There was no difference between the groups in cold dry air hyperreactivity, TMMCA1 and TMMCA2 measures of acoustic rhinometry, peak nasal inspiratory flow (PNIF), mucosal sensitivity to capsaicin, mucosal sensitivity to touch (for both epicritic and protopathic sensitivity), heart rate, or systolic and diastolic blood pressure at any time point.

Additional outcomes

Additional outcomes were not reported for this comparison.

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Capsaicin compared to budesonide for non-allergic rhinitis						
Patient or population: patients with non-allergic rhinitis Settings: tertiary university hospital Intervention: capsaicin Comparison: budesonide						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Budesonide	Capsaicin				
Nasal obstruction during the 4th week of treatment Number of responders Follow-up: 4 weeks	Study population		RR 1.11 (0.93 to 1.31)	40 (1 study)	⊕⊕○○ low ^{1,2,3}	Higher number indicates more patients responding to capsaicin compared to those responding to budesonide
	90 per 100	100 per 100 (84 to 100)				
	Moderate					
	90 per 100	100 per 100 (84 to 100)				
Aggregate relief score during the 4th week of treatment Follow-up: 4 weeks	The mean aggregate relief score during the 4th week of treatment in the control group was 3.65	The mean aggregate relief score during the 4th week of treatment in the intervention group was 2.5 higher (1.06 to 3.94 higher)	-	40 (1 study)	⊕⊕○○ low ^{1,2,3}	Higher scores indicate more relief of symptoms
Treatment-related adverse events	Not reported	Not reported	-	-	-	-

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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; **RR:** risk ratio

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹Pseudo-randomisation was performed on an odds and evens basis.

²Small sample size (40 patients total).

³Single study.

Five capsaicin treatments in one day compared to daily capsaicin treatment for five days for non-allergic rhinitis						
Patient or population: patients with non-allergic rhinitis Settings: tertiary university hospital Intervention: 5 capsaicin treatments in 1 day Comparison: daily capsaicin treatment for 5 days						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Daily capsaicin treatment for 5 days	5 capsaicin treatments in 1 day				
Smell testing University of Pennsylvania Smell Identification Test (UPSIT) Scale from: 0 to 40 Follow-up: 12 weeks	The mean smell testing in the control groups was 29 units	The mean smell testing in the intervention groups was 3 higher (1.5 lower to 7.5 higher)	-	30 (1 study)	⊕⊕⊕○ moderate ¹	Higher score indicates better smell sensation
Treatment-related adverse events	Not reported	Not reported	-	-	-	-
*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (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 GRADE Working Group grades of evidence High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate.						

¹Small sample size (30 total).

DISCUSSION

Summary of main results

We were unable to pool the data from the included studies into a meta-analysis. This would have been possible only with daily record chart symptom score data. However, due to the lack of numerical data from the [Blom 1997/1998](#) publication, pooling of daily record chart data was not possible.

All studies included patients with the classic non-allergic rhinitis subtype of idiopathic rhinitis (previously called NANIPER). In this aspect, populations in the included studies were quite uniform. Three studies examined the effects of capsaicin versus placebo; one compared different doses of placebo to each other (within the same placebo-controlled study), and one further study examined the regimen of capsaicin application. Finally, another study compared capsaicin with budesonide, an intranasal corticosteroid. Outcome measures were mostly clinically based, and most studies included a measure of patients' symptoms in the form of a daily record chart or visual analogue scale (VAS) score. Several studies also attempted to measure objective parameters of nasal function (e.g. airflow, smell, etc). Finally, [Blom 1997/1998](#) investigated the molecular aspects of the effect of capsaicin in non-allergic rhinitis.

The reporting of results in the included studies was suboptimal. In several instances, summary data were not presented in narrative, tabular or graphic form, and hence could not be included in the current review.

Comparing capsaicin with placebo and using the clinically meaningful data that could be extracted from the studies, one study reported a statistically significant improvement in overall nasal symptoms as measured on a VAS at post-treatment weeks two, 12 and 36 ([Blom 1997/1998](#)). Another study reported a statistically significant improvement of daily record chart symptom scores at four weeks with 4 µg of capsaicin per puff, but not with 1 µg or 2 µg per puff ([Ciabatti 2009](#)).

The included studies reported no significant differences between the groups for several measures: daily record chart ([Blom 1997/1998](#)), levels of leukotrienes C₄/D₄/E₄, prostaglandin D₂ and tryptase in the nasal lavage ([Blom 1997/1998](#)), expression of CD1, CD3, CD25, CD68, IgE, MBP (i.e. BMK13 antibody), chymase, tryptase, synaptophysin and neurofilament ([Blom 1998](#)), or side effects in the form of nasal blockage, itching, sneezing and coughing ([Ciabatti 2009](#)).

Comparing different doses of capsaicin, [Ciabatti 2009](#) demonstrated that 4 µg per puff of capsaicin was more effective than 1 µg per puff. Given that no other studies made direct dose comparisons, pooling of data was not possible.

[van Rijswijk 2003](#) compared two different regimens of capsaicin application: five treatments in one day, one hour apart versus five treatments given every two to three days during two weeks. They reported significant improvements of rhinorrhoea in the group treated five times in one day. However, there was no significant

difference between the groups for the other measured symptoms, despite there being a reported improvement in the time trend for resolution of some symptoms. There were also no significant differences in smell, nasal airflow, mucosal sensitivity testing, or heart rate and blood pressure.

Comparing capsaicin to budesonide, an intranasal corticosteroid, aggregate scores and aggregate relief scores were better with capsaicin, while there was no significant difference for all other symptoms.

Overall, the data from individual studies indicate that capsaicin may significantly improve overall nasal symptoms either measured on a VAS or as a responder derivative of daily record chart symptom scores. Higher doses of capsaicin are better than low doses, with no significant increase in side effects with doses up to 4 µg per puff. However, even higher doses were used in [Blom 1997/1998](#) and [van Rijswijk 2003](#). Application of capsaicin five times during the same day appears to be non-inferior to application once every two to three days to a total of five doses. In addition, capsaicin seems to be more effective than budesonide when overall relief of symptoms is considered.

Overall completeness and applicability of evidence

The lack of the opportunity to pool data from several studies does not allow us to draw a strong conclusion regarding the effectiveness of capsaicin in non-allergic rhinitis. Individual studies appear to suggest that cumulative nasal symptoms (overall nasal symptoms, daily record chart, overall response to treatment) fare better when treated with capsaicin compared to placebo or intranasal corticosteroids. Subgroup analysis indicates that higher doses of capsaicin may result in improvement in the proportion of responders, without significantly increasing side effects. No conclusions can be drawn from this review regarding the effects of capsaicin in non-allergic rhinitis of different types or severity, or with different forms of delivery of capsaicin.

The findings of this review apply to patients with idiopathic rhinitis, given that the included studies involved patients with this specific type of non-allergic rhinitis (idiopathic rhinitis, NANIPER, vasomotor rhinitis or intrinsic rhinopathy). Studies excluded specific types of non-allergic rhinitis, including those relating to smoking, pregnancy, hormonal changes, rhinitis medicamentosa or senile rhinitis. None of the studies included a mixed group of patients with non-allergic rhinitis of various aetiologies.

Interestingly, the ratio of men in the included studies was 54.46% of all patients, while most epidemiological studies report a larger proportion of affected females. We believe that the discrepancy of gender distribution in our study compared to larger epidemiological ones can be explained by the relatively small number of included patients.

Considering the limitations of the data presented, further studies are required to build upon the currently available evidence and

further describe the role of capsaicin in the treatment of non-allergic rhinitis.

Quality of the evidence

The quality of studies included in this review is low to moderate (see [Summary of findings for the main comparison](#); [Summary of findings 2](#); [Summary of findings 3](#)). Specifically, quality was low to moderate for comparisons between capsaicin and placebo, low for comparisons between capsaicin and budesonide, moderate for comparisons of capsaicin treatment regimens and low for comparisons of capsaicin doses. The limitations included the small sample sizes of the included studies, the availability of only a single study for each comparison and pseudo-randomisation of some studies. Many of the studies suffered from either selective reporting of results or reporting that did not allow the isolation of summary data for treatment groups. Given that none of the authors contacted could provide further summary data, in several instances we had to recalculate these data from figures. The most consistent evidence is presented for measures of overall nasal symptoms (measured using a VAS or daily record chart, or summarised as a responder/non-responder analysis). Overall, the risk of bias was low to unclear.

Potential biases in the review process

We excluded one study including 42 patients from this review ([Bernstein 2011](#)). This included patients with both non-allergic rhinitis and mixed rhinitis. The latter was defined as having one or more clinically relevant positive skin prick test (wheal ≥ 3 mm in diameter with surrounding erythema compared with saline control in conjunction with a positive histamine control) to a panel of aeroallergens that correlated with clinical symptoms and significant upper respiratory symptoms induced by chemical irritants, strong odours, weather or temperature changes. Total nasal symptom score (TNSS) was considered as the primary endpoint and individual symptoms were considered as secondary endpoints, while the Rhinitis Quality of Life Questionnaire (RQLQ) was considered an additional endpoint, and automated olfactometry was considered a part of the safety analysis. Considering this mixed group of patients, ICX72 (Sinus Buster, containing homeopathic doses of capsaicin), resulted in a significant improvement over placebo in TNSS change from baseline, and an improvement in nasal congestion, sinus pain, sinus pressure and headache at five, 10, 15 and 30 minutes, as well as at 60 minutes for nasal congestion and sinus pain.

We were able to get in touch with the authors of the study, who were able to isolate from the study's population a group of nine patients with non-allergic rhinitis: four treated with ICX72 (i.e. Sinus Buster) and five treated with placebo. Re-analysing the available data, we found no significant differences in TNSS, individual symptom scores or the RQLQ and its individual components.

We ultimately decided to not include this study in the review, because the treatment arm alone was contaminated by eucalyptus co-treatment. The latter is known to stimulate cold receptors in the nose and hence can alter the perception of the effect of capsaicin alone ([Behrendt 2004](#)). In addition, the study only used a homeopathic dose of capsaicin and this dose could not be identified by the study authors.

Another potential point of bias could be the data obtained from the studies. Most data were not presented numerically, therefore we had to recalculate some of the data from the narrative text or from figures, as we were unable to obtain raw or summary data from study authors.

In the case of figures, we calculated pixels from the baseline (x-axis) to a known point on the y-axis to determine the scale, followed by a calculation of individual pixels for each data point (e.g. mean or standard deviation (SD) or CI). Given that this calculation may not be completely precise, there is potential for an additional bias, however we cannot strongly assume that the bias would benefit either the treatment or control group, as it would be random.

Another potential bias is that one of our lead authors (WJF) is also the lead author of two of the five included studies, Blom 1998 and [van Rijswijk 2003](#). The first study (published as [Blom 1997/1998](#)) was the first randomised controlled trial (RCT) on capsaicin in non-allergic rhinitis, while the second one established no differences when patients were treated with capsaicin every two to three days for a total of five days versus administration of all treatments in one day. In order to avoid any bias, another author (CMvD) was brought in to participate in study selection and data analysis. While WJF conceived the idea for the review and participated in drafting the protocol and the final manuscript, she had no participation in study selection or data analysis.

Agreements and disagreements with other studies or reviews

There are no other systematic reviews or meta-analyses on non-allergic rhinitis.

We identified an interesting conference abstract describing a RCT that compared capsaicin with ipratropium bromide for vasomotor rhinitis ([Cuilty-Siller 1996](#)). The outcomes measures were nasal resistance and airflow measured by rhinomanometry. It was not possible to conclude from the abstract whether one or the other medication was more effective in treating vasomotor rhinitis. We were unable to obtain raw data or a full-text publication from the authors.

[Lacroix 1991](#) described the effects of capsaicin in 16 patients with non-allergic rhinitis and 17 controls. In non-allergic rhinitis patients, capsaicin resulted in significant improvement of individual nasal symptoms (obstruction, rhinorrhoea and sneezing) up to six months after application.

[Marabini 1991](#) reported on the effects of capsaicin in patients with known vasomotor rhinitis. Patients recorded their symptoms

over one month. Capsaicin reduced the symptom scores of nasal obstruction and nasal secretion, as well as overall symptom scores. These two studies, [Lacroix 1991](#) and [Marabini 1991](#), conducted prior to the first RCT on capsaicin, provided grounds for further investigation, and overall agree with the results of the RCTs, even though the effects are less pronounced than in the RCTs.

[Sanico 1998](#) measured the effects of capsaicin in patients with non-allergic rhinitis, patients with allergic rhinitis and healthy controls. Immediately after application, capsaicin produced burning, lacrimation and rhinorrhoea, which were not different in the three groups. This study did not, however, provide any meaningful clinical information about the long-term post-treatment effects of capsaicin.

As already indicated, the study by [Bernstein 2011](#), performed in a mixed group of patients with both non-allergic rhinitis and mixed rhinitis, showed an effect of Sinus Buster over placebo. However, recalculations for the non-allergic rhinitis group alone did not show any statistically significant changes.

AUTHORS' CONCLUSIONS

Implications for practice

Capsaicin may be included in the treatment of idiopathic non-allergic rhinitis. It appears to have beneficial effects on overall nasal symptoms up to 36 weeks after treatment, based on the results of individual studies. It is given in a form of brief treatments, usually during the same day. The overall quality of evidence in the included studies is low to moderate.

Intranasal capsaicin is used only in a handful of countries, so it is beneficial for individual practitioners to know that capsaicin preparations of at least 4 µg per puff provide a benefit over placebo with no documented short-term side effects. Despite the lack of availability of capsaicin in pharmacies in many countries, it can be prepared by hospital pharmacies or upon request, and may provide clinics with another treatment option for non-allergic rhinitis. In other countries, capsaicin is available as over-the-counter

combination homeopathic preparations, such as Sinus Buster in the United States or Nasol in Canada. Given the homeopathic doses of capsaicin and the inclusion of other active ingredients, it is hard to judge whether these preparations are effective and this review certainly did not aim to address them. We also do not have conclusive evidence regarding the risk of harm. The most common immediate side effects include burning, lacrimation, rhinorrhoea and cough, however long-term risks of harm are unknown.

Given the overall scarcity of options in the treatment of non-allergic rhinitis, capsaicin is a viable option in those with idiopathic non-allergic rhinitis.

Implications for research

Pooling of results for a meta-analysis was not possible in this review, due to the scarcity of randomised controlled trials and lack of uniform presentation of data. Well-conducted randomised controlled trials are required to further advance our understanding of the effectiveness of capsaicin in non-allergic rhinitis. Many aspects require further study, including the effect of capsaicin in patients with non-allergic rhinitis of different types and severity, and the effect of different methods of delivery of capsaicin. Standardisation of the reporting of clinically meaningful data, including patient-reported outcomes (symptom scores, validated questionnaires), as well as objective measurements, will help to paint a more comprehensive picture of the effects of capsaicin in this condition.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Blom 1997/1998

Methods	Allocation: randomised, double-blind, placebo-controlled; 42 weeks duration (36 weeks post-treatment) Design: parallel-group study
Participants	Number: 35 patients were randomised; 25 patients were included after exclusion criteria applied Age: 16 to 64 years Gender: 16 males, 9 women Setting: tertiary university hospital in The Netherlands Eligibility criteria: Patients with NANIPER (history of nasal complaints such as nasal obstruction, sneezing and rhinorrhoea for a period of over 1 year) with symptoms at least 1 hour per day for at least 5 days during a period of 14 days Symptom duration: perennial Severity: at least moderate or severe based on daily record chart or symptom scores on VAS Exclusion criteria: allergic rhinitis, positive SPT, positive serum IgE, nasal or paranasal sinus infection, nasal surgery within the previous 6 weeks, history of nasal polyps, anatomical nasal disorders, pregnancy, lactation, systemic disorders, smoking, use of systemic or inhaled corticosteroids, inhaled sodium cromoglycate, nedocromil sodium, or astemizole within the previous month, inability of the patient to stop taking medication affecting nasal function, a serious and/or unstable disease, abnormal blood work or urine analysis, or abnormal findings at physical examination
Interventions	Intervention group: capsaicin n = 14 - 0.1 mmol/L, consisted of pelargonic acid vanillylamide dissolved in 3 ml alcohol (96%) and diluted in 1 L NaCl solution (0.9%), applied in the form of a spray ("puff") - Dose: 0.5 ml solution was sprayed in each nostril (0.15 mg capsaicin) - Frequency: every 2 or 3 days for a total of 7 treatments in 2 weeks - 1 patient could not complete treatments due to influenza Comparator group: placebo n = 11 - Sodium chloride solution (0.9%) Use of additional interventions: co-intervention in both groups 15 minutes prior to intervention: - 3 applications of xylometazoline hydrochloride 0.1% (Otrivin® nebuliser) in each nostril - 3 applications (10 mg/puff) of lidocaine base (100 mg/ml) (Xylocaine® 10% spray) in each nostril
Outcomes	Daily record chart (DRC), 6 items total: nasal blockage, clear nasal discharge, sneezing, coughing, green/yellow or brown mucus production and eye irritation - 4 items (nasal blockage, clear nasal discharge, sneezing and coughing) on a 0 to 3 scale

	- 2 items (green/yellow or brown mucus production and eye irritation) on a 0 to 1 scale - Lower score indicates better outcome Overall nasal symptoms (VAS, 0 to 10) Levels of leukotrienes C4/D4/E4, prostaglandin D2 and tryptase in nasal lavage Blood and urine chemistry Expression of CD1, CD3, CD25, CD68, IgE, MBP, chymase and tryptase in the epithelium and lamina propria (Blom 1997/1998) Expression of synaptophysin and neurofilament	
Funding sources	Funding: not reported	
Declarations of interest	None declared	
Notes	Some results not reported for DRC This article, along with Blom 1998, is from the same study Participants lost to follow-up: 1 patient could not complete treatment due to influenza	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: “This study was performed in a double-blind placebo-controlled fashion.”
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: “This study was performed in a double-blind placebo-controlled fashion.”
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 patient could not complete capsaicin treatment due to influenza with fever. We judged that this patient’s withdrawal before treatment would not affect the results of the study, and hence we judged the risk of bias to be low
Selective reporting (reporting bias)	High risk	DRC results are not fully reported VAS results reported only in “figure 2”
Other bias	Low risk	None identified

Methods	Allocation: quasi-randomised study (patient assigned according to the date of their visit) ; 8 weeks total (4 weeks before and 4 weeks after treatment) Design: parallel-group study
Participants	Number: 208 patients randomised Age: not reported Gender: 115 males, 93 females Setting: tertiary university hospital in Italy Eligibility criteria: Patients with idiopathic rhinitis (history of nasal breathing obstruction, sneezing, coughing, rhinorrhoea and nasal itching for ≥ 1 year) with duration of symptoms ≥ 1 hour per day for at least 5 days during the 14 days preceding the day of the first visit and no beneficial effect of nasal corticosteroid spray (for a period of at least 6 weeks) Symptom duration: perennial Severity: not reported Exclusion criteria: allergic rhinitis, nasal surgery within the previous 6 weeks, history of nasal polyps, anatomical disorder affecting nasal function, pregnancy, lactation, systemic disorders, smoking, use of systemic or inhaled corticosteroids, inhaled sodium cromoglycate, nedocromil sodium, or astemizole within the previous month, inability of the patient to stop taking medication affecting nasal function, a serious and/or unstable disease, abnormal blood work or urine analysis, or abnormal findings at physical examination Baseline characteristics: baseline differences not reported
Interventions	Intervention group A: capsaicin 1 $\mu\text{g}/\text{puff}$ n = 52 Intervention group B: capsaicin 2 $\mu\text{g}/\text{puff}$ n = 52 Intervention group C: capsaicin 4 $\mu\text{g}/\text{puff}$ n = 52 Intervention group D: placebo 0 $\mu\text{g}/\text{puff}$ n = 52 Capsicum oleous nasal spray 1 $\mu\text{g}/\text{puff}$ (70 ml/puff) or other doses, respectively, 1 puff/nostril was administered 3 times a day, at 30-minute intervals, for 3 consecutive days Placebo: consistency not described Use of additional interventions: none
Outcomes	Daily record chart (DRC), 5 items total: nasal blockage, sneezing, itching, coughing, green/yellow mucus production - 4 items on a 0 to 3 scale, and 1 item on a 0 to 1 scale - Total score 0 to 7; lower score indicates better outcome - Outcomes reported as resolution (DRC score = 0) and persistence (DRC score ≥ 1) Adverse events Nasal blockage, itching/sneezing, coughing
Funding sources	Not reported
Declarations of interest	None declared

Notes	Adverse events are also symptoms of disease, therefore would be difficult to differentiate Participants lost to follow-up: none	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Patients assigned according to the date of their visit (quasi-randomisation)
Allocation concealment (selection bias)	High risk	Likely high risk, as specific measures to ensure allocation concealment were not described in this quasi-randomised study
Blinding of participants and personnel (performance bias) All outcomes	High risk	Likely high risk, given the quasi-randomised study design and the lack of co-intervention with an anaesthetic to conceal the effect of capsaicin
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients accounted for in every outcome
Selective reporting (reporting bias)	High risk	Pre-treatment DRC recorded but not reported
Other bias	High risk	Studied adverse events are also symptoms of disease, hence differentiation would be difficult

Havas 2002

Methods	Allocation: quasi-randomised study (on odds and even basis); 31 days total (3 days prior to treatment and 4 weeks of treatment) Design: parallel-group study
Participants	Number: 40 patients randomised 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 Setting: Department of Otolaryngology - Head and Neck Surgery in Australia Eligibility criteria: Patients with perennial non-allergic rhinitis (IgE < 100 and RAST negative) examined by the senior author

	Symptom duration: perennial Severity: not reported 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: capsaicin (each dose containing 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. Then once weekly self administration of 2 puffs of capsaicin in each nostril weekly for 4 weeks Comparator group: budesonide (64 micrograms/dose), 2 puffs of the spray in each nostril qAM and qPM for 2 weeks, after administration of lignocaine/phenylephrine (co-phenylcaine) before the 1st treatment	
Outcomes	1. Symptom sheet (VAS), assessed separately for each side, 3 days prior to treatment and during last 3 days of treatment: - Headache - PND - Rhinorrhoea - Nasal blockage - Sore throat - Sneezing 2. Aggregate total relief (decrease of symptom scores after treatment: sum of relief scores for all 6 symptoms) 3. Improved versus worse (or unchanged)	
Funding sources	Disclosures: no financial interest with company supplying capsaicin	
Declarations of interest	None declared	
Notes	Participants lost to follow-up: none declared	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Pseudo-randomisation was performed on an odds and evens basis
Allocation concealment (selection bias)	High risk	High risk due to pseudo-randomisation
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

Havas 2002 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcomes reported
Selective reporting (reporting bias)	Low risk	No selective outcome reporting identified
Other bias	Low risk	No other sources of bias identified

van Rijswijk 2003

Methods	Allocation: randomised, double-blind, double-dummy; 310 days (38 weeks post-treatment) Design: parallel-group study
Participants	Number: 30 patients randomised Age: 16 to 65 years (mean age, 36 years) Gender: 14 males, 16 females Setting: tertiary university hospital in The Netherlands Eligibility criteria: Patients with idiopathic rhinitis (history of nasal complaints such as nasal obstruction, sneezing and/or rhinorrhoea for a period of over 1 year) with 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 and with no benefit from nasal corticosteroid spray for a period of at least 6 weeks) Symptom duration: perennial Severity: at least moderate or severe based on daily record chart or symptom scores on VAS Exclusion criteria: allergic rhinitis, positive SPT, positive serum IgE, nasal or paranasal sinus infection, nasal surgery within the previous 6 weeks, history of nasal polyps, anatomical nasal disorders, pregnancy, lactation, systemic disorders, smoking, use of systemic or inhaled corticosteroids, inhaled sodium cromoglycate, nedocromil sodium, or astemizole within the previous month, inability of the patient to stop taking medication affecting nasal function, a serious and/or unstable disease, abnormal blood work or urine analysis, or abnormal findings at physical examination Baseline characteristics: baseline differences not reported
Interventions	Intervention group: first treated with capsaicin 5 times on a single day at 1-hour intervals. After 2 weeks, they received a total of 5 treatments with dummy placebo once every 2nd or 3rd day n = 15 Comparator group: first received dummy placebo 5 times on a single day at 1-hour intervals. This was followed 2 weeks later by a total of 5 treatments with capsaicin once every 2nd or 3rd day n = 15 Capsaicin: (0.1 mmol/l) consisted of 30.3 mg pelargonic acid vanillylamide dissolved in 3 ml alcohol (96%) and diluted in 1 L NaCl solution (0.9%) Placebo: capsaicin solvent only Dose: 0.27 ml of solution (3 applications) sprayed into each nostril with a metered nasal spray (0.09 ml per actuation, coefficient of variation 4%)

	Use of additional interventions: co-intervention in both groups 15 minutes prior to intervention: - 3 applications of xylometazoline hydrochloride 0.1% (Otrivin® nebuliser) in each nostril - 3 applications (10 mg/puff) of lidocaine base (100 mg/ml) (Xylocaine® 10% spray) in each nostril	
Outcomes	Daily record chart (DRC), 5 items total: nasal blockage, clear nasal discharge, sneezing, coughing, green/yellow mucus production. 4 items on a 0 to 3 scale, and 1 item on a 0 to 1 scale. Lower score indicates better outcome Nasal symptoms, measured by VAS (0 to 10): overall nasal symptoms, rhinorrhoea, nasal obstruction, sneezing Smell measured by UPSIT Cold dry air hyperreactivity Nasal patency measured by acoustic rhinomanometry Nasal patency measured by PNIF Mucosal sensitivity to capsaicin Mucosal sensitivity to touch - epicritic and protopathic sensitivity Blood pressure and heart rate	
Funding sources	Not reported	
Declarations of interest	None declared	
Notes	Numerical data not reported for many outcomes and time points Participants lost to follow-up: none	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised, double-blind study. Description provided of how this was done
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "This study was performed in a double-blind randomized fashion."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "This study was performed in a double-blind randomized fashion."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Low risk	All outcomes reported, though not always in straightforward ways

Other bias	Low risk	No other sources of bias identified
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DRC: daily record chart
 IgE: immunoglobulin E
 NaCl: sodium chloride
 NANIPER: non-allergic, non-infectious perennial allergic rhinitis
 PND: post-nasal drip
 PNIF: peak nasal inspiratory flow
 qAM: every morning
 qPM: every afternoon/evening
 RAST: radioallergosorbent test
 SPT: skin prick test
 UPSIT: University of Pennsylvania Smell Identification Test
 VAS: visual analogue scale

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Bernstein 2011	1. Population: patients with both allergic and non-allergic rhinitis. After communicating with the study's author, it was possible to isolate only patients with non-allergic rhinitis. However, we excluded this study for the following reasons: 2. Eucalyptol co-intervention in the capsaicin treatment group only a. Eucalyptus is known to result in temporary alleviation of nasal symptoms alone and affects cold receptors in the nose b. Despite a "homeopathic" dose of capsaicin, given a strong reaction to Eucalyptol, we can reasonably suspect that blinding of patients would have been difficult to achieve

Characteristics of ongoing studies [ordered by study ID]

NCT02288156

Trial name or title	'Elaboration of patient-friendly treatment strategy with capsaicin nasal spray in patients with idiopathic rhinitis'
Methods	Randomised, parallel-group, double-blind trial
Participants	Inclusion criteria: Aged 18 to 65 years; both genders Idiopathic rhinitis patients with at least 2 persistent (> 12 weeks) rhinological symptoms (nasal discharge, sneezing, nasal congestion) for an average of at least 1 hour per day Idiopathic rhinitis patients with a total nasal symptoms score (TNS) of 5 or more on a visual analogue scale (VAS)

Interventions	Capsaicin nasal spray 0.01 mM (2 puffs/nostril/day) over 4 weeks Capsaicin nasal spray 0.001 mM (2 puffs/nostril/day) over 4 weeks Capsaicin nasal spray 0.1 mM (5/day administered on a single day) (current treatment) Placebo
Outcomes	Primary outcome measure: Change in VAS for major nasal symptoms (week 4). Patients score their main nasal complaints from 0 to 10 on a scale, with 0 meaning no complaints and 10 meaning the worst complaints. This is done at baseline and after 4 weeks of treatment Secondary outcome measures: Change in VAS for individual nasal symptoms (week 4). Patients score all kinds of nasal symptoms from 0 to 10 on a scale, with 0 meaning no complaints and 10 meaning the worst complaints. This is done at baseline and after 4 weeks of treatment Change in therapeutic response in all treatment regimes (week 4) Evaluation of the therapeutic response (TRE) on a scale from 1 (= no relief of symptoms) to 5 (= total relief of symptoms) Change of nasal hyperreactivity in all treatment modalities (week 4) Evaluation of appearance of adverse events in all treatment groups (week 4 and 12) Evaluation of recurrence of symptoms in all treatment modalities (week 4, 12 and 26)
Starting date	January 2015 (completion date estimated December 2017)
Contact information	Sofie Mees (sofie.mees@med.kuleuven.be); Emily Dekimpe (emily.dekimpe@uzleuven.be) Principal investigator: Prof. Dr. Peter Hellings, UZ Leuven
Notes	-

DATA AND ANALYSES

Comparison 1. Capsaicin versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall nasal symptoms 2 weeks post-treatment	1	24	Mean Difference (IV, Fixed, 95% CI)	-3.34 [-5.24, -1.44]
2 Overall nasal symptoms 12 weeks post-treatment	1	24	Mean Difference (IV, Fixed, 95% CI)	-3.73 [-5.45, -2.01]
3 Overall nasal symptoms 36 weeks post-treatment	1	24	Mean Difference (IV, Fixed, 95% CI)	-3.52 [-5.55, -1.48]
4 Daily record chart symptom resolution at 4 weeks post-treatment (capsaicin 1 µg/puff versus placebo)	1	104	Risk Ratio (M-H, Fixed, 95% CI)	1.5 [0.58, 3.91]
5 Daily record chart symptom resolution at 4 weeks post-treatment (capsaicin 2 µg/puff versus placebo)	1	104	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.81, 4.93]
6 Daily record chart symptom resolution at 4 weeks post-treatment (capsaicin 4 µg/puff versus placebo)	1	104	Risk Ratio (M-H, Fixed, 95% CI)	3.17 [1.38, 7.29]

Comparison 2. Capsaicin versus budesonide

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Aggregate score during the 4th week of treatment	1	40	Mean Difference (IV, Fixed, 95% CI)	-2.46 [-4.28, -0.63]
2 Aggregate relief score during the 4th week of treatment	1	40	Mean Difference (IV, Fixed, 95% CI)	2.50 [1.06, 3.94]
3 Nasal obstruction (responder/non-responder analysis) during the 4th week of treatment	1	40	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.93, 1.31]
4 Headache during the 4th week of treatment	1	40	Mean Difference (IV, Fixed, 95% CI)	0.05 [-0.60, 0.69]
5 Postnasal drip during the 4th week of treatment	1	40	Mean Difference (IV, Fixed, 95% CI)	-0.50 [-1.32, 0.33]
6 Rhinorrhoea during the 4th week of treatment	1	40	Mean Difference (IV, Fixed, 95% CI)	-0.25 [-0.99, 0.48]
7 Nasal blockage during the 4th week of treatment	1	40	Mean Difference (IV, Fixed, 95% CI)	-1.19 [-2.45, 0.06]

8 Sneezing during the 4th week of treatment	1	40	Mean Difference (IV, Fixed, 95% CI)	-0.15 [-0.74, 0.43]
9 Sore throat during the 4th week of treatment	1	40	Mean Difference (IV, Fixed, 95% CI)	-0.44 [-1.04, 0.15]

Comparison 3. Different regimens of capsaicin administration

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 UPSIT at 12 weeks post-treatment	1	30	Mean Difference (IV, Fixed, 95% CI)	3.0 [-1.50, 7.50]

Comparison 4. Different doses of capsaicin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Daily record chart symptom resolution at 4 weeks post-treatment (capsaicin 1 μ g versus 2 μ g/puff)	1	104	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.35, 1.63]
2 Daily record chart symptom resolution at 4 weeks post-treatment (capsaicin 1 μ g versus 4 μ g/puff)	1	104	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.24, 0.95]
3 Daily record chart symptom resolution at 4 weeks post-treatment (capsaicin 2 μ g versus 4 μ g/puff)	1	104	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.34, 1.16]

CONTRIBUTIONS OF AUTHORS

AG, CG and RR were responsible for drafting the protocol, selecting the studies, data extraction and analysis, and drafting the final manuscript. CMvD participated in study selection, data analysis and drafting the final manuscript. WJF conceived the idea and participated in drafting the protocol and the final manuscript.

DECLARATIONS OF INTEREST

Wytske Fokkens received private sector support for research and/or clinical trials related to treatment of allergic and non-allergic rhinitis from Allergopharma, GlaxoSmithKline (GSK) and Bioinspire, as well as public sector research support from InterUniversity Attraction Poles (Belgium), ZonMW (The Netherlands), and Global Allergy and Asthma European Network (EU). WJ Fokkens has also received royalties for legal consultation/expert witness testimony for Stallergens. WJF is also the lead author of two of the five included studies, [Blom 1997/1998](#) and [van Rijswijk 2003](#).

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We decided to define patients over 16 years of age as adults ([Types of participants](#)). This was dictated by the fact that most studies had a cut-off of 16 years for definition of an adult. Given that we were unable to obtain further information about the included studies from the authors, we were also unable to exclude those patients aged between 16 and 18 years.

The specific types of non-allergic rhinitis included are now listed in [Types of participants](#).

We have included a 'Summary of findings' table and described the method used in the [Methods](#) section.

We have specified that quasi-randomisation is acceptable in included studies ([Types of studies](#)).