INTRANASAL CORTICOSTEROIDS FOR NON-ALLERGIC RHINITIS

Rens Reeskamp
Studentnummer: 6064809
Tel: +31634479212
E-mail: lfreeskamp@amc.uva.nl

Senior Supervisor:
Prof. dr. W. Fokkens
Chairman Department of Otorhinolaryngology
Academic Medical Centre
Tel: +31205663789
E-mail: w.j.fokkens@amc.uva.nl

Daily Supervisor
Artur Gevorgyan, MD, MSc, FRCSC
Clinical Fellow, Advanced Rhinology and Skull Base Surgery
Department of Otorhinolaryngology Academic Medical Centre
E-mail: artur.gevorgyan@mail.utoronto.ca

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ABSTRACT

Introduction: Non-allergic rhinitis (NAR) is a disease of the nasal mucosa, which is diagnosed by exclusion of allergic rhinitis and infectious rhinitis. Typical symptoms are rhinorrhea, sneezing, blockage and itching and can occur through the whole year. Different types of NAR are known: occupational (irritant) rhinitis, drug-induced rhinitis (rhinitis medicamentosa), hormonal, rhinitis of the elderly, non-allergic rhinitis with eosinophilia syndrome (NARES), smoking rhinitis and idiopathic rhinitis. Currently, first choice of treatment is the use of intranasal corticosteroids (INCS). However the effectiveness of treatment with INCS is unclear. This systematic review aims to assess the effectiveness of INCS in the treatment of NAR.

Methods: We searched the PubMed database to identify relevant studies. Inclusion criteria were: patients of 16 years and older with all types of non-allergic rhinitis, including but not limited to occupational, smoking, gustatory, hormonal, senile, atrophic, drug-induced, local allergic, vasomotor and idiopathic rhinitis, non-allergic, non-infectious perennial rhinitis (NANIPER) and NARES. Patients were excluded if they had allergic rhinitis, rhinitis of clearly infectious etiology, acute or chronic rhinosinusitis, autoimmune rhinitis, or rhinitis related to anatomical abnormalities. Data of the included studies was extracted by two authors (RR and RG) separately using a data-extraction form. Risk of bias was assessed by two authors as well. Primary outcome was improvement of total symptom scores (TSS). Secondary outcomes were individual symptom scores (rhinorrhea, sneezing, blockage and itching).

Results: Nine studies were included in this review. Two studies found a significant difference in TSS, favoring INCS over placebo. One study found a significant difference in individual symptom scores, favoring INCS over placebo. Five studies did not found a significant difference in TSS. One study compared INCS with ipratropium, but did not find a significant difference for individual symptom scores. Two studies compared different doses of INCS with each other. Both trials did not find a significant difference between different dosages of INCS.

Conclusion: This systematic review suggests that treatment of NAR with INCS is not effective. It is unclear if dosage, treatment duration or type of INCS influences the effectiveness of INCS treatment. Further studies should are required to investigate the effectiveness of INCS in various subtypes of NAR.

INTRODUCTION

DESCRIPTION OF THE CONDITION

Rhinitis is an inflammation of the nasal mucosal membrane. Rhinitis can be divided into 3 large types: infectious, allergic and non-allergic. Infectious rhinitis is generally a self-limiting disease, resolving in one or two weeks.(1) Allergic and non-allergic rhinitis have the same symptoms and can therefore be differentiated only based on allergy examination (history, skin prick testing, measurement of serum-specific IgE antibodies).(2) The symptoms consist of nasal blockage, rhinorrhea, sneezing, and nasal itching. Rhinitis can be intermittent or perennial, and symptoms can range from mild to debilitating.(3) Several types of non-allergic rhinitis (NAR) are recognized: occupational (irritant) rhinitis, drug-induced rhinitis (rhinitis medicamentosa), hormonal, rhinitis of the elderly, non-allergic rhinitis with eosinophilia syndrome (NARES), smoking rhinitis and idiopathic rhinitis.

Chronic rhinitis (allergic and non-allergic) affects up to 20% of the general population.(1) In most clinics a 50-50% division between allergic and non-allergic rhinitis is reported.(4) One study reported 43% of patients having AR, 23% having NAR, and 34% having a form of mixed rhinitis (both AR and NAR).(5)

DESCRIPTION OF THE INTERVENTION

There are different interventions used as treatment for patients with NAR. When rhinitis is caused by a non-allergic and non-infectious trigger, e.g. smoke, the main treatment consists of avoiding those triggers.(3) Besides avoiding triggers, there are several medications that can be prescribed, like antihistamine spray, local corticosteroids, ipratropium bromide and capsaicin. Some drugs are particularly used in one type of NAR. For example, ipratropium bromide is used in the treatment of rhinitis of the elderly, because it has a positive effect on the main symptom of this type, i.e. rhinorrhea.(2) Intranasal antihistamines are usually prescribed when sneezing is the main symptom of NAR.(3) Capsaicin, (8-methyl-nvanillyl-6-nomamide) the pungent component of red peppers, also seems to have a therapeutic effect in NAR. This therapy is tried after failing of treatment with local corticosteroids.(2)

Topical (local) intranasal corticosteroids (INCS) are considered the first choice of treatment in NAR, and are administered via a nasal spray or drops. Corticosteroids are steroid hormones produced by the adrenal cortex of the human body. Synthetic corticosteroids are widely used as anti-inflammatory medications in several conditions. Treatment with INCS should be attempted for at least several weeks, as it takes a few weeks to reach the maximum therapeutic effects.(6;7) Several INCS are available and differ by their pharmacological and pharmacokinetic properties, such as bioavailability, side effects and lipid solubility. Currently used INCS are beclomethasone dipropionate, triamcinolone acetonide, flunisolide, budesonide, fluticasone propionate, fluticasone furoate and mometasone furoate.(8)

If medications don't have a positive effects in NAR, surgery can be considered. Surgery focuses on two procedures: modifying the size of the inferior turbinate or blocking the autonomic innervation of the nose.(2)

HOW THE INTERVENTION MIGHT WORK

Corticosteroids have immunosuppressant and anti-inflammatory effects. INCS have a big range of anti-inflammatory effects, e.g. preventing fluid exudation and reducing the amount of inflammatory cells in the nose, such as lymphocytes, mast cells, basophils, eosinophils, macrophages and neutrophils. They also have a suppressing effect on the release and production of chemokines by those inflammatory cells.(9)

The use of INCS can result in local side effects in the nose, e.g. dryness, burning and stinging. Epistaxis occurs in 5 to 10% of the patients.(10)

WHY IT IS IMPORTANT TO DO THIS REVIEW

Currently, local corticosteroids are the first choice of treatment in NAR. Several studies suggest that local corticosteroids are effective in reducing the symptoms of NAR. Webb et al. have demonstrated that treatment with 200 µg of fluticasone propionate is effective in reducing symptoms of NAR compared with a placebo.(11) Another study reported that 200 µg of fluticasone propionate once daily led to reduction of nasal obstruction then placebo.(12) However, there are other studies that claim that INCS in NAR do not lead to improvement of NAR symptoms. For example, Lundblad concluded that mometasone furoate 200 µg/day for 6 weeks did not lead to any improvement in symptoms of NAR.(13) Given the equipoise in the literature on the effects of INCS in NAR, a systematic review of randomized controlled trials is hoped to provide further information about the effectiveness of this intervention.

OBJECTIVE

To assess the effectiveness of intranasal corticosteroids versus no therapy, placebo, other drugs or two or more of the above therapies in combination for the treatment of non-allergic rhinitis.

METHODS

This bachelor thesis is largely written following the Cochrane Collaboration guidelines described in Cochrane Handbook for Systematic Reviews of Interventions.(14) Parts of this thesis can be similar to parts of a Cochrane Protocol on this subject, which was published by the Cochrane Library in June 2013.(8) The full Cochrane systematic review will be published in due time.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

TYPES OF STUDIES

Randomized controlled trials (RCTs), irrespective of publication status, date of publication or language.

TYPES OF PARTICIPANTS

Patients of 16 years and older with all types of non-allergic rhinitis, including but not limited to occupational, smoking, gustatory, hormonal, senile, atrophic, drug-induced, local allergic, vasomotor and idiopathic rhinitis, non-allergic, non-infectious perennial rhinitis (NANIPER) and NARES. Patients were excluded if they had allergic rhinitis, rhinitis of clearly infectious etiology, acute or chronic rhinosinusitis, autoimmune rhinitis, or rhinitis related to anatomical abnormalities.

TYPES OF INTERVENTIONS

Interventions

Intranasal corticosteroids at any dose and duration.

Control

No therapy, placebo, or other drugs

TYPES OF OUTCOME MEASURES

PRIMARY OUTCOMES

Improvement of total symptom scores

SECONDARY OUTCOMES

Symptoms measured on a daily record chart (DRC) or visual analogue scale (VAS), like:

- Blockage
- Rhinorrhea
- Sneezing
- Nasal itching

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

ELECTRONIC SEARCHES

We performed an electronic search in PubMed with the following search strategy:

#1	rhinitis
#2	"Steroids"[Mesh]
#3	"Anti-Inflammatory Agents"[Mesh]
#4	"Anti-Inflammatory Agents, Non-Steroidal"[Mesh]
#5	#3 NOT #4
#6	steroid* OR corticosteroid* OR glucocorticoid* OR corticoid*
#7	#2 OR #5 OR #6
#8	"Administration, Intranasal"[Mesh]
#9	spray OR aerosol OR intranasal* OR intra-nasal OR topical*
#10	#8 OR #9
#11	#7 AND #10
#12	#1 AND #11
#13	#1 AND #11 Filters: Randomized Controlled Trial; Humans; English

SEARCHING OTHER RESOURCES

References of identified studies were checked to identify other relevant studies.

DATA COLLECTION AND ANALYSIS

SELECTION OF STUDIES

Two authors (RR and RG) independently assessed the title and abstract of the identified studies for inclusion. Disagreement on the inclusion of the studies was resolved through consensus and discussion. If necessary, disagreement was resolved through discussion with another author (AG).

Full texts of studies identified through title and abstract search were obtained, and were further assessed by two authors (RR and RG) independently. Reasons for exclusions were noted (Appendix 3 – Characteristics of excluded studies).

DATA EXTRACTION AND MANAGEMENT

Data was extracted by two authors independently (RR and RG) with a predetermined data extraction form (Appendix 1 – Data extraction form). Disagreements was resolved through consensus and discussion, and when necessary through a third author (AG).

ASSESSMENT OF RISK OF BIAS IN INCLUDED STUDIES

The Cochrane Collaboration 'Risk of bias' tool was used to assess the quality of included studies.(14) Seven specific domains (namely sequence generation, allocation concealment, blinding of participants, blinding of personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting) will be assessed and scored by assigning a judgment of 'Low risk' of bias, 'High risk' of bias, or 'Unclear risk' of bias. RR and RG independently assessed the methodological quality of all included studies. The authors resolved disagreement on this assessment through consensus and discussion, and when needed through a third party (senior author, AG).

DATA SYNTHESIS

Data extracted with the data extraction forms was assessed in a qualitative synthesis. Missing data was recorded in the data extraction form and reported in the Risk of Bias table.

SUBGROUP ANALYSIS

Three comparisons were made in this review. INCS were compared with placebo. INCS were compared with other interventions. Finally, different doses of INCS were compared with each other.

RESULTS

DESCRIPTION OF STUDIES

See Appendix 2 - Characteristics of Included studies; Appendix 3 - Characteristics of Excluded Studies.

RESULTS OF THE SEARCH

The original search in PubMed identified 563 studies. Through reference checking, we identified three more studies. A total of 566 titles and abstracts were screened, of which 524 studies were excluded for not meeting inclusion criteria. Of a total of 42 studies, the full-texts were retrieved and assessed for eligibility. 33 of those studies were excluded due to a variety of reasons (see Appendix 1 - PRISMA flowchart). Nine studies (Varricchio 2011(15); Lundblad 2001(13); Blom 1997(16); Jessen 1990(17); Day 1990(18); Turkeltaub 1982(19); Malm 1981(20); Incaudo 1980(21); Lofkvist 1976(22)) were included in this qualitative synthesis (see Appendix 2 – Characteristics of included studies).

INCLUDED STUDIES

STUDY DESIGN

Five studies (Lundblad 2001; Blom 1997; Day 1990; Turkeltaub 1982; Incaudo 1980) were randomized, double-blind, placebo controlled parallel-group trials. Three of them (Lundblad 2001; Day 1990; Incaudo 1980) had a treatment period of six weeks, preceded by a two week baseline period. The studies of Blom 1997 and Turkeltaub 1982 included respectively a treatment period of 8 and 12 weeks, both preceded by a two week baseline period. Varricchio 2011 was a randomized single-blind, placebo-controlled parallel-group trial, with duration of 8 weeks.

Three studies (Jessen 1990; Malm 1981; Lofkvist 1976) were randomized double-blind crossover trials. Malm 1981 and Lofkvist 1976 were placebo-controlled, while Jessen 1990 was double-dummy and ipratropium controlled. Malm 1981 started with a two week baseline period followed by two weeks of treatment with three different doses of active treatment or placebo, all separated by one week washout periods. On the other hand Jessen 1990 and Lofkvist 1976 did not start with a baseline period but included only two treatment periods of two weeks plus two weeks washout (Jessen 1990) or four weeks plus one week washout (Lofkvist 1976).

SETTING

Lundblad 2001 was a multicenter study in Northern Europe, including seven sites in Sweden, three in Denmark, four in Finland and four in Norway. Three studies (Malm 1981; Lofkvist 1976; Jessen 1990) took place in Sweden. The study of Blom 1997 was done in the Netherlands. Three studies were done in North America: one (Day 1990) in Canada and two (Turkeltaub 1982; Incaudo 1980) in the USA.

PARTICIPANTS

There were a total of 663 patients randomized in the nine included studies. Except for Blom 1997, all studies included adult patients. Blom 1997 included patients of 17 years and older. All studies included patients with a diagnosis of rhinitis and performed a skin prick test to exclude patients with allergic or seasonal rhinitis. Only Day 1990, Turkeltaub 1982, and Incaudo 1980 included allergic and non-allergic patients, but in those studies data of non-allergic patients was reported separately from the data of the patients with allergic rhinitis and could be used for this review. Eight studies (Lundblad 2001; Blom 1997; Jessen 1990; Day 1990; Turkeltaub 1982; Malm 1981; Incaudo 1980; Lofkvist 1976) excluded patients with nasal polyps. Five of those studies (Blom 1997; Jessen 1990; Day 1990; Malm 1981; Lofkvist 1976) also excluded patients with asthma. Varricchio 2011 did not exclude patients with nasal polyps or with asthma. Pregnant patients were excluded by Blom 1997, Day 1990 and Lofkvist 1976. Incaudo 1980 included only male patients.

INTERVENTIONS

During an eight-week intervention period Varricchio 2011 used 2 ml intranasal flunisolide (0.5 mg/ml) twice daily as active treatment and compared this with a placebo consisting of normal saline solution. Lundblad 2001 compared Mometasone Furoate nasal spray 200 µg once daily with a placebo, during six weeks. After randomization, patients of the Blom 1997 study were treated for eight weeks with one of four treatment regimens: twice daily placebo for eight weeks, 200 µg fluticasone once daily plus once daily a placebo, twice daily 200 µg fluticasone for eight weeks (400 µg/day), or once daily 200 µg fluticasone plus once daily placebo for four weeks (200 µg/day), followed by four weeks of twice daily 200 µg fluticasone nasal spray (400 µg/day). Jessen 1990 treated subjects in a double-dummy crossover setting with an aerosol 400 µg/day beclomethasone plus an aerosol with placebo for two weeks or with an aerosol 160 µg/day ipratropium plus an aerosol of placebo for two weeks. Between the two treatment periods a washout period of 2 weeks took place. The Day 1990 study used two puffs per nostril twice daily with budesonide (400µg/day) for four weeks as active treatment and compared it with placebo. Turkeltaub 1982 treated patients for twelve weeks with flunisolide (300 µg/day) or placebo (three times daily two puffs per nostril). A crossover trial with three different doses of Budesonide was performed by Malm 1981. Patients received either 50 µg, 200 µg, or 800 µg of budesonide per day or placebo for two weeks (twice daily on puff into each nostril). Every treatment period was separated with a one week washout period. As active treatment Incaudo 1980 used 200 µg/day flunisolide and compared it with placebo. Active treatment and placebo were given twice daily, two sprays in each nostril during six weeks. Lofkvist 1976 treated participants with beclomethasone 300 µg/day or with placebo (both three times daily, one puff into each nostril) for four weeks in a crossover setting. Between the two treatment periods was a one week washout period.

Rescue medication was allowed and/or provided in five studies. Blom 1997 and Day 1990 used terfenadine 60 mg as rescue medication, Malm 1981 phenylpropanolamine 50 mg, and Lundblad 2001 loratadine 10 mg. In the study of Jessen 1990 patients received a third aerosol containing ipratropium during the ipratropium treatment or placebo during the beclomethasone treatment, which they could use every second hour if needed.

Outcome measures

Individual symptoms, rhinorrhea, sneezing and blockage, were measured and reported by five studies (Blom 1997; Jessen 1990; Day 1990; Malm 1981; Lofkvist 1976). Patients recorded their symptoms on a scale from 0 (no symptoms) to 3 (severe symptoms) to describe the severity of their symptoms. Only Jessen 1990 used a scale from 0 (no symptoms) to 4 (severe symptoms). In addition Day 1990 and Lofkvist 1976 measured the symptom itching and Blom 1997 also measured the symptoms coughing, mucus production and eye-irritation. Those five studies combined the individual symptoms to a total symptom scores (TSS). The four other included studies also reported a TSS (Varricchio 2011; Lundblad 2001; Turkeltaub 1982; Incaudo 1980), using different scales to combine individual symptoms. Varricchio 2011 and Lundblad 2001 used the 0-3 scale, Incaudo 1980 used a scale from 1 to 4, and Turkeltaub 1982 measured symptoms on a scale from 0 to 6 and added this to a medication score (number of tablets and nasal sprays required to control symptoms). In addition to symptom scores, Blom 1997 used a Visual Analogue Scale (VAS) to assess the severity of symptoms; 0 meaning absence of symptoms and 10 meaning most severe intensity of symptoms.

Excluded studies

Thirty-three studies were excluded after full text analysis (See Appendix 3 – Characteristics of Excluded Studies) (6;7;11;23-52). Reasons for exclusion were: inclusion of children (<16 years), not a randomized controlled trial, no discrimination between non-allergic and allergic rhinitis, and the use of healthy subjects as participants.

Risk of bias in included studies

Risk of bias was judged by two authors independently and will be addressed below. For a summary and a risk of bias table see Figure 1 and 2. For a description of risk of bias per study see Appendix 2 – Characteristics of Included Studies.

Random sequence generation

Not one of the studies described how a random sequence was generated; therefore all studies were judged as 'unclear' for random sequence generation bias.

Allocation

Allocation concealment was judged as unclear in eight studies (Lundblad 2001; Blom 1997; Jessen 1990; Day 1990; Turkeltaub 1982; Malm 1981; Incaudo 1980; Lofkvist 1976). None of these studies described how allocation concealment was accomplished. Varricchio 2011 was a single-blind study, and therefore assessed as having a high risk of bias for allocation concealment.

Blinding

Except for Varricchio 2011, all studies were double-blind. Varricchio 2011 has a high risk for blinding of participants and personnel, and for blinding of outcome assessment.

INCOMPLETE OUTCOME DATA

Four studies (Blom 1997; Day 1990; Incaudo 1980; Lofkvist 1976) were judged as having an unclear risk of incomplete outcome data bias. These five studies did not describe if there were patients who withdrew during the study (Blom 1997; Incaudo 1980), or how they analyzed the data of the withdrawals (Day 1990; Lofkvist 1976). Three studies (Jessen 1990; Turkeltaub 1982; Malm 1981) were assessed with having a high risk of incomplete outcome data. Turkeltaub 1982 and Jessen 1990 didn't include patients who withdrew during the study in the efficacy analysis, and Malm 1981 excluded patients not having a symptom from the evaluation of that individual symptom.

SELECTIVE REPORTING

Most studies had a low risk of bias for selective outcome reporting. Two studies, Lofkvist 1982 and Jessen 1990, were judges as having a high risk. Lofkvist 1982 performed a medical examination of the nose for lividity, redness and edema on a scale from 0 (no symptoms) to 3 (sever symptoms), but did not report the outcomes of this examination. Jessen 1990 examined the nasal smears of patients, but the results of this examination were not reported.

OTHER POTENTIAL SOURCES OF BIAS

No other potential sources of bias were found.

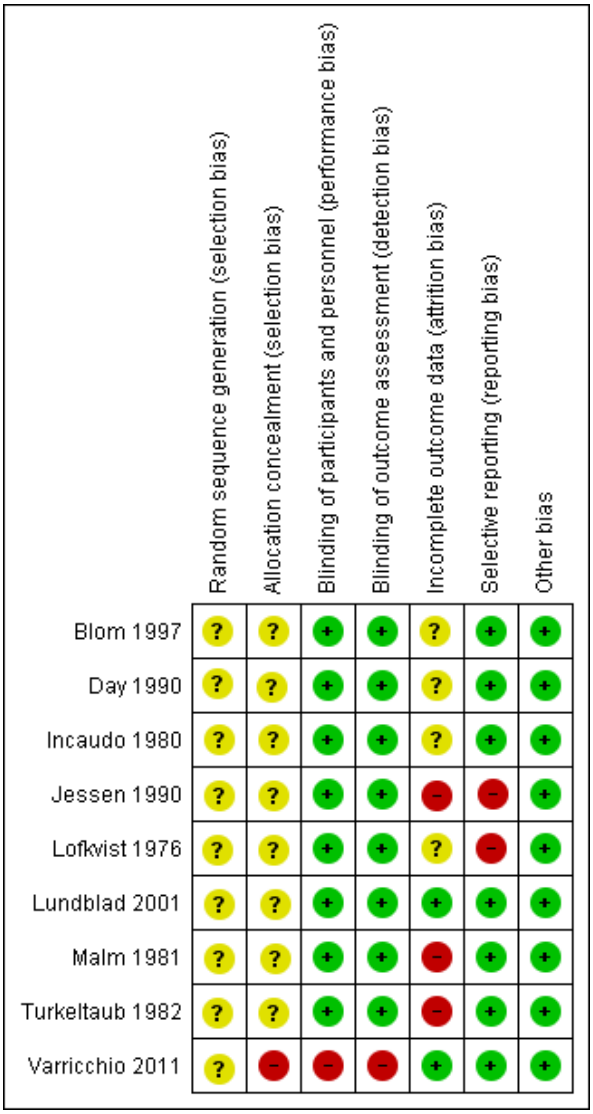

FIGURE 1: RISK OF BIAS SUMMARY: REVIEW AUTHORS' JUDGEMENTS ABOUT EACH RISK OF BIAS ITEM FOR EACH INCLUDED STUDY.

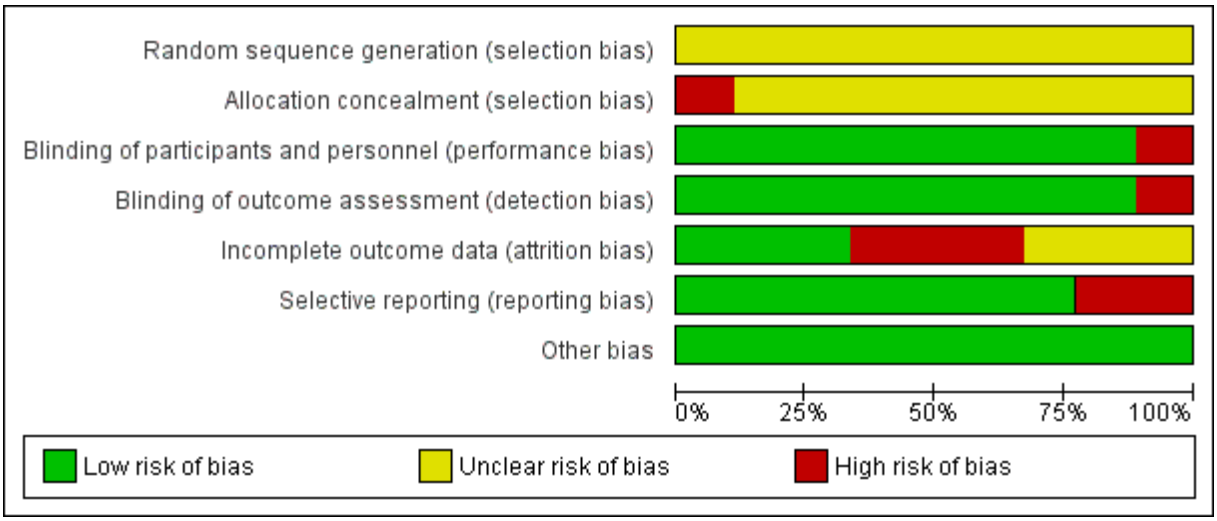

FIGURE 2: RISK OF BIAS GRAPH: REVIEW AUTHORS' JUDGEMENTS ABOUT EACH RISK OF BIAS ITEM PRESENTED AS PERCENTAGES ACROSS ALL INCLUDED STUDIES.

EFFECTS OF INTERVENTIONS

INTRANASAL CORTICOSTEROIDS VERSUS PLACEBO

The measured outcomes of the included studies are summarized in Appendix 4 – Summary of Outcomes.

PRIMARY OUTCOME

TOTAL SYMPTOM SCORES

From the seven studies reporting a Total Symptom Score (TSS), two studies (Varricchio 2011; Lofkvist 1976) found an improvement in TSS, however there were differences in the used scales.

Varricchio 2011 found an improvement in TSS from 8.3±1.8 at the beginning of the study to a score of 3.4±1.1 (P=0.0036) 8 weeks after treatment with beclomethasone. The placebo group improved their score from 8.9±2 to a score of 9.7±2 (not significant).

Lofkvist 1976 performed a crossover study and after 4 weeks a significant change in TSS was found for the group treated with beclomethasone compared with placebo (-2 points versus -0.7 points, P<0.01) After crossover the TSS of the group treated with beclomethasone improved 1.5 points versus an increase of 0.6 points for the placebo group (P<0.01).

Lundblad 2001 reported TSS as improvement rate during double-blind period. In the group treated with mometasone furoate for six weeks, 56% of the subjects improved their symptom scores compared with 49% of the subjects in the placebo group (P=0.25, or P=0.11 when stratified by baseline score).

In the Blom 1997 study, no significant difference was found in TSS between the four active treatment regimens and placebo. The placebo group started with a mean score of 2.8±1.6 and ended after 8 weeks with a score

2.6±1.7. Patients treated with 200 µg fluticasone had a baseline score of 3.0±1.1 and after eight weeks 2.7±2.1. The group treated with 200 µg for the first four weeks and after that with 400µg for four weeks, went from 3.1±1.7 to 1.9±1.3. Patients treated with 400 µg went from 3.2±0.9 to 2.2±1.3. For the symptoms measured on a visual analogue scale (VAS), combined to a combined symptom score, was also a not significant improvement found. The placebo group improved from a VAS score of 50±23 to a score of 41±24 after 8 weeks. The groups treated with 200 µg improved from 48.5±22.5 to 38±21, 200/400µg from 49±26 to 35±22 and 400µg from 46.5±21.5 to 30.5±22.5

Day 1980 reported no significant difference between mean change in TSS from baseline to treatment between budesonide and placebo. After 4 weeks of treatment the group on active treatment had a mean change of -1.46±1.79 points versus a mean change of -0.32±1.07 points in the placebo group (P=0.071).

Turkeltaub 1982 reported no significant difference between the group treated with flunisolide for twelve weeks and the placebo group (improvement of 2.75 points versus 1.12 points, SD and/or P-value are unknown).

In the Incaudo 1980 study, TSS improvement from 2.7 points to 2.45 points was not significant for patients treated with flunisolide and from 3.3 to 2.4 in the placebo group.

SECONDARY OUTCOMES

Five studies (Blom 1997; Jessen 1990; Day 1990; Malm 1981; Lofkvist 1976) reported individual symptoms (rhinorrhea, sneezing, blockage or itching).

RHINORRHEA

Blom 1997 measured an increase of 4% in symptom free days for rhinorrhea in the placebo group after 8 weeks of treatment. In the subgroups treated with 200 µg, 200/400µg, or 400µg per day, an increase of -2.5%, 21.5% and 7% respectively was measured. None of these increases were significant compared with placebo.

Day 1990 reported no significant difference (P=0.48) in change from baseline for the symptom rhinorrhea after treatment for six weeks with budesonide (-0.38±0.72) or placebo (-0.21±0.39).

Malm 1981 found a significant difference in rhinorrhea symptom score when budesonide was compared to placebo after 2 week treatment periods in a crossover trial (P<0.05). The group treated with 50 µg budesonide had a score of 0.6±0.1 post-intervention, the 200 µg budesonide group 0.7±0.1, the 800µg budesonide group 0.5±0.1 and the placebo group 0.85±0.2.

Lofkvist 1976 measured a significant reduction of blockage symptom score for the group of patients treated with beclomethasone compared with placebo in a crossover trial with 4 week treatment periods (P<0.01). In the first treatment period, patients on active treatment had a decrease in symptom score of 0.4 points compared to a decrease of 0.2 points for patients treated with placebo. After crossover, the beclomethasone group decreased 0.55 points compared to an increase of 0.05 points in the placebo group.

SNEEZING

Blom 1997 measured a decrease of 4% in symptom free days for sneezing in the placebo group after 8 weeks of treatment. In the subgroups treated with 200 µg, 200/400µg, or 400µg per day, an increase of -15%, 14.5% and 27% respectively was measured. Only the increase of 27% in the group treated with a dose of 400 µg fluticasone was significant compared with placebo ($P<0.05$).

Day 1990 reports no significant difference ($P=0.11$) in change from baseline for the symptom sneezing after treatment for six weeks with budesonide (-0.44±0.67) or placebo (-0.04±0.47).

Malm 1981 found a significant difference in sneezing symptom score when budesonide was compared to placebo after 2 week treatment periods in a crossover trial ($P<0.05$). The group treated with 50 µg budesonide had a score of 0.45±0.1 post-intervention, the 200 µg budesonide group 0.45±0.15, the 800µg budesonide group 0.3±0.1 and the placebo group 0.7±0.1.

Lofkvist 1976 measured a significant reduction of sneezing symptom score for the group of patients treated with beclomethasone compared with placebo in a crossover trial with 4 week treatment periods ($P<0.01$). In the first treatment period, patients on active treatment had a decrease in symptom score of 0.5 points compared to a decrease of 0.6 points for patients treated with placebo. After crossover, the beclomethasone group decreased 0.25 points compared to an increase of 0.2 points in the placebo group.

BLOCKAGE

Blom 1997 measured an increase of 6 % in symptom free days for blockage in the placebo group after 8 weeks of treatment. In the subgroups treated with 200 µg, 200/400µg, and 400µg per day, an increase of 9%, 4% and 15% respectively was measured. None of these increases were significant compared with placebo.

Day 1990 reports a significant difference ($P=0.048$) in change from baseline for the symptom blockage after treatment for six weeks with budesonide (-0.43±0.34) or placebo (-0.06±0.47).

Malm 1981 found a significant difference in blockage symptom score when budesonide was compared to placebo after 2 week treatment periods in a crossover trial ($P<0.01$). The group treated with 50 µg budesonide had a score of 0.0.85±0.2 post-intervention, the 200 µg budesonide group 0.75±0.15, the 800µg budesonide group 0.65±0.15 and the placebo group 1.2±0.2.

Lofkvist 1976 measured a significant reduction of blockage symptom score for the group of patients treated with beclomethasone compared with placebo in a crossover trial with 4 week treatment periods ($P<0.01$). In the first treatment period, patients on active treatment had a decrease in symptom score of 0.9 points compared to an unchanged score for patients treated with placebo. After crossover, the beclomethasone group decreased 0.45 points compared to an unchanged score in the placebo group.

ITCHING

Day 1990 reported no significant difference (P=0.23) in change from baseline for the symptom itching after treatment for six weeks with budesonide (-0.21±0.39) or placebo (0.01±0.45).

Lofkvist 1976 measured a significant reduction of sneezing symptom score for the group of patients treated with beclomethasone compared with placebo in a crossover trial with 4 week treatment periods (P<0.05). In the first treatment period, patients on active treatment had a decrease in symptom score of 0.35 points compared to a decrease of 0.05 points for patients treated with placebo. After crossover, the beclomethasone group decreased 0.2 points compared to a decrease of 0.05 points in the placebo group.

THERAPEUTIC RESPONSE

Therapeutic response was measured by Lundblad 2001 and reported after a follow-up period following 6 weeks of treatment with mometasone furoate or placebo. A not significant improvement in the group on active treatment was found compared to the placebo group (P=0.14). 16 patients treated with mometasone reported complete relief compared to 8 patients in the placebo group; 32 versus 28 showed marked relief; 34 versus 29 showed moderate relief; 22 versus 29 showed slight relief; 63 versus 68 had treatment failure.

INTRANASAL CORTICOSTEROIDS VERSUS OTHER INTERVENTIONS

The study done by Jessen 1990, compared intranasal beclomethasone 400 µg/day with ipratropium 160 µg/day and did not found a significant difference for the symptoms rhinorrhea, sneezing and blockage between the beclomethasone and the ipratropium group.

SECONDARY OUTCOMES

RHINORRHEA, SNEEZING AND BLOCKAGE

Jessen 1990 did not find a significant difference in rhinorrhea, sneezing or blockage symptoms when beclomethasone was compared with ipratropium in a crossover trial with treatment periods of two weeks. For Rhinorrhea the mean symptom score was 18.0±2.5 post-intervention for ipratropium and 19.8±3.3 post-intervention for beclomethasone, the mean symptom score for sneezing was 12.8±1.8 post-intervention for ipratropium and 11.4±1.9 post-intervention for beclomethasone. And the mean symptom score for nasal blockage was 8.0±2.0 post-intervention for ipratropium and 6.1±1.8 post-intervention for beclomethasone.

COMPARISON BETWEEN DIFFERENT DOSES OF INTRANASAL CORTICOSTEROIDS

PRIMARY OUTCOME

TOTAL SYMPTOM SCORES

Blom 1997 did not find a significant difference in TSS when different doses of fluticasone were compared to each other. Patients treated with 200 µg/day fluticasone had a baseline score of 3.0±1.1 and after eight weeks

2.7±2.1. The group treated with 200 µg/day for the first four weeks and after that with 400 µg/day for four weeks, went from 3.1±1.7 to 1.9±1.3. Patients treated with 400 µg/day went from 3.2±0.9 to 2.2±1.3. For the symptoms measured on a visual analogue scale (VAS), combined to a total symptom score, was also a not significant improvement found. The groups treated with 200 µg/day improved from a VAS score of 48.5±22.5 to 38±21, 200/400 µg/day from 49±26 to 35±22 and 400 µg/day from 46.5±21.5 to 30.5±22.5 after 8 weeks of treatment.

SECONDARY OUTCOMES

Due to the reporting style of Blom 1997, the different doses of fluticasone cannot be compared with each other for the secondary outcomes.

RHINORRHEA, SNEEZING AND BLOCKAGE

Malm 1981 did not found a significant difference in the rhinorrhea, sneezing or blockage symptom scores when a dosage of budesonide was compared to another dosage after 2 week treatment periods in a crossover trial. The group treated with 50 µg budesonide had a rhinorrhea score of 0.6±0.1 post-intervention, the 200 µg budesonide group 0.7±0.1, the 800µg budesonide group 0.5±0.1. For sneezing, the group treated with 50 µg budesonide had a score of 0.45±0.1 post-intervention, the 200 µg budesonide group 0.45±0.15, and the 800µg budesonide group 0.3±0.1. And for blockage the group treated with 50 µg budesonide had a score of 0.0.85±0.2 post-intervention, the 200 µg budesonide group 0.75±0.15, and the 800µg budesonide group 0.65±0.15.

DISCUSSION

We included only nine studies in accordance with our inclusion criteria. Among the excluded studies were many studies which included patients with perennial rhinitis with or without an allergic component. Although intranasal corticosteroids are an efficient treatment in allergic rhinitis, the effects of corticosteroids in NAR are not quite clear. (53;54) Therefore, we tried to study the isolated effects of INCS on NAR patients only.

Among the nine included trials in this review, two (Varricchio 2011; Lofkvist 1976) studies showed a significant improvement of total symptom scores (TSS) in patients treated with an intranasal corticosteroid compared with placebo. Five (Lundblad 2001; Blom 1997; Day 1990; Turkeltaub 1982; Incaudo 1980) of the nine included studies did not show a significant difference in TSS between the use of corticosteroids or placebo in patients with NAR. Two studies (Jessen 1990; Malm 1980) did not report TSS, but did reported individual symptoms. Malm 1981 found a significant difference in symptom score for secretion, sneezing and nasal obstruction, favoring corticosteroids. On the other hand Jessen 1990 found no significant difference in TSS between treatment with beclomethasone or ipratropium for the same symptoms.

Budesonide was the corticosteroid of choice in two of the four studies (Day 1990; Malm 1981) showing a positive effect of treatment with INCS. Flunisolide was used in three studies (Varricchio 2011; Turkeltaub 1982; Incaudo 1980) of which only Varricchio 2011 reports a significant improvement in symptoms favoring the active treatment group over the group treated placebo. Two trials (Jessen 1990; Lofkvist 1976) gave beclometasone as active treatment and compared it with placebo. Jessen 1980 reports no effects of treatment with a dose of 400 µg/day, while Lofkvist 1976 measured a significant improvement of symptoms when treated with 300 µg/day compared to placebo. We can conclude from the studies described above, that it is unclear whether the type of INCS used is of any influence on the effectiveness of INCS for NAR.

The dosage of INCS used in the included studies ranged from 50 µg/day (Malm 1981) to 2000 µg/day (Varricchio 2011). According to the results, there seems to be no relation between dosage of INCS used and relief in symptoms. Among the trials reporting significant improvements in symptom scores, only Varricchio 2011 used a much higher dose (2000 µg/day) compared to the trials not reporting a significant improvement of symptom scores.

The treatment duration varied from 2 weeks to 12 weeks in the nine trials. Malm 1981 and Lofkvist 1976, both favoring steroid over placebo, had relative short treatment periods (two and four weeks in crossover) compared to the studies which did not find a significant difference favoring steroids. We have to take into account that Malm 1981 treated patients four times two weeks with placebo or different doses of Budesonide (50, 200, 800 µg) giving patients a total duration of active treatment of 6 weeks. Given the heterogeneity of the treatment periods it is unclear if longer treatment periods will give better results for INCS treatment.

Taking the number of included participants per study in perspective, it is clear that of the total of 639 included patients, 515 were included in the seven studies showing no significant difference between the use of INCS

compared with placebo. Hundred and twenty four patients were included in a trial favoring INCS over placebo. Among the nine included studies, were small ones. Some studies (Jessen 1990; Malm 1981) included few patients; others included rhinitis patients of which a few had non-allergic rhinitis (Day 1990; Incaudo 1980). Lundblad 2001 was the largest study with a total of 329 randomized participants. To improve the quality of the evidence more and larger randomized controlled trials are required.

Patients under 16 years of age were not included in this review, with the consequence that three studies which included patients of 12 years or older (Kalpaklioglu 2010(24); Jacobs 2009(25); Schulz 1978(42)) were excluded from this review. Including those trials might have an effect on the conclusions of this review since they had a total of 900 patients, whereas a total of 663 patients are currently included. Jacobs 2009 is the largest of the excluded study with a total of 699 participants. It concluded that treatment with fluticasone is not effective in the treatment of patients with weather dependent vasomotor rhinitis. We are hoping to receive further information from this study on patients >16 years of age for inclusion in the final version of the Cochrane review that is currently written.

The diagnosis of NAR covers many types of rhinitis, e.g. vasomotor rhinitis, NARES, rhinitis of the elderly, drug-induced rhinitis, etcetera. Since NAR is a diagnosis of exclusion (by a negative skin prick test), the group of patients from the included studies includes various forms of NAR. It might be that some specific type of NAR encounters benefit from the use of INCS, while other types don't. A study done by Small et al has shown that treatment with beclomethasone dipropionate can be effective in patients with NARES(55). In this review, only Jessen 1980 included patients with a specific type of NAR (cholinergic NAR). The symptoms in those patients did not respond to treatment with an INCS. It is interesting to notice that Incaudo 1980 only included male participants. We can only speculate that they did this to exclude female patients with pregnancy rhinitis.

Some methodological differences between studies could be observed. Three studies were of a crossover design (Jessen 1990; Malm 1981; Lofkvist 1976). Varricchio 2011, Jessen 1990 and Lofkvist 1976 did not have a baseline period in which the symptoms of the subjects were measured without active treatment. In the measurement of outcomes, Turkeltaub 1981 added symptom score measured on a scale from 0 to 6 to a medication score to get a TSS. However, it is unclear how this medication score differs between patients; was rescue medication provided or were patients free to use as many sprays of flunisolide or placebo as the needed? Overall, the reporting of results was not standardized, making it difficult to compare results between studies. Although, performing a meta-analysis might be possible, it goes beyond the purpose of this review.

According to the risk of bias assessment, the included trials have many unclear biases and a few biases judged as high risk. None of the studies reported how a random sequence was generated or how allocation concealment was accomplished. Most of the included studies are marked unclear/high risk of bias for the incomplete data report assessment. It is clear that most studies were not thorough in reporting their full methodology or all their data. One study, Varricchio 2011, was single-blind and scored high for bias on three points (allocation concealment, blinding of participants and personal, and blinding of outcome assessment).

Excluding this study, because of his risk of bias from our review, makes it more likely that INCS do not improve symptom scores in patients with NAR.

During the writing of this review a few concessions were made, which could compromise the completeness of this review. First of all, we decided to only use clinically relevant outcomes, while some of the studies also reported other outcomes (such as turbinate hypertrophy, rhinomanometry, investigators overall evaluation). Secondly, we did not contact the authors of the included studies, because of a lack of time, to retrieve missing data, or to retrieve data in a way it could be analyzed and used in a meta-analysis. These points will be further addressed in the full systematic review and meta-analysis being prepared for the Cochrane Library. A current version of the protocol of this study can be accessed through the Cochrane Library.

CONCLUSION

After full assessment of the nine-included studies we can conclude that intranasal corticosteroids are probably not effective in the treatment of non-allergic rhinitis. It is unclear whether this depends on dose of INCS, sort of INCS or duration of treatment. Furthermore, it is unclear if INCS can be effective in different subtypes of NAR. To be able to make harder statements, more and bigger randomized trials should be done, especially trials which assess the effects of INCS in a subtype of NAR.

A Cochrane systematic review is currently being prepared. We hope to perform a meta-analysis after contacting all authors of included study to retrieve raw data. This full review is hoped to give answer to more questions about the effects of INCS as the treatment of NAR

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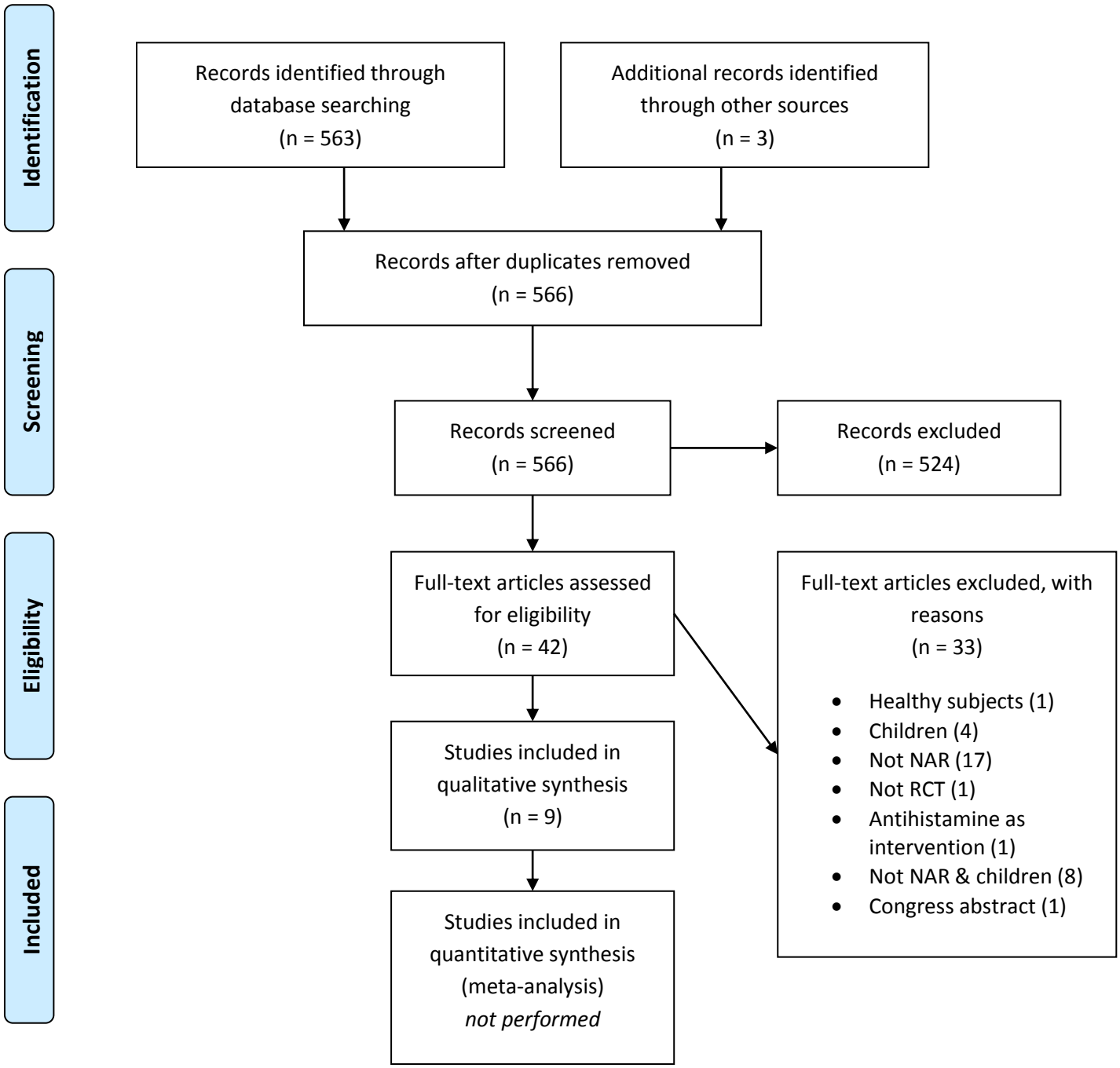
APPENDIX 1 – PRISMA FLOWCHART

PRISMA 2009 Flow Diagram



FROM: MOHER D, LIBERATI A, TETZLAFF J, ALTMAN DG, THE PRISMA GROUP (2009). *PREFERRED REPORTING ITEMS FOR SYSTEMATIC REVIEWS AND META-ANALYSES: THE PRISMA STATEMENT*. PLOS MED 6(6): E1000097. DOI:10.1371/JOURNAL.PMED1000097

APPENDIX 2 – CHARACTERISTICS OF INCLUDED STUDIES (ordered by date)

Varricchio 2011

Methods	Randomized, single-blind, placebo-controlled parallel trial Duration: 8 weeks Study setting: 2 hospitals in Naples, Italy	
Participants	Patients with non-allergic rhinitis 60 patients were randomized Mean age 42.8 years (range, 21-63 years) 39 males, 21 females Inclusion criteria: • Diagnosis of NAR (history of nasal symptoms, like sneezing, rhinorrhea, and nasal obstruction dependent on exposure to triggers (odors, irritants, weather changes) • Presence of inflammatory cells on nasal smear • Negative skin prick test (tested for house dust mites, cat, dog, grasses mix, Compositea mix, Parietaria judaica, birch, hazal tree, olive tree, cypress, Alternaria tenuis, Cladosporium, and Aspergilli mix) Exclusion criteria: • Acute or chronic upper respiratory infections, anatomic nasal defects, documented sensitization, using intranasal or oral corticosteroids, nasal or oral decongestants, antileukotrienes, and intranasal or oral antihistamines during the previous 4 weeks, or history of chronic epistaxis, immunodeficiency, or hypersensitivity to flunisolide	
Interventions	Intranasal flunisolide 2ml (0.5 mg/ml) or 2 ml placebo (saline solution) dispensed twice daily	
Outcomes	Nasal symptoms: measured at first treatment day (day 1) and at the end of treatment (end of week 8), on a scale from 0 (absence of symptoms) to 3 (severe symptoms). Turbinate hypertrophy: measured at day 1 and at the end of week 8 during nasal endoscopy. Measured on the basis of the distance between the medial wall of the inferior turbinate and the lateral wall of the septum: 0 = distance > 10 mm, 1 = distance < 10 mm and > 5 mm, 2 = < 5 mm, 3 = 0 mm. Percentage of inflammatory cells on nasal cytology: cytological samples obtained at day 1 and at the end of week 8 and. Assessed under a microscope. Data were expressed as percentage of inflammatory cells to total recovered cells	
Notes		
Risk of bias		
Item	*Authors' judgment*	*Description*
Random sequence generation	Unclear	Not described
Allocation concealment	High	Study was single-blind
Blinding of participants and personnel	High	Study was single-blind
Blinding of outcome assessment	High	Study was single-blind
Incomplete outcome data	Low	No patients withdrew during the trial
Selective outcome reporting	Low	Results from all measured outcomes are reported
Other bias	Low	Not found

Lundblad 2001

Methods	Randomized, double-blind, placebo-controlled parallel trial 2 week screening period 6 week treatment period 3 week follow-up period Study setting: 16 sites total, 7 in Sweden, 3 in Denmark, 4 in Finland and 4 in Norway.	
Participants	Patients with perennial non-allergic rhinitis 329 patients were randomized 78 withdrawals during study 167 males, 162 females Age 18-82 years (no mean age provided) Inclusion criteria: • A score of ≥2 for rhinorrhea or congestion and at least a moderate score during the month prior to the trial for at least 1 hour daily and for at least 4 days per week. Scale: 0= no symptoms to 3 severe symptoms. • Negative skin prick test (tested for birch, timothy, Artemisia vulgaris, dog, horse, cat, mite, Aspergillus fumigatus, Cladosporium herbarum and Alternaria alternata, as well as positive histamine and negative histamine controls) Exclusion criteria: • Intolerance to aspirin or NSAID's • Significant septal deviations or other structural deformities • Nasal polyps	
Interventions	Mometasone Furoate nasal spray 200 µg or placebo once daily for 6 weeks Rescue medication: Loratadine 10 mg	
Outcomes	Subjects overall evaluation: defined as a reduction (compared to screening period) of at least one point in the overall symptoms score, based on individual symptoms (rhinorrhea, nasal stuffiness/congestion, nasal itching and sneezing), recorded daily on scale from 0 (no symptoms) to 3 (severe symptoms). Investigators overall evaluation: based on individual symptoms, measured at day 0 (start of treatment), 14, 42 (end of treatment) en 63(end of follow-up), measured on the same scale the subjects used to assess their own symptoms. Therapeutic response: measured at day 14, 42 and 63 with the following scale: 1=complete relief, 2=marked relief, 3=moderate relief, 4=slight relief, 5=treatment failure.	
Notes	Intention to treat analysis was performed	
Risk of bias		
Item	*Authors' judgment*	*Description*
Random sequence generation	Unclear	Not described
Allocation concealment	Unclear	Not described
Blinding of participants and personnel	Low	Double-blind study, probably done correctly
Blinding of outcome assessment	Low	Double-blind study, probably done correctly
Incomplete data outcome	Low	ITT analysis was performed
Selective outcome reporting	Low	Results from all measured outcomes are reported
Other bias	Low	Not found

Blom 1997

Methods	Randomized, double-blind, placebo-controlled parallel trial. 2 week run in period 8 week treatment period (one of four different treatment regimens) Study setting: Leyenburg Hospital in Den Haag, The Netherlands and Dijkzigt University Hospital in Rotterdam, The Netherlands
Participants	Patients with non-allergic, non-infectious perennial rhinitis 65 patients were randomized 32 male, 33 female Mean age 34 years (17-62 years) Inclusion criteria: • Age between 16 and 64 years • Negative skin prick test response to house dust mite, tree pollen mix, grass pollen mix, bijvoet, Alternaria, Aspergillus, Cladosporiurn, Penicillurn, dog, cat, parakeet, rabbit, hamster, horse, guinea pig • Negative Phadiatop result • Symptoms for more than 1 year • Periods of nasal discharge, sneezing, and congestion for an average of at least 1 hour per day for at least 5 days during a period of 14 days Exclusion criteria: • Use of systemic or inhaled corticosteroids within the previous month • Use of inhaled sodium cromoglycate or nedocromil sodium within the previous month • Use of astemizole within the previous month • Inability of the patient to stop taking medication affecting nasal function • A serious and/or unstable disease • Nasal surgery within the previous 6 weeks • Nasal polyps or a history of nasal polyps • Significant anatomic abnormalities affecting nasal function • Nasal or paranasal sinus infection (abnormal sinus roentgenogram) • Pregnancy or lactation • Abnormal laboratory results for • Blood: Na, K, Ca, total protein, albumin, urea, creatinine, bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, γglutamyl transpeptidase, hemoglobin, red blood cell count, plasma cell volume, mean corpuscular volume, platelets, total white blood cell count, neutrophils, lymphocytes, monocytes, eosinophils, and basophils • Urine: blood, protein, and glucose • Abnormal findings at physical examination Ethnicity of patients: 1 Oriental, 56 white, 2 black, and 6 Asian
Interventions	Run in: placebo aqueous spray twice daily Treatment period: • Twice daily placebo; • Once daily fluticasone 200 µg for 8 weeks + once daily placebo; • Twice daily fluticasone 200 µg for 8 weeks • Once daily fluticasone 200 µg + once daily placebo for 4 weeks, followed by fluticasone 200 µg twice daily for 4 weeks Rescue medication: Terfenadine tablets (60 µg)
Outcomes	Symptom score: Daily Record Chard for rhinorrhea, sneezing and obstruction, ranging from 0 (absence of symptom) up to 3 (most severe level of symptoms). Reported as mean increase in the percentage of symptom-free days. Total symptom score: Mean sum score (sum of individual symptoms rhinorrhea,

	sneezing and obstruction). And a Visual Analogue Scale (0 to 10 cm, 0=absence of symptoms, 10 most severe intensity of symptoms) was used to assess nasal symptoms for the last 3 days at entry, end of run in period, week 4 and 8.	
Notes		
Risk of bias		
Item	*Authors' judgment*	*Description*
Random sequence generation	Unclear	Not described
Allocation concealment	Unclear	Not described
Blinding of participants and personnel	Low	Double-blind, probably done correctly
Blinding of outcome assessment	Low	Double-blind, probably done correctly
Incomplete data reporting	Unclear	Unclear how many patients withdrew from study during treatment and what was done with their data
Selective outcome reporting	Low	Results from all measured outcomes are reported
Other bias	Low	Not found

Jessen 1990

Methods	Randomized double-blind, double-dummy, ipratropium-controlled, crossover trial 2 week treatment with beclomethasone, 2 week washout, followed by 2 weeks of treatment with ipratropium, or in reversed order Study setting: Malmö General Hospital, University of Lund, Sweden	
Participants	Patients with cholinergic non-allergic rhinitis 24 patients were randomized 14 male, 10 female Mean age 49 years (20-77 years) Inclusion criteria: • Negative skin prick test • Excessive nasal secretion from a half to 30 years Exclusion criteria: • Asthma or nasal polyps • No benefit of ipratropium challenge	
Interventions	Aerosol with beclomethasone 400 µg and aerosol with placebo, both two times a day two puffs to each nostril Aerosol with Ipratropium 160 µg and aerosol with placebo, both two times a day two puffs to each nostril. Rescue medication: every second hour a third aerosol containing ipratropium during ipratropium treatment period or placebo during beclomethasone treatment period, if needed.	
Outcomes	Individual symptoms (secretion, sneezing, blockage), recorded daily on a scale from 0 (no symptoms) to 4 (severe symptoms) Nasal Airway resistance was measured with rhinomanometry (time-point unknown). Nasal smear examination	
Notes	Results not reported for nasal smear examination	
Risk of bias		
Item	*Authors' judgment*	*Description*
Random sequence generation	Unclear	Not described

Allocation concealment	Unclear	Not described
Blinding of participants and personnel	Low	Double-blind, probably done correctly
Blinding of outcome assessment	Low	Double-blind, probably done correctly
Incomplete outcome data	High	No ITT analysis
Selective outcome reporting	High	Nasal smear examination results are not reported
Other bias	Low	Not found

Day 1990

Methods	Randomized, double-blind, placebo-controlled, parallel trial 2 week baseline period 4 week treatment period Study setting: Kingston General Hospital, Ontario, Canada.	
Participants	Adults with rhinitis 48 patients were randomized (24 with non-allergic rhinitis) 20 male, 28 female Age 22-65 years Inclusion criteria: • Perennial rhinitis over a period of at least 2 years • Currently not receiving therapy for rhinitis • Negative skin prick test (non-allergic patients) Exclusion criteria: • Pregnant • Tuberculosis • Respiratory infection • Additional nasal disease • Asthma	
Interventions	Budesonide (400 µg daily dose) or placebo , two puffs per nostril each morning and evening Rescue medication: terfenadine 60 mg	
Outcomes	Individual symptoms (blocked nose, itchy nose, runny nose and sneezing), measured as mean change in symptoms scores, measured daily on a scale from 0 (no symptoms) to 3 (severe symptoms) Combined symptom scores measured as for individual symptom scores	
Notes	Characteristics not known for the non-allergic rhinitis subgroup	
Risk of bias		
Item	*Authors' judgment*	*Description*
Random sequence generation	Unclear	Not described
Allocation concealment	Unclear	Not described
Blinding of participants and personnel	Low	Double-blind, probably done correctly
Blinding of outcome assessment	Low	Double-blind, probably done correctly
Incomplete outcome data	Unclear	1 patient in the placebo group failed to return for a visit mid-treatment. Unclear whether intention to treat analysis, or not?
Selective outcome	Low	Results from all measured outcomes

reporting		are reported
Other bias	Low	Not found

Turkeltaub 1982

Methods	Randomized, double-blind, placebo controlled, parallel trial 2 week run in period 12 week treatment period Long-term follow-up period for patients who continued flunisolide treatment Date: Study started 1 month after the first frost and continued through the winter months Study setting: John Hopkins University School of Medicine, Baltimore, USA	
Participants	125 patients (50 with seasonal and 75 with perennial rhinitis) Age and sex for the perennial group is not described All perennial rhinitis patients were tested with skin prick test with the following test panel: giant/short ragweed, perennial rye grass, bermuda, Alterneria Sp., house dust, cat and dog. Any reaction larger than the control was considered positive. Inclusion criteria: • Year-round nasal symptoms severe enough to require medication (over-the-counter and/or prescription) Exclusion criteria: • Sinusitis • Underlying nasal pathology resulting in fixed occlusion of a nostril • Medication which might suppress symptoms of perennial rhinitis	
Interventions	Flunisolide 300 µg/day or placebo, three times daily two puffs per nostril	
Outcomes	Total symptom score, consisting of daily recorded symptom scores (sneezing, runny nose, stuffy nose, eye itch and throat itch) on a scale from 0 (symptom definitely absent) to 6 (symptom definitely present 6 hours or more), added to the number of tablets and nasal sprays required to control nasal symptoms	
Notes	It is unclear whether rescue medication was used Per protocol analysis was performed (15 patients were not included in the analysis)	
Risk of bias		
Item	*Authors' judgment*	*Description*
Random sequence generation	Unclear	Not described
Allocation concealment	Unclear	Not described
Blinding of participants and personnel	Low	Double-blind, probably done correctly
Blinding of outcome assessment	Low	Double-blind, probably done correctly
Incomplete outcome data	High	Patients who dropped out were not included in the efficacy analysis
Selective data reporting	Low	Results from all measured outcomes are reported
Other bias	Low	Not found

Malm 1981

Methods	Randomized double-blind placebo-controlled crossover trial 2 week run in period 2 week treatment

	1 week wash-out period between treatments Study setting: Malmo General Hospital, Malmö, Sweden
Participants	Patients with perennial non-allergic rhinitis 23 patients were randomized 1 withdrawal Mean age 42 years (20-68 years) 5 males, 17 females Inclusion criteria: • Two or more of the symptoms of nasal obstruction, nasal secretion, sneezing attacks for at least 1 year • Negative skin prick test Exclusion criteria: • Bronchial asthma • Nasal polyposis
Interventions	Budesonide 50 µg or 200 µg or 800 µg or placebo as pressurized aerosols, one puff into each nostril twice daily Rescue medication: phenylpropanolamine 50 mg
Outcomes	Obstruction symptom score, measured daily with a scale from 0 (no symptoms) to 3 (severe symptoms) Secretion symptom score, measured daily with a scale from 0 (no symptoms) to 3 (severe symptoms) Sneezing attacks symptom score, measured daily with scale: 0= no attacks, 1= 1-5 attacks, 2=6-16 attacks, 3= more than 15 attacks Rhinomanometry nasal resistance in degrees, in sitting position and recumbent position. Measured at end of the first week of run-in and the day after each treatment period
Notes	Unclear at what point withdrawal took place

Risk of bias		
Item	*Authors' judgment*	*Description*
Random sequence generation	Unclear	Not described
Allocation concealment	Unclear	Not described
Blinding of participants and personnel	Low	Double-blind, probably done correctly
Blinding of outcome assessment	Low	Double-blind, probably done correctly
Incomplete outcome data	High	Included patients not having a symptom were excluded from the evaluation of that individual symptom
Selective data reporting	Low	Results from all measured outcomes are reported
Other bias	Low	Not found

Incaudo 1980

Methods	Randomized double blind placebo-controlled parallel group trial 2 week baseline period 6 week treatment Study setting: 3 medical centers in San Diego, USA
Participants	Patients with perennial rhinitis 56 patients were randomized (31 skin prick positive, 22 skin prick negative) Mean age: 34,7 years (19-62 years) All patients were male Inclusion criteria:

	• Perennial rhinitis consisting primarily of nasal stuffiness, rhinorrhea, or sneezing for at least 2 years Exclusion criteria: • Nasal polyps	
Interventions	Flunisolide 200 µg/day (twice daily, two sprays in each nostril) or placebo consisting of aqueous propylene glycol/polyethylene glycol (twice daily, two sprays in each nostril)	
Outcomes	Symptom severity score measured daily on a scale 1 (absence of symptoms) to 3 (severe symptoms). Reported end of week 2 (baseline), and end of week 4, 6, and 8.	
Notes		
Risk of bias		
Item	*Authors' judgment*	*Description*
Random sequence generation	Unclear	Not described
Allocation concealment	Unclear	Not described
Blinding of participants and personnel	Low	Double-blind, probably done correctly
Blinding of outcome assessment	Low	Double-blind, probably done correctly
Incomplete outcome data	Unclear	Withdrawals are not described
Selective data reporting	Low	Results from all measured outcomes are reported
Other bias	Low	Not found

Lofkvist 1976

Methods	Randomized double-blind placebo-controlled crossover trial Date: February 1975-April 1975 Duration: 4 weeks treatment period, 1 week wash-out, 4 weeks placebo, or in reversed order. Study setting: University Hospital, Lund, Sweden
Participants	Patients with a history of perennial, vasomotor rhinitis for many years 41 patients were randomized 2 withdrawals Mean age 39 years (19-66 years) 19 males and 20 females Inclusion criteria: • Negative allergy test (6 dust extracts, 2 mould extracts, 8 animal epithelium extracts, and 10 pollen extracts) Exclusion criteria: • Nasal polyposis • Obvious septum deviation • Bronchial asthma • Pregnancy
Interventions	Beclomethasone dipropionate 300 µg/day (three times daily, one puff into each nostril) or placebo (three times daily, one puff into each nostril)
Outcomes	Individual symptoms: nasal catarrh, blockade, sneezing and itching, measured daily on a scale 0 (no symptoms) to 3 (severe symptoms) Total nasal symptom score: individual symptoms combined Medical examination of the nose: lividity, redness, edema and purulent discharge, measured before entry and last day of active and placebo treatment period on a scale 0 (no symptoms) to 3 (severe symptoms)

Notes	Medical examination results are not reported	
Risk of bias		
Item	*Authors' judgment*	*Description*
Random sequence generation	Unclear	Not described
Allocation concealment	Unclear	Not described
Blinding of participants and personnel	Low	Double-blind, probably done correctly
Blinding of outcome assessment	Low	Double-blind, probably done correctly
Incomplete outcome data	Unclear	2 patients withdrew, not clear when (baseline or during treatment) and how it is analyzed (per protocol or ITT)
Selective outcome reporting	High	Medical examination of the nose is not reported.
Other bias	Low	Not found

APPENDIX 3 – CHARACTERISTICS OF EXCLUDED STUDIES (ordered by date)

Study	Reason for exclusion
Vaidyanathan 2010	Healthy subjects
Kalpaklioglu 2010	Children included, >14 years
Jacobs 2009	Children included, >12 years
Rinne 2002	No discrimination between NARES and perennial allergic rhinitis
Webb 2002	Not randomized controlled
Ellegard 2001	No discrimination between allergic rhinitis and non-allergic rhinitis
Kivisaari 2001	No discrimination between allergic rhinitis and non-allergic rhinitis Children included, >12 years
Purello-DÁmbrosio 1999	Comparing loratadine (antihistamine) with placebo
Dockhorn 1999	Children included, > 8 years
Graf 1998	No discrimination between allergic rhinitis and non-allergic rhinitis
Hallen 1997	No discrimination between allergic rhinitis and non-allergic rhinitis
Scadding 1995	No discrimination between allergic rhinitis and non-allergic rhinitis Children included, >12 years
Haye 1993	No discrimination between allergic rhinitis and non-allergic rhinitis
Studham 1993	No discrimination between allergic rhinitis and non-allergic rhinitis
Wight 1992	No discrimination between allergic rhinitis and non-allergic rhinitis
Bunnag 1992	No discrimination between allergic rhinitis and non-allergic rhinitis
Lau 1990	No discrimination between allergic rhinitis and non-allergic rhinitis
Svendsen 1989	No discrimination between allergic rhinitis and non-allergic rhinitis
Hartley 1985	No discrimination between allergic rhinitis and non-allergic rhinitis
Joubert 1983	No discrimination between allergic rhinitis and non-allergic rhinitis
Arbesman 1983	No discrimination between allergic rhinitis and non-allergic rhinitis
Small 1982	No discrimination between allergic rhinitis and non-allergic rhinitis Children included, >14 years
Warland 1982	No discrimination between allergic rhinitis and non-allergic rhinitis
Clayton 1981	No discrimination between allergic rhinitis and non-allergic rhinitis Children included, >13 years
Jones 1979	No discrimination between allergic rhinitis and non-allergic rhinitis Children included, >15 years
Schulz 1978	Children included, >15 years
Tarlo 1977	No discrimination between allergic rhinitis and non-allergic rhinitis
Blair 1977	No discrimination between allergic rhinitis and non-allergic rhinitis Children included, >11 years
Harding 1976	No discrimination between allergic rhinitis and non-allergic rhinitis Children included, >9 years
Gibson 1974	No discrimination between allergic rhinitis and non-allergic rhinitis
Hansen 1974	No discrimination between allergic rhinitis and non-allergic rhinitis Children included, >15 years
Czarny 1968	No discrimination between allergic rhinitis and non-allergic rhinitis

APPENDIX 4 - SUMMARY OF OUTCOMES (Green = significant, red = not significant, yellow = subgroup significant)

	TSS	Rhinorrhea	Sneezing	Blockage	Itching
Varricchio 2011	Favors steroid over saline solution (P=0.0036)	NA	NA	NA	NA
Lundblad 2001	No significant difference between steroid and placebo (P=0.11)	NA	NA	NA	NA
Blom 1997	No significant difference between steroid and placebo (P not shown)	No significant difference between steroid and placebo (P not shown)	Only significant in group treated with 400 µg/day steroid (P<0.05)	No significant difference between steroid and placebo (P not shown)	NA
Jessen 1990	NA	No significant difference between steroid and ipratropium (P not shown)	No significant difference between steroid and ipratropium (P not shown)	No significant difference between steroid and ipratropium (P not shown)	NA
Day 1990	No significant difference between steroid and placebo (P=0.071)	No significant difference between steroid and placebo (P=0.48)	No significant difference between steroid and placebo (P=0.11)	Favors steroid over placebo (P=0.048)	No significant difference between steroid and placebo (P=0.23)
Turkeltaub 1982	No significant difference between steroid and placebo (P not shown)	NA	NA	NA	NA
Malm 1981	NA	Favors steroid over placebo (P<0.05)	Favors steroid over placebo (P<0.05)	Favors steroid over placebo (P<0.01)	NA
Incaudo 1980	No significant difference between steroid and placebo (P not shown)	NA	NA	NA	NA
Lofkvist 1976	Favors steroid over placebo (P<0.01)	Favors steroid over placebo (P<0.01)	Favors steroid over placebo (P<0.01)	Favors steroid over placebo (P<0.01)	Favors steroid over placebo (P<0.05)

APPENDIX 5 – DATA EXTRACTION FORM

Data collection form

Review title or ID	Intranasal corticosteroids in non-allergic rhinitis
Study ID *(surname of first author and year first full report of study was published e.g. Smith 2001)*	
Report ID	
Report ID of other reports of this study	

General Information

Date form completed *(dd/mm/yyyy)*	
Name/ID of person extracting data	Rens Reeskamp
Reference citation	
Study author contact details	
Study country	
Publication type *(e.g. full report, abstract, letter)*	
Notes:	

Study eligibility

Study Characteristics	Eligibility criteria *(Insert inclusion criteria for each characteristic as defined in the Protocol)*	Eligibility criteria met? Yes No Unclear	Location in text or source *(pg & ¶/fig/table/other)*

Type of study	Randomised Controlled Trial	☐ ☐ ☐	
	Quasi-randomised Controlled Trial	☐ ☐ ☐	
Participants		☐ ☐ ☐	
Types of intervention		☐ ☐ ☐	
Types of comparison		☐ ☐ ☐	
Types of outcome measures		☐ ☐ ☐	
INCLUDE ☐		EXCLUDE ☐	
Reason for exclusion			
Notes:			

DO NOT PROCEED IF STUDY EXCLUDED FROM REVIEW

Characteristics of included studies

Methods

	Descriptions as stated in report/paper	**Location in text or source** *(pg & ¶/fig/table/other)*
Aim of study *(e.g. efficacy, equivalence, pragmatic)*		

Design*(e.g. parallel, crossover, non-RCT)*			
Unit of allocation *(by individuals, cluster/ groups or body parts)*			
Start date			
End date			
Duration of participation *(from recruitment to last follow-up)*			
Ethical approval needed/ obtained for study	☐ Yes ☐ No ☐ Unclear		
Notes:			

Participants

	Description *Include comparative information for each intervention or comparison group if available*	Location in text or source *(pg & ¶/fig/table/other)*
Population description *(from which study participants are drawn)*		
Setting *(including location and social context)*		

Inclusion criteria		
Exclusion criteria		
Method of recruitment of participants *(e.g. phone, mail, clinic patients)*		
Informed consent obtained	☐ Yes ☐ No ☐ Unclear	
Total no. randomised *(or total pop. at start of study for NRCTs)*		
Clusters *(if applicable, no., type, no. people per cluster)*		
Baseline imbalances		
Withdrawals and exclusions *(if not provided below by outcome)*		
Age		
Sex		
Race/Ethnicity		
Severity of illness		
Co-morbidities		
Other relevant sociodemographics		
Subgroups measured		
Subgroups reported		
Notes:		

Intervention groups

Copy and paste table for each intervention and comparison group

Intervention Group 1

	Description as stated in report/paper	Location in text or source *(pg & ¶/fig/table/other)*
Group name		
No. randomised to group *(specify whether no. people or clusters)*		
Theoretical basis *(include key references)*		
Description *(include sufficient detail for replication, e.g. content, dose, components)*		
Duration of treatment period		
Timing *(e.g. frequency, duration of each episode)*		
Delivery *(e.g. mechanism, medium, intensity, fidelity)*		
Providers *(e.g. no., profession, training, ethnicity etc. if relevant)*		
Co-interventions		
Economic information *(i.e. intervention cost, changes in other costs as result of intervention)*		

Resource requirements *(e.g. staff numbers, cold chain, equipment)*		
Integrity of delivery		
Compliance		
Notes:		

Outcomes

Copy and paste table for each outcome.

Outcome 1

	Description as stated in report/paper	Location in text or source *(pg & ¶/fig/table/other)*
Outcome name		
Time points measured *(specify whether from start or end of intervention)*		
Time points reported		
Outcome definition *(with diagnostic criteria if relevant)*		
Person measuring/ reporting		
Unit of measurement *(if relevant)*		
Scales: upper and lower limits *(indicate whether high or low score is good)*		

Is outcome/tool validated?	☐ Yes ☐ No ☐ Unclear		
Imputation of missing data *(e.g. assumptions made for ITT analysis)*			
Assumed risk estimate *(e.g. baseline or population risk noted in Background)*			
Power *(e.g. power & sample size calculation, level of power achieved)*			
Notes:			

Risk of Bias assessment

See Chapter 8 of the Cochrane Handbook. Additional domains may be added for non-randomised studies.

Domain	Risk of bias Low High Unclear	Support for judgement *(include direct quotes where available with explanatory comments)*	Location in text or source *(pg & ¶/fig/table/other)*
Random sequence generation *(selection bias)*	☐ ☐ ☐		
Allocation concealment *(selection bias)*	☐ ☐ ☐		
Blinding of participants and personnel *(performance bias)*	☐ ☐ ☐	Outcome group: All/	

(if separate judgement by outcome(s) required)	☐ ☐ ☐	Outcome group:	
Blinding of outcome assessment *(detection bias)*	☐ ☐ ☐	Outcome group: All/	
(if separate judgement by outcome(s) required)	☐ ☐ ☐	Outcome group:	
Incomplete outcome data *(attrition bias)*	☐ ☐ ☐	Outcome group: All/	
(if separate judgement by outcome(s) required)	☐ ☐ ☐	Outcome group:	
Selective outcome reporting? *(reporting bias)*	☐ ☐ ☐		
Other bias	☐ ☐ ☐		
Notes:			

Data and analysis

Copy and paste the appropriate table for each outcome, including additional tables for each time point and subgroup as required.

Dichotomous outcome

	Description as stated in report/paper	Location in text or source *(pg & ¶/fig/table/other)*
Comparison		
Outcome		

Subgroup					
Time point *(specify from start or end of intervention)*					
Results	Intervention		Comparison		
	No. with event	Total in group	No. with event	Total in group	
Any other results reported *(e.g. odds ratio, risk difference, CI or P value)*					
No. missing participants					
Reasons missing					
No. participants moved from other group					
Reasons moved					
Unit of analysis *(by individuals, cluster/groups or body parts)*					
Statistical methods used and appropriateness of these *(e.g. adjustment for correlation)*					
Reanalysis required? *(specify, e.g. correlation adjustment)*	☐ Yes	☐ No	☐ Unclear		
Reanalysis possible?	☐ Yes	☐ No	☐ Unclear		
Reanalysed results					
Notes:					

Continuous outcome

	Description as stated in report/paper						Location in text or source *(pg & ¶/fig/table/other)*
Comparison							
Outcome							
Subgroup							
Time point *(specify from start or end of intervention)*							
Post-intervention or change from baseline?							
Results	Intervention			Comparison			
	Mean	SD *(or other variance, specify)*	No. participants	Mean	SD *(or other variance, specify)*	No. participants	
Any other results reported *(e.g. mean difference, CI, P value)*							
No. missing participants							
Reasons missing							
No. participants moved from other group							
Reasons moved							

Unit of analysis *(individuals, cluster/ groups or body parts)*			
Statistical methods used and appropriateness of these *(e.g. adjustment for correlation)*			
Reanalysis required? *(specify)*	☐ Yes ☐ No ☐ Unclear		
Reanalysis possible?	☐ Yes ☐ No ☐ Unclear		
Reanalysed results			
Notes:			

Other outcome

	Description as stated in report/paper				Location in text or source *(pg & ¶/fig/table/other)*
Comparison					
Outcome					
Subgroup					
Time point *(specify from start or end of intervention)*					
No. participants	Intervention		Control		
Results	Intervention result	SE (or other variance)	Control result	SE (or other variance)	

	Overall results		SE (or other variance)		
Any other results reported					
No. missing participants					
Reasons missing					
No. participants moved from other group					
Reasons moved					
Unit of analysis *(by individuals, cluster/groups or body parts)*					
Statistical methods used and appropriateness of these					
Reanalysis required? *(specify)*	☐ Yes ☐ No ☐ Unclear				
Reanalysis possible?	☐ Yes ☐ No ☐ Unclear				
Reanalysed results					
Notes:					

Other information

	Description as stated in report/paper	**Location in text or source** *(pg & ¶/fig/table/other)*

Key conclusions of study authors		
References to other relevant studies		
Correspondence required for further study information *(from whom, what and when)*		
Notes:		

Other

Study funding sources *(including role of funders)*		
Possible conflicts of interest *(for study authors)*		
Notes:		