Etiology, diagnosis and treatment of non-allergic rhinitis

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Voor mijn ouders

Etiology, diagnosis and treatment of non-allergic rhinitis

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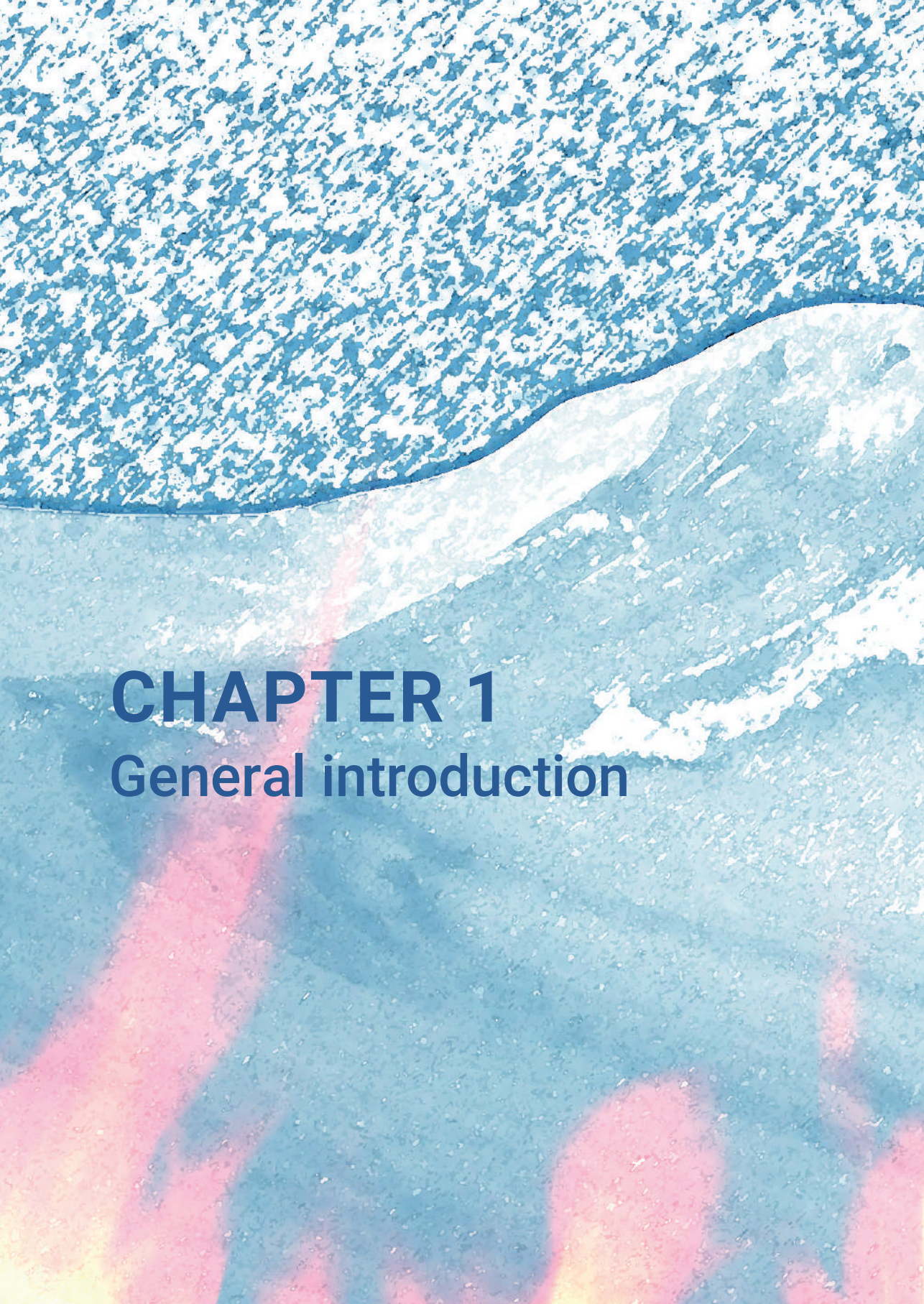
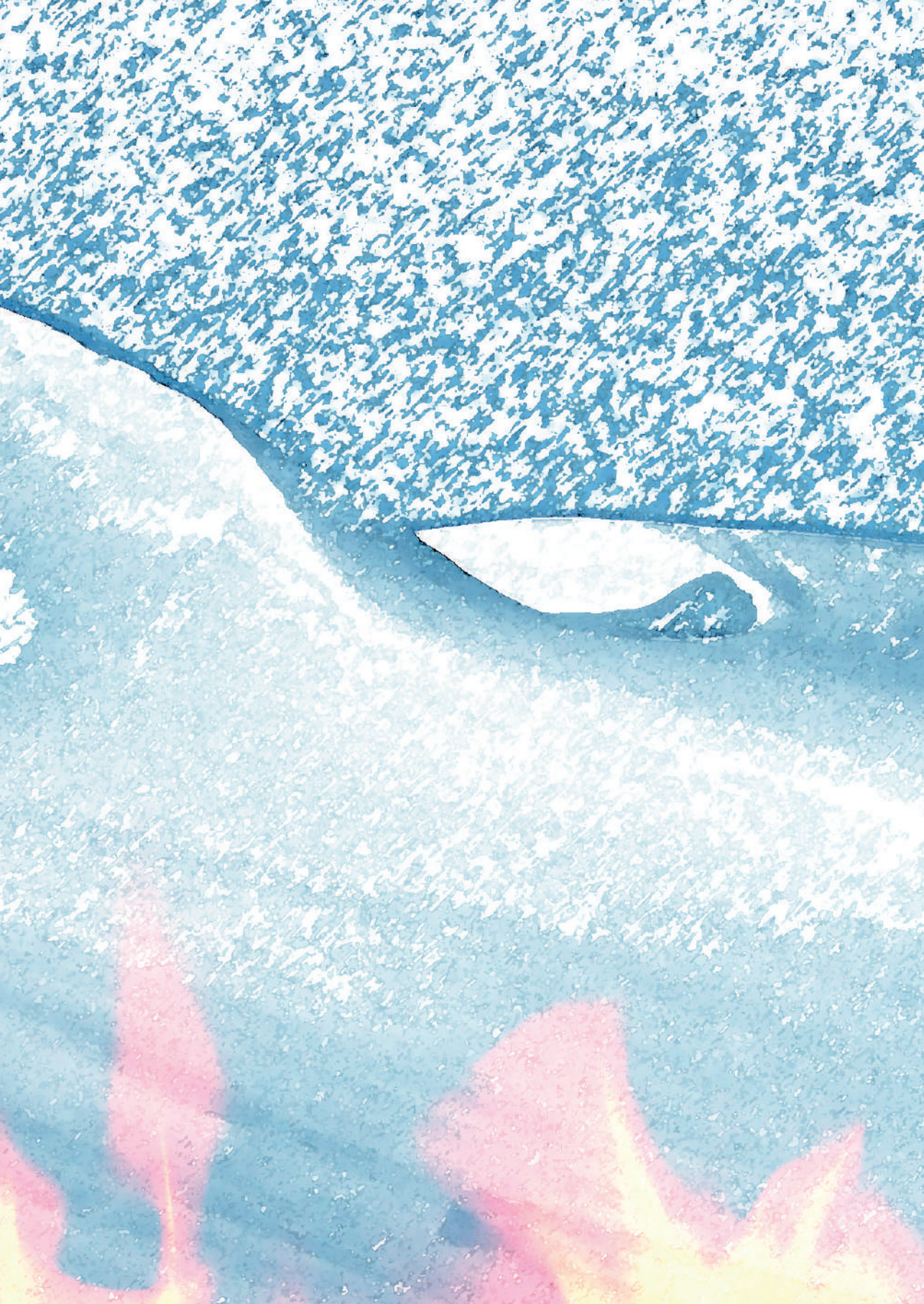
CONTENTS



CHAPTER 1
General introduction



GENERAL INTRODUCTION

Non-allergic rhinitis

Definitions in rhinitis

Rhinitis is an umbrella term used to describe nasal symptoms such as nasal congestion/obstruction, rhinorrhea, sneezing, and pruritus resulting from inflammation ('itis') and/or dysfunction. One can differentiate infectious rhinitis, allergic rhinitis (AR) and non-allergic rhinitis (NAR) (1-3).
Most of the cases of infectious rhinitis are acute, self-limiting viral infections ('common cold'), lasting not much longer than one week. Sometimes these infections are prolonged because of a secondary bacterial superinfection like in patients with a septal perforation, nose picking, and/or corpus alienum, but even then they are usually self-limiting. More rare is chronic infectious rhinitis, an example of which is atrophic rhinitis.
AR is defined as an inflammatory condition caused by an IgE-mediated response to environmental allergens such as pollens, dust mites, cockroaches, animal dander, molds, and occupational allergens. The presence of systemic allergen-specific IgE can be tested by skin prick test (SPT) or in serum. Symptoms can be either intermittent or persistent and with varying severity (mild to moderate-severe) as defined in the ARIA classification (3) (4) (5). AR can be further differentiated into phenotypes that have either mono- or polysensitization and that come with or without concurrent asthma (1).
NAR is a dysfunction and non-infectious inflammation of the nasal mucosa that is caused by factors/provoking agents other than allergens or microbes, although often the exact cause is not known (2, 6).

NAR was known by several names and definitions in the past, like non-infectious non-allergic rhinitis (NINAR) and non-allergic non-infectious perennial rhinitis (NANIPER) (2). NAR and idiopathic rhinitis are often -but wrongly- used interchangeably (for explanation of the difference see section below on *phenotypes)*. The assessment of prevalence rate and other epidemiologic data of NAR can therefore be hampered by variation in definition and diagnostic criteria. Besides the need of uniform definitions and diagnostic criteria, to reliably assess prevalence rates there is a need for population-based cohort studies. These however, unfortunately are rather limited when it comes to NAR. Population-based cohort studies (a representative sample of the population or an entire population) have the benefit of no to little risk of selection-bias but bring high costs and resources. A Finnish population study assessing prevalence rates of asthma, eczema and allergic rhinitis in military recruits (98% of the Finnish men between age 18-19 years old are examined on their fitness for military service) between 1966 and 2003, reported a prevalence rate of AR of 8.9% but did not report on NAR (7). A population cohort-study in a representative sample of the Belgium population of 4959 patients of 15 years or older using questionnaires, showed a high prevalence rate of self-declared chronic rhinitis patients, with a three times higher prevalence

rate of presumed AR (prevalence rate 29.8%) than presumed NAR (prevalence rate 9.6%) (8). A cross-sectional population-based study in Italy using questionnaires that were sent to a random sample of the Italian population reported prevalence rates of 15.6-26.6% in AR and 7.5-12.0% in NAR, depending on the age-class of the sampled individuals (9). Studies assessing prevalence rates in either the first-, second- or third-line of health care are more common but have the risk of patient selection bias and could therefore be unreliable.

Within NAR one can differentiate several disease subgroups (or *phenotypes*) based on clinically relevant characteristics (3). The different phenotypes have more or less well-defined underlying triggers or mechanisms that cause rhinitis symptoms. Change in temperature is an important trigger in NAR with an almost linear relationship between decrease in temperature and increase in NAR symptoms (10). Also atmospheric pollution or meteorological conditions are able to trigger NAR symptoms like humidity, NO, O_3, O_x, atmospheric pressure, wind velocity and cloudiness (10). One can distinct the following phenotypes, i.e. non-allergic occupational rhinitis, smoking rhinitis, hormonal rhinitis, drug-induced rhinitis, gustatory rhinitis, rhinitis of the elderly (senile rhinitis), non-allergic rhinitis with eosinophilia syndrome (NARES), local allergic rhinitis (LAR) and idiopathic rhinitis. NAR *endotypes* describe disease subtypes based on cellular and molecular mechanisms. In NAR we can distinct a neurogenic, inflammatory or idiopathic endotype (table 1) (3).

Table 1. Pheno- and endotypes in NAR*

Neurogenic	Inflammatory	Idiopathic
Idiopathic rhinitis with nasal hyper-reactivity		Idiopathic rhinitis
Gustatory rhinitis	NARES[1]	
Occupational		Occupational
Senile rhinitis	LAR[2]	
Smoking		Smoking
Hormonal		
Drug-induced		Drug-induced

* Columns represent endotypes and rows represent phenotypes.

(1) NARES: non-allergic rhinitis with eosinophilia syndrome
(2) LAR: local allergic rhinitis

The prevalence rates of the distinct phenotypes within NAR are unclear because of differences in classification across studies. In case no underlying causal trigger or mechanism can be identified, a patient is diagnosed as having idiopathic rhinitis (IR) (3). Often one considers the idiopathic subtype in NAR as the most common one,

however this is not confirmed by objective data. Although we think that nasal hyper-reactivity is an important feature of IR, it is unclear from the literature whether it is a necessity.

Nasal hyper-reactivity is an increased sensitivity of the nasal mucosa to various nonspecific stimuli like changes in temperature, air humidification or barometric pressure, strong odors, fumes or tobacco smoke, exercise, emotions and stress. The golden standard to diagnose nasal hyper-reactivity is cold dry air provocation (11). However, simply asking for symptoms of nasal hyper-reactivity and recognizing hyper-reactivity symptoms during ENT-examination -i.e. rhinitis symptoms when performing nasal endoscopy- can easily lead the way to the diagnosis of this symptom in clinical practice.

In case AR and NAR are combined in one patient, this is called mixed rhinitis (3). An example is a patient with a clinically relevant seasonal allergen sensitization (AR) in combination with continuing rhinitis symptoms outside pollen season (NAR). Diagnosis of mixed rhinitis can be complicated in case of a persistent (perennial) allergen sensitization like house dust mite.

Phenotypes in NAR

As mentioned above, within NAR one can differentiate several phenotypes, i.e. environmental (occupational, smoking), hormonal (pregnancy, anti-conceptive medication), drug-induced, gustatory, age (rhinitis of the elderly), inflammatory (NARES/LAR) and idiopathic.

Occupational rhinitis

Non-allergic occupational rhinitis is defined as a non-allergen driven, Th2-inflammation of the nasal mucosa due to exposure to a particular factor in work environment (1) (12).

It can be the result of exposure to airborne irritants like chemicals, metal salts, wood dust or animal dander. Low molecular weight agents are thought to be responsible for non-allergic occupational rhinitis.

Besides from an inflammatory reaction, also nasal hyper-reactivity to these agents can be responsible for symptoms. A proportion of non-allergic occupational rhinitis can develop into non-allergic asthma (3) (13) (14).

Smoking rhinitis

Cigarette smoke (in both active as passive smoking and in both adults as children) is known for its irritating effect on the mucosa of the respiratory tract. It can induce a mucosal cellular infiltration with a Th2-like profile, including eosinophils, IgE positive

cells and increased interleukin 4 (IL-4) levels, resulting in rhinitis symptoms (15) (16) (17).

Hormonal rhinitis

Hormonal imbalances are often associated with NAR (3). Elevation of estrogens/ progesterone during pregnancy can induce rhinitis symptoms by means of elevation of histamine H-1 receptors resulting in vasodilatation in the nasal mucosa and influencing function of eosinophils. In general, elevation of estrogen levels is thought to induce vascular engorgement and with that nasal congestion (3) (18) (19) (20). Smoking is thought to be a risk factor for pregnancy rhinitis (21). But also fluctuation of the level of estrogen or progesterone hormones during menstruation, puberty and menopause or during the use of oral anti-conceptive (OAC) medication can induce rhinitis symptoms. In postmenopausal women the hormonal imbalance can additionally result in atrophic nasal mucosa. Thyroid or growth hormones (mucosal hypertrophy) are also thought to be able to induce rhinitis symptoms, although it is rarely reported (1) (20) (22).

Drug-induced rhinitis

Several types of medication are able –by means of different and sometimes unknown mechanisms- to induce non-allergic rhinitis symptoms; examples are NSAIDS and aspirin, anti-depressants, ACE-inhibitors, calcium-antagonists and anti-psychotics (1) (3) (23) (24). Drug-induced rhinitis can be differentiated into three endotypes depending on the mechanism of disease, i.e. local inflammatory, neurogenic and idiopathic (1). The most well known type of drug-induced rhinitis is *rhinitis medicamentosa*, a result of use of xylometazoline or oxymetazoline for more than 10 days (25). Xylometazoline has an α-adrenergic agonistic (sympathomimetic) activity inducing improvement of nasal airflow by means of nasal vessel constriction. Unfortunately, this also results in a compensatory upregulation of the parasympathetic innervation of the nasal mucosa leading to rhinorrhea and nasal blockage. This stimulates the repetitive use of xylometazoline and ends in a vicious cycle of temporary improvement in nasal airflow after use of xylometazoline, evolving to renewed nasal blockage and re-use of xylometazoline.

Aspirin and non-steroidal anti-inflammatory drugs (NSAID) are able to induce rhinitis symptoms and aggravate lower airway disease, also summarized by the term NSAID-exacerbated respiratory disease (NERD). Rhinitis symptoms are the result of inhibition of cyclooxygenase-1 (COX-1) with overproduction of cysteinyl leukotrienes. This disease entity is also associated with chronic rhinosinusitis with nasal polyps and asthma. Besides from the drug hypersensitivity reaction, NERD-patients tend to have a more severe course of both upper (chronic rhinosinusitis with nasal polyposis) and lower airway disease (asthma) with eosinophilic hyperplastic inflammation of the upper and lower airways (24) (26).

Gustatory rhinitis
Gustatory rhinitis is characterized by the acute onset of watery rhinorrhea after ingestion of food, often hot or spicy food (1) (3) (27) (28).

Rhinitis of the elderly
Rhinitis of the elderly is defined as late-onset, bilateral watery nasal secretions without endonasal mucosal and/or anatomic pathology and it is not associated with a specific trigger. It often occurs in the male, elderly (>65 years old) patient (3) (29, 30).

NARES
Non-allergic rhinitis with eosinophilia syndrome (NARES) is defined as rhinitis in NAR patients that have the defining feature of eosinophilia in nasal mucosal smears. Patients often have symptoms of hyposmia/anosmia and of bronchial hyper-responsivess. It can develop into (micro-) nasal polyposis and aspirin hypersensitivity (1) (31, 32).

LAR
Local allergic rhinitis (LAR) is characterized by the presence of a nasal Th2-inflammatory response with local production of allergen-specific IgE antibodies and a positive response to a nasal allergen provocation test (NAPT) without evidence of systemic atopy (33). It can be diagnosed by means of nasal allergen provocation tests (NAPT), to which LAR patients will respond with both clinical symptoms of rhinitis as with elevation of local allergen-specific IgE in nasal mucosa (33, 34).

Idiopathic rhinitis
Patients with chronic rhinitis with no underlying causal trigger or mechanism are identified as idiopathic rhinitis (IR). Most often these patients have symptoms of nasal hyper-reactivity (1, 3).

Rhinitis diagnosis and examination
Diagnosis of the different types of NAR starts by taking an ENT-history and includes the onset of symptoms, duration and time relationships, severity, possible triggers (allergens and nonspecific stimuli), aggravating and mitigating factors, smoking, and use (and success of) previous medication. The next step is performing an ENT-examination including anterior rhinoscopy and nasal endoscopy to assess both anatomical abnormalities as pathology of the nasal mucosa and/or secretions.

To assess allergen sensitization a skin prick test (SPT) and/or blood test for allergen-specific IgE in serum (like ImmunoCAP or RAST) is performed (4).

To objectify a reduction in nasal airflow, a peak nasal inspiratory flow (PNIF), acoustic rhinometry or rhinomanometry can be performed.

To diagnose LAR a nasal allergen provocation test (NAPT) with one or more allergens can be performed, assessing both symptoms of rhinitis (rhinitis questionnaire, PNIF, amount of nasal secretions etc.) and allergen-specific IgE in nasal mucosa and/or nasal secretions (33, 34).

To assess impairment of quality of life (QoL) validated and disease specific quality of life (QoL) questionnaires are available for AR but to our knowledge not for NAR (35).

Endotypes in NAR

Within NAR roughly three main endotypes are recognized: the inflammatory endotype, the neurogenic endotype and the idiopathic endotype (1, 3). More than one endotype can be present within one phenotype. Besides these three major endotypes, most likely there is a (primary or secondary) role for dysfunction of epithelial cells or ciliae (36).

The **inflammatory endotype** is a mainly Th2-inflammatory endotype. Primarily, NARES and LAR belong to the inflammatory endotype. To a certain extent also drug-induced rhinitis (NSAIDs, aspirin), hormonal rhinitis and environmental -occupational and smoking- rhinitis belong to the inflammatory endotype (1, 3).

Within the **neurogenic endotype** there are several neurogenic mechanisms that involve different nerve fibers of both the central nervous system and locally in the nasal mucosa. A number of mediators might play a role and have their effect on nasal mucosal blood vessels, glands and epithelial cells (figure 1). The below described mechanisms intertwine and interact. They are responsible for normal nasal mucosal defense mechanisms in healthy people. Only when they are unbalanced, upregulated or otherwise disturbed, they can cause rhinitis symptoms. This is not only limited to NAR, but also in other types of chronic rhinitis these mechanisms might play a role (37) (38). Finally, it is important to emphasize there is still a lot unknown about the neurogenic endotype.

To start, there might be an autonomic imbalance with an overactivity of the parasympathetic autonomic nervous system and/or an underactivity of the sympathetic autonomic nervous system (38, 39, 40). The vidian nerve innervates the nasal mucosa and contains both sympathetic and parasympathetic nerve fibers that have opposite activity. In healthy conditions this opposite activity is balanced. Parasympathetic nerve fibers activate both subepithelial mucosal blood vessels and exocrine nasal glands. They secrete acetylcholine (Ach) that mainly acts on vessel dilatation and the neuropeptide vasoactive intestinal peptide (VIP) that mainly acts on glandular hypersecretion. Overactivity of the parasympathetic activity therefor results in respectively both nasal congestion and rhinorrhea. Sympathetic nerve fibers secrete norepinephrine and neuropeptide Y (NPY) and innervate mainly subepithelial mucosal vessels. In healthy conditions the sympathetic nervous system is dominant and thereby maintains a

(normal) vascular tonus. Underactivity of sympathetic nerve fibers results in vessel dilatation and symptoms of nasal congestion (37) (41, 42). An example of a NAR phenotype with a neurogenic dysbalance endotype is rhinitis of the elderly, with symptoms as result of hyperactivity of the parasympathetic nervous system. Also, rhinitis medicamentosa (xylometazoline abuse with fluctuating sympathetic overactivity and underactivity and a relative overdrive of the parasympathetic nervous system), some other types of drug-induced rhinitis phenotypes (like sildenafil with parasympathetic action) and gustatory rhinitis (for a part the result of overactivity of parasympathetic nervous system) belong to this endotype.

Secondly, there seems to be an important role for intraepithelial and perivascular nonadrenergic noncholinergic (NANC) sensory nerve fibers in the nasal mucosa, mainly unmyelinated trigeminal sensory C-fibers. These fibers contain neuropeptides, i.e. vasoactive intestinal peptide (VIP), substance P, calcitonin gene-related peptide (CGRP) and neurokinin A and B (NKA and NKB) (41) (43, 44, 45, 46, 47). These neuropeptides are released after activation of the sensory nerve fibers by nonspecific stimuli (temperature changes, changes in osmolality etc.) or inflammatory mediators like histamine and bradykinin, but also nicotine, cigarette smoke or capsaicin (42, 48). Capsaicin, together with other physical or chemical stimuli, is capable of activating (depolarizing) sensory C-fibers by means of activation of the TRPV-1 receptor -a nociceptive transducer and member of the transient receptor potential (TRP) receptor family-, which is present on the sensory trigeminal nerve endings. Both TRPV-1 and TRPA-1 receptors can respond to nonspecific stimuli, inducing symptoms of nasal hyper-reactivity (41) (48).

The released neuropeptides from the sensory fibers are thought to induce rhinitis symptoms by acting on epithelial submucosal blood vessel dilatation/transudation and permeability and/or glandular function.

Either an upregulation of the NANC system and/or an upregulation or hyperactivity of TRPV-1 or TRPA-1 receptors is thought to induce symptoms of nasal hyper-reactivity, as in idiopathic rhinitis with nasal hyper-reactivity (3).

It is assumed that activation of the NANC system and release of neuro-inflammatory mediators might also upregulate the parasympathetic activity of the autonomic nervous system, thereby interacting with each other. The combination of these two mechanisms within the neurogenic endotype is clearly represented in gustatory rhinitis in which there is both an upregulation of the parasympathetic nervous system and upregulation of the NANC system. In addition to idiopathic rhinitis with nasal hyper- reactivity and gustatory rhinitis that both have a clear neurogenic inflammatory endotype, there also seems to be a role for neurogenic inflammation in smoking rhinitis and occupational rhinitis (12) (3).

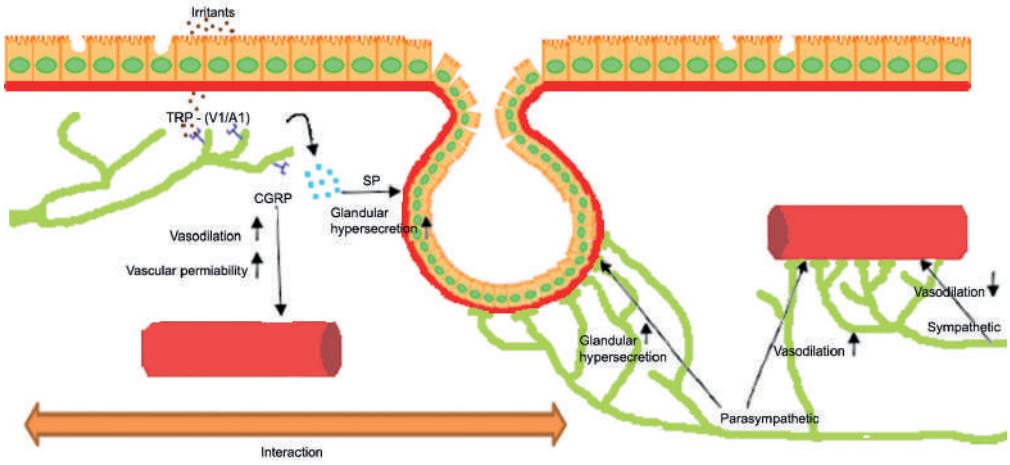


Figure 1. Neurogenic endotype

In idiopathic rhinitis the underlying mechanisms -besides from the mechanism of nasal hyper-reactivity that is described above- are still largely unknown, and for that reason IR belongs to both the neurogenic and the **idiopathic endotype** (3). Also the other phenotypes have an important share in the idiopathic endotype.

Treatment

In the past, NAR patients were often unsuccessfully treated in a so-called 'trial and error' approach.

The increasing knowledge on pheno- and endotyping in the previous years, shifts treatment from a 'trial and error' approach to an endotype-specific treatment in the upper airways (3, 49).

Intranasal corticosteroids

Intranasal corticosteroids (INCS) have immunosuppressant and anti-inflammatory effects, modifying and reducing inflammation. They suppress the synthesis of pro-inflammatory cytokines, pro-inflammatory enzymes, inhibit lymphocyte proliferation and chemotaxis (50).

They are (one of) the first-line therapy options in AR and chronic rhinosinusitis (CRS) (51) (52) (53). INCS have been extensively studied in NAR however with inconclusive results and a study with large patient numbers cannot show a positive treatment effect (54). It is likely that INCS work better in the inflammatory endotypes like LAR and NARES although evidence in this direction is moderate and hampered by definition of NAR patient groups (55) (56).

INCS can also be considered as an alternative treatment in case of rhinitis medicamentosa when patients have to stop the use of xylometazoline, although evidence is limited (57) (58).

Anti-histamines

In general, as histamine does not seem to play a role in NAR, an anti-histamine therapy would not be expected to be an effective therapy for this patient group.

Oral anti-histamines

No strong recommendations can be made for the use of oral anti-histamines in NAR (1).

Intranasal anti-histamines

Azelastine, a second-generation anti-histamine was shown to be effective for treatment of idiopathic rhinitis with nasal hyper-reactivity in two multicenter double-blind placebo controlled trials (59) (60). One of the possible explanations is that it works on neurogenic inflammatory processes. The latter could be the result of TRPV-1 receptor desensitization by influencing intracellular calcium homeostasis (61).

Combinations of INCS and anti-histamine

There are very few study data available for this combination treatment in NAR patients only, showing a beneficial effect (62).

Intranasal anticholinergics

An intranasal anticholinergic, like ipratroprium bromide nasal spray (Atronase) with antimuscarinic activity seems to be a very effective treatment in NAR patients with overactivity of the parasympathetic system and in whom rhinorrhea is the most important symptom (1) (3). The effectiveness of ipratroprium bromide is studied in perennial non-allergic rhinitis (in combination with other therapy), common cold and healthy volunteers during skiing (63, 64, 65, 66). NAR phenotypes for whom this treatment can be considered are rhinitis of the elderly, idiopathic rhinitis and gustatory rhinitis (1). However, it has to be mentioned that randomized placebo-controlled trials on the effectiveness of ipratroprium bromide for these specific phenotypes are not available.

Iptratroprium bromide acts as an antagonist of the acetylcholine-receptor in the same way as ipratroprium (for example Atrovent) acts on this receptor in the lower airways in asthmatic patients with bronchial hyper-reactivity (41). It has very few local and systemic side effects (65) (67).

Oral corticosteroids

There is no evidence-based recommendation of oral steroids in NAR (1).

Nasal irrigations
There is no evidence-based recommendation of saline nasal irrigations in NAR (1, 3).

Capsaicin
Capsaicin (8-methyl-N-vanillyl-6-nonenamide) is the therapeutic component of the red-hot chili pepper. After a shown degeneration of sensory C-fibers in nasal mucosa of animals after treatment with capsaicin and a therapeutic effect in rhinosinusitis patients, several studies in NAR patients followed (68, 69).

The study of Blom et al was the first placebo-controlled randomized trial in a clear defined group of IR to confirm the therapeutic effect of capsaicin in IR (70, 71). Recently was shown that capsaicin works on the TRPV-1 receptors that are present on sensory C-fibers in the nasal mucosa. Being a TRPV-1 agonist, capsaicin induces massive release of neurogenic inflammatory mediators like substance-P and calcitonin gene-related peptide (CGRP) from sensory C-fibers, resulting in symptoms of rhinitis like rhinorrhea, sneezing, itching and a burning sensation of the nose and eyes. After that, the sensory C-fibers enter a refractory state resulting in a decreased hyper-reactivity to nonspecific irritants. The sensory C-fibers seem to desensitize and degenerate (reversible over time) and the concentration of TRPV-1 receptors decreases together with the concentration of neuro-inflammatory mediators (42, 48) (72). Capsaicin therefor seems to be effective in endotypes with neurogenic inflammation and elevated TRPV-1. The effectiveness of capsaicin in different pheno- and endotypes of NAR are unknown, and there are no clear recommendations for treatment regimen or dosage.

Vidian neurectomy
Vidian neurectomy can be considered in case of persisting watery rhinorrhea in the neurogenic dysbalance endotype (hyperactivity of the parasympathetic nervous system) like in senile rhinitis, when all other treatment options failed (73) (74). However, evidence for this treatment modality is weak as it mainly consists out of (non-randomized) case series and is hampered by heterogeneity in (definition of) patient groups.

Inferior turbinate reduction
Several studies have looked at the effect of inferior turbinate reduction in rhinitis but not many specifically in non-allergic rhinitis only, let alone in individual phenotypes and endotypes. Studies on this topic are hampered by variation in patient selection and definition. No clear recommendation for inferior turbinate reduction in NAR can therefore be made.

Aim and outline of this thesis
The aim of this thesis is to better understand the diagnosis of NAR, its impact on quality of life (QoL) and to evaluate treatment options in the light of different phenotypes.

In explaining NAR to patients, doctors often referred to the concept of nasal hyper-reactivity. For that reason, NAR -or idiopathic rhinitis- was also called vasomotor rhinitis in the past. However, in literature it is not clear whether nasal hyper-reactivity strictly belongs to NAR or can also occur in AR or other chronic rhinitis patients. In the lower airways, bronchial hyper-responsiveness is a nonspecific symptom of lower airway inflammation.

Years ago, the Food and Drug Association (FDA) proposed a strict division in two types of nasal hyper-reactivity, i.e. chemical hyper-reactivity (rhinitis symptoms in response to chemical nonspecific stimuli like strong odors/perfumes/tobacco smoke) and physical hyper-reactivity (symptoms in response to physical nonspecific stimuli like temperature changes, osmolality or changes in air humidification) (54). Whether one should distinct two separate groups of hyper-reactivity patients, i.e. patients with strictly chemical or strictly physical hyper-reactivity, is another point of debate. Although the golden standard to assess nasal hyper-reactivity is cold dry air provocation (CDA), in clinical practice -for practical reasons- we often simply ask about symptoms of hyper-reactivity.

Therefore, in **chapter 2** we assessed the prevalence rate of nasal hyper-reactivity in AR and NAR patients by means of both subjective (questionnaires) and objective (cold dry air provocation, CDA) measurements. We also evaluated whether it is possible to differentiate a strictly physical and chemical type of nasal hyper-reactivity.

Endotyping of NAR is of interest as it guides the way to endotype-specific treatment. The most clinically relevant phenotype to unravel is the one of idiopathic rhinitis because of lack of effective treatment options. Besides from neurogenic inflammation being responsible for symptoms of nasal hyper-reactivity in idiopathic rhinitis, one could question whether there is a role for Th2-inflammation or Th1-inflammation in idiopathic rhinitis. This question is important when one thinks about treatment effectiveness of intranasal corticosteroids in these patients. In the past, no clear inflammatory profile in idiopathic rhinitis could be found (75). However, these studies focused on a limited panel of inflammatory mediators related to IgE-inflammation, i.e. IgE, IL-5 and eosinophils. Another relevant question relates to the role of (ongoing) Th2-inflammation in the group of mixed rhinitis patients, a patient group that shows features of both AR and NAR.

Therefore, in **chapter 3** we assessed a wide panel of inflammatory mediators in NAR (mainly idiopathic rhinitis), AR and mixed rhinitis patients and healthy controls. To have a better profile of the non-allergic part of mixed rhinitis patients, this assessment was done unrelated to allergen exposure.

Awareness of the socioeconomic burden and (non-) healthcare related costs in NAR are important for future investments in research. As pointed out above, although NAR is very much comparable to AR in both its rhinitis symptoms and (estimated) prevalence rate, data on quality of life (QoL) in NAR are lacking. In contrast to AR, no validated QoL questionnaires are available for NAR. Besides from epidemiologic purposes, QoL questionnaires have an important role in the diagnostic process as it can give an estimation of a patients' individual severity and burden of disease in the outpatient clinic.

Therefore, in **chapter 4**, we performed both a validation of the mini-RQLQ questionnaire for NAR patients and assessed QoL in NAR patients, compared to AR and healthy controls. Secondly, the use of the different available treatment options and the resulting treatment satisfaction in NAR patients is unknown. Therefore, we assessed by means of questionnaires both the type and number of used treatment modalities and the general treatment satisfaction of NAR patients.

Intranasal corticosteroids (INCS) are one of the most often prescribed effective drugs in (inflammatory) diseases of the upper airways, like allergic rhinitis, chronic rhinosinusitis (CRS) with or without nasal polyposis and inflammation of adenoid tissue. Studies on the effectiveness of INCS in NAR show contradicting results although in number they seem to lean towards the conclusion that INCS are not effective in NAR. Heterogeneity of selected NAR patient groups, small patient numbers and the use of different types or dosages of INCS and so on make it difficult to make a firm recommendation when it comes to the use of INCS in NAR.

Therefore, in **chapter 5** we performed a meta-analysis of the performed randomized controlled trials (RCT's) to assess the effectiveness of INCS in NAR.

The shown effectiveness of capsaicin in NAR has been very promising (71). Only a few randomized controlled trials were performed on the effectiveness in NAR. These studies often had only small numbers of participants and variation in dosage and schedule of capsaicin administration. The now known working-mechanism of capsaicin as TRPV-1 agonist resulting in treatment of neurogenic inflammation, does not answer the question in which phenotypes of NAR capsaicin can be effective and what is the optimal dosage or treatment schedule.

In **chapter 6** we performed a meta-analysis of RCT's to give better recommendations on the effectiveness of capsaicin, together with when and how (dosing and schedule of administration) to use capsaicin.

As upregulation of TRPV-1 receptors in nasal mucosa plays an important role in neurogenic inflammation, and capsaicin as TRPV-1 agonist has proven therapeutic

effectiveness in idiopathic rhinitis (IR), a relevant question is whether a TRPV-1 antagonist (SB-705498) can also be effective in IR.

Therefore, in **chapter 7**, we assess the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of intranasal SB-705498, a selective TRPV-1 antagonist.

REFERENCES

1. Papadopoulos NG et al. Phenotypes and endotypes of rhinitis and their impact on management: a PRACTALL report. Allergy, 2015. 70 (5): p. 474-94.

2. van Rijswijk JB et al. Idiopathic rhinitis, the ongoing quest. Allergy, 2005. 60(12): p. 1471-81.

3. Hellings PW et al. Non-allergic rhinitis: Position paper of the European Academy of Allergy and Clinical Immunology. Allergy, 2017. 72(11): p. 1657-1665.

4. Bousquet J et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA (2)LEN and AllerGen). Allergy, 2008. 63 Suppl 86: p. 8-160.

5. Brozek JL et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines-2016 revision. J Allergy Clin Immunol, 2017. 140 (4): p. 950-958.

6. Bousquet J et al. Important research questions in allergy and related diseases: nonallergic rhinitis: a GA2LEN paper. Allergy, 2008. 63 (7): p. 842-53.

7. Haahtela T et al. Trends in prevalence of asthma and allergy in Finnish young men: nationwide study, 1966-2003. BMJ 2005; 330(7501): 1186–1187.

8. Bachert C et al. Prevalence, classification and perception of allergic and nonallergic rhinitis in Belgium. Allergy, 2006. 61 (6): p. 693-8.

9. Cazzoletti L et al. The gender, age and risk factor distribution differs in self-reported allergic and non-allergic rhinitis: a cross-sectional population-based study. Allergy Asthma Clin Immunol, 2015. 11: p. 36.

10. Braat JP et al. Pollutional and meteorological factors are closely related to complaints of non-allergic, non-infectious perennial rhinitis patients: a time series model. Clin Exp Allergy, 2002. 32 (5): p. 690-7.

11. Braat JP et al. Intranasal cold dry air is superior to histamine challenge in determining the presence and degree of nasal hyper-reactivity in nonallergic noninfectious perennial rhinitis. Am J Respir Crit Care Med, 1998. 157(6 Pt 1): p. 1748-55.

12. Hox V et al. Occupational upper airway disease: how work affects the nose. Allergy, 2014. 69 (3): p. 282-91.

13. Karjalainen A et al. Risk of asthma among Finnish patients with occupational rhinitis. Chest, 2003. 123 (1): p. 283-8.

14. Shusterman D. Occupational irritant and allergic rhinitis. Curr Allergy Asthma Rep, 2014. 14 (4): p. 425.

15. Benninger MS. The impact of cigarette smoking and environmental tobacco smoke on nasal and sinus disease: a review of the literature. Am J Rhinol, 1999. 13 (6): p. 435-8.

16. Vinke JG et al. Passive smoking causes an 'allergic' cell infiltrate in the nasal mucosa of non-atopic children. Int J Pediatr Otorhinolaryngol, 1999. 51 (2): p. 73-81.

17. Eriksson J et al. Cigarette smoking is associated with high prevalence of chronic rhinitis and low prevalence of allergic rhinitis in men. Allergy, 2013. 68 (3): p. 347-54.

18. Hamano N et al. Expression of histamine receptors in nasal epithelial cells and endothelial cells-the effects of sex hormones. Int Arch Allergy Immunol, 1998. 115 (3): p. 220-7.

19. Ellegard EK. The etiology and management of pregnancy rhinitis. Am J Respir Med, 2003. 2 (6): p. 469-75.

20. Ellegard EK et al. Rhinitis in the menstrual cycle, pregnancy, and some endocrine disorders. Clin Allergy Immunol, 2007. 19: p. 305-21.

21. Ellegard EK et al. The incidence of pregnancy rhinitis. Gynecol Obstet Invest, 2000. 49 (2): p. 98-101.

22. Ellegard EK. Clinical and pathogenetic characteristics of pregnancy rhinitis. Clin Rev Allergy Immunol, 2004. 26 (3): p. 149-59.

23. Varghese MMC et al. Drug-induced rhinitis. Clin Exp Allergy, 2010. 40 (3): p. 381-4.

24. Kirsche H et al. ASA-intolerance syndrome and persistent rhinosinusitis : Differential diagnosis and treatment). HNO, 2015. 63 (5): p. 357-63.

25. Ramey JTE et al. Rhinitis medicamentosa. J Investig Allergol Clin Immunol, 2006. 16 (3): p. 148-55.

26. Kowalski ML et al. Diagnosis and management of NSAID-Exacerbated Respiratory Disease (N-ERD)-a EAACI position paper. Allergy, 2019. 74 (1): p. 28-39.

27. Raphael G et al. Gustatory rhinitis: a syndrome of food-induced rhinorrhea. J Allergy Clin Immunol, 1989. 83 (1): p. 110-5.

28. Waibel KH et al. Prevalence and food avoidance behaviors for gustatory rhinitis. Ann Allergy Asthma Immunol, 2008. 100 (3): p. 200-5.

29. Settipane RA. Other causes of rhinitis: mixed rhinitis, rhinitis medicamentosa, hormonal rhinitis, rhinitis of the elderly, and gustatory rhinitis. Immunol Allergy Clin North Am, 2011. 31 (3): p. 457-67.

30. Rodriguez KE et al. Clear anterior rhinorrhea in the population. Int Forum Allergy Rhinol, 2015. 5(11): p. 1063-7.

31. Bousquet J et al. Allergic rhinitis and its impact on asthma. J Allergy Clin Immunol, 2001. 108(5 Suppl): p. S147-334.

32. Moneret-Vautrin DA et al. NARES: a model of inflammation caused by activated eosinophils? Rhinology, 1992. 30 (3): p. 161-8.

33. Rondon CG et al. Local allergic rhinitis: a new entity, characterization and further studies. Curr Opin Allergy Clin Immunol, 2010. 10 (1): p. 1-7.

34. Rondon CG et al. Nasal allergen provocation test with multiple aeroallergens detects polysensitization in local allergic rhinitis. J Allergy Clin Immunol, 2011. 128 (6): p. 1192-7.

35. Juniper EF et al. Validation of the standardized version of the Rhinoconjunctivitis Quality of Life Questionnaire. J Allergy Clin Immunol, 1999. 104(2 Pt 1): p. 364-9.

36. Kortekaas Krohn I et al. MP29-02 reduces nasal hyper-reactivity and nasal mediators in patients with house dust mite-allergic rhinitis. Allergy, 2018. 73 (5): p. 1084-1093.

37. Baraniuk JN. Sensory, parasympathetic, and sympathetic neural influences in the nasal mucosa. J Allergy Clin Immunol, 1992. 90(6 Pt 2): p. 1045-50.

38. Baraniuk JN et al. Neuroregulation of human nasal mucosa. Ann N Y Acad Sci, 2009. 1170: p. 604-9.

39. Baraniuk JN et al. Neuropeptide Y (NPY) in human nasal mucosa. Am J Respir Cell Mol Biol, 1990. 3 (2): p. 165-73.

40. Baroody FM. Nonallergic Rhinitis: Mechanism of Action. Immunol Allergy Clin North Am, 2016. 36 (2): p. 279-87.

41. Bernstein JA et al. Neural Abnormalities in Nonallergic Rhinitis. Curr Allergy Asthma Rep, 2015. 15 (4): p. 18.

42. Van Gerven LG et al. Up-date on neuro-immune mechanisms involved in allergic and non-allergic rhinitis. Rhinology, 2012. 50 (3): p. 227-35.

43. Lundblad L et al. Origin and distribution of capsaicin-sensitive substance P-immunoreactive nerves in the nasal mucosa. Acta Otolaryngol, 1983. 96(5-6): p. 485-93.

44. Baraniuk JN et al. Vasoactive intestinal peptide in human nasal mucosa. J Clin Invest, 1990. 86 (3): p. 825-31.

45. Baraniuk JN et al. Substance P and neurokinin A in human nasal mucosa. Am J Respir Cell Mol Biol, 1991. 4 (3): p. 228-36.

46. Lacroix JS et al. Neutral endopeptidase activity and concentration of sensory neuropeptide in the human nasal mucosa. Eur Arch Otorhinolaryngol, 1995. 252 (8): p. 465-8.

47. Heppt W et al. Innervation of human nasal mucosa in environmentally triggered hyperreflectoric rhinitis. J Occup Environ Med, 2002. 44 (10): p. 924-9.

48. Van Gerven L et al. Capsaicin treatment reduces nasal hyper-reactivity and transient receptor potential cation channel subfamily V, receptor 1 (TRPV-1) overexpression in patients with idiopathic rhinitis. J Allergy Clin Immunol, 2014. 133 (5): p. 1332-9, 1339 e1-3.

49. Muraro A et al. European symposium on precision medicine in allergy and airways diseases: report of the European Union parliament symposium (October 14, 2015). Rhinology, 2015. 53 (4): p. 303-7.

50. Klimek L et al. Mechanism of action of nasal glucocorticosteroids in the treatment of allergic rhinitis. Part 1: Pathophysiology, molecular basis). HNO, 2012. 60 (7): p. 611-7.

51. Al Sayyad JJ et al. Topical nasal steroids for intermittent and persistent allergic rhinitis in children. Cochrane Database Syst Rev, 2007 (1): p. CD003163.

52. Kalish L et al. Topical steroids for nasal polyps. Cochrane Database Syst Rev, 2012. 12: p. CD006549.

53. Chong LY et al. Intranasal steroids versus placebo or no intervention for chronic rhinosinusitis. Cochrane Database Syst Rev, 2016. 4: p. CD011996.

54. Jacobs R et al. Weather/temperature-sensitive vasomotor rhinitis may be refractory to intranasal corticosteroid treatment. Allergy Asthma Proc, 2009. 30 (2): p. 120-7.

55. Kirtsreesakul V et al. Clinical efficacy of nasal steroids on nonallergic rhinitis and the associated inflammatory cell phenotypes. Am J Rhinol Allergy, 2015. 29 (5): p. 343-9.

56. Webb DR et al. Intranasal fluticasone propionate is effective for perennial nonallergic rhinitis with or without eosinophilia. Ann Allergy Asthma Immunol, 2002. 88 (4): p. 385-90.

57. Graf PM et al. One year follow-up of patients with rhinitis medicamentosa after vasoconstrictor withdrawal. Am J Rhinol, 1997. 11 (1): p. 67-72.

58. Elwany S et al. Treatment of rhinitis medicamentosa with fluticasone propionate--an experimental study. Eur Arch Otorhinolaryngol, 2001. 258 (3): p. 116-9.

59. Banov, CHP et al. Vasomotor Rhinitis Study, Efficacy of azelastine nasal spray in the treatment of vasomotor (perennial nonallergic) rhinitis. Ann Allergy Asthma Immunol, 2001. 86 (1): p. 28-35.

60. Gehanno P et al. Vasomotor rhinitis: clinical efficacy of azelastine nasal spray in comparison with placebo. ORL J Otorhinolaryngol Relat Spec, 2001. 63 (2): p. 76-81.

61. Singh U et al. Azelastine desensitization of transient receptor potential vanilloid 1: a potential mechanism explaining its therapeutic effect in nonallergic rhinitis. Am J Rhinol Allergy, 2014. 28 (3): p. 215-24.

62. Guo L et al. Clinical study of the combination therapy with intranasal antihistamine and nasal corticosteroids in the treatment of nasal obstruction of persistent non-allergic rhinitis. Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi, 2015. 29 (3): p. 243-5, 251.

63. Finn AF Jr et al. Ipratropium bromide nasal spray 0.03% provides additional relief from rhinorrhea when combined with terfenadine in perennial rhinitis patients; a randomized, double-blind, active-controlled trial. Am J Rhinol, 1998. 12 (6): p. 441-9.

64. Bonadonna P et al. Cold-induced rhinitis in skiers--clinical aspects and treatment with ipratropium bromide nasal spray: a randomized controlled trial. Am J Rhinol, 2001. 15 (5): p. 297-301.

65. Bronsky EA et al. A clinical trial of ipratropium bromide nasal spray in patients with perennial nonallergic rhinitis. J Allergy Clin Immunol, 1995. 95(5 Pt 2): p. 1117-22.

66. Wood CC et al. Product characteristics and pharmacokinetics of intranasal ipratropium bromide. J Allergy Clin Immunol, 1995. 95(5 Pt 2): p. 1111-6.

67. Georgitis JW et al. Ipratropium bromide nasal spray in non-allergic rhinitis: efficacy, nasal cytological response and patient evaluation on quality of life. Clin Exp Allergy, 1994. 24(11): p. 1049-55.

68. Lacroix JS et al. Improvement of symptoms of non-allergic chronic rhinitis by local treatment with capsaicin. Clin Exp Allergy, 1991. 21 (5): p. 595-600.

69. Lundblad L. Protective reflexes and vascular effects in the nasal mucosa elicited by activation of capsaicin-sensitive substance P-immunoreactive trigeminal neurons. Acta Physiol Scand Suppl, 1984. 529: p. 1-42.

70. Blom HM et al. The effect of nasal steroid aqueous spray on nasal complaint scores and cellular infiltrates in the nasal mucosa of patients with nonallergic, noninfectious perennial rhinitis. J Allergy Clin Immunol, 1997. 100(6 Pt 1): p. 739-47.

71. Blom HM et al. Intranasal capsaicin is efficacious in non-allergic, non-infectious perennial rhinitis. A placebo-controlled study. Clin Exp Allergy, 1997. 27 (7): p. 796-801.

72. Fokkens W et al. Capsaicin for Rhinitis. Curr Allergy Asthma Rep, 2016. 16 (8): p. 60.

73. Robinson SR et al. Endoscopic vidian neurectomy. Am J Rhinol, 2006. 20 (2): p. 197-202.

74. Harvey R. From legacy to novel: vidian neurectomy and eustachian tube balloon dilatation in modern ENT practice. J Laryngol Otol, 2016. 130 Suppl 4: p. S1.

75. van Rijswijk JB et al. Inflammatory cells seem not to be involved in idiopathic rhinitis. Rhinology, 2003. 41 (1): p. 25-30.

CHAPTER 2

Nasal hyper-reactivity is a common feature in both allergic and non-allergic rhinitis

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ABSTRACT

Background

Nasal hyper-reactivity is an increased sensitivity of the nasal mucosa to various nonspecific stimuli. Both allergic rhinitis (AR) and non-allergic rhinitis (NAR) patients can elicit nasal hyper-reactivity symptoms. Differences in the prevalence or type of nasal hyper-reactivity in AR and NAR patients are largely unknown. In this study, we quantitatively and qualitatively assessed nasal hyper-reactivity in AR and NAR.

Methods

In the first part, an analysis of a prospectively collected database was performed to reveal patient-reported symptoms of hyper-reactivity. In the second part, cold dry air provocation (CDA) was performed as a hyper-reactivity measure in AR and NAR patients and healthy controls, and symptoms scores, nasal secretions and peak nasal inspiratory flow were measured. Comparisons were made between AR and NAR patients in both studies.

Results

The database analysis revealed high hyper-reactivity prevalence in AR (63.4%) and NAR (66.9%). There were no differences between AR and NAR in terms of the number or type of hyper-reactivity stimuli. Hyper-reactivity to physical stimuli did not exclude a response to chemical stimuli, or vice versa. CDA provocation resulted in a significant increase in rhinitis symptoms and the amount of nasal secretions in AR and NAR patients, but not in controls.

Conclusions

We found no quantitative or qualitative differences in nasal hyper-reactivity between AR and NAR patients. It is not possible to differentiate NAR subpopulations based on physical or chemical stimuli.

INTRODUCTION

Nasal hyper-reactivity is an increased sensitivity of the nasal mucosa to everyday nonspecific stimuli, both physical and chemical, such as sudden temperature changes, cigarette smoke or chemical pollutants (1, 2). Nasal hyper-reactivity can be found in different types of rhinitis, varying from common cold to both allergic and non-allergic chronic rhinitis (3, 4). However, specific data on prevalence and type of nasal hyper-reactivity in different types of rhinitis are very limited. There is only one small epidemiological study by Shusterman et al. (5), which evaluated self-reported nasal hyper-reactivity in allergic rhinitis (AR) (31 patients) and non-allergic rhinitis (NAR) (29 patients). The only study with patient groups of sufficient size that compared nasal hyper-reactivity of AR with that of NAR is the study of Lindberg et al. (6). In this study, however, they reported only symptoms after the chemical exposure to cigarette smoke and perfumes to be similar in both groups, and hyper-reactivity to other physical stimuli was not investigated. Another limitation of this study was the lack of a control group.

The lack of assessment of physical stimuli is relevant because in recent years, the Food and Drug Association (FDA) imposed to differentiate NAR patients based on hyper-reactivity to chemical and physical sensitivity only (7). Bronchial hyper-reactivity is a common and aspecific symptom of diseased lower airway mucosa without exclusive sensitivity to chemical or physical stimuli only. It seems likely that the same applies to nasal hyper-reactivity in the upper airways. This would assume no differences in nasal hyper-reactivity between types of rhinitis or in sensitivity to types of aspecific stimuli between patients.

In this study, we investigated quantitative and qualitative aspects of nasal hyper-reactivity in AR and NAR by means of patient-reported responses to different forms of nasal hyper-reactivity. We also addressed whether it is possible to identify subtypes of hyper-reactivity based on responses to physical or chemical stimuli only. To further validate the patient-reported outcomes, we performed cold dry air (CDA) provocation in a random selection of AR and NAR patients and healthy controls.

METHODS

Study design

We performed a prospectively collected database analysis of chronic rhinitis patients (Database study) to elucidate the rate of hyper-reactivity based on patient-reported symptoms. To validate these results, we performed a CDA provocation study to measure hyper-reactivity in AR and NAR patients and healthy controls (Figures 1 and 2).

Database study

Patient characteristics

The patients were prospectively recruited from the outpatient clinic of the Department of Otorhinolaryngology of the Academic Medical Centre, Amsterdam, the Netherlands. All patients had a positive history of rhinitis symptoms and were referred to our tertiary care outpatient clinic by their general practitioner or another otorhinolaryngology clinic. AR patients had at least one positive skin prick test result and clinical symptoms relevant to their sensitization. NAR was defined as clinically relevant symptoms of rhinitis without positive skin prick test results. Severity of symptoms was assessed according to Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines (8). We excluded patients with chronic rhinosinusitis (CRS) with or without nasal polyposis, nasal surgery within the previous 3 months, a serious and/or unstable disease and history of immunotherapy and patients with other causes of rhinitis (infectious or anatomic). Patients were not allowed to use antihistamines 14 days before inclusion, and patients using medication affecting nasal function were excluded. All patients in whom symptoms could not be explained by sensitization only were excluded, leaving only those with classic AR and NAR.

Skin prick test

To assess allergic sensitization, we used the Global Allergy and Asthma European Network's (GA^2LEN) standardized method of skin prick test (SPT) (9). Patients were asked to stop their antihistamine medication 14 days before SPT. A positive reaction to SPT was defined as a skin reaction > 3 mm for one or more of the 18 tested allergens and no reaction to the negative control.

Patient-reported outcomes

All rhinitis patients were routinely asked to fill in a questionnaire regarding symptoms of rhinitis, allergy and nasal hyper-reactivity. In regard to nasal hyper-reactivity, patients were asked to report sensitivity to temperature change, tobacco smoke or scents, exercise, emotional stress and humidity. Patients were allowed to choose more than one option. Patients were asked to report number and type of rhinitis symptoms, duration and periods of symptoms and severity according to ARIA classification (8).

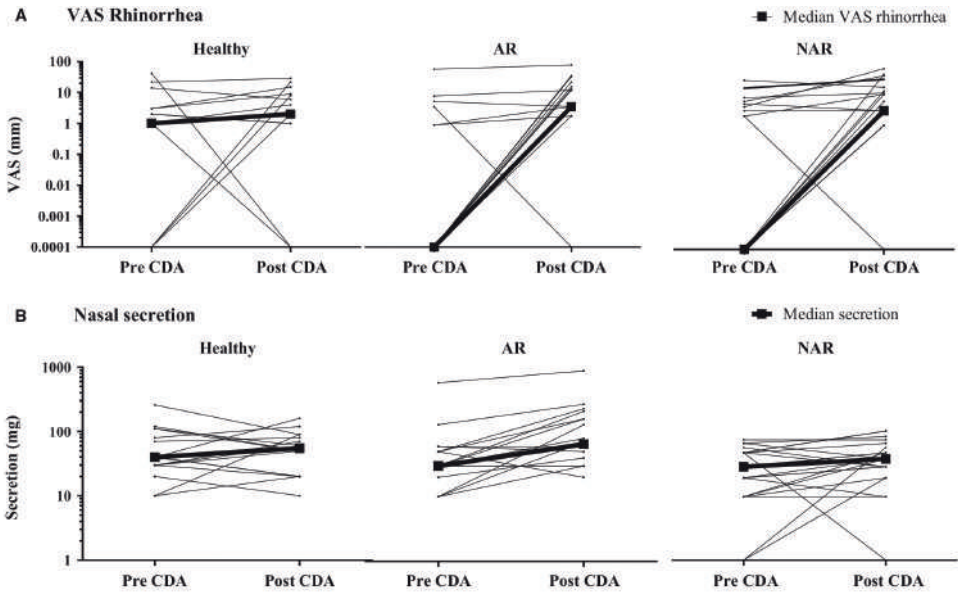


Figure 1 A and B. Subjective report of rhinorrhea (A) and objective amount of nasal secretion (B) in Healthy controls, AR and NAR patients before and after CDA provocation
Individual patient results are shown in small circles; median results for each group are shown in large squares

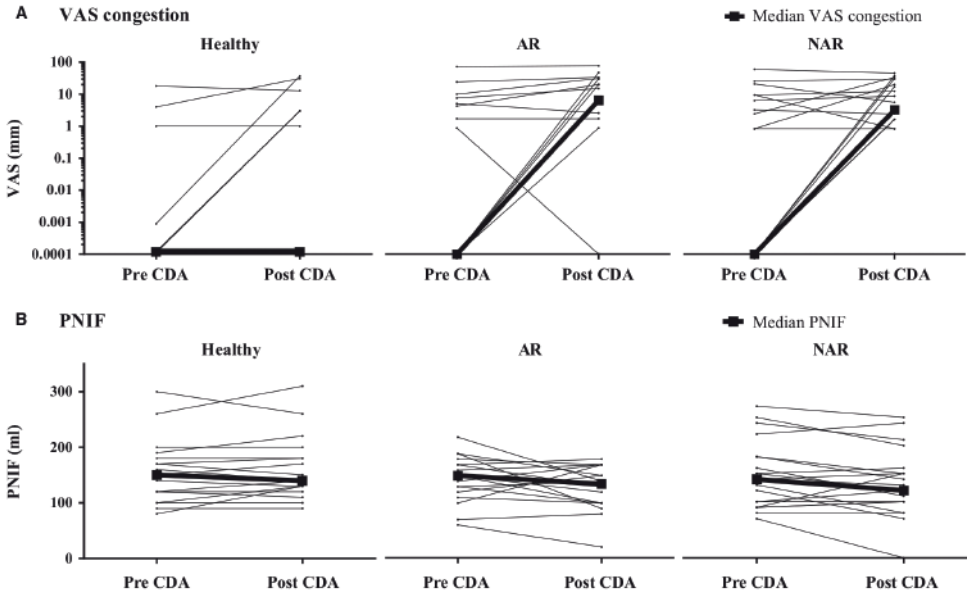


Figure 2 A and B. Subjective report of nasal congestion (A) and objective PNIF values (B) in Healthy controls, AR and NAR patients before and after CDA provocation
Individual patient results are shown in small circles; median results for each group are shown in large squares

CDA provocation study

Patient characteristics

Cold dry air provocation was performed in a random selection of the database patients (AR and NAR) as well as in healthy volunteers. Patients were classified according to ARIA guidelines (8). Patients were asked to stop antihistamine medication 4 weeks before CDA provocation and any medication possibly influencing nasal function, including all nasal medication, 2 weeks before provocation. A healthy control group consisted of individuals, recruited via advertisement, who had no medical history of rhinitis and a negative skin prick test to allergens. All subjects signed an informed consent form. This study was approved by the institutional Medical Ethics Committee.

Dose escalation CDA provocation

Patients were first provoked with a vehicle, that is, air at room temperature and humidity for 1 min. Following this, patients were provoked with CDA at a temperature of at least 10°C and humidity of around 20% in 5 dose-escalating steps as described in the validated protocol of CDA provocation by Braat et al. (10).

Questionnaires during the CDA provocation

At 1, 5 and 10 min after each provocation (including with the vehicle), patients were asked to assess their symptoms of rhinorrhea, nasal congestion, burning, itching and sneezing on visual analogue scale (VAS, 0–100 mm).

Nasal secretion during the CDA provocation

To assess the amount of nasal secretions, 2 min after each provocation, a 3.5-cm Ivalon® Post-Op Sinus Packing (Endovision BVBA, Holsbeek, Belgium) was placed anteriorly in the same nostril for 3 min. The nasal dressing, placed in a 3-ml BD Falcon™ tube (BD Biosciences, San Jose, CA, USA), was weighed before and after provocation to measure the amount (in mg) of nasal secretions.

Peak nasal inspiratory flow (PNIF) during the CDA provocation

To measure nasal inspiratory flow, we used PNIF 5 min after each provocation. Patients were instructed to exhale through their mouth, place the mask over their nose and mouth in a way that the nose would not be compressed and inspire air through their nose with their mouth closed. Patients were allowed to perform the PNIF exercise three times. The highest recorded value (ml) was used for analysis.

Statistical Analyses

In both studies, all statistical analyses were performed using SPSS, version 19.0 for Windows (IBM Corporation, New York, NY, USA). Despite multiple testing, the cut-off value of statistically significance was kept at P values of < 0.05. Bonferroni correction was not performed because we did not want to underestimate potential differences between the groups.

Database study
The Fisher's exact test was used to compare hyper-reactivity between NAR and AR based on total prevalence and type of different provoking stimuli.

CDA provocation study
Due to data being not normally distributed, nonparametric statistics was used. The Wilcoxon signed rank test was used to compare rhinitis symptoms before and after CDA provocation measured by means of VAS (0–100 mm), PNIF (ml) and amount of nasal secretions (mg). Median values were used.

RESULTS

Database study

Patient characteristics
Table 1 demonstrates patient characteristics, the use of medication and ARIA classification in the database study. There were no significant differences between both patient groups for age, gender, smoking and ARIA classification, with an exception of asthma, which was more prevalent in the AR group ($P < 0.0001$, Fisher's exact test). Table 1 also demonstrates the type and frequency of medication use in the previous 4 weeks.

Skin prick test
The five most frequent sensitizations (not exclusive of each other) were grass mix (61.9%), house dust mites (56.6%), birch (46.8%), dog (46.5%) and hazel (41.5%).

Patient-reported outcomes
Nasal hyper-reactivity is a common feature in AR and NAR.
Table 2 demonstrates the number and type of hyper-reactivity provoking stimuli in AR and NAR patients. There were no differences between AR and NAR patients.

No specificity in the reaction to individual stimuli or to classes of stimuli.
No significant differences were seen in the type of provoking stimuli reported by AR and NAR patients, with the highest prevalence in both groups being for 'temperature changes' and 'smoke/scents' (Table 2). We selected individuals who reported 'temperature change' and determined whether this would exclude a response to 'smoke/scents' (7). In both AR and NAR, a majority of those reporting sensitivity to 'temperature change' also reported sensitivity to 'smoke/scents' (58.9% in AR and 53.8% in NAR). As expected in the reciprocal analysis of individuals responding to smoke/scents, we saw no indication of this precluding a response to temperature changes (63.6% in AR and 65.6% in NAR responded to both smoke/scents and temperature stimuli).

Hyper-reactivity is not different between individuals suffering from intermittent or persistent rhinitis.

We investigated whether individuals diagnosed with either intermittent or persistent rhinitis (AR or NAR) would demonstrate a different pattern of responsiveness in terms of the number and type of stimuli causing hyper-reactivity (Table 3). There were no significant differences in the number or type of provoking stimuli between intermittent or persistent rhinitis patients. The exclusion was the significantly higher frequency of a single hyper-reactivity stimulus per patient in intermittent vs persistent NAR.

Table 1. Patient characteristics, the use of medication and ARIA classification in the database study

Total, n = 993	**AR, n = 585**	**NAR, n = 408**
Male (%)	45.6	34.3
Mean age (years)	39.0	43.3
Smoking N (%)	122 (20.9)	93 (22.8)
Asthma N (%)	100 (17.1)	34 (8.3)
Sensitizations (skin prick testing) N (%)	585 (100.0)	0 (0)
Medication use (per patient) N (%)		
Medication	292 (49.9)	225 (55.1)
No medication	122 (20.9)	88 (21.6)
Unknown	171 (29.2)	95 (23.3)
Type of medication last 4 weeks N (%)		
Nasal corticosteroids	243 (41.5)	217 (53.1)
Oral antihistamines *	54 (9.2)	8 (2.0)
Xylometazoline (intermittent use)	5 (0.9)	2 (0.5)
Nasal sodium cromoglicate	2 (0.3)	0 (0.0)
Other medication	3 (0.5)	0 (0.0)
ARIA grading N (%)		
Mild intermittent	10 (1.7)	15 (3.7)
Moderate-severe intermittent	112 (19.1)	64 (15.7)
Mild persistent	13 (2.2)	12 (2.9)
Moderate-severe persistent	403 (68.9)	281 (68.9)
Undefined	47 (8.0)	36 (8.8)

AR – allergic rhinitis; ARIA – Allergic Rhinitis and its Impact on Asthma; NAR – non-allergic rhinitis
** Antihistamines were stopped 14 days before inclusion*

Table 2. Prevalence of the number and type of hyper-reactivity provoking stimuli per AR or NAR patient, based on questionnaire reports in the database study

	AR, N (%)	NAR, N (%)	AR vs. NAR (p, Fisher's Exact Test)
Number of hyper-reactivity stimuli per patient			
None	214 (36.6)	135 (33.1)	*NS*
At least one	*371 (63.4)*	*273 (66.9)*	*NS*
One	129 (22.1)	87 (21.3)	*NS*
Two	138 (23.6)	91 (22.3)	*NS*
Three	68 (11.6)	58 (14.2)	*NS*
Four	24 (4.1)	26 (6.4)	*NS*
Five	12 (2.1)	11 (2.7)	*NS*
Total	585	408	
Types of hyper-reactivity provoking stimuli			
Temperature changes	246 (42.1)	195 (47.8)	*NS*
Smoke, smells	228 (39.0)	160 (39.2)	*NS*
Exercise	127 (21.7)	110 (27.0)	*NS*
Emotional stress	101 (1.7)	85 (20.8)	*NS*
Humidity	63 (10.8)	52 (12.7)	*NS*
Total	765	602	

AR – allergic rhinitis; NAR – non-allergic rhinitis
NS: not significant, p> 0.05
Italic values denote *P* = 0.2798 (comparing AR and NAR for responding to at least 1 stimulus).

CDA provocation study

Patient characteristics

We performed CDA provocation as a reliable measure of nasal hyper-reactivity in a subpopulation of rhinitis patients [18 patients with AR (mean age 40.3) and 21 with NAR (mean age 47.0), as well as 17 healthy controls (mean age 31.8). There were no significant differences for gender ratio (AR: NAR, NAR: healthy: *P* = 0.2753, AR: healthy: *P* = 1.000, Fisher's exact test). There were no significant differences in age in AR and NAR between the database and the CDA provocation studies (AR: *P* = 0.682, Mann–Whitney U-test; NAR: *P* = 0.213, Mann–Whitney U-test).

In AR and NAR, respectively, 83.3% and 72.6% of patients were classified as moderate--to-severe persistent according to ARIA classification, and 5.6% of AR and 14.3% of NAR classified as moderate-to-severe intermittent and 5.6% of AR mild intermittent (8).

Skin prick testing

The five most frequent sensitizations were grass mix (94.1%), hazel (47.1%), alder (47.1%), birch (47.1%) and house dust mites (35.3%).

Results of CDA provocation

In contrast to controls, patients with AR and NAR react to CDA provocation. Patient with both AR and NAR demonstrated a significant response to CDA provocation, while the control population did not (Table 4). Specifically, both patient groups demonstrated a significant increase in rhinitis symptoms after CDA provocation (rhinorrhea, congestion and burning, with a trend of congestion in NAR and sneezing in AR) and a significant increase in the amount of secretion. This was in contrast with the control group that did not demonstrate any significant reaction to CDA.

The median PNIF after CDA provocation decreased in AR and NAR, with a trend in NAR and not reaching significance in AR. There was no change in PNIF in control patients.

Table 3. Prevalence of the number and type of hyper-reactivity provoking stimuli per patient as a function of rhinitis duration (intermittent or persistent) in the database study*

Number of stimuli per patient	**Intermittent AR N (%)**	**Persistent AR N (%)**	***Intermittent vs. persistent AR p (Fisher's Exact test)***	**Intermittent NAR, N (%)**	**Persistent NAR, N (%)**	***Intermittent vs. persistent NAR p (Fisher's Exact test)***
Number of hyper-reactivity stimuli per patient						
None	43 (35.2)	150 (36.1)	NS	21 (26.6)	102 (34.8)	NS
At least one	*79 (64.8)*	*266 (63.9)*	*NS*	*58 (73.4)*	*191 (65.2)*	*NS*
One	27 (20.0)	91 (22.9)	NS	**26 (32.9)**	**49 (16.7)**	NS
Two	37 (30.0)	90 (21.6)	NS	21 (26.6)	64 (218)	NS
Three	13 (10.0)	52 (12.5)	NS	6 (7.6)	49 (16.7)	$P = 0.049$
Four	2 (0)	21 (5.0)	NS	4 (5.1)	20 (6.8)	NS
Five	0 (0)	12 (2.9)	NS	1 (1.3)	9 (3.1)	NS
Total	122 (100)	416 (100)		79 (100)	293 (100)	
Types of hyper-reactivity provoking stimuli						
Temperature changes	50 (33.8)	180 (31.5)	NS	40 (37.4)	140 (31.2)	NS
Smoke, smells	52 (35.1)	165 (28.9)	NS	26 (24.3)	121 (26.9)	NS
Exercise	22 (14.9)	96 (16.8)	NS	18 (16.8)	84 (18.7)	NS
Emotional stress	13 (8.8)	80 (14.0)	NS	13 (12.1)	64 (14.3)	NS
Humidity	11 (7.4)	50 (8.8)	NS	10 (9.3)	40 (8.9)	NS
Total	148 (100)	571 (100)		107 (100)	449 (100)	

Table continued

*ARIA classification (intermittent or persistent) is missing on 47 patients with AR and 36 patients with NAR.
AR – allergic rhinitis; ARIA – Allergic Rhinitis and its Impact on Asthma; NAR – non-allergic rhinitis
NS: not significant, P > 0.05
Italic values denote *P* = 0.9147 (comparing intermittent AR and persistent AR for responding to at least 1 stimulus); *P* = 0.1802 (comparing intermittent NAR and persistent NAR for responding to at least 1 stimulus).
Bold values denote *P* = 0.0025 (comparing intermittent NAR and persistent NAR for responding to 1 stimulus only).

Table 4. Response to CDA provocation in AR patients

Outcome parameter	Median pre-CDA (25-75th inter-quartiles)	Median post-CDA (25-75th interquar-tiles)	Median Delta	Pre- vs. post -CDA (*p*, Wilcoxon Signed Rank Test)
Allergic rhinitis				
Rhinorrhea (VAS, mm)	**0 (0.00-1.75)**	**4 (0.00-0.20)**	**2.5**	***P* = 0.008**
Congestion (VAS, mm)	**0 (0.00-6.75)**	**7.5 (0.00-36.50)**	**6.5**	***P* = 0.04**
Burning (VAS, mm)	**0 (0.00-3.00)**	**6 (0.00-25.00)**	**6**	***P* = 0.013**
Sneezing (VAS, mm)	0 (0.00-1.50)	0 (0.00-0.50)	0	NS
Itching (VAS, mm)	0 (0.00-4.50)	0 (0.00-8.00)	0	NS
Nasal secretion (mg)	**30 (30.00-50.00)**	**65 (30.00-170.00)**	**40**	***P* = 0.003**
PNIF (ml)	150 (117.50-172.50)	135 (100.0-170.00)	-15	NS
Non-allergic rhinitis				
Rhinorrhea (VAS, mm)	**0 (0.00-4.50)**	**3 (0.00-15.00)**	**1**	***P* = 0.020**
Congestion (VAS, mm)	0 (0.00-10.00)	4 (1.00-32.50)	2	NS
Burning (VAS, mm)	**0 (0.00-0.00)**	**0 (0.00-1.00)**	**0**	***P* = 0.039**
Sneezing (VAS, mm)	0 (0.00-0.00)	0 (0.00-0.00)	0	NS
Itching (VAS, mm)	0 (0.00-4.00)	0 (0.00-1.00)	46	NS
Nasal secretion (mg)	**30 (10.00-50.00)**	**40 (30.00-80.00)**	**20**	***P* = 0.021**
PNIF (mL)	140 (95.00-180.00)	120 (100.00-155.00)	-10	NS
Healthy				
Rhinorrhea (VAS, mm)	1 (0.00-3.50)	2 (0.00-8.50)	0	NS
Congestion (VAS, mm)	0 (0.00-0.00)	0 (0.00-3.00)	0	NS
Burning (VAS, mm)	0 (0.00-0.00)	0 (0.00-2.00)	0	NS
Sneezing (VAS, mm)	0 (0.00-0.00)	0 (0.00-0.00)	0	NS
Itching (VAS, mm)	0 (0.00-0.00)	0 (0.00-0.00)	0	NS
Nasal secretion (mg)	40 (30.00-100.00)	55 (20.00-90.00)	0	NS
PNIF (ml)	150 (110.00-185.0)	140 (125.00-140.00)	0	NS

CDA – cold dry air; PNIF – peak nasal inspiratory flow; VAS – visual analogue scale
NS: not significant; bold denotes significant value (*P* < 0.05).

DISCUSSION

In accordance with the concept of nasal hyper-reactivity being a general outcome of disturbed nasal mucosa of the upper airways, our patient-reported outcomes demonstrated no differences in quantitative or qualitative aspects of nasal hyper-reactivity between AR and NAR (11). Within NAR, the higher frequency of a single hyper-reactivity stimulus per patient in patients with intermittent vs persistent symptoms could be explained by less severe rhinitis symptoms in the former. Hyper-reactivity has been shown to be a phenomenon of uncontrolled disease in rhinitis, conjunctivitis and asthma (12–14).

As we did not perform nasal provocation tests, it is possible that some of the NAR patients had local allergic rhinitis (LAR) causing confounding of patient groups (15). However, in the past, several studies were performed in our clinic assessing inflammatory cells and cytokines in nasal secretions of NAR patients, and no sign of inflammation was demonstrated in these patients (16–18).

The FDA recently imposed a distinction between nasal hyper-reactivity symptoms exclusively elicited to either physical or chemical stimuli (7). This distinction, however, was not confirmed in our database analysis. Most AR and NAR patients responded to both physical and chemical stimuli.

To validate the patient-reported outcomes, a CDA provocation was performed. Hyper-reactivity can be objectively determined with either direct (histamine, methacholine, capsaicin) or indirect (CDA provocation) stimuli. CDA provocation, contrary to histamine, is able to distinguish patients with hyper-reactivity from healthy controls (8, 10, 19–21). In bronchial hyper-reactivity, indirect stimuli, such as CDA, exercise and adenosine monophosphate, also appear to be more clinically relevant and better correlate with eosinophilic inflammation than direct stimuli (22–26). For this purpose, we randomly selected 25 patients per group from the database study. Unfortunately, not all patients who originally indicated that they were willing to participate did so, because of time and other practical constraints. As we aimed to perform the provocation outside pollen season, we decided to stop further inclusion. This resulted in smaller and unequal sized patient groups for CDA provocation than originally planned. As a result of relatively small group sizes in the latter, there were some differences between patient groups. ARIA classification in the CDA provocation study showed a higher proportion of moderate-to-severe persistent rhinitis compared with the database patient group. Therefore comparisons based on severity of symptoms cannot be performed.

Reactions to CDA were significant for symptoms of rhinorrhea, congestion and burning. This was accompanied by a significant increase in nasal secretions in both AR and NAR, but not in healthy patients. PNIF decreased in both groups; however, it

did not reach a statistically significant level. Most likely, this was caused by the large variation in PNIF values and relatively small groups sizes. These results are in agreement with a recent study by Hellings et al. demonstrating a significant response to CDA in both AR and NAR patients compared with controls (27).

As our results demonstrate that nasal hyper-reactivity is as common in NAR, as in AR, while no inflammatory cells or markers are present in NAR (according to previous studies), the question of the underlying mechanism causing nasal hyper-reactivity remains unknown (16–18, 28). Possible explanations of nasal hyper-responsiveness can be an upregulation of the nervous system with a (para-)sympathetic dysbalance or neurogenic inflammation with release of neuropeptides as part of an antidromic reflex in the nose. Another hypothesis refers to the release of substance P from the trigeminal nerve (28–30). Substance P is suggested to induce hyper-reactivity in allergic and non-allergic airway disease by directly and indirectly (via histamine and mast cell degranulation) affecting smooth muscle tissue and vasculature (31, 32). While hyper-reactivity is the result of smooth muscle contraction in lower airway disease, the absence of muscle tissue in the upper airways suggests another pathogenic mechanism, that is, vasodilation and increased vascular permeability. Another interesting aspect of airway hyper-reactivity is a (dysfunctional) role of the mucosal membrane barrier and its phospholipid composition (11, 33).

In conclusion, nasal hyper-reactivity seems to be an indistinctive feature of upper airway disease, irrespective of inflammation.

Conflicts of interest

C.M. van Drunen and W.J. Fokkens receive private sector support for research and/or clinical trials related to the treatment of allergic and non-allergic rhinitis from Allergopharma, ALK-Abello, GlaxoSmithKline, HAL Allergy, MSD, Optinose UK, as well as public sector research support from InterUniveristy Attraction Poles (Belgium), ZonMW (the Netherlands), and Global Allergy and Asthma European Network (EU). C.M. van Drunen has received royalties for legal consultation/expert witness testimony from Stallergens; W.J. Fokkens has received royalties for legal consultation/expert witness testimony for Stallergens, GSK, MSD. Other authors have no potential conflict of interest. Peter W. Hellings is the recipient of unrestricted research grants of GlaxoSmithKline, MSD, and Stallergens and participated in clinical trials on allergic rhinitis of HAL and GlaxoSmithKline.

REFERENCES

1. van Wijk RG et al. Nasal hyper-reactivity. Rhinology 1999;37(2):50-55.

2. Marquez F et al. Nasal hyper-reactivity to methacholine measured by acoustic rhinometry in asymptomatic allergic and perennial nonallergic rhinitis. Am J Rhinol 2000;14(4):251-256.

3. Cassano M et al. May nasal hyper-reactivity be a sequela of recurrent common cold? J Biol Regul Homeost Agents 2011;25(2):299-301.

4. Vaidyanathan S et al. Nasal AMP and histamine challenge within and outside the pollen season in patients with seasonal allergic rhinitis. J Allergy Clin Immunol 2011;127(1):173-178, 178 e171-173.

5. Shusterman D et al. Nasal hyper-reactivity in allergic and non-allergic rhinitis: a potential risk factor for non-specific building-related illness. Indoor Air 2007;17(4):328-333.

6. Lindberg S et al. Comparison of allergic rhinitis and vasomotor rhinitis patients on the basis of a computer questionnaire. Allergy 1993;48(8):602-607.

7. Jacobs R et al. Weather/temperature-sensitive vasomotor rhinitis may be refractory to intranasal corticosteroid treatment. Allergy Asthma Proc 2009;30(2):120-127.

8. Bousquet J et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). Allergy 2008;63 Suppl 86:8-160.

9. Bousquet J et al. Practical guide to skin prick tests in allergy to aeroallergens. Allergy 2012;67(1):18-24.

10. Braat JP et al. Intranasal cold dry air is superior to histamine challenge in determining the presence and degree of nasal hyper-reactivity in nonallergic noninfectious perennial rhinitis. Am J Respir Crit Care Med 1998;157(6 Pt 1):1748-1755.

11. Golebski K et al. The multi-faceted role of allergen exposure to the local airway mucosa. Allergy 2013;68(2):152-160.

12. Leonardi A et al. Ocular allergy: recognizing and diagnosing hypersensitivity disorders of the ocular surface. Allergy 2012;67(11):1327-1337.

13. Brannan JD. Bronchial hyperresponsiveness in the assessment of asthma control: Airway hyperresponsiveness in asthma: its measurement and clinical significance. Chest 2010;138(2 Suppl):11S-17S.

14. Hellings PW et al. Uncontrolled allergic rhinitis and chronic rhinosinusitis: where do we stand today? Allergy 2013;68(1):1-7.

15. Rondon C et al. Local allergic rhinitis: concept, pathophysiology, and management. J Allergy Clin Immunol 2012;129(6):1460-1467.

16. Blom HM et al. Mast cells, eosinophils and IgE-positive cells in the nasal mucosa of patients with vasomotor rhinitis. An immunohistochemical study. Eur Arch Otorhinolaryngol 1995;252 Suppl1:S33-39.

17. Blom HM et al. The effect of nasal steroid aqueous spray on nasal complaint scores and cellular infiltrates in the nasal mucosa of patients with nonallergic, noninfectious perennial rhinitis. J Allergy Clin Immunol 1997;100(6 Pt 1):739-747.

18. Blom HM et al. The long-term effects of capsaicin aqueous spray on the nasal mucosa. Clin Exp Allergy 1998;28(11):1351-1358.

19. Kim YH et al. Use of cold dry air provocation with acoustic rhinometry in detecting nonspecific nasal hyper-reactivity. Am J Rhinol Allergy 2010;24(4):260-262.

20. Hellings PW et al. Executive summary of European Task Force document on diagnostic tools in rhinology. Rhinology 2012;50(4):339-352.

21. Scadding G et al. Diagnostic tools in Rhinology EAACI position paper. Clin Transl Allergy 2011;1(1):2.

22. Cockcroft DW et al. Diagnostic and therapeutic value of airway challenges in asthma. Curr Allergy Asthma Rep 2009;9(3):247-253.

23. Hassan NM et al. Airway responsiveness to indirect challenges in COPD. COPD 2010;7(2):133-140.

24. Rundell KW et al. Exercise and other indirect challenges to demonstrate asthma or exercise-induced bronchoconstriction in athletes. J Allergy Clin Immunol 2008;122(2):238-246; quiz 247-238.

25. Sverrild A et al. Airway hyperresponsiveness to mannitol and methacholine and exhaled nitric oxide: a random-sample population study. J Allergy Clin Immunol 2010;126(5):952-958.

26. Stern DA et al. Wheezing and bronchial hyper-responsiveness in early childhood as predictors of newly diagnosed asthma in early adulthood: a longitudinal birth-cohort study. Lancet 2008;372(9643):1058-1064.

27. Van Gerven L et al. Up-date on neuro-immune mechanisms involved in allergic and non-allergic rhinitis. Rhinology 2012;50(3):227-235.

28. van Rijswijk JB et al. Idiopathic rhinitis, the ongoing quest. Allergy 2005;60(12):1471-1481.

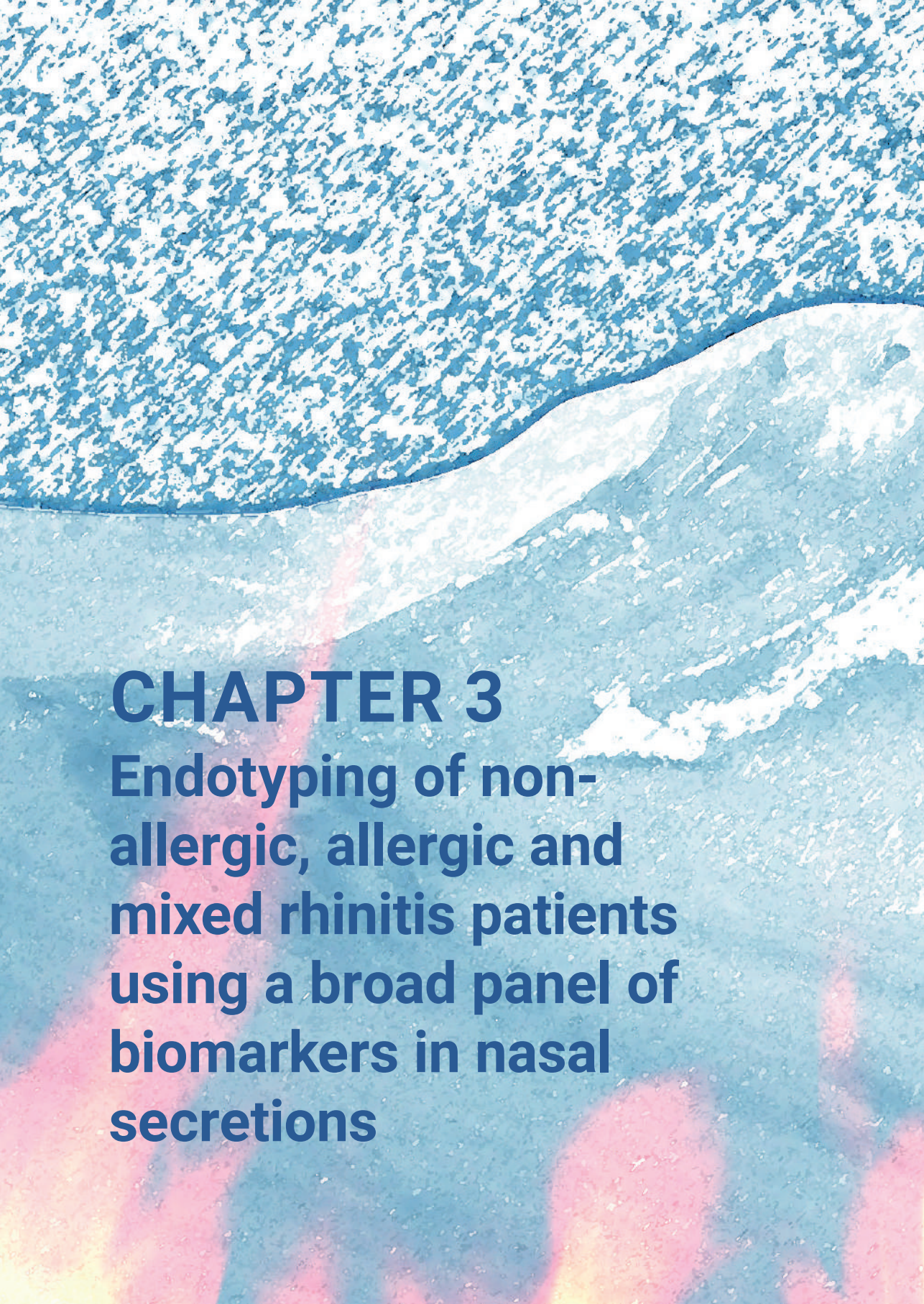
29. Bousquet J et al. Important research questions in allergy and related diseases: nonallergic rhinitis: a GA2LEN paper. Allergy 2008;63(7):842-853.

30. Taylor-Clark TE et al. Nasal sensory nerve populations responding to histamine and capsaicin. J Allergy Clin Immunol 2005;116(6):1282-1288.

31. Baumgarten CR et al. Substance P is generated in vivo following nasal challenge of allergic individuals with bradykinin. Clin Exp Allergy 1997;27(11):1322-1327.

32. Hanf G et al. Substance P induced histamine release from nasal mucosa of subjects with and without allergic rhinitis. Inflamm Res 2000;49(10):520-523.

33. Bohm M et al. Liposomes: a new non-pharmacological therapy concept for seasonal-allergic-rhinoconjunctivitis. Eur Arch Otorhinolaryngol 2012;269(2):495-502



CHAPTER 3

Endotyping of non-allergic, allergic and mixed rhinitis patients using a broad panel of biomarkers in nasal secretions

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ABSTRACT

Background
Endotyping chronic rhinitis has proven hardest for the subgroup of non-allergic rhinitis (NAR) patients. While IgE-related inflammation is typical for allergic rhinitis (AR), no markers have been found that can be seen to positively identify NAR. A further complication is that AR and NAR might co-exist in patients with mixed rhinitis. As previous studies have considered only a limited number of inflammatory mediators, we wanted to explore whether a wider panel of mediators could help us refine the endotyping in chronic rhinitis patients.

Objective
To endotype chronic rhinitis, and non-allergic rhinitis in particular, with help of molecular or cellular markers.

Method
In this study we included 23 NAR patients without allergen sensitizations and with persistent rhinitis symptoms, 22 pollen sensitized rhinitis patients with seasonal symptoms, 21 mixed rhinitis patients with pollen-related symptoms and persistent symptoms outside of the pollen season, and 23 healthy controls without any symptoms. Nasal secretions were collected outside of pollen season and differences between the endotypes were assessed for a broad range of inflammatory mediators and growths factors using a multiplex ELISA.

Results
Although we were able to identify two new nasal secretion markers (IL-12 and HGF) that were low in mixed and AR patients versus NAR and healthy controls, the most intriguing outcome is that despite investigating 29 general inflammatory mediators and growth factors no clear profile of non-allergic or mixed rhinitis could be found.

Conclusion
Classical inflammatory markers are not able to differentiate between non-allergic or mixed rhinitis patients and healthy controls.

INTRODUCTION

Rhinitis can be subdivided into a number of discrete pheno- and endotypes (1). The characterization of phenotypes is hampered by limited clinical tools (2). Identifying the molecular processes underlying rhinitis in a particular patient may help us to identify different endotypes more readily and may help to optimize treatment for these patients (3).

If we disregard infectious rhinitis, the most common rhinitis phenotype is allergic rhinitis (AR), in which a clinical response to an otherwise innocent environmental factor or allergen results in symptoms. This clinical response, in combination with specific IgE targeting aeroallergens constitutes allergic rhinitis. The second most common rhinitis phenotype is non-allergic rhinitis (NAR), which is defined as a form of non-infectious rhinitis in which it is not possible to identify an allergic component (1) (4). NAR can be subdivided into the following phenotypes: environmental (occupational, smoking), hormones (pregnancy), medication-induced (*rhinitis medicamentosa*, NSAIDS (non-steroidal anti-inflammatory drugs), aspirin etc.), gustatory, age (rhinitis of the elderly) and/or inflammation (non-allergic rhinitis with eosinophilia syndrome (NARES) or local allergic rhinitis (LAR)). However, in a significant proportion of patients, none of these triggers are present and the disease is considered to be idiopathic (1) (3) (5). However, the phenotypes are dynamic and overlapping, and they may evolve into one another (1).

For a long time, nasal hyper-reactivity was seen as a symptom that made it possible to differentiate between patients affected by idiopathic rhinitis (former known as *vasomotor rhinitis*) and other chronic rhinitis patients. However, we recently showed that nasal hyper-reactivity is a widespread symptom that is common to both AR and NAR patients (6, 7). Furthermore, quality of life (QoL) is equally impaired in both NAR and AR patients (8).

In addition to phenotypes, NAR can be subdivided into inflammatory, neurologic and idiopathic endotypes (4, 9) (Table 1). The prevalence of the different endotypes of NAR is unknown and this area will require research in the future. The inflammatory endotype includes two clear subendotypes: local allergic rhinitis (LAR) and NARES (non-allergic rhinitis with eosinophilia syndrome) (1) (10). These two usually have a Th2 endotype involving an increase in eosinophils, IL-5, IL-4, IL-13 and, in the case of LAR, specific IgE (1) (9). This endotype may also include the environmental phenotype (occupational, smoking)–with low-molecular-weight substances initiating a Th2 response by means of TSLP, IL-33 etc.–, the drug-induced inflammatory endotype (NAIDS, aspirin) and hormonal rhinitis involving histamine H1-receptor overexpression (1) (4). Although there is no hard evidence one can expect that the NAR inflammatory

endotype will be successfully treated with a combination of intranasal corticosteroids and/or antihistamines.

Table 1. NAR phenotypes and endotypes

Phenotypes [4]	**Endotypes** [1, 4, 9]
NARES/LAR	Th2-inflammation
Occupational	Neurogenic inflammation, Th2-inflammation
Medication-induced	Neurogenic dysbalance, Th2-inflammation, idiopathic
Hormonal	Neurogenic dysbalance, Th2-inflammation
Idiopathic rhinitis	Neurogenic inflammation, idiopathic
Rhinitis of the Elderly	Neurogenic dysbalance
Gustatory	Neurogenic dysbalance and neurogenic inflammation

In the case of the neurological endotype, one can differentiate between neurological inflammation in idiopathic rhinitis with nasal hyper-reactivity and disease attributed to hyperactivity in the parasympathetic nervous system (primarily senile and gustatory rhinitis, but also, to a certain extent, hormonal and drug-induced rhinitis). In idiopathic rhinitis, studies have indicated that neurogenic signs of disease (transient potential receptor channels (TRP receptors)) affect trigeminal nerves, substance P, and calcitonin gene-related peptide (11). Capsaicin treatment in these patients induces the reduction of TRPV-1 receptors in nasal mucosa, reducing the symptoms of nasal hyper-reactivity (11) (12) (13). Recent literature shows that azelastine (nasal antihistamine) can achieve the same effect in TRP desensitization (14). In patients with senile and gustatory rhinitis, ipratroprium nasal spray (atronase) reduces parasympathetic activity in the nose (15). When all other treatments fail, vidian neurectomy may be a way of disrupting the parasympathetic innervation of the nose and stopping rhinorrhea (16).

We are not aware of a type 1 or type 3 inflammatory endotype (INF-y, IL-17, TNF) in NAR; type 1 inflammation would seem to be related mainly to infectious rhinitis and not to NAR phenotypes (4).

It is also important to realize that the underlying mechanism of NAR can also be present in AR. When there is a seasonal allergen sensitization accompanied by perennial symptoms, symptoms outside the pollen season may be the result of ongoing, minimal persistent, allergic inflammation or the same underlying mechanism as in NAR may be responsible for symptoms (9, 17).

Studies to assess single cellular or molecular markers (or combinations of these markers) with the aim of defining the endotype of AR and NAR are scarce (3) (18). Unfortunately, it is difficult to combine the data from these studies due to differences

in the inclusion criteria that resulted in unclear phenotypes. In general terms, these studies have mainly identified differences between AR and NAR that are linked to cells and markers related to IgE inflammation in AR: total and specific IgE, eosinophils, mast cells, and IL-5 (19). However, some of these studies showed comparable levels of allergic inflammation in AR and NAR patients, possibly indicating some form of local allergic inflammation in these NAR patients (20) (21). In cases where idiopathic rhinitis patient were studied, levels of inflammatory mediators or cells were found to be the same as in healthy controls (22).

We wondered whether the endotyping of chronic rhinitis patients–and non-allergic rhinitis patients in particular–with molecular or cellular markers could be helpful. In this cross-sectional study we studied nasal secretions for the presence of potentially relevant mediators related to different rhinitis endotypes. We looked at non-allergic rhinitis patients (selected to represent idiopathic rhinitis), grass-pollen-allergic rhinitis patients (outside allergen exposure) as an example of minimal persistent, allergic inflammation, mixed rhinitis patients and healthy controls (17).

MATERIAL AND METHODS

Inclusion and exclusion criteria

Patients were recruited from the outpatient clinic of the Department of Otorhinolaryngology of the Academic Medical Center, Amsterdam, the Netherlands. Medical ethical approval was obtained (MEC 08/356) by the Institutional Medical Ethics Review Committee (MRTC) of the Academic Medical Centre of Amsterdam (AMC) and all participants gave their written informed consent. A patient information document (approved by the Institutional Medical Ethics Review Committee) was signed per included patient. All rhinitis patients had a positive history of rhinitis symptoms at least one year and were referred to our tertiary care outpatient clinic by their general practitioner or another otorhinolaryngology clinic.

Only pollen-sensitized AR patients were included, excluding AR patients with a perennial allergen sensitization like for example house dust mite. Pollen-sensitized AR patients had at least one positive SPT result for a pollen allergen (defined as: a wheal equal in size or larger than 3 mm and no response to the negative control) and clinical symptoms relevant to their sensitization and no symptoms outside the pollen season when they were included in the study. NAR was defined as clinically relevant symptoms of rhinitis without a positive SPT. In this study, we selected non-allergic rhinitis patients and excluded smoking, senile, gustatory, occupational, medication-induced and pregnancy rhinitis. Mixed rhinitis patients had perennial rhinitis symptoms with peak symptoms during the pollen season and a positive SPT for one or more

pollen allergens, mixed rhinitis patients with perennial allergen sensitizations were excluded as well. The healthy control group had no symptoms of rhinitis and a negative SPT.

The exclusion criteria for all patient groups were anatomic abnormalities, or any systemic disease or medication influencing nasal function. Patients had to be free of symptoms of upper airway infection for at least 1 week. Patients with symptoms of chronic rhinosinusitis (CRS) (diagnosed according to EPOS criteria, i.e. two or more symptoms of the following: nasal congestion/blockage, (anterior/posterior) rhinorrhea, hyposmia/anosmia, facial pain/pressure; with at least either nasal congestion or rhinorrhea, combined with signs of CRS with nasal endoscopy and/or CT sinus) with or without nasal polyposis were excluded, as were patients who had undergone nasal surgery in the previous 3 months, patients with a history of immunotherapy or asthma, and patients who smoked (23).

STUDY DESIGN

Data collection

Nasal secretions were collected to compare molecular biological parameters in nasal secretions of 23 pollen-sensitized AR patients outside the season, 23 symptomatic NAR patients, 23 symptomatic pollen-sensitized mixed rhinitis patients and 23 healthy controls. Nasal secretions were obtained outside the pollen season from September to March-May, with the latter limit depending on the patient's seasonal sensitizations.

Screening visit

Patients were seen for a screening visit and a sampling visit, both outside the pollen season. Patients were asked to stop with their antihistamines for 48 hours before both visits and with nasal corticosteroid medication or any other medication influencing nasal function for at least 4 weeks. The screening visit included a skin prick test (SPT), and an Ear-Nose-Throat (ENT) history and examination. Patients were categorized using the ARIA classification system (24).

Sampling visit

The sampling visit included an assessment of nasal symptoms (rhinorrhea, nasal congestion, itch and sneezing) with a Visual Analogue Scale (VAS) (maximum 100 mm per nasal symptom) and a nasal airflow assessment based on Peak Nasal Inspiratory Flow (PNIF). To collect the secretion, a small merocel (Ivalon, ThinPack™) was inserted into the inferior meatus of one nostril for three minutes. Which nostril was used depended on the anatomical situation of the individual patient. The merocel was weighed before and after application to calculate total secretion weights and the secretion was eluted by soaking in 3 mL (0.9% w/v) NaCl at 4°C for two hours and

collected after centrifugation for 15 min at 1,500g. Aliquots were stored at -80°C until use in a multiplex ELISA.

Protein multiplex ELISA

The samples collected from the three patient groups and healthy control group were used to determine protein levels for a broad range of inflammatory mediators and growth factors (the lower detection limit for each mediator is stated in pg/mL between brackets): IL-1RA (13.4 pg/mL), IL-1β (3.7 pg/mL), IL-2R (10.5 pg/mL), IL-2 (4.7 pg/mL), IL-4 (16.6 pg/mL), IL-5 (4.2 pg/mL), IL-6 (2.7 pg/ml), IL-8 (2.4 pg/mL), IL-10 (9.5), IL-12 (4.6), IL-13 (5.0), IL-15 (11.0), IL-17 (8.6 pg/mL), eotaxin (1.6 pg/mL), TNF-α (3.9 pg/mL), INF-α (6.7 pg/mL), IFN-γ (11.0 pg/mL), MCP-1 (4.9) pg/mL), GM-CSF (10.3 pg/mL), G-SCF (26.8 pg/mL), VEGF (3.5 pg/mL), FGF-β (1.6 pg/mL), EGF (3.3 pg/mL), HGF (6.8 pg/mL), IP-10 (1.9 pg/mL), MIG (1.7 pg/mL), RANTES (5.4 pg/mL), MIP1-α (6.9 pg/mL), MIP1-β (3.3 pg/mL).

The function of the measured cytokines and their relation to an underlying endotype can be found in Figure 1.

General inflammatory mediators

IL-1 family	
IL-1β:	- Activation of multiple cells (lymphocytes, B cells, fibroblasts) - Induces FGF and EGF expression
IL-1RA:	Binds IL-1R and prevents activation
IL17:	T-cell-produced, induces GCSF/GMCSF/IL-6, IL-1β, TGFβ, TNFα, IL8, Gro-α (CXCL1- neutrophil chemokine), MCP1 (CCL2)
IFNα:	Activates B cells, anti-tumor and anti-viral response
TNFα:	Induces apoptosis (anti-tumor), and IL1 β, membrane-bound intermediate

T-cell-related

IL-2 family (IL-4, IL-7, IL-9, IL-15, IL-21) share ɣ-chain in their receptor	
IL-2:	Stimulation, proliferation, and survival of T and NK cells allowing differentiation of all Th's
IL-4:	Allows Th0 to Th2 differentiation, conversion of B cells to plasma cells, IgE class switch
IL-15:	Constitutively expressed by epithelium, inhibits apoptosis of T cells in absence of antigen
IL-10:	In the role of Th2, inhibits Th1, B cell survival hallmark regulatory T cells, inhibits inflammatory mediators (IFN, IL-2, TNF, GMCSF)
IL-12:	Required for Th1 differentiation, inhibits Th2, induces INF in T cells, blocks formation of new blood vessels
IL-13:	Links adaptive response to tissue effects (MMP induction, goblet hyperplasia)
IL-17:	Secreted by TH17/22 cells and recruits neutrophils
IFNɣ:	Hallmark Th1 cytokine, activates antiviral response
MIG (CXCL9):	Induced by IFNɣ, T cell chemokine
IP10 (CXCL10):	Induced by IFNɣ, T cell chemokine (also macrophages, NK, dendritic cells)
RANTES:	Chemokine also for eo's

Neutrophilia

IL-17:	Chemokine
MIP-1α (CCL3):	Also eo's, basophils, mast cells
MIP-1 β (CCL4):	Also eo's, basophils, mast cells
IL-8:	Chemokine
GMCSF:	Induces neutrophils and eosinophils from stem cells
GCSF:	Induces mostly neutrophils

Eosinophilia

Eotaxin:	Eo chemokine
RANTES (CCL5):	Chemokine also for T cells
MCP1:	Only monocytes and basophils, but after removal of N-terminal amino acid it recruits eo's but no longer basophils
GMCSF:	Induces neutrophils and eosinophils from stem cells

Growth factors

VEGF:	Endothelium
FGF:	Fibroblasts
EGF:	Epithelium – counteracts effect of TGF driving EPI to FIB transformation
HGF:	Epithelium – counteracts effect of TGF driving EPI to FIB transformation

Figure 1. Function of measured cytokines

Cytokine levels were measured with a Human Cytokine Thirty-Plex Antibody Bead Kit (Biosource, USA) in combination with a Bio-Plex workstation (Bio-Rad, NL). All standards were diluted in HBSS medium as required by the manufacturer. All standards were diluted in HBSS medium (3 mL) as required by the manufacturer. Luminex software was employed for the protein concentration calculations and all these concentrations–after correcting for the different amounts of nasal secretions collected–were expressed in pg/mL.

Statistics and principal component analysis

SPSS 20.0 (Chicago, IL, USA) was used for statistical analysis. Cytokine, chemokine, and growth factor values that were below the detection limits were recoded to the lowest measurable value. The distribution of the data was not normal and Kruskal-Wallis non-parametric tests were therefore performed to check for significant between-group variability. Where significant between-group variability was found, Mann-Whitney-U non-parametric tests were performed for between-group comparisons. The level of statistical significance was set to <0.003 after Bonferroni correction for multiple testing (0.05/15). Principal component analysis involving the extraction of 11 components in a rotated component matrix (Varimax with Kaiser normalization) took place to determine whether a combination of cytokines could distinguish between groups of patients.

RESULTS

Characterization of participants

The patient groups were comparable in terms of age, gender and percentage of patients with moderate-severe persistent disease (Table 2).

Table 2. Patient characteristics

	Healthy Controls (n = 23)	Mixed Rhinitis (n = 21)	Non-Allergic rhinitis (n = 23)	Allergic rhinitis (outside season) (n = 22)	Significance levels over the groups
Gender (male %)	34.8%	19.0%	34.8%	36.4%	$p = 0.540$ [a]
Mean age (years)	32.7	38.8	41.7	36.2	$p = 0.160$ [b]
ARIA class. (% moderate-severe persistent)	Not relevant	85.7%	82.6%	68.2%	$p = 0.230$ [a]
Allergen sensitization	n.a.	Only trees (23.8%)	n.a.	Only trees (9.1%)	
		Only grass (23.8%)		Only grass (31.8%)	
		Only plants (4.8%)		Only plants (0%)	
		Mixture of above: (47.6%)		Mixture of above: (59.1%)	
VAS rhinorrhea					$p = 0.185$ †
Median (range)	0.0 (0–28)	0.0 (0–79)	2.0 (0–88)	0.0 (0–48)	
Mean (SD)	5.4 (8.5)	12.1 (25.0)	13.0 (23.9)	4.7 (11.5)	
VAS congestion					$p = 0.001$†
Median (range)	1.0 (0–51)	14.0 (0–83)	30.0 (0–98)	3.5 (0–47)	
Mean (SD)	6.4 (11.7)	21.1 (25.1)	41.2 (38.1)	9.0 (12.5)	
VAS itch					$p = 0.011$†
Median (range)	0.0 (0–23)	2.0 (0–80)	1.0 (0–67)	0.0 (0–29)	
Mean (SD)	2.5 (5.5)	17.1 (24.7)	11.7 (20.3)	3.0 (7.4)	
VAS burning					$p = 0.012$†
Median (range)	0.0 (0–2.0)	0.0 (0–63)	0.0 (0–71)	0.0 (0–7)	
Mean (SD)	0.26 (0.54)	10.5 (19.9)	7.4 (16.9)	0.4 (1.5)	
VAS sneezing					$p = 0.160$†
Median (range)	0.0 (0–33)	0.0 (0–69)	1.0 (0–60)	0.0 (0–40)	
Mean (SD)	2.7 (7.4)	8,4 (18.8)	9.6 (17.4)	4.7 (10.3)	
PNIF					$p = 0.052$† $p = 0.446$ ‡
Median (range)	140.0 (70–260)	105.0 (40–230)	110.0 (60–270)	115.0 (40–200)	
Mean (SD)	147.4 (45.8)	107.9 (50.7)	125.9 (48.0)	120.7 (41.4)	

a: Chi Square Test
b: Kruskal Wallis
†: Kruskal Wallis over all groups
‡: Kruskal Wallis over patient groups only

The NAR and the mixed rhinitis group had significantly ($p< 0.001$) higher total VAS scores and VAS scores for congestion and itch ($p< 0.001$ and $p< 0.011$ respectively) than healthy controls and allergic rhinitis patients (outside the season). Although the PNIF was higher in the healthy controls than in the patient groups, the differences were not statistically significant. Two patients in the mixed rhinitis group and one in the allergic rhinitis group were excluded: one patient in the mixed rhinitis group started smoking again and the other was found to have a perennial allergen sensitization for cat combined with daily exposure to this allergen, and the bothersome symptoms of rhinitis disappeared in the patient in the AR group.

Nasal secretion analysis

Nasal secretions of non-allergic rhinitis patients cannot be differentiated from healthy controls

Above the detection levels were:
IL-8, IL-12, IL1RA, MCP1, MIP1α, MIP1β, EGF, VEGF, HGF, INFα, RANTES, IP10, IL7, FGFβ and MIG. No significant differences were found between non-allergic rhinitis and healthy controls for any of the mediators above detection level. The functions of these mediators can be found in Figure 1.

Levels of IL-12 and HGF are low in nasal secretions of mixed and allergic rhinitis patients

There was a significant difference between patient groups (Kruskal-Wallis, $p < 0.003$) for two mediators above detection level, IL-12 and HGF (Table 3). Median IL-12 levels were significantly higher in the NAR group than in the AR and mixed groups. Median IL-12 levels in AR and mixed rhinitis were lower than in healthy controls but they reached significance in the mixed patient group only. A similar pattern was seen for HGF but it was not found to be significant when we set the level of significance at $p < 0.003$ for the correction of multiple testing (Figure 2A and 2B).

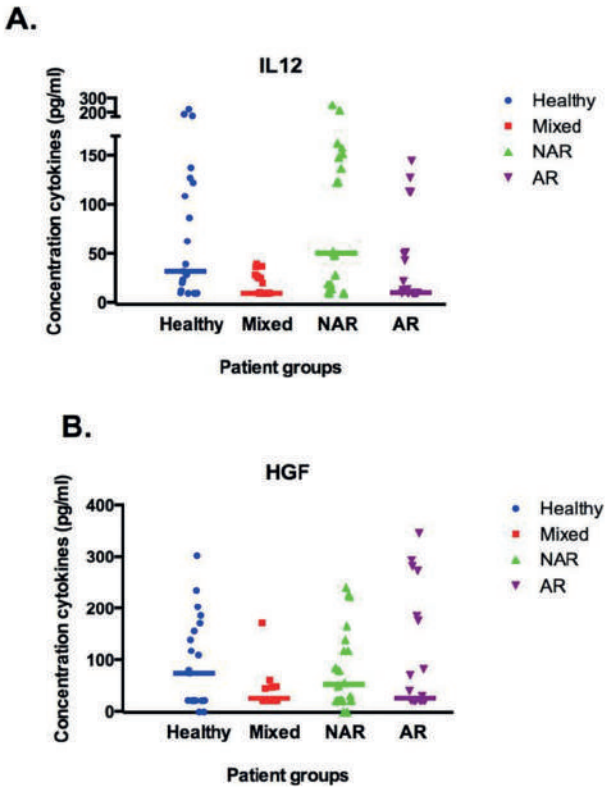


Figure 2 (A and B). Cytokines that were (significantly) different between groups: IL12 (A) and HGF (B)
(A and B): Expression of cytokines (pg/mL) in nasal lavage fluid in a healthy control group and in mixed, non-allergic (NAR) and allergic (AR) rhinitis patient groups. Individual concentrations are represented with a symbol; median concentration levels per group are represented with a horizontal line.
** IL12 is significantly lower in mixed versus healthy controls.*
*** IL12 is significantly lower in AR and mixed versus NAR.*

Table 3. Cytokine levels in nasal secretions

Mediator	Controls Median (*range*) Mean (*SD*)	Mixed Rhinitis Median (*range*) Mean (*SD*)	Non-Allergic Median (*range*) Mean (*SD*)	Allergic Median (*range*) Mean (*SD*)	Kruskal Wallis (*p*)
EGF	8.0 (3.4–12.5) 9.2 (4.8)	3.5 (3.4–67.5) 13.6 (15.2)	5.1 (3.4–20.2) 6.2 (3.9)	3.4 (3.4–37.8) 10.4 (9.7)	$p = 0.392$
HGF	74.6 (74.6–301.9) 110.2 (84.0)	20.6 (20.5–171.4) 41.1 (32.1)	50.1 (20.8–240.5) 88.2 (71.5)	20.8 (20.5–344.6) 96.2 (107.4)	$p = 0.021$
IL-12	32.0 (20.3–221.1)[a] 69.4 (67.8)	9.30 (9.2–39.4)[a,b] 19.4 (9.5)	51.1 (9.3–253.0)[b] 84.1 (76.7)	10.8 (9.2–144.2)[b] 38.1 (43.6)	$p = 0.001$
IL-8	357.1 (567.9–3667.1) 835.5 (1032,5)	217.2 (250.0–2072.5) 441.5 (559.7)	254.7 (159.0–1681.3) 452.4 (491.5)	509.9 (51.7–3072.6) 785.3 (849.8)	$p = 0.148$
RANTES	21.7 (16.2–41.3) 22.2 (13.0)	16.4 (16.2–57.7) 22.5 (12.6)	16.7 (16.3–27.3) 17.7 (6.0)	16.4 (16.2–44.7) 18.9 (6.4)	$p = 0.562$
IL-1RA	311.8 (39.8–1583.5) 360.9 (338.1)	151.6 (39.9–2431.9) 355.3 (545.0)	194.0 (39.9–2587.7) 335.9 (542.1)	179.4 (39.9–1111.9) 334.0 (314.4)	$p = 0.622$
INF-α	42.6 (6.2–77.2) 38.7 (24.1)	6.3 (6.2–79.5) 28.6 (23.1)	43.9 (6.2–81.6) 40.9 (26.3)	6.3 (6.2–99.9) 33.5 (27.3)	$p = 0.108$
MCP1	38.1 (14.9–128.3) 46.2 (31.5)	33.7 (14.8–186.0) 61.7 (58.0)	24.3 (5.0–120.3) 30.5 (24.1)	32.6 (14.9–134.7) 47.7 (38.2)	$p = 0.336$
IP10	45.0 (6.3–863.0) 131.8 (199.3)	20.5 (5.6–2447.5) 212.9 (533.0)	28.8 (5.7–1465.1) 69.1 (105.9)	39.0 (5.7–1195.1) 124.4 (273.1)	$p = 0.336$
MIG	22.4 (5.1–77.5) 131.8 (199.3)	16.3 (5.1–218.1) 212.9 (533.0)	22.5 (5.1–65.5) 69.1 (105.9)	17.3 (5.1–106.0) 124.4 (273.1)	$p = 0.720$
MIP-1β	10.0 (9.9–22.1) 12.1 (3.7)	9.9 (9.9–13.4) 10.8 (0.9)	10.0 (9.9–18.4) 11.1 (2.2)	10.0 (9.9–20.5) 11.7 (3.0)	$p = 0.358$
MIP-1α	20.8 (20.6–41.9) 25.9 (6.6)	20.7 (20.6–22.8) 23.0 (2.3)	20.8 (20.6–50.2) 26.1 (8.0)	20.8 (20.6–47.7) 25.9 (6.7)	$p = 0.091$
VEGF	5.1 (3.4–24.0) 8.8 (4.9)	3.4 (3.4–12.3) 8.1 (3.4)	4.3 (3.4–10.1) 5.7 (2.5)	3.4 (3.4–37.9) 9.0 (8.3)	$p = 0.065$
IL-15	33.2 (32.9–276.0) 57.7 (56.1)	33.4 (32.9–418.0) 84.8 (91.7)	33.1 (32.9–68.6) 37.1 (10.1)	33.2 (32.9–417.4) 66.7 (90.3)	$p = 0.568$
IL-7	9.8 (9.7–157.9) 58.3 (46.7)	9.8 (9.7–177.2) 59.8 (52.7)	9.8 (9.7–67.3) 56.7 (49.4)	10.1 (9.7–174.4) 52.9 (50.7)	$p = 0.583$
FGF-β	4.8 (4.7–12.9) 11.2 (2.8)	4.8 (4.7–9.6) 9.6 (3.4)	4.8 (4.7–5.1) 11.8 (2.3)	4.8 (4.8–9.6) 10.1 (3.5)	$p = 0.782$

a: Kruskal Wallis $p < 0.003$ mixed versus healthy

b: Kruskal Wallis $p < 0.003$ AR and mixed versus NAR

Principal component analysis reveals high inter- and intra-group variance as a consequence of the large dynamic range of expression for multiple mediators

As has been shown above, some of the individual cytokines showed significant differences between the groups, but neither the three patient groups nor the healthy controls expressed a feature cytokine. We used principal component analysis to explore whether the use of combinations of mediators rather than single mediators could improve molecular characterization for our study population.

Mapping individual patients in multi-dimensional space showed that we could reduce the dataset to the first five principal components with eigenvalues over 1 that together account for more than 75% of total variance (Figure 3) in all samples.

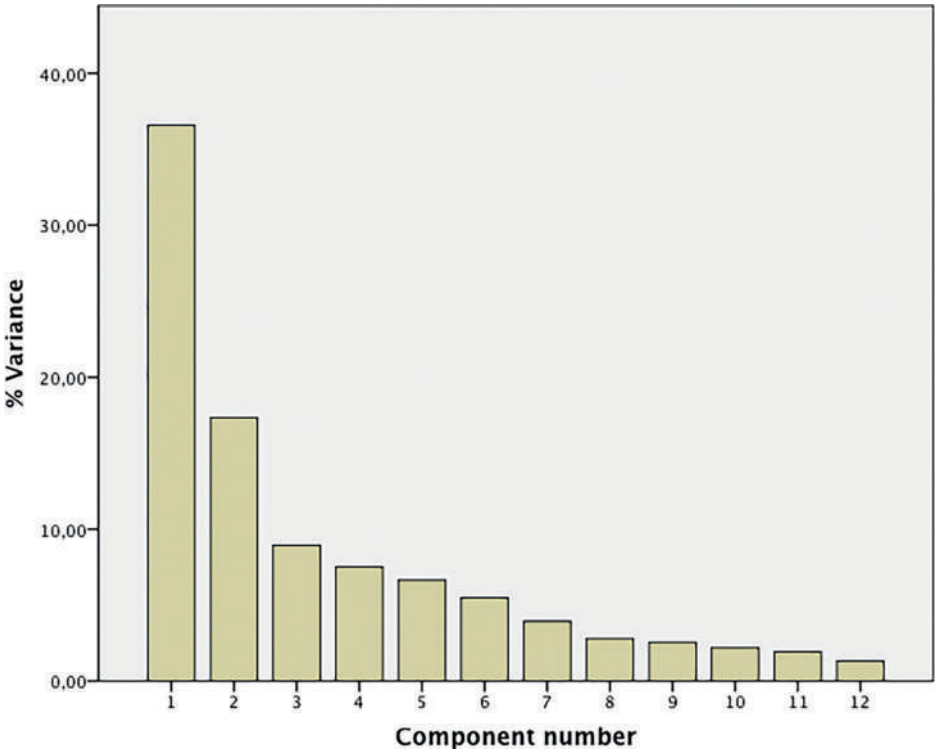
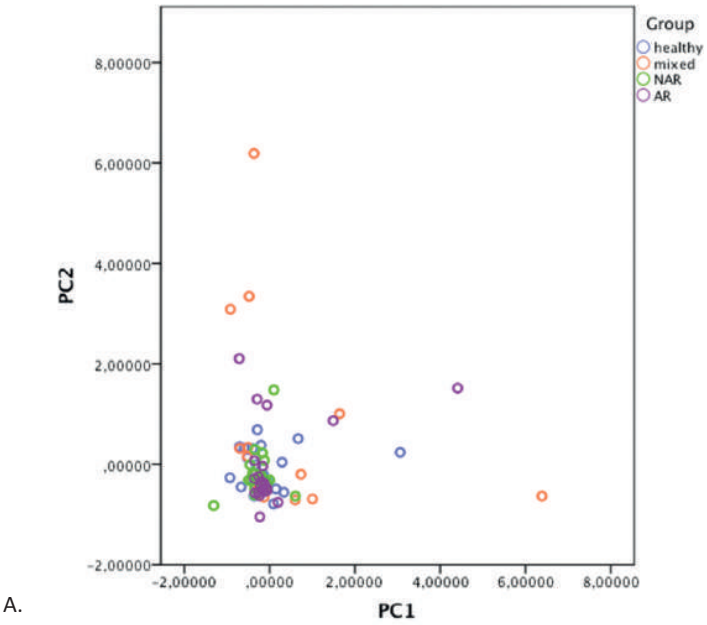


Figure 3. Proportion of contribution to total variance of principal components

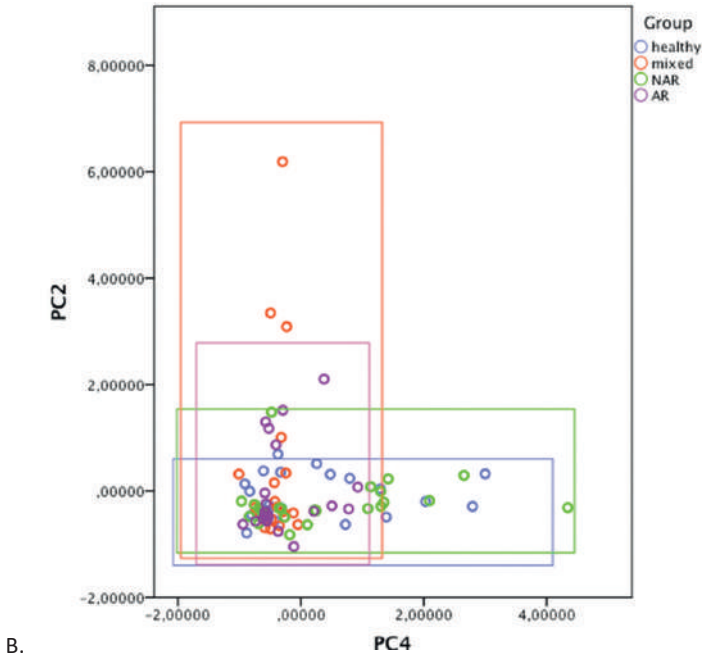
Table 4 shows the relative contribution of each of the mediators to these five principal components. The first three principal components showed significant loading of more than 0.5 for multiple mediators: MCP1, IP10, and IL-15 on PCA1, EGF and MCP1 on PCA2, and the related mediators MIP1α and MIP1β on PCA3. The last two principal components seemed to depend on single mediators: PCA4 on IL-12 and PCA5 on IL-17. Pairwise plotting of the five principal components did not result in a full separation of an individual patient group; the plot of PCA1/PCA2 is shown in Figure 4A as an example. The best separation of groups was obtained when PCA4 was involved. For instance, plotting PCA2 against PCA4 (Figure 4B) revealed the unique low vales for the mixed rhinitis group.

Table 4. Contribution of individual cytokines to the principal components

Cytokine	PCA 1	PCA 2	PCA 3	PCA 4	PCA 5
EGF	+ 0.15	**+ 0.94**	+ 0.07	- 0.01	+ 0.05
HGF	+ 0.04	+ 0.09	+ 0.34	+ 0.38	+ 0.22
IL12	- 0.04	- 0.02	+ 0.19	**+ 0.95**	- 0.03
IL8	0	+ 0.18	+ 0.11	+ 0.10	+ 0.04
RANTES	+ 0.29	+ 0.06	+ 0.22	+ 0.11	+ 0.23
IL1RA	+ 0.32	+ 0.13	+ 0.04	- 0.03	+ 0.03
INFA	+ 0.06	- 0.05	+ 0.22	+ 0.03	+ 0.21
MCP1	**+ 0.53**	**+ 0.65**	+ 0.10	- 0.02	+ 0.09
IP10	**+ 0.94**	+ 0.10	+ 0.01	0	- 0.02
MIG	+ 0.33	+ 0.25	+ 0.02	+ 0.04	+ 0.14
MIP1B	+ 0.05	0.09	**+ 0.91**	+ 0.19	+ 0.02
MIP1A	+ 0.05	0.05	**+ 0.58**	+ 0.04	+ 0.09
VEGF	+ 0.12	0.23	+ 0.21	+ 0.17	+ 0.19
IL15	**+ 0.92**	0.02	+ 0.08	- 0.03	+ 0.12
IL7	+ 0.08	0.07	+ 0.03	- 0.01	**+ 0.96**
FGFB	0.07	0.17	+ 0.27	- 0.01	+ 0.07



A.



B.

Figure 4 (A and B). Principal component analysis

(A): PC1 versus PC2: no distinction between groups

(B): PC2 versus PC4: distinction between mixed and AR patients (with low values for PC4) and healthy and NAR (with low values for PC2).

We evaluated potential correlations between mediators on the basis of the significant loadings of multiple mediators for each principal component. Indeed, Pearson's correlation coefficient was highly significant for mediators that weighted PCA1 (MCP1, IP10, and IL-15): MCP1 versus IP10 (r = 0.642, *P* = < 0.0001), MCP1 versus IL-15 (r = 0.669, *P* = < 0.0001), and IP10 versus IL-15 (r = 0.907, *P* = < 0.0001). The same picture emerges for the mediators weighting PCA2 (EGF versus MCP1, r = 0.776, *P* = < 0.0001) and for MIP1α versus MIP1β (r = 0.764, *P* = < 0.0001) on PCA3.

DISCUSSION

The most important outcome of this study is that, looking at a wide panel of mediators related to endotypes of (general/Th2/Th1) inflammation, no clear profile could be found in non-allergic rhinitis patients. In the past, only a limited panel of mainly Th2 mediators–examples being IL-5, IgE, and eosinophils–were taken into account when comparing non-allergic rhinitis patients with allergic rhinitis patients (18). The aim of this study was to broaden that panel in order to establish a wider picture, and to assess a large number of mediators and chemokines related to growth, inflammation (general/Th1/Th2/Th3), eosinophils, and neutrophils. In NAR patients, none of the levels of these mediators differed significantly from those in healthy controls, emphasizing that no distinction can be made between the inflammatory patterns in non-allergic rhinitis (mainly idiopathic rhinitis) and healthy controls (Table 3). We have to acknowledge that in this study we have not looked at the typical neurogenic inflammatory markers in NAR patients. This might have shown a distinctive pattern in NAR compared to healthy controls.

On a phenotype level, it is important to realize that -although we excluded NAR patients with senile, gustatory, occupational, medication-induced and pregnancy rhinitis- we cannot objectively claim to have excluded NARES or LAR. The history of NAR patients was however not suggestive for an allergen sensitization. Differentiating at a phenotype level between AR–particularly when there is concomitant perennial sensitization–and mixed rhinitis can be extremely complicated. AR and mixed patients in this study were therefore pollen-sensitized only and the study was performed outside the pollen season. At the phenotype level, this meant that AR patients did not have symptoms during the study but that mixed and NAR patients did and that molecular differences between AR, NAR and mixed patients were independent of allergic inflammation. We aimed to identify, where present, the specific endotype of the NAR profile in NAR and mixed patients.

In a broad panel of inflammatory mediators, the mediator profile of non-allergic rhinitis patients resembles that of healthy controls whereas the profile of mixed rhinitis patients resembles that of allergic rhinitis patients. The analysis of multiple

inflammatory mediators did reveal differences in the levels of the mediators IL-12 and HGF (which were significantly lower in AR and mixed rhinitis than in NAR and healthy controls) that have not been extensively explored previously in the context of different forms of rhinitis.

Traditionally, IL-12 has been seen as a hallmark Th1 cytokine produced by dendritic cells that skews native T lymphocytes to produce INF-gamma. As we know, there is cross-regulation of anti-viral Th1 and allergic Th2 responses by the mutual inhibitory effects of IL-12 on Th2, and IL-4 on Th1, responses. It might therefore be assumed that, in our study, the AR patients with a predominant Th2-skewed inflammation would have lower levels of IL-12 than healthy controls or non-allergic rhinitis patients. Nevertheless, IL-12 levels in these pollen-allergic patients were very low, even when taking into consideration the fact that these patients were seen outside of the pollen season. We also failed to detect IL-4, IL-5, and IL-13 in nasal secretions, which suggest that it is unlikely that low IL-12 levels are a result of active Th2-dominated inflammation. This suggests that the low IL-12 levels could be an intrinsic characteristic of pollen-allergic patients.

A similar pattern in the nasal secretion levels was seen for HGF. This mediator is known to regulate dendritic cell migration, inhibit epithelial apoptosis, and reduce airway eosinophilia in OVA-allergic mice (25) (26). HGF can also suppress IL-13-induced eotaxin expression in airway epithelial cells (27) (28). The low level of HGF may therefore facilitate Th2 responses in AR and mixed rhinitis patients.

The overall low expression of IL-12 and HGF in mixed rhinitis patients may be a small step towards this goal and it does show that a more unbiased approach may help to reveal new aspects of a disease that have not been previously considered.

Although IL-12 is best known in relationship to dendritic cells, it has been shown that other cells such as epithelium produce IL-12 in substantial quantities; we have shown that IL-12 expression in an epithelial cell line can be up-regulated through the activation of the cells by pollen allergen (29) (30). Epithelial cells can also secrete HGF, which is in line with the concept that proteins from the nasal epithelium could dominate the protein content of nasal secretion. The potential contribution of nasal epithelium and the potential intrinsically low level of IL-12 and HGF in pollen-allergic individuals outside the pollen season could concur with our observations of the nasal epithelium of HDM-allergic individuals, which seems to stay activated when these cells are cultured *ex vivo* in the absence of allergen exposure (31). How the differences we have observed may contribute to the pathological mechanisms of allergic rhinitis or idiopathic rhinitis remains to be explored. However, low levels of IL-12 and HGF could facilitate a stronger Th2 response upon allergen exposure. In addition to the obvious targets of the nasal mediators we may also need to consider potential contributions from the family of innate lymphoid cells. Type 2 innate lymphoid cells (ILC2) play an

important role in chronic inflammatory airway diseases (such as chronic rhinosinusitis and diseases of the lower airways). IL-12 and IL-4 can switch the function of ILC2 into either type 1 or type 2 inflammation (32), (33).

Also looking at groups of mediators instead of only individual mediators–as was done in the principal component analysis–did not help us in differentiation between patient groups. Principal component analysis showed us that the cytokines present on the first principal component contribute most to variation between patient groups. The clinical implications, however, remain unknown as the numbers and types of cytokines and/or the defined sets of phenotypes cannot differentiate between groups of patients.

In conclusion, looking at a broad panel of mediators did not allow us to identify a mediator profile that links non-allergic rhinitis to a general or Th2/Th1 inflammatory or neurogenic endotype. Nor could we identify a specific combination of mediators that differentiate between non-allergic rhinitis and healthy controls. This confirms previous data that looked at a limited number of mediators in idiopathic rhinitis patients (mainly at IgE, eosinophils, IgE, mast cells) and found no differences from healthy controls (19, 22).

The panel of inflammatory mediators was still limited in number and function: we did not look at, for example, neuropeptides such as SP or CGRP as markers of neurogenic inflammation. Further research to assess differences in a completely unbiased way –in other words at the mRNA level (micro-array) and including mediators related to neurogenic inflammation–may help us to identify the distinct features of this patient group, for which treatment is unsatisfactory owing to our lack of understanding of the underlying etiology.

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REFERENCES

1 Papadopoulos NG et al. Phenotypes and endotypes of rhinitis and their impact on management: a PRACTALL report. Allergy. 2015;70(5):474-94. doi: 10.1111/all.12573.

2. Papadopoulos NG et al. Rhinitis Subtypes, Endotypes, and Definitions. Immunology and allergy clinics of North America. 2016;36(2):215-33.

3. Muraro A et al. Precision medicine in patients with allergic diseases: Airway diseases and atopic dermatitis-PRACTALL document of the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma & Immunology. The Journal of allergy and clinical immunology. 2016;137(5):1347-58.

4. De Greve G et al. Endotype-driven treatment in chronic upper airway diseases. Clinical and translational allergy. 2017;7:22. doi: 10.1186/s13601-017-0157-8.

5. van Rijswijk JB et al. Allergy. 2005;60(12):1471-81.

6. Segboer CL et al. Nasal hyper-reactivity is a common feature in both allergic and nonallergic rhinitis. Allergy. 2013;68(11):1427-34.

7. Van Gerven L et al. Up-date on neuro-immune mechanisms involved in allergic and non-allergic rhinitis. Rhinology. 2012;50(3):227-35.

8. Segboer CL et al. Quality of life is significantly impaired in non-allergic rhinitis patients. Allergy. 2017.

9. Hellings PW et al. Non-allergic rhinitis: Position paper of the European Academy of Allergy and Clinical Immunology. Allergy. 2017;72(11):1657-65.

10. Campo P et al. Local Allergic Rhinitis. Immunology and allergy clinics of North America. 2016;36(2):321-32.

11. Van Gerven L et al. Capsaicin treatment reduces nasal hyper-reactivity and transient receptor potential cation channel subfamily V, receptor 1 (TRPV-1) overexpression in patients with idiopathic rhinitis. The Journal of allergy and clinical immunology. 2014;133(5):1332-9,

12. Van Rijswijk JB et al. Intranasal capsaicin reduces nasal hyper-reactivity in idiopathic rhinitis: a double-blind randomized application regimen study. Allergy. 2003;58(8):754-61.

13. Gevorgyan A, Segboer C et al. Capsaicin for non-allergic rhinitis. Cochrane Database Syst Rev. 2015;(7)

14. Gehanno P et al. Vasomotor rhinitis: clinical efficacy of azelastine nasal spray in comparison with placebo. ORL J Otorhinolaryngol Relat Spec. 2001;63(2):76-81.

15. Bronsky EA et al. A clinical trial of ipratropium bromide nasal spray in patients with perennial nonallergic rhinitis. The Journal of allergy and clinical immunology. 1995;95(5 Pt 2):1117-22.

16. Robinson SR et al. Endoscopic vidian neurectomy. Am J Rhinol. 2006;20(2):197-202.

17. Ricca V et al. Minimal persistent inflammation is also present in patients with seasonal allergic rhinitis. The Journal of allergy and clinical immunology. 2000;105(1 Pt 1):54-7.

18. Bachert C et al. Advances in rhinitis and rhinosinusitis in 2015. The Journal of allergy and clinical immunology. 2016;138(5):1277-83.

19. Blom HM et al. Mast cells, eosinophils and IgE-positive cells in the nasal mucosa of patients with vasomotor rhinitis. An immunohistochemical study. Eur Arch Otorhinolaryngol. 1995;252

20. Comoglu S et al. Inflammatory cell patterns in the nasal mucosa of patients with idiopathic rhinitis. American journal of rhinology & allergy. 2012;26(2):e55-62.

21. Klimek L et al. Local (exclusive) IgE production in the nasal mucosa. Evidence for local allergic rhinitis). Hno. 2013;61(3):217-23.

22. van Rijswijk J et al. Inflammatory cells seem not to be involved in idiopathic rhinitis. Rhinology. 2003;41(1):25-30.

23. Fokkens WJ et al. EPOS 2012: European position paper on rhinosinusitis and nasal polyps 2012. A summary for otorhinolaryngologists. Rhinology. 2012;50(1):1-12.

24. Bousquet J et al. Allergic Rhinitis and its Impact on Asthma (ARIA): achievements in 10 years and future needs. The Journal of allergy and clinical immunology. 2012;130(5):1049-62.

25. Baek JH et al. The HGF receptor/Met tyrosine kinase is a key regulator of dendritic cell migration in skin immunity. Journal of immunology (Baltimore, Md : 1950). 2012;189(4):1699-707.

26. Togo S et al. Hepatic growth factor (HGF) inhibits cigarette smoke extract induced apoptosis in human bronchial epithelial cells. Experimental cell research. 2010;316(20):3501-11.

27. Okunishi K et al. Intratracheal delivery of hepatocyte growth factor directly attenuates allergic airway inflammation in mice. International archives of allergy and immunology. 2009;149 Suppl 1:14-20.

28. Reh DD et al. The role of hepatocyte growth factor/c-Met in chronic rhinosinusitis with nasal polyps. American journal of rhinology & allergy. 2010;24(4):266-70.

29. Junghans V et al. Epidermal cytokines IL-1beta, TNF-alpha, and IL-12 in patients with atopic dermatitis: response to application of house dust mite antigens. The Journal of investigative dermatology. 1998;111(6):1184-8.

30. Roschmann K et al. Timothy grass pollen extract-induced gene expression and signalling pathways in airway epithelial cells. Clinical and experimental allergy: journal of the British Society for Allergy and Clinical Immunology. 2011;41(6):830-41.

31. Vroling A et al. Primary nasal epithelium exposed to house dust mite extract shows activated expression in allergic individuals. American journal of respiratory cell and molecular biology. 2008;38(3):293-9.

32. Kortekaas Krohn I et al. Emerging roles of innate lymphoid cells in inflammatory diseases: clinical implications. Allergy. 2017. doi: 10.1111/all.13340.


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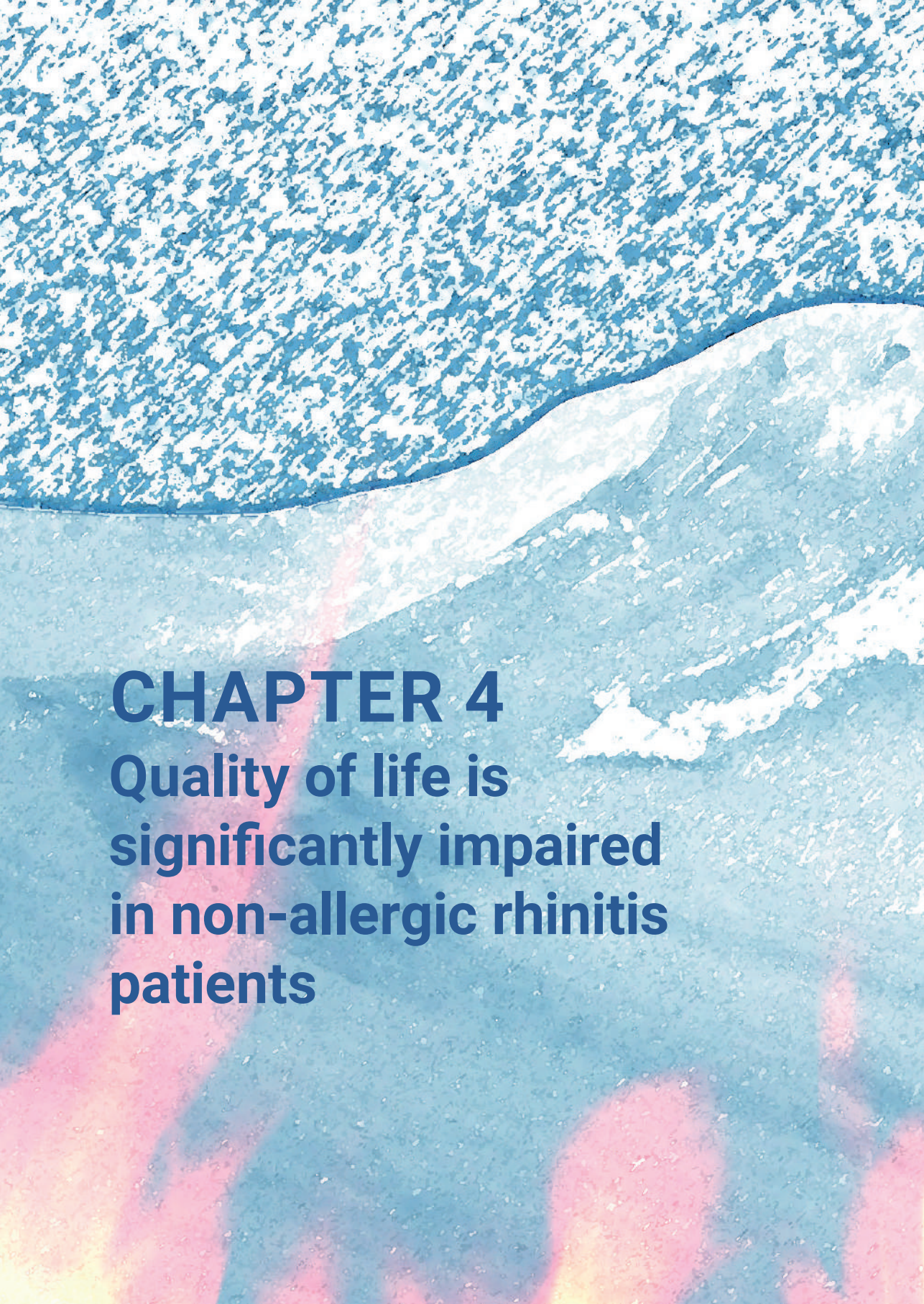

CHAPTER 4
Quality of life is significantly impaired in non-allergic rhinitis patients

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ABSTRACT

Background

In contrast to the well-known significant impairment of quality of life (QoL) in allergic rhinitis (AR), the degree of impairment in QoL in non-allergic rhinitis(NAR) remained unknown for a long time, due to a lack of a validated questionnaire to assess QoL in the NAR patient group. In this study, a validation of the mini-RQLQ questionnaire in NAR patients was performed, followed by an assessment of QoL in NAR patients compared to AR and healthy controls. Secondly, use of medication and treatment satisfaction in AR and NAR was assessed.

Methods

The study was an observational cohort study in 287 AR and 160 NAR patients. Patients with symptoms of rhinitis were recruited from a tertiary care outpatient clinic of the Otorhinolaryngology Department. Allergic rhinitis (AR) was defined as one or more positive results on skin prick testing and clinically relevant symptoms of rhinitis related to their sensitization. Non-allergic rhinitis (NAR) was defined as clinically relevant symptoms of rhinitis but without positive results on skin prick testing. The mini-RQLQ was successfully validated in this study for NAR patients.

Results

Quality of life (QoL) in NAR patients was equally—and for some aspects even more—impaired compared to AR. More than half of both AR and NAR patients were unsatisfied with treatment.

Conclusion

These results demonstrate a significant impairment in both AR and NAR patients in their QoL combined with a low treatment satisfaction, emphasizing the need for adequate treatment, especially in the NAR patient group.

INTRODUCTION

Both allergic rhinitis (AR) and non-allergic rhinitis (NAR) are amongst the most common chronic diseases with a significant impact on quality of life (QoL). Allergic rhinitis (AR) is an inflammatory condition caused by an IgE-mediated response to allergen exposure (1). Patients with NAR have similar symptoms without clinical evidence for an infectious, anatomic, or allergic aetiology (1).

The worldwide estimated prevalence of NAR exceeds 200-400 million people (2). Around half of the adult rhinitis patients (20% to 70%) are considered to have NAR (2, 3, 4).

Clinically, NAR shows largely the same symptoms of rhinitis as AR (5). Also, NAR and AR patients have the same prevalence and type of nasal hyper-reactivity, although in the past nasal hyper-reactivity was considered a hallmark of NAR patients only (6). However, some characteristic features of AR and NAR do exist. AR patients will have allergen induced rhinitis symptoms that usually is accompanied with symptoms of conjunctivitis, more often seasonality and other signs of the atopic syndrome. Data on lower airway involvement are contradictory indicating lower or the same level of lower airway involvement in NAR compared to AR (4, 7-10).

A number of subphenotypes can be discerned within the context of NAR: drug-induced rhinitis, gustatory rhinitis, hormonal-induced rhinitis, rhinitis of the elderly, atrophic rhinitis, NARES, LAR and idiopathic rhinitis (1) (11).

When considering pathophysiology, a subdivision in a neurogenic and an inflammatory endotype is often made. Although not proven, one may consider anti-inflammatory treatment to be more effective in the inflammatory endotype like NARES and LAR and capsaicin to be more effective in the neurogenic endotype (12).

A consequence of the lack of evidence-based treatment for NAR patients compared to AR, is that many NAR patients are unsuccessfully treated. This could cause a high impairment of quality of life in NAR. In contrast to the significant literature on the impairment of the QoL seen in patients with AR (13-17), the degree of impairment of health-related QoL in NAR patients is under-evaluated (3) (18, 19). For this reason, we wanted to assess the QoL of NAR patients in comparison to AR and healthy controls.

In contrast to AR however, for NAR no disease specific and validated questionnaires to measure quality of life were available until now (20).

Van Oene *et al.* showed that for measurement of health related quality of life in AR patients, the RQLQ(S) and the mini-RQLQ were the best tests with optimal discriminant

validity and responsiveness (13). For that reason, we first validated the RQLQ for evaluation of QoL in patients with NAR. Then we assessed QoL in NAR compared to healthy controls and AR patients as a positive control group.

Finally, we assessed the use of nasal medication in NAR, and compared NAR with AR for number and type of nasal medication and treatment satisfaction.

METHODS

Study design

An observational cohort study was performed using questionnaires

Quality of life was assessed by comparing NAR with both healthy controls as with AR as a positive control group. The use of nasal medication was assessed by comparing NAR with AR.

Allergic rhinitis (AR) and non-allergic rhinitis (NAR) patients were recruited between June 2006 and February 2015 from a database composed of rhinitis patients visiting the outpatient clinic of the Ear-Nose-Throat Department of the Academic Medical Centre (Amsterdam, The Netherlands) that went for skin prick testing. If patients met inclusion and exclusion criteria based on history, Ear-Nose-Throat routine examination and allergy skin prick testing, two sets of questionnaires (assessing quality of life and use of nasal medication) were sent to patient's home address. Questionnaires were sent between October 2011 and February 2015.

Inclusion criteria

AR patients

Allergic rhinitis (AR) patients had at least one positive skin prick test result and chronic rhinitis symptoms relevant to their sensitization. Rhinitis was defined as one or more of the following symptoms: watery, anterior rhinorrhea, paroxysmal sneezing, nasal obstruction and/or nasal pruritus. Patients were classified as having intermittent or persistent symptoms of rhinitis according to ARIA classification. This classification was done with help of a questionnaire that accompanied the skin prick test, assessing duration of symptoms (< or >4 days per week and/or < or >4 weeks per year) and severity of symptoms (influence on daily life). To assess allergic sensitization, we used the GA2LEN standardized method of skin prick testing (SPT) (21). A positive reaction to SPT was defined as a skin reaction larger than 3 mm for one or more of the 18 tested allergens, and no reaction to the negative control. Patients were asked to stop their antihistamine medication 48 hours before allergy testing.

NAR patients

Non-allergic rhinitis (NAR) was defined as clinically relevant symptoms of chronic rhinitis without positive skin prick test results and no other reason for rhinitis symptoms (see Exclusion Criteria). Intermittent or persistent rhinitis was defined in the same way as in AR (according to ARIA classification).

Controls

To validate the mini-RQLQ for use in NAR patients, 49 healthy controls were included. Healthy controls were employees from the AMC and were randomly recruited between December 2012 and January 2013. Healthy controls had to be free of rhinitis symptoms.

Exclusion criteria

Patients with anatomical deformities or other forms of nasal obstruction, such as septal deviation, septal perforation, choanal atresia and/or nasal valve collapse or dysfunction being responsible for nasal obstruction, were excluded. Also, patients with signs of infectious rhinitis (purulent/discoloured discharge, fever) and/or chronic rhinosinusitis (CRS) with or without nasal polyposis based on nasal endoscopy (purulent/discoloured discharge, nasal polyps) and/or CT scan were excluded, as were pregnant patients, patients with nasal/sinus surgery within the previous 3 months, a serious and/or unstable disease affecting nasal function, unilateral nasal symptoms and/or patients with a history of immunotherapy.

Questionnaires

Both the mini Rhinoconjunctivitis Quality-of-Life Questionnaire (mini-RQLQ) and a questionnaire assessing use and success rate of nasal medication were sent to patients' home address.

Mini-RQLQ questionnaire

The mini-RQLQ was used to assess quality of life in AR and NAR patients and healthy controls. This questionnaire was primarily developed to assess QoL in AR and includes 14 questions divided into 5 subdomains assessing daily activities, practical issues, complaints of nose and eyes.

Validation of the RQLQ for NAR

The psychometric properties of the questionnaire, reliability, validity, responsiveness and clinically significant change have been described for AR (22). Because symptomatology of NAR and AR is quite similar, we expected the content of the mini-RQLQ to be valid for NAR patients. Internal reliability was measured estimated by calculating Cronbach's α. Test-retest reliability was not measured because we did not expect it to be different from AR patients. We determined convergent construct validity by comparing the outcomes of the mini-RQLQ in NAR patients to the ARIA classification.

The discriminant construct validity was determined by comparing the NAR patients group to healthy controls. The clinically significant change was expected to be comparable to AR and not evaluated separately for the NAR group (13).

Nasal medication questionnaire

To assess the use of nasal medication in NAR and AR, patients completed a questionnaire concerning present and past medication in the last 2 years, assessing number and type of medication use, rate of improvement of different treatment modalities and overall treatment satisfaction with current treatment. Patients were asked if they were on medication at the moment of filling in the questionnaire and/or in the previous years. Subsequently, they filled in the name of (a) currently used medicament(s) and -if applicable- the name(s) of medicaments they used in the past. As a supplement, we attached a list of allergy and nasal drugs in case patients forgot the name of their medicament. We included space for "description in own words." Per medicament patients had to tick a box for "duration of use" and "rate of improvement." Duration of use was classified as: incidentally, less than 4 weeks, 1-6 months and more than 6 months. Rate of improvement was classified as: no improvement, small improvement, large improvement and no more symptoms.

Finally, patients had to tick a box whether they were satisfied or unsatisfied with their treatment.

Statistics

The Kolmogorov-Smirnov test showed that data of the mini-RQLQ results were not normally distributed. Therefore, a Mann-Whitney U test was used to compare mini-RQLQ results between AR and NAR patients and between NAR and healthy controls. A general linear model (GLM) analysis was performed to assess the influence of patient characteristics age and sex on outcome results of QoL. Chi-square test was used to compare AR and NAR nonresponders and responders according to ARIA classification. Fisher's exact test was performed to compare type and rate of improvement of treatment modalities between AR and NAR.

RESULTS

Validation of mini-RQLQ in NAR

Because symptomatology of NAR and AR is quite similar, we expected the content of the mini-RQLQ to be valid for NAR patients. Non-allergic rhinitis (NAR) patients indeed had comparable outcomes to AR in the different domains of the questionnaire. The Cronbach's α of 0.883 indicated high internal consistency between mini-RQLQ outcomes within the NAR patient group. A test-retest analysis in 36 patients demonstrated a Pearson's correlation coefficient of 0.717 with a significance level of $P <$

.0001. Previously performed language validation of the (mini-)RQLQ showed that its Dutch translation is adequately adapted to be used in the Dutch population (23). The convergent construct validity showed higher values in the mini-RQLQ in patients with moderate to severe symptoms as defined by the ARIA classification than patients with mild symptoms. On all subdomains of the mini-RQLQ, NAR patients had significantly higher outcomes compared to healthy controls (Table 1).

Table 1. Mini-rhinoconjunctivitis quality of life questionnaire (Mini-RQLQ) in non-allergic rhinitis (NAR) versus healthy controls

	NAR, n=160		Healthy, n=49		NAR vs Healthy
Mini – RQLQ domains	**Median (range)**	**Mean (SD)**	**Median (range)**	**Mean (SD)**	**Mann – Whitney U test (p)**
Activitities	2.67 (0.00 – 6.00)	2.63 (1.58)	0.00 (0.00 – 3.33)	0.46 (0.84)	< 0.0001
Practical problems	3.00 (0.50 – 6.00)	3.04 (1.50)	0.00 (0.00 – 4.50)	0.67 (1.01)	< 0.0001
Nose symptoms	2.67 (0.33 – 6.00)	2.84 (1.28)	0.33 (0.00 – 3.00)	0.49 (0.76)	< 0.0001
Eye symptoms	1.00 (0.00 – 6.00)	1.52 (1.70)	0.00 (0.00 – 4.33)	0.35 (0.76)	< 0.0001
Other symptoms	2.17 (0.00 – 6.00)	2.47 (1.72)	0.67 (0.00 – 2.67)	0.71 (0.79)	< 0.0001
Overall	2.36 (0.29 – 5.64)	2.46 (1.20)	0.43 (0.00 – 2.57)	0.53 (0.62)	< 0.0001

Response rate

We selected AR and NAR patients who fulfilled the inclusion and exclusion criteria based on ENT history and examination from our database of patients who visited our outpatient clinic with symptoms of rhinitis and/or allergy and who received a skin prick test. This resulted in 556 allergic rhinitis patients and 329 non-allergic rhinitis patients. The questionnaires were sent to these patients home address followed by a reminder a month later. Patients who did not return the questionnaire after the first postal reminder were repeatedly tried to be reached by postal mail, telephone and/or email. 31 AR and 19 NAR patients were untraceable (“sample loss”) because of changed address, telephone number and/or email. In AR 216 and in NAR 108 patients did not respond (not to the postal questionnaire nor to postal, email, or telephone reminders). 22 AR and 42 NAR patients refused to participate. Finally, completed questionnaires of 287 AR (response rate 54.7%) and 160 NAR (response rate 51.6%) patients were analysed.

Patient characteristics

Table 2 shows the patient characteristics of both patient groups. Patients with AR and NAR had a comparable mean age. Distribution by ARIA (Allergic Rhinitis and its Impact on Asthma) classification concerning duration and severity of symptoms was also comparable between the two groups. In the NAR group, a significant higher proportion of patients smoked (21.3% vs 13.9%, P = .046, chi-square test, without Yates correction). In the AR group, there was a higher proportion of patients with asthma than in the NAR group (16.4% vs 7.5%, P = .008, chi-square test, without Yates correction).

Table 2. Patient characteristics

	NAR, *n*=160	**AR, *n*=287**
Male: female	1: 2.1	1: 1.2
Mean age	47.4	42.4
Smoking (%)	34 (21.3%)	40 (13.9%)
Asthma (%)	12 (7.5%)	47 (16.4%)
ARIA grading	Moderate-severe persistent 115/151 (76.2%)	Moderate-severe persistent 204/279 (73.1%)
Perennial sensitization	Not applicable	218
House dust mite	Not applicable	156
Strictly seasonal sensitzation	Not applicable	69

Questionnaire outcomes

Mini-RQLQ outcome

Table 3 shows the results of impairment of QoL as assessed by means of the mini-RQLQ-questionnaire. A higher score means a higher level of impairment indicating a lower QoL. Non-allergic rhinitis (NAR) patients had an overall trend of having higher mini-RQLQ scores than AR (P=.053). Non-allergic rhinitis (NAR) patients were significantly more bothered by nasal complaints. Other complaints such as tiredness and lack of sleep were also more prominent in NAR patients. A general linear model (GLM) analysis did not show a significant influence of age and gender on QoL results in both patient groups. A separate analysis per mini-RQLQ domain comparing NAR and AR patients is shown in Table 4. Non-allergic rhinitis (NAR) patients have significantly higher scores for blocked and running nose compared to AR patients.

Table 3. Mini-rhinoconjunctivitis quality of life questionnaire (Mini-RQLQ) in non-allergic rhinitis (NAR) versus allergic rhinitis (AR)

	NAR, *n*=160		AR, *n*=287		NAR vs AR
Mini – RQLQ domains	**Median (range)**	**Mean (SD)**	**Median (range)**	**Mean (SD)**	**Mann – Whitney U test (p)**
Activities	2.67 (0.00 – 6.00)	2.63 (1.58)	2.33 (0.00 – 6.00)	2.39 (1.68)	0.116
Practical problems	3.00 (0.50 – 6.00)	3.04 (1.50)	2.50 (0.00 – 6.00)	2.71 (1.67)	0.056
Nose symptoms	2.67 (0.33 – 6.00)	2.84 (1.28)	2.33 (0.00 – 6.00)	2.49 (1.52)	0.005
Eye symptoms	1.00 (0.00 – 6.00)	1.52 (1.70)	1.33 (0.00 – 6.00)	1.70 (1.62)	0.095
Other symptoms	2.17 (0.00 – 6.00)	2.47 (1.72)	1.67 (0.00 – 6.00)	1.91 (1.55)	0.001
Overall	2.36 (0.29 – 5.64)	2.46 (1.20)	2.07 (0.00 – 5.50)	2.21 (1.24)	0.053

Table 4. Mini-rhinoconjunctivitis quality of life questionnaire (mini-RQLQ) domain scores in non-allergic rhinitis (NAR) versus allergic rhinitis (AR)

	NAR (n=160)		AR (n=287)		
	Median (range)	**Mean (SD)**	**Median (range)**	**Mean (SD)**	**NAR vs AR Mann-Whitney U test (P)**
1. Activities	2.67 (0.00 – 6.00)	2.63 (1.58)	2.33 (0.00 – 6.00)	2.39 (1.68)	0.116
Regular activities at home and at work	3.00 (0.00 – 6.00)	2.71 (1.74)	3.00 (0.00 – 6.00)	2.64 (1.91)	0.631
Recreational activities	3.00 (0.00 – 6.00)	2.68 (1.81)	2.00 (0.00 – 6.00)	2.47 (1.93)	0.232
Sleep	3.00 (0.00 – 6.00)	2.50 (2.01)	2.00 (0.00 – 6.00)	2.06 (2.08)	0.023
2. Practical problems	3.00 (0.50 – 6.00)	3.04 (1.50)	2.50 (0.00 – 6.00)	2.71 (1.66)	0.056
Need to rub nose/ eyes	3.00 (0.00 – 6.00)	2.66 (1.88)	3.00 (0.00 – 6.00)	2.76 (1.99)	0.622
Need to blow nose repeatedly	3.50 (0.00 – 6.00)	3.42 (1.65)	3.00 (0.00 – 6.00)	2.67 (1.87)	< 0.001
3. Nose symptoms	2.67 (0.33 6.00)2	.84 (1.28)	2.33 (0.00 6.00)	2.49 (1.52)	0.005
Sneezing	2.00 (0.00 – 6.00)	2.43 (1.75)	2.00 (0.00– 6.00)	2.50 (1.84)	0.802

Table continued

Stuffy blocked mose	3.00 (0.00 – 6.00)	3.50 (1.78)	3.00 (0.00 – 6.00)	2.80 (2.04)	< 0.001
Runny nose	3.00 (0.00 – 6.00)	2.58 (1.94)	2.00 (0.00 – 6.00)	2.14 (1.93)	0.022
4. Eye symptoms	1.00 (0.00 6.00)	1.52 (1.70)	1.33 (0.00 – 6.00)	1.70 (1.61)	0.095
Itchy eyes	1.00 (0.00 – 6.00)	1.59 (1.81)	2.00 (0.00 – 6.00)	2.09 (2.00)	0.008
Sore eyes	0.00 (0.00 – 6.00)	1.36 (1.85)	0.00 (0.00 – 6.00)	1.42 (1.89)	0.561
Watery eyes	1.00 (0.00 – 6.00)	1.58 (2.04)	1.00 (0.00 – 6.00)	1.57 (1.85)	0.577
5. Other symptoms	2.17 (0.00 6.00)	2.47 (1.72)	1.67 (0.00 – 6.00)	1.91 (1.55)	0.001
Tiredness and/or fatigue	3.00 (0.00 6.00)	2.99 (2.00)	2.00 (0.00 – 6.00)	2.55 (1.97)	0.022
Thirst	2.00 (0.00 6.00)	2.19 (2.06)	1.00 (0.00 – 6.00)	1.50 (1.81)	0.001
Feeling irritable	2.00 (0.00 6.00)	2.23 (2.07)	1.00 (0.00 – 6.00)	1.70 (1.89)	0.009

Medication questionnaire outcome

Table 5 shows the proportion of AR and NAR patients using medication now or in the past. Non-allergic rhinitis (NAR) patients used significantly less medication than AR patients. In NAR, 71.6% used only one medicament, 20.9% used two medicaments, and 7.5% used three medicaments. In AR, 60.3% used only one medicament, 27.8% used two medicaments, and 11.9% used three medicaments. Table 6 shows the four most frequent used nasal drugs at the moment of filling in the questionnaire for both AR and NAR. Corticosteroid nasal spray and antihistamine tablets were the most frequent used drugs in AR, compared to corticosteroid nasal spray and xylometazoline in NAR. A significant higher proportion of AR patients used anti-histamine tablets compared to NAR (P = .0001). Treatment satisfaction was not significantly different (Fisher's exact test, P = .6588) between AR and NAR. Both AR and NAR patients were not very satisfied with their current treatment with a treatment satisfaction rate of 43.3% in NAR and 47.0% in AR.

Table 5. Use of medication

Use of medication	NAR, n = 160 Number of patients (%)	AR, n = 287 Number of patients (%)	Fisher's Exact Test (p)
Current use	67 (41.9%)	151 (52.6%)	0.0305
No current use but use of medication last two years	43 (26.9%)	82 (28.6%)	0.7423
Only use of medication > 2 years ago	23 (14.4%)	25 (8.7%)	0.0791
Never used medication	27 (16.9%)	29 (10.1%)	0.0518

Table 6. Type of medication

Type of medication	NAR *n* (% of patients currently on medication) *	AR *n* (% of patients currently on medication) *	Fisher's Exact Test *(p)*
Corticosteroid nasal spray	57 (85.1%)	107 (70.9%)	0.0273
Xylometazoline	16 (23.9%)	22 (14.6%)	0.1210
Antihistamine tablet	6 (9.0%)	67 (44.4%)	0.0001
Antihistamine nasal spray	2 (3.0%)	4 (2.6%)	1.0000
Other	10 (14.9%)	29 (19.2%)	0.5663

* A proportion of patients used more than one medicament

DISCUSSION

There have been a substantial number of studies assessing several social-economic aspects, including QoL in AR, in contrast to NAR (24). This is the first study assessing QoL in NAR patients with a validated questionnaire. Until now, there was no validated questionnaire to assess QoL in NAR patients. In this study, we performed a validation of the mini-RQLQ in NAR patients, showing a high discriminant construct validity (strongly significant higher outcomes in the NAR group compared to healthy controls), a Cronbach's alpha indicating strong internal consistency and a high convergent construct validity by comparing the mini-RQLQ in NAR to the ARIA classification. Use of the (now validated for NAR) mini-RQLQ questionnaire showed that the QoL in NAR patients is equally -and for some aspects even more- impaired compared to AR, emphasizing the need for adequate treatment in NAR.

For the mini-RQLQ subdomains "nasal complaints" and "other complaints" (ie, tiredness), NAR scored significantly higher compared to AR. The subdomain "practical problems" nearly reached significance with a higher burden in NAR. Only, for the subdomain "eye complaints," AR scored slightly higher compared to NAR, as expected.

One might explain the higher impairment of nasal symptoms, practical problems, etc. in NAR by the lack of effective treatment options in this patient group, because of lack of knowledge of underlying pathophysiology. The higher impairment of eye symptoms in AR can be explained by the fact that allergic conjunctivitis is an intrinsic feature of AR (19).

Interpretation of these QoL results seems complicated by the fact that not all AR patients were allergen exposed during the time of completion of the questionnaire. Unfortunately, this was inevitable because some patients did not respond directly but after several reminders. However, assessment of mini-RQLQ scores in AR patients with and without allergen exposure surprisingly did not show significant differences between the two, not even in strictly seasonal AR patients. This might be influenced by the fact that around half of patients were using medication at time of filling in the questionnaire, independent of allergen exposure. Whether patients were not using medication because of mild symptoms or because of severe symptoms unresponsive to treatment remains an almost impossible question to answer. This study was combined with an assessment of the use of numbers and types of (nasal) medication and the (subjective) efficacy of these medications in the different patient groups.

The "use of medication" questionnaire showed that a smaller proportion of NAR patients use medication for their symptoms compared to AR.

This is likely to be the result of a lack of effective treatment options in this difficult to treat patient group, also shown in a treatment satisfaction rate of 43.3%. Also, AR patients have a less than 50% treatment satisfaction. Looking at these results, it is necessary to keep in mind that we are assessing an academic (thirdline) patient group, with a risk of selecting more treatment-resistant AR patients. For NAR patients, it is possible that referral to an ENT clinic will happen sooner when atopy cannot be demonstrated by the GP and nasal (corticosteroid) spray is unsuccessful. One can speculate that comparing AR and NAR in a general population, the difference in QoL and treatment satisfaction will be even larger.

Assessing the numbers of patients using different types of medication, one notices that most NAR patients end up with the longterm use of a corticosteroid nasal spray. A proportion of 23.9% of NAR patients admits to use xylometazoline (Table 6). Unknown is the duration and frequency of use of this medicament in these individuals and thereby whether one can define these patients as actual "rhinitis medicamentosa." Moreover, for some patients, there was a (small) time gap between this ENT assessment at the outpatient clinic and the completion of the questionnaire, allowing a change in use of medication to take place.

Concluding, these results demonstrate a clinically relevant impairment in both AR and NAR patients in their QoL combined with a low treatment satisfaction, emphasizing the need for adequate treatment. This is especially of importance in the NAR patient group where lack of understanding of its underlying mechanism hampers finding adequate treatment solutions.

REFERENCES

1. Papadopoulos NG et al. Phenotypes and endotypes of rhinitis and their impact on management: a PRACTALL report. Allergy. 2015;70(5):474-94.

2. Bousquet J et al. Important research questions in allergy and related diseases: nonallergic rhinitis: a GA2LEN paper. Allergy. 2008;63(7):842-53.

3. Bousquet J et al. Unmet needs in severe chronic upper airway disease (SCUAD). The Journal of allergy and clinical immunology. 2009;124(3):428-33.

4. Molgaard E et al. Differences between allergic and nonallergic rhinitis in a large sample of adolescents and adults. Allergy. 2007;62(9):1033-7.

5. Van Gerven L et al. Up-date on neuro-immune mechanisms involved in allergic and non-allergic rhinitis. Rhinology. 2012;50(3):227-35.

6. Segboer CL et al. Nasal hyper-reactivity is a common feature in both allergic and nonallergic rhinitis. Allergy. 2013;68(11):1427-34.

7. Chawes BL et al. Children with allergic and nonallergic rhinitis have a similar risk of asthma. The Journal of allergy and clinical immunology. 2010;126(3):567-73.e1-8.

8. Hakansson K et al. Nonallergic rhinitis and its association with smoking and lower airway disease: A general population study. American journal of rhinology & allergy. 2011;25(1):25-9.

9. Kim SW et al. Bronchial hyperresponsiveness in pediatric rhinitis patients: the difference between allergic and nonallergic rhinitis. American journal of rhinology & allergy. 2013;27(3):e63-8.

10. Rondon C et al. Nonallergic rhinitis and lower airway disease. Allergy. 2017;72(1):24-34.

11. Hellings PW et al. Non-allergic rhinitis: Position paper of the European Academy of Allergy and Clinical Immunology. Allergy. 2017.

12. Gevorgyan A et al. Capsaicin for non-allergic rhinitis. The Cochrane database of systematic reviews. 2015;7:CD010591.

13. van Oene CM et al. Quality-assessment of disease-specific quality of life questionnaires for rhinitis and rhinosinusitis: a systematic review. Allergy. 2007;62(12):1359-71.

14. Canonica GW et al. A survey of the burden of allergic rhinitis in Europe. Allergy. 2007;62 Suppl 85:17-25.

15. Baiardini I et al. ARIA-suggested drugs for allergic rhinitis: what impact on quality of life? A GA2LEN review. Allergy. 2008;63(6):660-9.

16. Droessaert V et al. Real-life study showing better control of allergic rhinitis by immunotherapy than regular pharmacotherapy. Rhinology. 2016;54(3):214-20.

17. Fokkens WJ. Rhinitis, not to sniff at. Rhinology. 2016;54(3):193-4.

18. Gelardi M et al. Quality of life in non-allergic rhinitis depends on the predominant inflammatory cell type. J Biol Regul Homeost Agents. 2008;22(1):73-81.

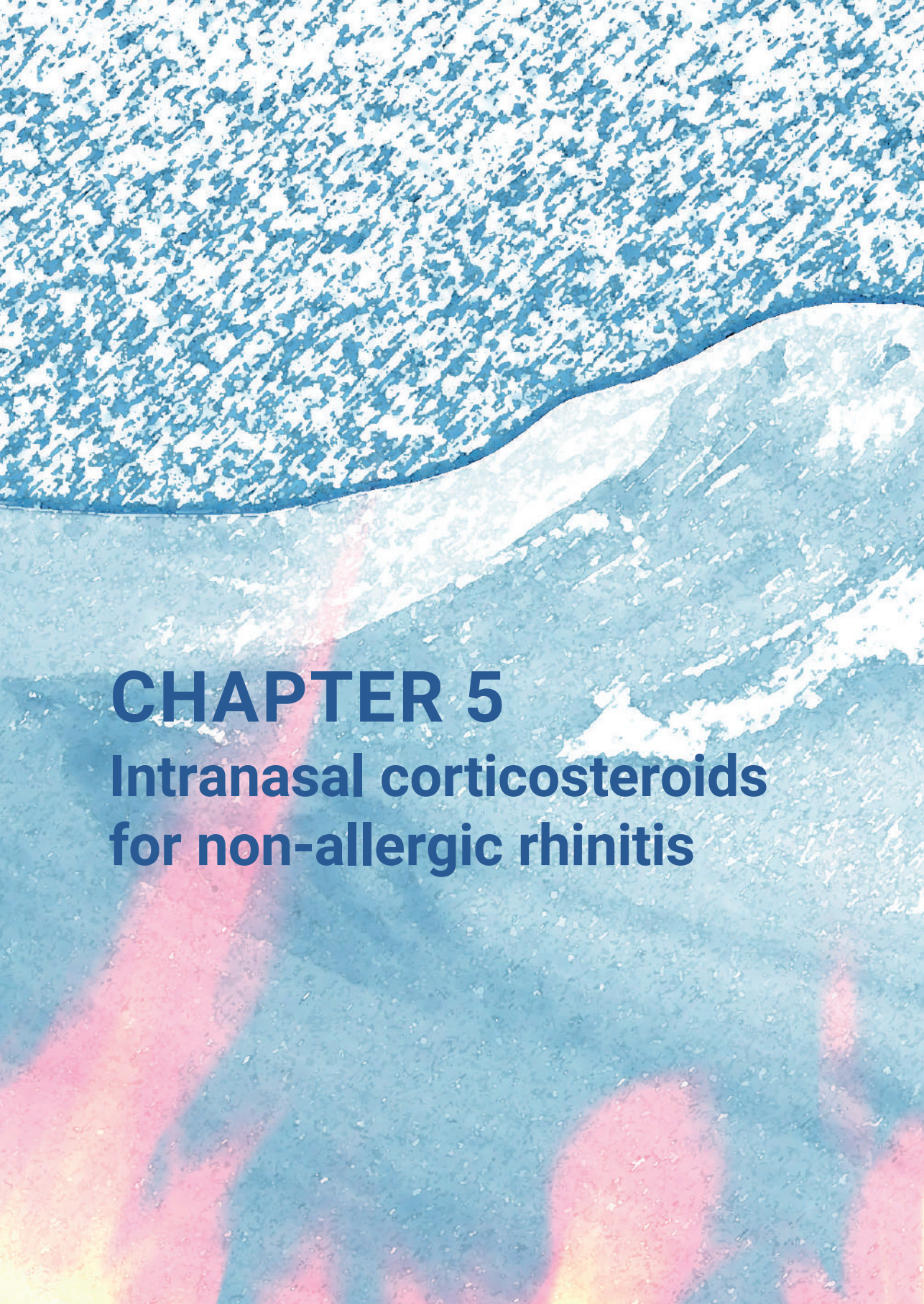
19. Kalpaklioglu AF et al. Allergic and nonallergic rhinitis: can we find the differences/similarities between the two pictures? J Asthma. 2009;46(5):481-5.

20. Juniper EF et al. Validation of the standardized version of the Rhinoconjunctivitis Quality of Life Questionnaire. J Allergy Clin Immun. 1999;104(2):364-9.

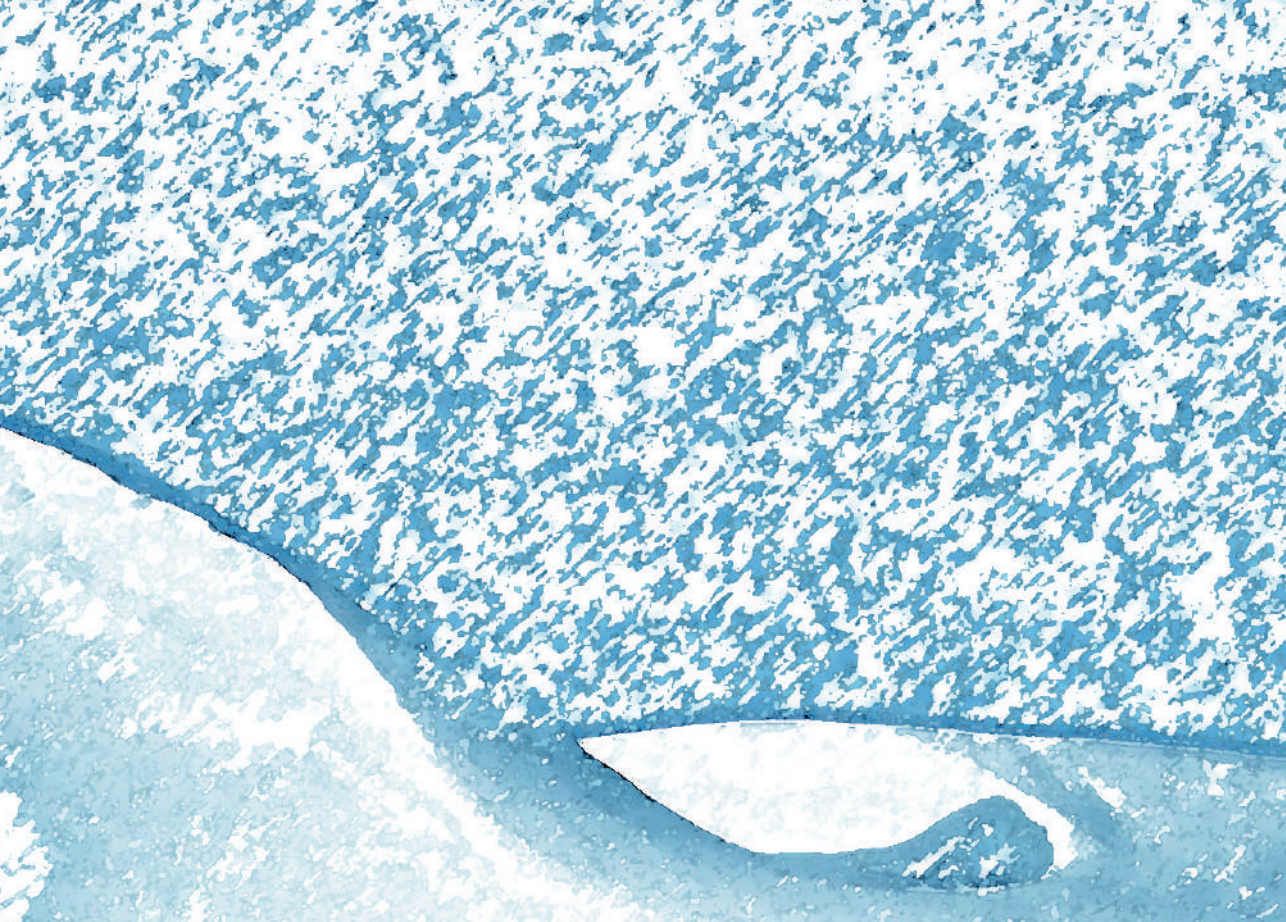
21. Heinzerling L et al. Standard skin prick testing and sensitization to inhalant allergens across Europe—a survey from the GALEN network. Allergy. 2005;60(10):1287-300.

22. Juniper EF et al. Development and validation of the mini Rhinoconjunctivitis Quality of Life Questionnaire. Clinical and experimental allergy: journal of the British Society for Allergy and Clinical Immunology. 2000;30(1):132-40.

23. Del Cuvillo A et al. Allergic rhinitis severity can be assessed using a visual analogue scale in mild, moderate and severe. Rhinology. 2017;55(1):34-8



CHAPTER 5
Intranasal corticosteroids for non-allergic rhinitis



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ABSTRACT

Background

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

Objectives

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

Search methods

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

Selection criteria

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

Data collection and analysis

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

Main results

We included 34 studies (4452 participants); however, only 13 studies provided data for our main comparison, intranasal corticosteroids versus placebo. The participants

were mainly defined as patients with perennial rhinitis symptoms and negative allergy tests. No distinction between different pheno- and endotypes could be made, although a few studies only included a specific phenotype such as pregnancy rhinitis, vasomotor rhinitis, rhinitis medicamentosa or senile rhinitis. Most studies were conducted in a secondary or tertiary healthcare setting. No studies reported outcomes beyond three months follow-up. Intranasal corticosteroid dosage in the review ranged from 50 µg to 2000 µg daily.

Intranasal corticosteroids versus placebo

Thirteen studies (2045 participants) provided data for this comparison. These studies used different scoring systems for patient-reported disease severity, so we pooled the data in each analysis using the standardised mean difference (SMD). Intranasal corticosteroid treatment may improve patient-reported disease severity as measured by total nasal symptom score compared with placebo at up to four weeks (SMD -0.74, 95% confidence interval (CI) -1.15 to -0.33; 131 participants; 4 studies; I^2 = 22%) (low-certainty evidence). Between four weeks and three months the evidence is very uncertain (SMD -0.24, 95% CI -0.67 to 0.20; 85 participants; 3 studies; I^2 = 0%) (very low-certainty evidence). Intranasal corticosteroid treatment may not mprove patient-reported disease severity as measured by total nasal symptom score change from baseline when compared with placebo at up to four weeks (SMD -0.54, 95% CI -1.18 to 0.10); 1465 participants; 4 studies; I^2 = 96%) (low-certainty evidence).

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

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

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

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

Intranasal corticosteroids versus other treatments

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

Authors' conclusions

Overall, the certainty of the evidence for most outcomes in this review was low or very low. It is unclear whether intranasal corticosteroids reduce patient-reported disease severity in non-allergic rhinitis patients compared with placebo when measured at up to three months.

However, intranasal corticosteroids probably have a higher risk of adverse effects such as epistaxis. There are very few studies comparing intranasal corticosteroids to other treatment modalities making it difficult to draw conclusions.

PLAIN LANGUAGE SUMMARY

Intranasal corticosteroids for non-allergic rhinitis

Review question

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

Background

Non-allergic rhinitis is a chronic disease of the nose, which is not caused by infection or allergies. People with non-allergic rhinitis experience symptoms that affect their quality of life, such as nasal obstruction, runny nose and sneezing. Non-allergic rhinitis patients can be divided into different subgroups who have different underlying causes for their disease. The underlying causes of non-allergic rhinitis are not fully understood, therefore treatment is often unsuccessful in these patients.

Topical (intranasal) corticosteroids are used with the aim of reducing inflammation. They are the most commonly prescribed drug in other chronic diseases of the nose

and sinuses, such as allergic rhinitis and chronic rhinosinusitis. Intranasal corticosteroid treatment can be delivered with sprays or drops and for different time periods.

Study characteristics

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

Key results

Intranasal corticosteroids compared with placebo

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

Intranasal corticosteroids compared with other treatments

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

Certainty of the evidence

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

Summary of findings

Intranasal corticosteroids compared to placebo for non-allergic rhinitis

Intranasal corticosteroids compared to placebo for non-allergic rhinitis							
Patient or population: adults and children > 12 with non-allergic rhinitis **Setting:** secondary/tertiary health care **Intervention:** intranasal corticosteroids **Comparison:** placebo							
Outcomes		**Anticipated absolute effects*** **(95% CI)**		**Relative effect (95% CI)**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
		Risk with placebo	**Risk with intranasal corticosteroids**				
Disease severity as mesured by patient-reported symptom score (total nasal symptom score)	Follow-up ≤ 4 weeks	—	SMD 0.74 lower (1.15 lower to 0.33 lower)	—	131 (4 RCTs)	⨁⨁⨀⨀ **low**[1]	Intranasal corticosteroids may improve patient-reported disease severity at a follow-up of up to 4 weeks compared to placebo. The mean difference in disease severity score was 0.74 standard deviations lower (1.15 lower to 0.33 lower) with intranasal corticosteroids compared to placebo. This represents a medium effect size (Cohen 1988).
	Follow-up > 4 weeks	—	SMD 0.24 lower (0.67 lower to 0.20 higher)	—	85 (3 RCTs)	⨁⨀⨀⨀ **very low**[2]	It is uncertain whether intranasal corticosteroids improve patient-reported disease severity with a follow-up of more than 4 weeks compared to placebo, because the certainty of the evidence is very low.
	Change from baseline Follow-up ≤ 4 weeks	—	SMD 0.15 lower (0.25 lower to 0.05 lower)	—	1465 (4 RCTs)	⨁⨁⨀⨀ **low**[3]	Intranasal corticosteroids may slightly improve patient-reported disease severity change from base- line with a follow-up of up to 4 weeks compared to placebo. The SMD of 0.15 represents a small ef-fect size. There are two large studies (Jacobs 2009; Webb 2002). Jacobs 2009 reports with a high degree of certainty a small improvement in favour of intranasal corticosteroids. Webb 2002 reports a less certain clinically relevant improvement in favour of intranasal corticosteroids. Jacobs 2009 has an adjusted SD value (presented SD are most likely SEM).

Significant adverse event: epistaxis Follow-up: 2 weeks to 33 days	Study population		RR 2.10 (1.24 to 3.57)	1174 (4 RCTs)	⊕⊕⊕⊖ **moderate**[4]	There is probably a higher risk of epistaxis with intranasal steroids compared to placebo.
	(31 per 1000)	65 per 1000 (39 to 111)				
Disease-specific health-related quality of life Short Form 12 (SF-12v2) (range 0 to 800) Follow-up: 1 month to 3 months	Just one study reported quality of life (Lin 2017). Quality of life was better in the intranasal corticosteroids group versus the placebo group, however while this difference was significant at a follow-up of 1 month (152.3 versus 145.6) it was barely noticeable at a follow-up of 3 months (148.4 versus 145.6).			49 (1 RCT)	⊕⊕⊖⊖ **low**[5]	There is not enough information (1 study) to conclude whether there is a difference.
Objective measurement of airflow: peak flow rate (expiratory) Follow-up: 2 weeks to 4 weeks	Just 2 studies reported objective measurement of airflow (Malm 1981; Spector 1980). However, they used different outcome measurements to measure outflow: rhinomanometry and expiratory peak flow rate (PEFR). Neither found a significant difference between groups: rhinomanometry (Malm 1981) (SMD -0.46, 95% CI -1.06 to 0.14; 44 participants); PEFR (Spector 1980) SMD 0.78, 95% CI -0.47 to 2.03; 11 participants).			55 (2 RCTs)	⊕⊖⊖⊖ **very low**[6]	There is not enough information (2 studies with different methods of measurement) to conclude whether there is a difference.
Other adverse events Follow-up: 1 month to 6 weeks	Study population		RR 0.99 (0.87 to 1.12)	1130 (3 RCTs)	⊕⊕⊕⊖ **moderate**[7]	Intranasal corticosteroids probably result in little or no difference in the risk of other adverse events compared to placebo.
	454 per 1000	450 per 1000 (395 to 509)				
*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI). **CI:** confidence interval; **RCT:** randomised controlled trial; **RR:** risk ratio; **SD:** standard deviation; **SEM:** standard error of the mean; **SMD:** standardised mean difference						

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

[1]Due to the small sample size we downgraded once for imprecision and once due to the risk of publication bias. The I^2 value in this pooled analysis was 22% so there was no reason to downgrade for heterogeneity.
[2]We downgraded twice for serious imprecision due to the small sample size and because the confidence interval includes both meaningful benefit and harm. We downgraded once for risk of publication bias due to the small sample size.
[3]We downgraded twice for serious inconsistency because the I^2 value is 96% and the confidence intervals for Jacobs 2009 and Webb 2002 do not overlap. Jacobs 2009 has an unlikely SD value, which does not match the mean, n and P values. It is likely that the SD value presented should actually be a standard error of the mean (SEM).
[4]We downgraded once due to study limitations (risk of bias) because there were unclear blinding domains, which could have influenced the significant adverse events (epistaxis) outcome. The I^2value in this pooled analysis is 0% so there is no reason to downgrade for heterogeneity. We judged that there were no other reasons to downgrade.
[5]Due to the small sample size we downgraded once for imprecision and once due to the risk of publication bias.
[6]We downgraded once for inconsistency (when the two studies are combined the I^2 value is 67%). The two studies used different methods for measuring objective airflow, which contributed to the heterogeneity. Due to the small sample size we downgraded once for imprecision and once due to the risk of publication bias.
[7]We downgraded once due to study limitations (risk of bias) as there were unclear blinding domains, which could have influenced the adverse events outcome. The I^2 value in the pooled analysis is 0% so there is no reason to downgrade for heterogeneity. We judged that there were no other reasons to downgrade.

BACKGROUND

Description of the condition

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

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

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

In the case of medication-induced rhinitis (rhinitis medicamentosa), several medications have been implicated (Varghese 2010). The most common is the misuse of topical sympathomimetics (e.g. oxyor xylometazoline) for more than 10 days, resulting

in dysregulation of the adrenergic receptors in the nasal mucosa and a relative increase of the parasympathetic drive, leading to significant rhinorrhoea and nasal obstruction. These symptoms cause the patients to continue using topical adrenergics, perpetuating a vicious cycle. Treatment is usually focused on cessation of the affecting agent, as well as support with intranasal corticosteroids.

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

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

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

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

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

Some medications are particularly useful in specific types of non-allergic rhinitis. Specifically, ipratropium bromide is mostly used in the treatment of rhinitis of the elderly, due to its alleviation of the main symptom, rhinorrhoea (van Rijswijk 2005). Intranasal antihistamines are usually prescribed when sneezing is the main symptom 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 trials (van Rijkwijk 2003, Ciabatti 2009).

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

Description of the intervention

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

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

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

How the intervention might work

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

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

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

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

Why it is important to do this review

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

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

OBJECTIVES

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

METHODS

Criteria for considering studies for this review

Types of studies

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

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

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

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

Types of participants

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

We excluded studies that included a majority of patients with:

- Allergic rhinitis;
- Infectious rhinitis;
- Acute or chronic rhinosinusitis;
- Auto-immune rhinitis;
- Rhinitis related to anatomical abnormalities.

Types of interventions

Intervention

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

First-generation intranasal corticosteroids:

- Beclomethasone dipropionate
- Triamcinolone acetonide
- Flunisolide
- Budesonide

Second-generation intranasal corticosteroids:

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

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

Comparisons

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

The main comparison pair was:

- Intranasal corticosteroids *versus* placebo

Other possible comparison pairs included:

- Intranasal corticosteroids *versus* saline irrigation
- Intranasal corticosteroids *versus* intranasal antihistamine
- Intranasal corticosteroids *versus* capsaicin
- Intranasal corticosteroids *versus* sodium cromoglycate
- Intranasal corticosteroids *versus* ipratropium

Types of outcome measures

Primary outcomes

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

Secondary outcomes

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

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

Search methods for identification of studies

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

Electronic searches

The Information Specialist searched:

- The Cochrane ENT Register (searched via the Cochrane Register of Studies 1 July 2019)

- The Cochrane Central Register of Controlled Trials (CENTRAL 2019, Issue 7) (searched via the Cochrane Register of Studies 1 July 2019)
- PubMed (1946 to 1 July 2019)
- Ovid EMBASE (1974 to 1 July 2019)
- EBSCO CINAHL (1982 to 1 July 2019)
- Ovid CAB Abstracts (1910 to 1 July 2019)
- LILACS (Latin American and Caribbean Health Science Information database), lilacs.bvsalud.org (searched 1 July 2019)
- Web of Science (1945 to 1 July 2019)
- ClinicalTrials.gov (searched via the Cochrane Register of Studies and clinicaltrials.gov 1 July 2019)
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP), www.who.int/ictrp (searched 1 July 2019)

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

Searching other resources

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

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

Data collection and analysis

Selection of studies

We merged the identified studies using the Covidence online reference management software. We removed any duplicate records of the same report.

Two authors (AG and CS, a rhinology fellow and a junior otorhinolaryngology trainee, respectively) independently examined the titles and abstracts of the studies and removed obviously irrelevant reports. We then retrieved the full texts of potentially

relevant articles. We linked multiple reports of the same study together. The same two authors independently examined the full-text reports for compliance of the studies with the eligibility criteria. We contacted the study authors, where appropriate, to clarify study eligibility. The two authors then independently made final decisions on study inclusion. Any disagreements on study inclusion were resolved by discussion. If necessary, disagreement was resolved by arbitration of a third author (KS). We noted the primary reason for exclusion.

Data extraction and management

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

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

Assessment of risk of bias in included studies

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

- Sequence generation
- Allocation concealment
- Blinding
- Incomplete outcome data
- Selective outcome reporting and
- Other sources of bias

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

Measures of treatment effect

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

Unit of analysis issues

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

Dealing with missing data

We recorded all missing data on the data collection form and reported this in the 'Risk of bias' tables. Whenever possible, we contacted the original investigators to request missing data and information for our risk of bias assessments.

Imputing total symptom scores

We planned to adopt the strategy outlined by Chong et al to deal with missing total disease severity outcomes (Chong 2016). Where a paper did not present information for the total disease severity in terms of patient-reported symptom scores but did present data for the results of individual symptoms, we used the symptoms rhinorrhoea, blockage and sneezing to calculate a total symptom score. Where mean final values or changes from baseline were presented in the paper for the individual symptoms we summed these to calculate a 'total symptom score'. We calculated standard deviations for the total symptom score as if the symptoms were independent, random variables that were normally distributed. We acknowledge that there is likely to be a degree of correlation between the individual symptoms, however we used this process because the magnitude of correlation between the individual symptoms is not currently well understood (no evidence found). If the correlation is high, the summation of variables as discrete variables is likely to give a conservative estimate of the total variance of the summed final score. If the correlation is low, this method of calculation will underestimate the standard deviation of the total score. However, the

average patient-reported symptom scores have a correlation coefficient of about 0.5; if this is also applicable to non-allergic rhinitis, the method used should have minimal impact (Balk 2012). As this method of calculation does not take into account weighting of different symptoms (no evidence found), we downgraded all the disease severity outcomes for lack of use of validated scales whenever this occurred.

Assessment of heterogeneity

To assess the heterogeneity of effect size across pooled studies, we calculated the I^2 statistic in RevMan 5. We did not plan to perform a meta-analysis if heterogeneity was considered substantial (50% to 90%) or considerable (75% to 100%), but because the study Jacobs 2009 is one of the most well-known and largest studies on the topic, we decided to include this study in the meta-analysis (with a random-effects model) although this results in high (I^2 = 96%) heterogeneity. The most likely reason for this high heterogeneity is explained in detail in the Results section.

Assessment of reporting biases

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

Data synthesis

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

Subgroup analysis and investigation of heterogeneity

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

- Different types of intranasal corticosteroids (type A versus type B)

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

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

Sensitivity analysis

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

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

GRADE and 'Summary of findings' table

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

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

- Study limitations (risk of bias)
- Inconsistency
- Indirectness of evidence
- Imprecision
- Publication bias

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

RESULTS

Description of studies

See Characteristics of included studies; Characteristics of excluded studies.

Results of the search

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

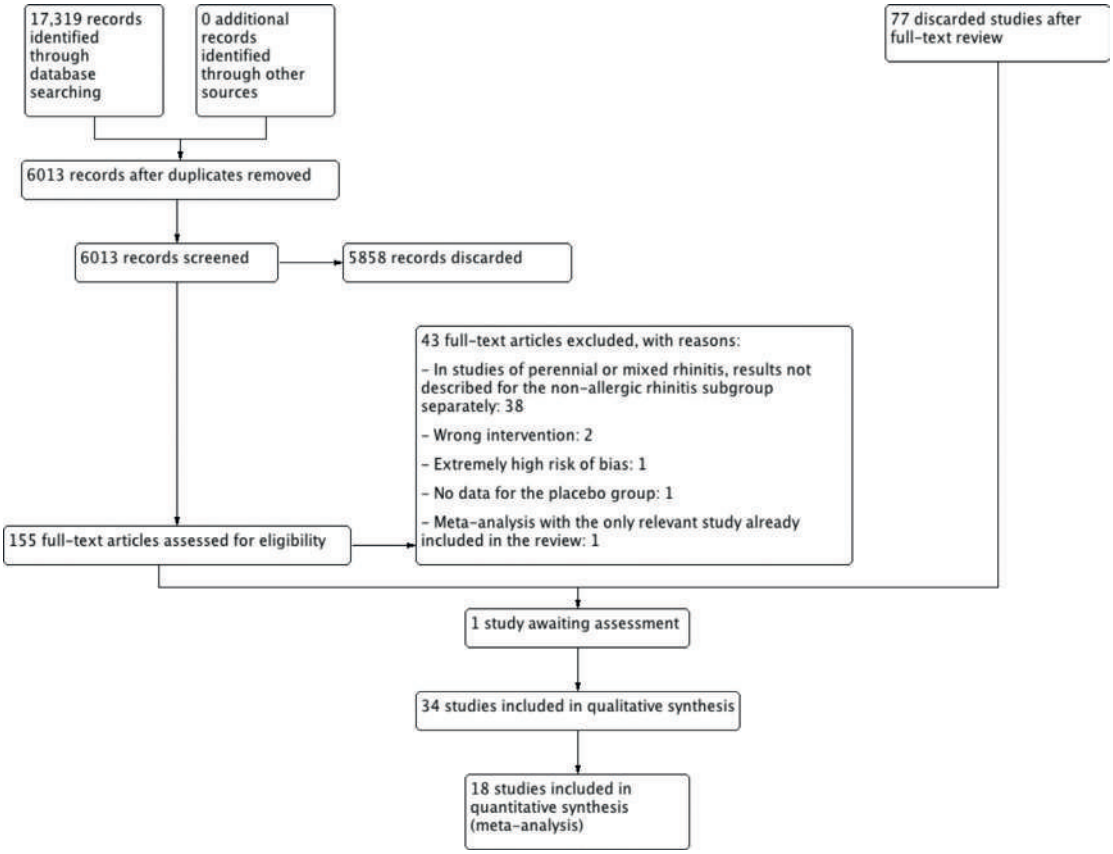

Figure 1. Process for sifting search results and selecting studies for inclusion

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

We did not identify any ongoing studies. One study is awaiting assessment (NCT04002349). This study is a randomised, open-label clinical trial comparing both nasal saline, intranasal corticosteroid, intranasal antihistamine and combination therapy in non-allergic rhinitis patients. The expected completion date of the study is 31 March 2020 (see Characteristics of studies awaiting classification).

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

Included studies

We included 34 studies in this review (Arikan 2006; Balle 1982; Behncke 2006; Boechat 2019; Blom 1997; Day 1990; Ellegård 2001; Guo 2015; Hallén 1997; Havas 2002; Hillas 1980; Incaudo 1980; Jacobs 2009; Jessen 1990; Kalpaklioglu 2010; Lin 2017; Löfkvist 1976; Lundblad 2001; Malm 1976; Malm 1981; Meltzer 1994; Miller 1969; O'Reilly 1991; Scadding 1995; Schulz 1978; Singh 2017; Song 2018; Spector 1980; Tantilipikorn 2010; Tarlo 1977; Turkeltaub 1982; Varricchio 2011; Warland 1982; Webb 2002). See Characteristics of included studies.

Design

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

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

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

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

Sample size

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

Setting

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

Participants

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

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

2001 was a study of pregnancy rhinitis in females. Behncke 2006 studied rhinitis symptoms in geriatric patients.

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

Description of non-allergic rhinitis in included patients

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

Interventions

Comparisons

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

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

Two studies compared azelastine combined with an intranasal corticosteroid to an intranasal corticosteroid alone (Guo 2015; Song 2018). One study compared

azelastine combined with fluticasone propionate to placebo (Singh 2017). Another study compared intranasal corticosteroids with capsaicin (Havas 2002).

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

Types of steroids

Fluticasone propionate was the most commonly used intranasal corticosteroid and was the main intervention in 10 studies (Arikan 2006; Behncke 2006; Blom 1997; Ellegård 2001; Guo 2015; Hallén 1997; Meltzer 1994; Scadding 1995; Singh 2017; Webb 2002). It was used in total daily doses (calculated as a sum of total dose for both nostrils) of 200 µg (Arikan 2006; Blom 1997; Ellegård 2001; Hallén 1997; Scadding 1995; Singh 2017; Webb 2002) or 400 µg daily (Blom 1997; Scadding 1995; Webb 2002). Singh 2017 and Guo 2015 used a combination of fluticasone propionate and azelastine. The length of treatment varied from two weeks to three months. Arikan 2006 used treatment for three months; Blom 1997, Blom 1997 and Ellegård 2001 for eight weeks; Guo 2015 for six weeks; Hallén 1997 and Singh 2017 for two weeks; Scadding 1995 for 12 weeks; and Webb 2002 for four weeks.

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

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

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

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

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

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

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

Steroid dosage

Different doses of the same intranasal corticosteroids were used in six studies in addition to the placebo comparison (Balle 1982; Blom 1997; Malm 1976; Malm 1981; Scadding 1995; Webb 2002). Balle 1982 used budesonide at daily doses of 200 µg and 400 µg in a cross-over study design. Blom 1997 (parallel-group study) used fluticasone propionate respectively 200 µg once daily and twice daily in different regimens: a) fluticasone propionate 200 µg once daily and placebo once daily for eight weeks; b) fluticasone propionate 200 µg once daily and placebo once daily for four weeks followed by fluticasone propionate 200 µg twice daily for four weeks; and c) fluticasone propionate 200 µg twice daily for eight weeks. Malm 1976 used 200 µg, 400 µg and 800 µg daily doses of beclomethasone dipropionate in a cross-over study design. Malm 1981, in comparison to the previous study, used budesonide at daily doses of 50 µg, 200 µg or 800 µg, also in a cross-over study design. Webb 2002 (parallel-group study) used fluticasone propionate respectively at 200 µg and 400 µg daily dosage. Finally, Scadding 1995 used both different doses of fluticasone and another intranasal corticosteroid beclomethasone. Specifically, they used fluticasone propionate 200 µg once daily, 200 µg twice daily and beclomethasone dipropionate 200 µg twice daily for 12 weeks.

Rescue medication

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

Outcomes

Primary outcomes

Disease severity as measured by patient-reported symptom score

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

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

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

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

Significant adverse events: epistaxis

Eight studies reported on the significant adverse event 'epistaxis' (Arikan 2006; Incaudo 1980; Jacobs 2009; Lin 2017; Lundblad 2001; Malm 1981; Scadding 1995; Tantilipikorn 2010). In almost all studies this adverse event was reported as the number of cases of epistaxis at the end of follow-up, either actively asked for by the investigator and/or spontaneously reported by the patient or recorded daily in a diary or on a question

form (Jacobs 2009). Scadding 1995 only mentioned "generally minor adverse events" and reported no explicit numbers.

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

Secondary outcomes

Disease-specific health-related quality of life

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

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

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

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

Other adverse events: local irritation, discomfort

Nineteen studies included 'adverse events' (besides epistaxis) as an outcome (Arikan 2006; Day 1990; Incaudo 1980; Jacobs 2009; Jessen 1990; Kalpaklioglu 2010; Lin 2017; Lundblad 2001; Malm 1976; Malm 1981; Miller 1969; O'Reilly 1991; Scadding 1995; Song 2018; Spector 1980; Tantilipikorn 2010; Tarlo 1977; Turkeltaub 1982; Varricchio 2011). In almost all studies these adverse events were reported as the number of cases of adverse events at the end of follow-up, either actively asked for by the investigator and/or spontaneously or recorded daily by the patient in a diary or on a question form (Day 1990; Jacobs 2009). Of these studies four were included in the meta-analysis (Jacobs 2009; Lundblad 2001; Song 2018; Tantilipikorn 2010). The studies that were not included in the meta-analysis either did not report data on non-allergic rhinitis patients separately, did not report numerical data or were excluded from the meta-analysis for other reasons (for example, too low or too high an intranasal corticosteroid dosage or unclear dosage subgroup).

Excluded studies

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

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

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

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

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

We also excluded 38 studies that were performed in patients with perennial rhinitis and did not present results for the non-allergic rhinitis subgroup separately (Adamopoulos

1995; Arbesman 1983; Balle 1982b; Basran 1995; Berger 2012; Bernstein 1997; Blair 1977; Bunnag 1992; Chatterjee 1974; Dieges 1978; Dockhorn 1999; Gibson 1974; Hansen 1974; Harding 1976; Hartley 1985; Haye 1993; Jones 1979; Joubert 1983; Juniper 1993; Kakumanu 2003; Kivisaari 1998; Kohan 1989; Lahdensuo 1977; Lau 1990; Lebowitz 1993; Malmberg 1988; McAllen 1969; McAllen 1980; Negreiros 1975; Price 2013; Rusnak 1981; Scadding 1991; Shaw 1979; Svendsen 1989; Sy 1979; Turner Warwick 1980; Webb 1977; Weckx 2001; Wight 1992). We contacted the authors of the studies in an attempt to obtain these results, without success.

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

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

Risk of bias in included studies

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

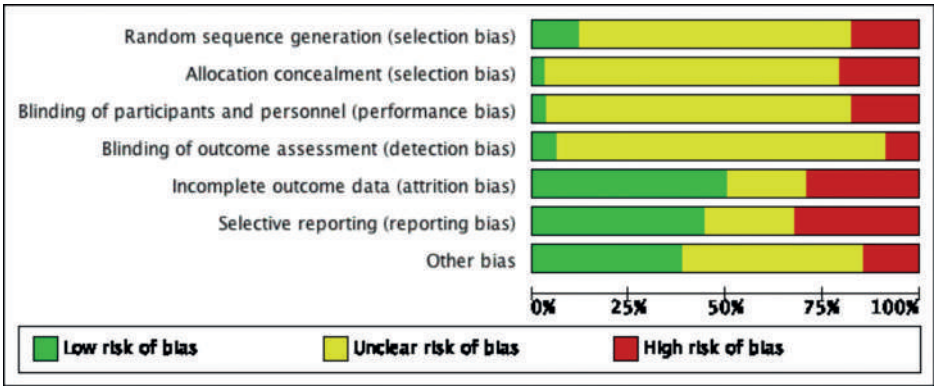

Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

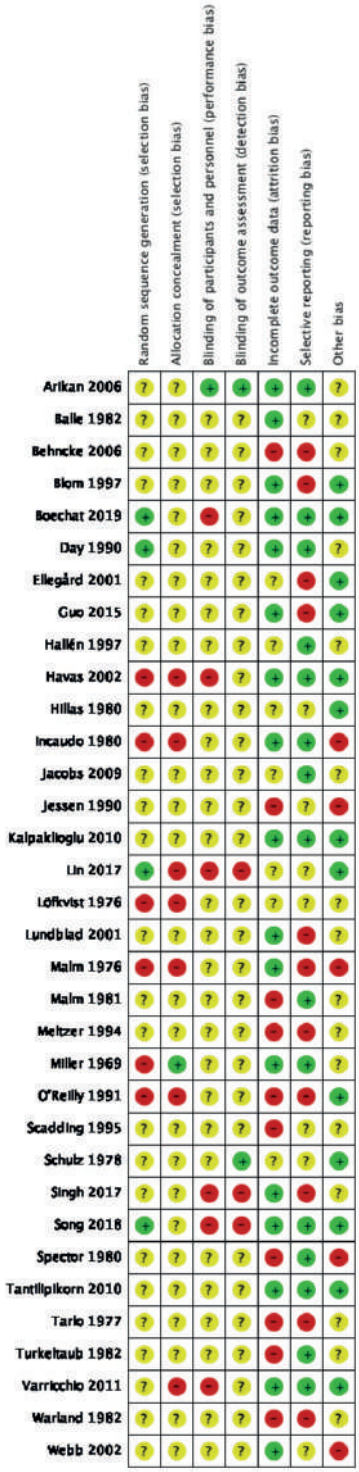

Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study

Allocation

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

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

Blinding

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

Incomplete outcome data

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

Selective reporting

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

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

Other potential sources of bias

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

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

Effects of interventions

See Summary of findings table 1 for the main comparison: 'Intranasal corticosteroids versus placebo'.

Intranasal corticosteroids versus placebo

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

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

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

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

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

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

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

Up to four weeks follow-up

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

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

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

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

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

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

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

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

Change from baseline, up to four weeks follow-up

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

These studies showed that patients treated with intranasal corticosteroids had no difference in total nasal symptom scores compared to placebo (SMD -0.54, 95% CI -1.18 to 0.10; 1465 participants; 4 studies; I^2 = 96%) (Analysis 1.3) (low-certainty evidence). This represents a medium effect size. We used a random-effects model due to the high heterogeneity.

The very high heterogeneity in this analysis is mainly driven by Jacobs 2009. Removing this study reduces the heterogeneity to 0%. Without Jacobs 2009 there is an improvement in favour of intranasal corticosteroids (SMD -0.23, 95% CI -0.37 to -0.09) (without Jacobs 2009 we used a fixed-effect model because of the low heterogeneity). The Jacobs 2009 study reports a very unlikely standard deviation (SD) value that does not match with the presented means, n and P values. The data would make more sense if the standard deviation (SD) presented values were actually standard error of the mean (SEM), which was confirmed by a re-analysis. As Jacobs 2009 is one of the larger and also one of the most well-known and frequently cited studies, we decided to keep the study included in the meta-analysis. Converting the as-presented SD values into SEM values does change the outcome of this individual study (i.e. no effect of intranasal corticosteroids), but it does not significantly change the overall outcome of this comparison ('Total nasal symptom score change from baseline, up to four weeks follow-up'), which is in favour of intranasal corticosteroids (SMD -0.15, 95% CI -0.25 to -0.05; 1465 participants; 4 studies; I^2 = 35%).

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

Webb 2002 also reports an improvement in favour of intranasal corticosteroids, however this is less certain than in Jacobs 2009. The amount of improvement is more clinically relevant than in Jacobs 2009, i.e. around a 10% improvement in total nasal symptom score. In general, the data from Webb 2002 seem to be far more reliable than the data from Jacobs 2009.

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

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

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

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

Significant adverse events: epistaxis

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

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

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

Three studies reported on epistaxis but were not included in the meta-analysis because the study did not report numerical data for the non-allergic rhinitis subgroup (Scadding 1995), due to lack of quality of the study (Lin 2017), or because no events were observed in either group (Arikan 2006). Scadding 1995 reported "generally minor" adverse events in the intranasal corticosteroids group and Lin 2017 reported two cases of epistaxis in a total group of 22 patients treated with budesonide versus no cases of epistaxis in the placebo group. Arikan 2006 reported no epistaxis in either the intervention group or the control group.

Disease-specific health-related quality of life

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

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

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

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

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

Hallén 1997 was not included in the meta-analysis as it compared intranasal corticosteroids versus placebo in a single separate subgroup of non-allergic rhinitis patients, i.e. participants with rhinitis medicamentosa. Hallén 1997 reported both acoustic rhinometry and PNIF after 13 days of treatment. The mean acoustic rhinometry outcome in the intranasal corticosteroids group was 0.28 cm^2 (SD 0.19) and the mean acoustic rhinometry outcome in the placebo group was 0.03 cm^2 (SD 0.17) (SMD -1.34, 95% CI -0.35 to -2.33). The mean PNIF outcome in the intranasal corticosteroids group was 121.2 L/min (SD 69.0) and the mean PNIF outcome in the placebo group was 128.7 L/min (SD 40.4) (SMD -0.13, 95% CI -0.75 to 1.00), i.e. there was no significant difference.

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

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

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

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

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

Other adverse events

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

Three studies included in the meta-analysis reported on 'other adverse events' besides epistaxis (Jacobs 2009; Lundblad 2001; Tantilipikorn 2010). We decided to combine the three studies and not to make a separation into up to four weeks and more than four weeks follow-up. Intranasal corticosteroids probably result in little or no difference in the risk of other adverse events compared to placebo (RR 0.99, 95% CI 0.87 to 1.12; 1130 participants; 3 studies; I^2 = 0%) (Analysis 1.7) (moderate-certainty evidence).

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

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

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

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

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

Subgroups and phenotypes

Within the comparison of intranasal corticosteroids versus placebo there were not enough data to perform a subgroup analysis for different subgroups/phenotypes of non-allergic rhinitis. Ellegård 2001evaluated intranasal corticosteroids in pregnancy rhinitis patients (see also under 'Objective measurement of airflow'). Overall, the study did not find a beneficial effect of intranasal corticosteroids over placebo. Hallén 1997 evaluated intranasal corticosteroids in rhinitis medicamentosa patients (see also 'Objective measurement of airflow'). They concluded that the symptom scores for nasal stuffiness showed a marked reduction during the treatment period in both groups, but there was a faster onset of symptom reduction after treatment with fluticasone propionate.

Intranasal corticosteroids versus saline

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

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

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

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

Significant adverse events: epistaxis

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

Disease-specific health-related quality of life

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

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

The study did not report objective measurements of nasal airflow.

Other adverse events

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

Intranasal corticosteroids versus intranasal antihistamine

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

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

In Song 2018, there was a non-significant difference in combined nasal symptom VAS score in favour of budesonide nasal spray (mean difference (MD) -0.25, 95% CI -0.69 to 0.19; 80 participants) (Analysis 2.1).

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

Significant adverse events: epistaxis

Epistaxis was not evaluated.

Disease-specific health-related quality of life

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

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

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

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

Other adverse events

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

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

Intranasal corticosteroids versus capsaicin

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

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

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

Significant adverse events: epistaxis

Epistaxis was not evaluated.

Disease-specific health-related quality of life

Quality of life was not evaluated.

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

Objective measurements of airflow were not evaluated.

Other adverse events

Other adverse events were not evaluated.

Intranasal corticosteroids versus sodium cromoglycate

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

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

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

Significant adverse events: epistaxis

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

Disease-specific health-related quality of life

Quality of life was not evaluated.

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

Objective measurements of airflow were not evaluated.

Other adverse events

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

Intranasal corticosteroids versus ipratropium bromide

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

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

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

Significant adverse events: epistaxis

Epistaxis was not evaluated.

Disease-specific health-related quality of life

Quality of life was not evaluated.

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

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

Other adverse events

No other adverse events were evaluated.

Intranasal corticosteroids versus intranasal corticosteroids combined with intranasal antihistamine

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

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

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

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

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

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

Guo 2015 reported a small but significant difference in total nasal symptom score (unclear scale and range) in favour of fluticasone dipropionate nasal spray combined

with azelastine after six weeks of treatment (SMD 0.37, 95% CI 0.06 to 0.68; 162 participants) (Analysis 5.1).

Song 2018 also reported a significant difference in total symptom VAS score (range 0 to 10) in favour of budesonide nasal spray combined with azelastine after eight weeks of treatment (SMD 0.75, 95% CI 0.48 to 1.02; 80 participants) (Analysis 5.1).

Significant adverse events: epistaxis

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

Disease-specific health-related quality of life

In Guo 2015, quality of life was not evaluated.

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

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

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

Other adverse events

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

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

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

Singh 2017 compared intranasal corticosteroids combined with azelastine to placebo instead of intranasal corticosteroids. It could not be included in the meta-analysis

because the total nasal symptom score was not reported numerically. Total nasal symptom score and objective measurement of airflow were both related to cold dry air provocation. The study did report that there were no statistically significant differences between the two treatments.

Intranasal corticosteroids versus intranasal corticosteroids combined with saline irrigation

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

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

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

Significant adverse events: epistaxis

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

Disease-specific health-related quality of life

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

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

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

Other adverse events

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

Intranasal corticosteroids with saline spray versus saline spray alone

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

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

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

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

Significant adverse events: epistaxis

The study reported no adverse events.

Disease-specific health-related quality of life

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

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

The peak nasal inspiratory flow (PNIF) measurements showed no significant difference between intranasal corticosteroid spray combined with isotonic saline spray (72.9 L/min (SD 25.5)) and isotonic nasal spray alone (82.1 L/min (SD 39.8)) after two weeks (MD -9.20, 95% CI -33.96 to 15.56; 28 participants) (Analysis 6.3). Pre-treatment PNIF for intranasal corticosteroid spray combined with isotonic saline spray was 77.1 (SD 25.8) and for nasal spray alone was 90.7 (SD 38.5). The reduction was non-significant (P = 0.688).

Other adverse events

The study reported no adverse events.

DISCUSSION

Summary of main results

See Summary of findings table 1.

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

Intranasal corticosteroids versus placebo

We were only able to identify a significant number of studies (25) for the main comparison, intranasal corticosteroids versus placebo; 13 of these studies could be included in the meta-analysis. However, the evidence was limited by the fact that most studies had only small numbers of patients and there was a high degree of variance in their results. The two largest studies did show a significant improvement in symptom scores (Jacobs 2009; Webb 2002). However, the study data in Jacobs 2009 are unlikely to be credible. The study presented very unlikely standard deviation (SD) values, which did not match the presented mean, n and P values, resulting in very high heterogeneity of the data for the outcome 'Total nasal symptom score, change from baseline'. Most likely the SD values should have been standard error of the mean (SEM) values, as was confirmed by re-analysis. The study authors did not reply to our questions about the data. If the as-presented SD values are actually SEM, the overall effect size in favour of intranasal corticosteroids for this comparison is only small.

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

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

One study assessed quality of life (Lin 2017). This study showed that quality of life was better in the intranasal corticosteroids group compared to the placebo group. However, while this difference was significant at one-month follow-up it was barely noticeable at three-month follow-up. Lin 2017 was not included in the meta-analysis because of lack of quality of the study data. Firstly, the study presents unexpected data with disappearance of benefit of intranasal corticosteroids with longer follow-up. Secondly, including the study in the meta-analysis resulted in a high level of heterogeneity. Finally, the SD values that are presented in the study do not match with presented means,

n and P values. The data make more sense if the as-presented SD values should actually be standard error of the mean (SEM), which was confirmed by a re-analysis.

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

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

Other comparisons

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

Three studies compared an intranasal corticosteroid with an intranasal corticosteroid combined with an intranasal antihistamine. Two studies reported a significant difference in favour of intranasal corticosteroids combined with an intranasal antihistamine versus intranasal corticosteroids alone (Guo 2015; Song 2018). The difference in favour of the combined treatment strategy in these two studies was significant [pooled result not shown in 'Effects of interventions']. The third study reported no statistically significant differences between the two treatments (Singh 2017).

Overall completeness and applicability of evidence

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

Quality of life, which is one of the most important outcomes for patients, was only included in three studies as an outcome measure (Boechat 2019; Lin 2017; Song 2018).

There is too little information, therefore, to establish whether intranasal steroids have an impact on patients' quality of life.

Quality of the evidence

The certainty of the evidence (GRADE assessment) for our primary outcome, disease severity as measured by patient-reported symptom score (total nasal symptom score), was in general low because most studies had small participant numbers resulting in high imprecision and high risk of publication bias. One of the only two studies with a large number of participants was Jacobs 2009. Unfortunately this study contributed to the very high heterogeneity in the study data because of unlikely standard deviation values that were most likely to be standard error of the mean values.

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

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

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

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

Potential biases in the review process

The primary outcome total nasal symptom score consisted of different nasal symptoms in different studies, measured on different measurement scales. When only individual nasal symptom scores were reported but no total nasal symptom score, we calculated a total nasal symptom scores for rhinorrhoea (secretion), nasal obstruction (blockage) and sneezing: the most common symptoms used to calculate a total nasal symptom score in the other included studies (Table 1). We decided not to include itching, as a previous study by our research group has shown that ocular itch plays a

less dominant role in non-allergic rhinitis compared to allergic rhinitis (Segboer 2018). However, given that itching was included in the total nasal symptom score of a few other studies, this may have resulted in a potential bias.

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

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

In the meta-analysis we included only studies with an intranasal corticosteroid dosage range of 200 µg to 400 µg. The reason for this was to prevent double counting of the same patients or controls (see Differences between protocol and review). This leads to a potential bias in the review as the meta-analysis is limited to certain dosages. However, only one study was excluded from the meta-analysis because of this dosage limitation (Varricchio 2011).

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

Agreements and disagreements with other studies or reviews

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

AUTHORS' CONCLUSIONS

Implications for practice

For people with non-allergic rhinitis and clinicians

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

For those funding health care

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

Implications for research

Evidence

As of July 2019, we have identified 34 studies that investigated the use of intranasal corticosteroids in non-allergic rhinitis. The studies were generally small, included different pheno-and endotypes of non-allergic rhinitis, and used different outcome

measurements for patient-reported disease severity at up to four weeks. The evidence identified indicates that there may be benefits in terms of patient-reported disease severity when compared with placebo but the range of unvalidated instruments used, along with heterogeneity in the study characteristics, made it difficult to draw definite conclusions.

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

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

Population

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

Intervention and comparison

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

Outcomes

- Studies should focus on outcomes that are important to patients with non-allergic rhinitis (symptom scores, quality of life) and use validated instruments to measure these, in particular using standard, validated, patient-reported disease severity

scores and disease-specific health-related quality of life scores (e.g. the (mini) Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ))

- The duration of the trial needs to be carefully considered. The current evidence only includes trials that had up to a three-month treatment duration. A duration of follow-up of 12 months is more likely to be meaningful given the chronicity of the condition
- Trials and other high-quality studies should use consistent outcomes and adhere to reporting guidelines, so that results can be compared across future trials. The development of a standardised set of outcomes, or core outcome set, for non-allergic rhinitis, agreed by researchers, clinicians and patients, would facilitate this process

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REFERENCES TO STUDIES

Included studies

Arikan 2006

Arikan OK, Koc C, Kendi T, Muluk NB, Ekici A. CT assessment of the effect of fluticasone propionate aqueous nasal spray treatment on lower turbinate hypertrophy due to vasomotor rhinitis. Acta Oto-Laryngologica 2006;126(1):37-42.

Balle 1982

Balle VH. The effect of budesonide in perennial rhinitis. European Journal of Respiratory Diseases. Supplement 1982;122:197-204.

Behncke 2006

Behncke VB, Alemar G, Kaufman DA, Eidelman FJ. Azelastine nasal spray and fluticasone nasal spray in the treatment of geriatric patients with rhinitis. Journal of Allergy and Clinical Immunology 2006;2 Suppl 1:S263.

Blom 1997

Blom HM, Godthelp T, Fokkens WJ, KleinJan A, Mulder PG, Rijntjes E. The effect of nasal steroid aqueous spray on nasal complaint scores and cellular infiltrates in the nasal mucosa of patients with non-allergic, noninfectious perennial rhinitis. Journal of Allergy and Clinical Immunology 1997;100(6 Pt 1):739-47.

Boechat 2019

Published and unpublished data

* Boechat JL. Re: RBR-498bnq The evaluation of the effectiveness of mometasone furoate plus isotonic nasal saline in geriatric patients with rhinitis: a randomized clinical trial. Email to C Segboer 8 July 2019.

Carvalho V, Olej B, De Moraes JR, Boechat JL. Mometasone furoate plus isotonic nasal saline versus isotonic nasal saline alone in geriatric chronic rhinitis: an open-label, active comparator, randomized trial. Allergy 2019;74(S106):376-853 [abstract TP0672].

RBR-498bnq. The effectiveness of mometasone furoate plus isotonic nasal saline in the elderly with rhinitis. www.who.int/trialsearch/Trial2.aspx?TrialID=RBR-498bnq (first received January 2018). [CENTRAL: CN-01900661; CRS: 10800361; CRSREP: 10800361]

Day 1990

Day JH, Andersson CB, Briscoe MP. Efficacy and safety of intranasal budesonide in the treatment of perennial rhinitis in adults and children. Annals of Allergy 1990;64(5):445-50.

Ellegård 2001
Ellegård EK, Hellgren M, Karlsson NG. Fluticasone propionate aqueous nasal spray in pregnancy rhinitis. Clinical Otolaryngology and Allied Sciences 2001 Oct;26(5):394-400.

Guo 2015
Guo L, Sun X, Yang J, Liu J, Wang D. Clinical study of the combination therapy with intranasal antihistamine and nasal corticosteroids in the treatment of nasal obstruction of persistent non-allergic rhinitis. Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi 2015;29(3):243-51.

Hallén 1997
Hallén H, Enerdal J, Graf P. Fluticasone propionate nasal spray is more effective and has a faster onset of action than placebo in treatment of rhinitis medicamentosa. Clinical and Experimental Allergy 1997;27(5):552-8.

Havas 2002
Havas TE, Taplin MA. Intranasal neuropeptide depletion using topical capsaicin for the control of symptoms in non-allergic, non-infectious perennial rhinitis (NANIPER). Australian Journal of Otolaryngology 2002;5(2):107-13.

Hillas 1980
Hillas J, Booth RJ, Somerfield S, Morton R, Avery J, Wilson JD. A comparative trial of intra-nasal beclomethasone dipropionate and sodium cromoglycate in patients with chronic perennial rhinitis. Clinical Allergy 1980;10(3):253-8.

Incaudo 1980
Incaudo G, Schatz M, Yamamoto F, Mellon M, Crepea S, Johnson JD. Intranasal flunisolide in the treatment of perennial rhinitis: correlation with immunologic parameters. Journal of Allergy and Clinical Immunology 1980;65(1):41-9.

Jacobs 2009
Jacobs R, Lieberman P, Kent E, Silvey M, Locantore N, Philpot EE. Weather/temperature-sensitive vasomotor rhinitis may be refractory to intranasal corticosteroid treatment. Allergy and Asthma Proceedings 2009;30(2):120-7.

Jessen 1990
Jessen M, Bylander A. Treatment of non-allergic nasal hypersecretion with ipratropium and beclomethasone. Rhinology 1990;28(2):77-81.

Kalpaklioglu 2010
Kalpaklioglu AF, Kavut AB. Comparison of azelastine versus triamcinolone nasal spray in allergic and non-allergic rhinitis. American Journal of Rhinology & Allergy 2010;24(1):29-33.

Lin 2017
Lin L, Lu Q, Tang XY, Dai F, Wei JJ. Nasal irrigation for the treatment of vasomotor rhinitis: a pilot study. Zhonghua Er Bi Yan Hou Tou Jing Wai Ke za Zhi [Chinese Journal of Otorhinolaryngology Head and Neck Surgery] 2017;52:446-52.

Löfkvist 1976
Löfkvist T, Svensson G. Treatment of vasomotor rhinitis with intranasal beclomethasone dipropionate (Becotide). Results from a double-blind cross-over study. Acta Allergologica 1976;31(3):227-38.

Lundblad 2001
Lundblad L, Sipilä P, Farstad T, Drozdziewicz D. Mometasone furoate nasal spray in the treatment of perennial non-allergic rhinitis: a Nordic, multicenter, randomized, double-blind, placebo-controlled study. Acta Oto-Laryngologica 2001;121(4):505-9.

Malm 1976
Malm L, Wihl JA. Intra-nasal beclomethasone dipropionate in vasomotor rhinitis. Acta Allergologica 1976;31(3):245-53.

Malm 1981
Malm L, Wihl JA, Lamm CJ, Lindqvist N. Reduction of metacholine-induced nasal secretion by treatment with a new topical steroid in perennial non-allergic rhinitis. Allergy 1981;36(3):209-14.

Meltzer 1994
Meltzer EO. Is the successful control of perennial rhinitis achievable? European Respiratory Review 1994;20:266-70.

Miller 1969
Miller J. Aerosol corticosteroid treatment of vasomotor rhinitis. Eye, Ear, Nose & Throat Monthly 1969;48:292-7.

O'Reilly 1991
O'Reilly BJ, Kenyon GS. A double-blind, placebo-controlled trial of beclomethasone dipropionate 600 µg/day in the treatment of non-atopic rhinitis. Journal of Laryngology and Otology 1991;105:12-3.

Scadding 1995
Scadding GK, Lund VJ, Jacques LA, Richards DH. A placebo-controlled study of fluticasone propionate aqueous nasal spray and beclomethasone dipropionate in perennial rhinitis: efficacy in allergic and non-allergic perennial rhinitis. Clinical and Experimental Allergy 1995;25(8):737-43.

Schulz 1978
Schulz JI, Johnson JD, Freedman SO. Double-blind trial comparing flunisolide and placebo for the treatment of perennial rhinitis. Clinical Allergy 1978;8(4):313-20.

Singh 2017
Singh U, Bernstein JA, Lorentz H, Sadoway T, Nelson V, Patel P, et al. A pilot study investigating clinical responses and biological pathways of azelastine/fluticasone in non-allergic vasomotor rhinitis before and after cold dry air provocation. International Archives of Allergy and Immunology 2017;173:153-64.

Song 2018
Song K, Gong ZP, Ma YF, Chen Y. Therapeutic effect of nasal corticosteroids combined with nasal antihistamine on vasomotor rhinitis. Lin Chuang Er Bi Yan Hou Ke za Zhi [Journal of Clinical Otorhinolaryngology] 2018;32(23):1783-7.

Spector 1980
Spector SL, English G, Jones L. Clinical and nasal biopsy response to treatment of perennial rhinitis. Journal of Allergy and Clinical Immunology 1980;66(2):129-37.

Tantilipikorn 2010
Tantilipikorn P, Thanaviratananich S, Chusakul S, Benjaponpitak S, Fooanant S, Chintrakarn C, et al. Efficacy and safety of once daily fluticasone furoate nasal spray for treatment of irritant (non-allergic) rhinitis. Open Respiratory Medicine Journal 2010;4:92-9.

Tarlo 1977
Tarlo SM, Cockcroft DW, Dolovich J, Hargreave FE. Beclomethasone dipropionate aerosol in perennial rhinitis. Journal of Allergy and Clinical Immunology 1977;59(3):232-6.

Turkeltaub 1982
Turkeltaub PC, Norman PS, Johnson JD, Crepea S. Treatment of seasonal and perennial rhinitis with intranasal flunisolide. Allergy 1982;37(5):303-11.

Varricchio 2011
Varricchio A, Capasso M, De Luca A, Avvisati F, Varricchio AM, Bettoncelli G, et al. Intranasal flunisolide treatment in patients with non-allergic rhinitis. International Journal of Immunopathology and Pharmacology 2011;24(2):401-9.

Warland 1982
Warland A. Evaluation of flunisolide nasal solution in the symptomatic treatment of perennial rhinitis. Allergy 1982;6:417-20.

Webb 2002
Webb DR, Meltzer EO, Finn AF Jr, Rickard KA, Pepsin PJ, Westlund R, et al. Intranasal fluticasone propionate is effective for perennial non-allergic rhinitis with or without eosinophilia. Annals of Allergy, Asthma & Immunology 2002;88(4):385-90.

Excluded studies

Adamopoulos 1995
Adamopoulos G, Manolopoulos L, Giotakis I. A comparison of the efficacy and patient acceptability of budesonide and beclomethasone dipropionate aqueous nasal sprays in patients with perennial rhinitis. Clinical Otolaryngology and Allied Sciences 1995;4:340-4.

Arbesman 1983
Arbesman C, Bernstein IL, Bierman CW, Bocles JS, Katz R, Lieberman PL, et al. Multicenter, double-blind, placebo-controlled trial of fluocortin butyl in perennial rhinitis. Journal of Allergy and Clinical Immunology 1983;6:597-603.

Astafieva 2012
Astafieva NG, Udovichenko EN, Gamova IV, Perfilova IA. Treatment of non-allergic rhinitis symptoms: the estimation of effectiveness, safety and clinical equivalence of generics, containing fluticasone propionate [Лечение симптомов неаллергического ринита: оценка эффективности, безопасности и клинической эквивалентности генерика, содержащего флутиказона пропиона]. Lechashii Vrach 2012;9.

Balle 1982
Balle VH, Pedersen U, Engby B. The treatment of perennial rhinitis with a new non-halogenated, topical, aerosol packed steroid, budesonide. Acta Oto-Laryngologica 1982;1-2:169-73.

Berger 2012
Berger W, Shah S, Price D, Hadley J, Gever L, Bhatia S. Long-term safety and efficacy of mp29-02 (novel intranasal formulation of azelastine hydrochloride and fluticasone

propionate) in patients with chronic rhinitis. In: Annals of Allergy, Asthma and Immunology. Vol. 109. 2012:A130.

Bernstein 1997
Bernstein DI, Nolop K, Mesarina-Wicki B. Evaluation of mometasone furoate (Nasonex) nasal spray in perennial rhinitis. Annals of Allergy, Asthma & Immunology 1997;154.

Blair 1977
Blair H, Butler AG. The treatment of perennial rhinitis with intranasal beclomethasone dipropionate. The Practitioner 1977;1304:283-5.

Bunnag 1992
Bunnag C, Jareoncharsri P, Wong EC. A double-blind comparison of nasal budesonide and oral astemizole for the treatment of perennial rhinitis. Allergy 1992;47(4 Pt 1):313-7.

Celiker 2011
Celiker S, Rosenblad A, Wilhelmsson B. A radiofrequency vs topical steroid treatment of chronic nasal obstruction: a prospective randomized study of 84 cases. Acta Oto-Laryngologica 2011;131(1):79-83.

Chatterjee 1974
Chatterjee SS, Nassar WY, Wilson O, Butler AG. Intra nasal beclomethasone dipropionate and intra nasal sodium cromoglycate: a comparative trial. Clinical Allergy 1974;4:343-8.

Dieges 1978
Dieges PH, Heeringa A. A study of the clinical effects of intranasal beclometasone inhalation in chronic vasomotor rhinitis. Nederlands Tijdschrift voor Geneeskunde 1978;122(21):744-8.

Dockhorn 1999
Dockhorn R, Aaronson D, Bronsky E, Chervinsky P, Cohen R, Ehtessabian R, et al. Ipratropium bromide nasal spray 0.03% and beclomethasone nasal spray alone and in combination for the treatment of rhinorrhea in perennial rhinitis. Annals of Allergy, Asthma & Immunology 1999;4:349-59.

Gibson 1974
Gibson GJ, Maberly DJ, Lal S, Ali MM, Butler AG. Double-blind cross-over trial comparing intranasal beclomethasone dipropionate and placebo in perennial rhinitis. British Medical Journal 1974;4(5943):503-4.

Hansen 1974
Hansen I, Mygind N. Local effect of intranasal beclomethasone dipropionate aerosol in perennial rhinitis. Acta Allergologica 1974;4:281-7.

Harding 1976
Harding SM, Heath S. Intranasal steroid aerosol in perennial rhinitis: comparison with an antihistamine compound. Clinical Allergy 1976;4:369-72.

Hartley 1985
Hartley TF, Lieberman PL, Meltzer EO, Noyes JN, Pearlman DS, Tinkelman DG. Efficacy and tolerance of fluocortin butyl administered twice daily in adult patients with perennial rhinitis. Journal of Allergy and Clinical Immunology 1985;75(4):501-7.

Haye 1993
Haye R, Gomez EG. A multicentre study to assess long-term use of fluticasone propionate aqueous nasal spray in comparison with beclomethasone dipropionate aqueous nasal spray in the treatment of perennial rhinitis. Rhinology 1993;31(4):169-74.

Jones 1979
Jones LM, Spector SL, English GM, Taylor-Dawson K. Treatment of perennial rhinitis with flunisolide corticosteroid spray. Annals of Allergy 1979;3:139-44.

Joubert 1983
Joubert JR. Flunisolide nasal spray in the treatment of perennial rhinitis. South African Medical Journal 1983;16:623-4.

Juniper 1993
Juniper EF, Guyatt GH, Andersson B, Ferrie PJ. Comparison of powder and aerosolized budesonide in perennial rhinitis: validation of rhinitis quality of life questionnaire. Annals of Allergy 1993;3:225-30.

Kakumanu 2003
Kakumanu SS, Mende CN, Lehman EB, Hughes K, Craig TJ. Effect of topical nasal corticosteroids on patients with chronic fatigue syndrome and rhinitis. Journal of the American Osteopathic Association 2003;103(9):423-7.

Kivisaari 1998
Kivisaari E, Baker RC, Richards DH, Karia N, Price MJ. Comparison of fluticasone propionate aqueous nasal spray (FPANS) 200mcg once a day with budesonide intranasal turbuhaler 200mcg once a day and placebo in patients with perennial rhinitis. Journal of Allergy and Clinical Immunology 1998;101(1):S245.

Kohan 1989
Kohan D, Jacobs JB, Nass RL, Gonzalez S. Rhinomanometric evaluation of two nasal steroid sprays in rhinitis. Otolaryngology Head and Neck Surgery 1989;4:429-33.

Lahdensuo 1977
Lahdensuo A, Haahtela T. Efficacy of intranasal beclomethasone dipropionate in patients with perennial rhinitis and asthma. Clinical Allergy 1977;3:255-61.

Lau 1990
Lau SK, Wei WI, Van Hasselt CA, Sham CL, Woo J, Choa D, et al. A clinical comparison of budesonide nasal aerosol, terfenadine and a combined therapy of budesonide and oxymetazoline in adult patients with perennial rhinitis. Asian Pacific Journal of Allergy and Immunology 1990;8(2):109-15.

Lebowitz 1993
Lebowitz RA, Jacobs JB. Rhinomanometric and clinical-evaluation of triamcinolone acetonide and beclomethasone dipropionate in rhinitis. American Journal of Rhinology 1993;7(3):121-4.

Malmberg 1988
Malmberg H, Holopainen E, Grahne B, Lindqvist N. A clinical comparison between budesonide aqueous suspension and flunisolide pump spray in patients suffering from perennial rhinitis. Allergy 1988;Suppl 7:107, Abstract No. L 5.

McAllen 1969
McAllen MK, Langman MJ. A controlled trial of dexamethasone snuff in chronic perennial rhinitis. Lancet 1969;7602:968-71.

McAllen 1980
McAllen MK, Portillo PR, Parr EJ, Seaton A, Engler C. Intranasal flunisolide, placebo and beclomethasone dipropionate in perennial rhinitis. British Journal of Diseases of the Chest 1980;74(1):32-6.

Negreiros 1975
Negreiros EB, Filardi C. Preliminary observations on the intranasal use of beclomethasone dipropionate aerosol in 13 patients with rhinitis. Postgraduate Medical Journal 1975;51 Suppl 4:III.

Price 2013
Price D, Shah S, Bhatia S, Bachert C, Berger W, Bousquet J, et al. A new therapy (MP29-02) is effective for the long-term treatment of chronic rhinitis. Journal of Investigational Allergology & Clinical Immunology 2013;23(7):495-503.

Rusnak 1981
Rusnak SL. Concurrent administration of flunisolide nasal solution with beclomethasone dipropionate bronchial aerosol in patients with both rhinitis and asthma. Annals of Allergy 1981;5 Pt 1:320-4.

Scadding 1991
Scadding GK, Lund VJ, Holmstrom M, Darby YC. Clinical and physiological effects of fluticasone propionate aqueous nasal spray in the treatment of perennial rhinitis. Rhinology. Supplement 1991;11:37-43.

Shaw 1979
Shaw JD. Intra-nasal beclomethasone dipropionate in perennial rhinitis: a double-blind study. Journal of Pharmacotherapy 1979;2(1):41-3.

Small 1982
Small P, Black M, Frenkiel S. Effects of treatment with beclomethasone dipropionate in subpopulations of perennial rhinitis patients. Journal of Allergy and Clinical Immunology 1982;70(3):178-82.

Svendsen 1989
Svendsen UG, Frølund L, Madsen F, Mygind N, Nielsen NH, Weeke B. Beclomethasone dipropionate versus flunisolide as topical steroid treatment in patients with perennial rhinitis. Clinical Otolaryngology and Allied Sciences 1989;14(5):441-5.

Sy 1979
Sy RK. Flunisolide intranasal spray in the treatment of perennial rhinitis. Archives of Otolaryngology 1979;11:649-53.

Synnerstad 1996
Synnerstad B, Lindqvist N. A clinical comparison of intranasal budesonide with beclomethasone dipropionate for perennial non-allergic rhinitis: a 12 month study. British Journal of Clinical Practice 1996;50(7):363-6.

Turner Warwick 1980
Turner Warwick M. Double-blind trial comparing 2 dosage schedules of beclomethasone dipropionate aerosol with a placebo in the treatment of perennial rhinitis for 12 months. Clinical Allergy 1980;10(3):239-51.

Webb 1977
Webb AK. Beclomethasone dipropionate aerosol in perennial rhinitis: preliminary results of medical Research Council/Brompton Hospital Cooperative long-term study. British Journal of Clinical Pharmacology 1977;4(Suppl 3):281S.

Weckx 2001
Weckx LLM, Fujita RR, Pignatari SSN, Morato Castro FF, Mocellin M, Castro NP, et al. Randomized open-label comparative study between triamcinolone acetonide nasal spray versus beclometasone dipropionate in perennial rhinitis in adults [Estudo clínico aberto, randomizado, comparativo de spray nasal de acetonido de triancinoloma versus dipropionato de beclometasona em adultos com rinite perene]. Revista Brasileira de Medicina 2001;10:774-80.

Wight 1992
Wight RG, Jones AS, Beckingham E, Andersson B, Ek L. A double blind comparison of intranasal budesonide 400 micrograms and 800 micrograms in perennial rhinitis. Clinical Otolaryngology and Allied Sciences 17;4:354-8.

Zucker 2019
Zucker SM, Barton BM, McCoul ED. Management of rhinitis medicamentosa: a systematic review. Otolaryngology Head and Neck Surgery 2019;160(3):429-38.

References to ongoing studies

NCT04002349
ZhangL, MengY. Study of medication for non-allergic rhinitis (NAR) based on cluster analysis. https://clinicaltrials.gov/ct2/show/NCT04002349 (first received 28 June 2019).

Additional references

Ameille 2013
Ameille J, Hamelin K, Andujar P, Bensefa-Colas L, Bonneterre V, Dupas D, et al. Occupational asthma and occupational rhinitis: the united airways disease model revisited. Occupational and Environmental Medicine 2013 Feb 6 [Epub ahead of print].

Bachert 2008
Bachert C, Jorissen M, Betrand B, Khaltaev N, Bousquet J. Allergic rhinitis and it impact on asthma update (ARIA 2008). The Belgian perspective. B-ENT 2008;73:253-7.

Balk 2012
Balk EM, Earley A, Patel K, Trikalinos TA, Dahabreh IJ. Empirical assessment of within-arm correlation imputation in trials of continuous outcomes [Internet]. Report No.: 12(13)-EHC141-EF. Rockville (MD): Agency for Healthcare Research and Quality, 2012.

Basran 1995
Basran GS, McGivern DV, Hanley S, Davies D. The efficacy of budesonide and beclomethasone dipropionate, delivered via a pressurized metered dose inhaler, in the treatment of perennial rhinitis: a randomized, double-blind, crossover study. American Journal of Rhinology 1995;5:285-90.

Benninger 2003
Benninger MS, Ahmad N, Marple BF. The safety of intranasal steroids. Otolaryngology Head and Neck Surgery 2003;129(6):739-50.

Bousquet 2008
Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). Allergy 2008;63 Suppl 86:8-160.

Bousquet 2008
Bousquet J, Fokkens W, Burney P, Durham SR, Bachert C, Akdis CA, et al. Important research questions in allergy and related diseases: non-allergic rhinitis: a GA2LEN paper. Allergy 2008;63(7):842-53.

Bruni 2009
Bruni FM, De Luca G, Venturoli V, Boner AL. Intranasal corticosteroids and adrenal suppression. Neuroimmunomodulation 2009;16(5):353-62.

Burns 2012
Burns P, Powe DG, Jones NS. Idiopathic rhinitis. Current Opinion in Otolaryngology & Head and Neck Surgery 2012;20(1):1-8.

Chong 2016
Chong LY, Head K, Hopkins C, Philpott C, Schilder AGM, Burton MJ. Intranasal steroids versus placebo or no intervention for chronic rhinosinusitis. Cochrane Database of Systematic Reviews 2016, Issue 4. Art. No.: CD011996. DOI: 10.1002/14651858.CD011996.pub2.

Ciabatti 2009
Ciabatti PG1, D'Ascanio L.. Intranasal Capsicum spray in idiopathic rhinitis: a randomized prospective application regimen trial.. Acta Otolaryngol. 2009;129(4):367-71.

Cohen 1988
Cohen J. Statistical Power Analysis in the Behavioral Sciences. 2nd edition. Hillsdale (NJ): Lawrence Erlbaum Associates, 1988.

Covidence
Covidence [Computer program]. Melbourne, Australia: Veritas Health Innovation, (accessed 1 July 2019). Available at covidence.org.

Ellis 2007
Ellis AK, Keith PK. Non-allergic rhinitis with eosinophilia syndrome and related disorders. Clinical Allergy and Immunology 2007;19:87-100.

Emin 2011
Emin O, Fatih M, Emre D, Nedim S. Lack of bone metabolism side effects after 3 years of nasal topical steroids in children with allergic rhinitis. Journal of Bone and Mineral Metabolism 2011;29(5):582-7.

Fokkens 2002
Fokkens WJ. Thoughts on the pathophysiology of non-allergic rhinitis. Current Allergy and Asthma Reports 2002;2(3):203-9.

Garzaro 2012
Garzaro M, Pezzoli M, Landolfo V, Defilippi S, Giordano C, Pecorari G. Radiofrequency inferior turbinate reduction: long-term olfactory and functional outcomes. Otolaryngology Head and Neck Surgery 2012;146(1):146-50.

Groger 2012
Groger M, Klemens C, Wendt S, Becker S, Canis M, Havel M, et al. Mediators and cytokines in persistent allergic rhinitis and non-allergic rhinitis with eosinophilia syndrome. International Archives of Allergy and Applied Immunology 2012;159(2):171-8.

Handbook 2011
Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Hellings 2017
Hellings PW, Klimek L, Cingi C, Agache I, Akdis C, Bachert C, et al. Non-allergic rhinitis: Position paper of the European Academy of Allergy and Clinical Immunology. Allergy 2017;72(11):1657-65.

Knudsen 2009
Knudsen TB, Thomsen SF, Nolte H, Backer V. A population-based clinical study of allergic and non-allergic asthma. Journal of Asthma 2009;46(1):91-4.

Merck 2012
Merck & Co Inc. Prescribing information for Nasonex, highlights of prescribing information. http://www.merck.com/product/usa/pi_circulars/n/nasonex/nasonex_pi.pdf March 2013.

Mizrachi 2012
Mizrachi A, Bachar G, Yaniv E, Hadar T, Vinker S. Effect of intranasal steroids on glucose and hemoglobin A1c levels in diabetic patients. American Journal of Rhinology & Allergy 2012;26(5):395-7.

Molgaard 2007
Molgaard E, Thomsen SF, Lund T, Pedersen L, Nolte H, Backer V. Differences between allergic and non-allergic rhinitis in a large sample of adolescents and adults. Allergy 2007;62(9):1033-7.

Mygind 2001
Mygind N, Nielsen LP, Hoffmann HJ, Shukla A, Blumberga G, Dahl R, et al. Mode of action of intranasal corticosteroids. Journal of Allergy and Clinical Immunology 2001;108(1 Suppl):S16-25.

Papadopoulos 2015
Papadopoulos NG, Bernstein JA, Demoly P, Dykewicz M, Fokkens W, Hellings PW, et al. Phenotypes and endotypes of rhinitis and their impact on management: a PRACTALL report. Allergy 2015;70(5):474-94.

RevMan 2014
Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Robinson 2006
Robinson SR, Wormald PJ. Endoscopic vidian neurectomy. American Journal of Rhinology 2006;20(2):197-202.

Rondon 2012
Rondon C, Campo P, Galindo L, Blanca-Lopez N, Cassinello MS, Rodriguez-Bada JL, et al. Prevalence and clinical relevance of local allergic rhinitis. Allergy 2012;67(10):1282-8.

Rondon 2012
Rondon C, Campo P, Togias A, Fokkens WJ, Durham SR, Powe DG, et al. Local allergic rhinitis: concept, pathophysiology, and management. Journal of Allergy and Clinical Immunology 2012;129(6):1460-7.

Schroer 2012
Schroer B, Pien LC. Non-allergic rhinitis: common problem, chronic symptoms. Cleveland Clinic Journal of Medicine 2012;79(4):285-93.

Segboer 2018
Segboer CL, Terreehorst I, Gevorgyan A, Hellings PW, van Drunen CM, Fokkens WJ. Quality of life is significantly impaired in non-allergic rhinitis patients. Allergy 2018;73(5):1094-100.

van Rijkwijk 2003
Van Rijswijk JB1, Boeke EL, Keizer JM, Mulder PG, Blom HM, Fokkens WJ.. Intranasal capsaicin reduces nasal hyper-reactivity in idiopathic rhinitis: a double-blind randomized application regimen study.. Allergy 2003;58(8):754-61.

van Rijswijk 2005
van Rijswijk JB, Blom HM, Fokkens WJ. Idiopathic rhinitis, the ongoing quest. Allergy 2005;60(12):1471-81.

Varghese 2010
Varghese M, Glaum MC, Lockey RF. Drug-induced rhinitis. Clinical and Experimental Allergy 2010;40(3):381-4.

Waibel 2008
Waibel KH, Chang C. Prevalence and food avoidance behaviors for gustatory rhinitis. Annals of Allergy, Asthma & Immunology 2008;100(3):200-5.

Characteristics of studies

Characteristics of included studies

Arikan 2006

Methods	Double-blind, parallel-group, randomised, placebo-controlled trial with 3 months duration of treatment
Participants	**Setting:** Otorhinolaryngology Head and Neck Surgery and Chest Disease Departments, Faculty of Medicine, Kirikkale University, Turkey **Sample size:** **Number randomised:** 35 patients (20 in intervention, 15 in control) **Number completed:** 35 patients **Participant (baseline) characteristics:** **Age:** not reported **Gender:** not reported *No significant age or sex differences **Symptom duration:** 1 to 8 years **Severity:** N/A **Inclusion criteria:** vasomotor rhinitis patients with bilateral inferior turbinate hypertrophy suffering from chronic nasal obstruction, whose allergic skin prick test and nasal cytologic examination for eosinophils were negative. **Exclusion criteria:** previous sinonasal surgery, acute rhinosinusitis, nasal polyps, clinically significant structural abnormalities, a history of hypersensitivity to corticosteroids or food allergy, a need for regular use of inhaled or systemic glucocorticosteroids for asthma and any systemic renal, endocrine, cardiovascular, gastrointestinal or hematological diseases or neuropsychiatric disorders, pregnant and lactating women; allergic rhinitis (presence of three out of four of the following symptoms: nasal obstruction, clear rhinorrhoea, repeated sneezing and itching of the nose for 1 year; and allergic status as confirmed by radioallergosorbent tests and a skin prick test using a range of common allergens).
Interventions	**Intervention group:** fluticasone propionate (n = 20) Dose: 50 µg, 1 puff each nostril (daily dose of 200 µg) Frequency: twice daily (morning and evening) Duration: 3 months Vehicle: pressurised aerosol spray **Comparator group:** placebo (vehicle) (n = 15) **Use of additional interventions:** none
Outcomes	1. **Nasal obstruction** VAS (0 to 10; 0 is better) Measured prior to trial and after 1, 2 and 3 months of double-blind treatment Reported as before and after treatment No numerical data provided 2. **Adverse effects**

Table continued

Funding sources	None
Declarations of interest	None declared
Notes	Summary data not reported to allow inclusion in meta-analysis: Outcomes reported as median, min, max and P value, so cannot derive mean and SD to include in meta-analysis. Study reports significantly greater relief of nasal obstruction with fluticasone propionate versus placebo, however summary data were not provided.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random component in the sequence generation process: "patients with vasomotor rhinitis were randomly assigned to receive a 3-month course of either an FP aqueous nasal spray or a matching intranasal placebo spray". The random sequence generation is not further explained.
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	Low risk	Double-blind study: "Clinical evaluation was performed prior to the trial and after 1, 2 and 3 months of double-blind treatment." "Fifteen patients in the control group were treated with placebo FP, which was administered in the same fashion as the active treatment." Blinding is not further described in detail. Both treatments consisted of nasal spray making adequate blinding possible. The outcomes consisted of a symptom-related questionnaire (outcome 1) completed by patients. The CT assessment of turbinate size (outcome 2) was done by a blinded radiologist. The symptom scores could have been influenced by inadequate blinding (blinding not further described) of the patients. The CT assessment is unlikely to have high risk of bias.
Blinding of outcome assessment (detection bias)	Low risk	"The radiologist was blinded regarding the study medication."
Incomplete outcome data (attrition bias)	Low risk	All participants that were randomised were reported in the 'Results' section.

Table continued

Selective reporting (reporting bias)	Low risk	All outcomes that were pre-defined in 'Materials and methods' were reported in the 'Results' section.
Other bias	Unclear risk	Data not reported in means and SDs, but rather median, mean, max and P values.

Balle 1982

Methods	Double-blind, cross-over, randomised, placebo-controlled trial of 5 weeks total: unclear run-in, 2 weeks treatment, 1 week wash-out, 2 weeks treatment
Participants	**Setting:** Departments of Otorhinolaryngology and Lung Medicine, Aalborg hospital in Aalborg, Denmark **Sample size:** **Number randomised:** 36 perennial rhinitis, 15 non-allergic rhinitis patients **Number completed:** 36 perennial rhinitis, 15 non-allergic rhinitis patients **Participant (baseline) characteristics:** **Age:** adults (specific age not described) **Gender:** not described **Symptom duration:** not described **Severity:** not described **Inclusion criteria:** patients with perennial rhinitis, with at least 2 of the 3 symptoms: nasal obstruction, rhinorrhoea, sneezing. Non-allergic rhinitis group was defined by negative cutaneous allergy or RAST testing. **Exclusion criteria:** diabetes, pregnancy, asthma, bronchitis
Interventions	**Intervention group:** budesonide 200 µg daily (n = 15) Dose: cross-over trial with 2 dosages of budesonide (200 µg and 400 µg daily) Frequency: unclear Duration: 2 weeks Vehicle: not described **Comparator group:** placebo (n = 15) **Use of additional interventions:** none
Outcomes	**Total nasal symptom score (mean score of obstruction, rhinorrhoea and sneezing)** Scale unclear, low indicates fewer symptoms Presented as mean and SEM **Individual symptom scores** Measured, but not reported for non-allergic rhinitis subgroup only
Funding sources	The role of the pharmaceutical company, AB Draco, besides providing the medication for the study, is not clarified.
Declarations of interest	None declared
Notes	Cross-over trial with 2 dosages of budesonide (200 µg and 400 µg) versus placebo. Dosage of 400 µg daily included in the meta-analysis. Single author reports this RCT. Non-allergic rhinitis data (15 patients with non-allergic rhinitis) available only for total nasal symptom score. Unclear scale.

Risk of bias

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

Behncke 2006

Methods	Open-label, parallel-group randomised controlled trial with a 6-week study period.
Participants	**Setting:** Otorhinolaryngology, Cleveland Clinic Florida, Weston, FL **Sample size:** **Number randomised:** 15 non-allergic rhinitis patients (negative SPT), 3 allergic rhinitis **Number completed:** 15 non-allergic rhinitis patients **Participant (baseline) characteristics:** **Age:** unclear **Gender:** unclear **Symptom duration:** 6-week study period **Severity:** moderate-to-severe rhinitis **Inclusion criteria:** 18 patients 65 years and older with a history of moderate-to-severe rhinitis **Exclusion criteria:** unclear
Interventions	**Intervention group:** intranasal corticosteroids: fluticasone 2 sprays per nostril daily (200 µg) (n = unclear) **Comparator group:** intranasal antihistamine: azelastine: azelastine nasal spray 2 sprays per nostril twice daily (1.1 mg) (n = unclear) **Use of additional interventions:** none
Outcomes	The primary outcome variable was quality of life as assessed by the Rhinitis Quality of Life Questionnaire (RQLQ). Patients completed the RQLQ at baseline and at week 3 and week 6. Patients also recorded symptoms and side effects each day in a diary. There is a stated significant improvement of symptom score from baseline, however no definition/scale/range or numerical data for this symptom score.
Funding sources	None
Declarations of interest	None declared
Notes	Study in geriatric patients No numerical data for non-allergic rhinitis subgroup Conclusion: No difference in effectiveness between intranasal corticosteroids and intranasal antihistamine. Azelastine nasal spray and fluticasone nasal spray improved RQLQ scores and rhinitis symptom scores in geriatric patients with either allergic or non-allergic rhinitis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised: "Eligible patients were randomized to treatment with either azelastine nasal spray 2 sprays per nostril bid (1.1 mg) or fluticasone 2 sprays per nostril qd (200 µg) for a 6-week study period". The random sequence generation is not further explained.
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias)	Unclear risk	No information
Blinding of outcome assessment (detection bias)	Unclear risk	No information
Incomplete outcome data (attrition bias)	High risk	No numerical data on allergic or non-allergic rhinitis subgroup.
Selective reporting (reporting bias)	High risk	No numerical data on allergic or non-allergic rhinitis subgroup.
Other bias	Unclear risk	No information

Blom 1997

Methods	Double-blind, multi-centre, parallel-group, randomised, placebo-controlled trial of 6 weeks total: 2 weeks run-in period, 8 weeks treatment
Participants	**Setting:** outpatient Ear, Nose, and Throat Departments of the Leyenburg Hospital in the Hague and the Dijkzigt University Hospital in Rotterdam, the Netherlands **Sample size:** **Number randomised:** 65 **Number completed:** 65 **Participant (baseline) characteristics:** **Age: m**ean age 34 years (range 17 to 62 years) **Gender:** 32 male, 33 female **Symptom duration:** over 1 year **Severity:** not described **Inclusion criteria:** patients with NANIPER, with a history of nasal complaints such as nasal obstruction, sneezing, and rhinorrhoea for a period of over 1 year; negative skin prick testing and Phadiatop. Periods of nasal discharge, sneezing and congestion for an average of at least 1 hour per day for at least 5 days during a period of 14 days. **Exclusion criteria:** allergic rhinitis, nasal or paranasal sinus infection, anatomic disorders affecting nasal function (e.g. septal deviation, septal perforation, synechia or bullous medial concha), pregnancy or lactation, systemic disorders, and/or the use of medication affecting nasal function; nasal polyps; use of systemic or inhaled corticosteroids, inhaled sodium cromoglycate or nedocromil sodium or astemizole within the previous; inability of the patient to stop taking medication affecting nasal function; a serious and/or unstable disease; nasal surgery within the previous 6 weeks; abnormal laboratory results or abnormal findings at physical examination.
Interventions	Parallel-group study; 4 different treatment regimens: **a.** Fluticasone propionate 200 µg once daily and placebo once daily for 8 weeks **b.** Fluticasone propionate 200 µg once daily and placebo once daily for 4 weeks after which patients will be treated for 4 weeks longer with FP 200 µg twice daily and placebo twice daily **c.** Fluticasone propionate 200 µg twice daily and placebo twice daily for 8 weeks **d.** Placebo twice daily for 8 weeks **Included in meta-analysis:** fluticasone propionate (200 µg) twice daily for 8 weeks (n = 15) Dose: a total daily dose of 400 µg for 8 weeks Frequency: twice daily Duration: 8 weeks Vehicle: aqueous nasal spray **Comparator group:** placebo twice daily for 8 weeks (n = 16) Frequency: twice daily Duration: 8 weeks **Use of additional interventions:** none

Table continued

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

Risk of bias

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

Boechat 2019

Methods	A randomised, open-label, active comparator trial, with 2 weeks treatment
Participants	**Setting:** outpatient allergy clinic at hospital, Universitario Antonio Pedro/ Universidade Federal Fluminense in the Metropolitan Region of Rio de Janeiro, Brazil **Sample size:** **Number randomised:** 40 (20 to each treatment group, per treatment group 14 non-allergic rhinitis patients, 28 non-allergic rhinitis patients in total). **Number completed:** 40 (28 non-allergic rhinitis patients in total). **Participant (baseline) characteristics:** **Age:** described for allergic and non-allergic rhinitis subgroups together**:** varies between 60 and 87 years old (mean 71 years). **Gender:** described for allergic and non-allergic rhinitis subgroups together: 31 (75%) female participants. **Symptom duration:** not described. **Severity:** not explicitly described, however at least 2 chronic symptoms of rhinitis, congestion, rhinorrhoea, itching of the nose or sneezing. Pre-treatment patients had combined nasal symptom scores of 5.0 to 5.8 on a 0 to 10 scale. **Inclusion criteria:** at least 2 chronic symptoms of rhinitis, congestion, rhinorrhoea, itching of the nose or sneezing. **Exclusion criteria:** primary or secondary immunodeficiency, mechanical obstruction of upper airways and respiratory infection in the last 2 weeks.
Interventions	**Intervention group:** intranasal steroid (mometasone furoate) + saline (n = 14) Dose: 200 µg Frequency: once a day Duration: 2 weeks Vehicle: nasal spray **Comparator group:** isotonic nasal saline spray (n = 14), 4 times a day. **Use of additional interventions:** no

Table continued

Outcomes	**Individual symptoms:** **Blocked nose** **Itchy nose** **Runny nose** **Sneezing** Measured on a scale of 0 to 3 daily. Mean change in symptom score from end of treatment to baseline reported. Data available for non-allergic rhinitis subgroup. **Combined symptom score** Combined nasal symptoms intensity score rated by a 10-point visual analogue scale (VAS) at 2 weeks, with 0 indicating no symptoms and 10 the worst possible discomfort. Measured pre-treatment and 2 weeks after treatment. Data available for non-allergic rhinitis subgroup. **Peak nasal inspiratory flow** 3 satisfactory maximal inspirations were obtained and the highest of the 3 results was taken as the PNIF. Measured pre-treatment and 2 weeks after treatment. Measured in L/min. **Quality of life** SNOT-22 (sinonasal outcome test) questionnaire of quality of life. SNOT-22 is the only questionnaire of quality of life in nasal chronic problem that is validated in Brazilian Portuguese. This consists of 22 questions scored between 0 and 5, with higher scores meaning greater problems. Data available for non-allergic rhinitis subgroup. Measured pre-treatment and 2 weeks after treatment. **Adverse events** No adverse events (evaluated type of adverse events not described).
Funding sources	Unclear/none reported
Declarations of interest	None declared
Notes	—

Risk of bias

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

Day 1990

Methods	Double-blind, parallel-group, randomised, placebo-controlled trial of 6 weeks total: 2 weeks baseline, 4 weeks treatment
Participants	**Setting:** Kingston General Hospital, Ontario, Canada **Sample size:** **Number randomised:** 107 patients enrolled including children and adults, of which 100 received treatment, and 99 were reported; out of these, there were 23 patients with non-allergic rhinitis (10 treated with budesonide and 13 with placebo). **Number completed:** 99 **Participant (baseline) characteristics:** **Age:** described for allergic and non-allergic rhinitis subgroups together: range 22 to 65 years (mean 41.9 years in budesonide, and 45.9 years in placebo groups). **Gender:** not described separately for allergic and non-allergic rhinitis subgroups. **Symptom duration:** at least 2 years **Severity:** not described Conclusion cannot be reached specifically about the non-allergic rhinitis subgroup. **Inclusion criteria:** perennial rhinitis over a period of at least 2 years, and currently not receiving therapy for rhinitis. Skin prick testing done either within the last 6 months, or at baseline. In this review, only patients with non-allergic rhinitis are included. **Exclusion criteria:** pregnancy, tuberculosis, respiratory infection, additional nasal disease, asthma requiring treatment with corticosteroids. In addition, all other rhinitis medications were discontinued besides terfenadine. Immunotherapy was allowed as long as antigens relative to that time of year were not involved.
Interventions	**Intervention group:** budesonide (n = 10) Dose: a total daily dosage of 400 µg Frequency: 2 puffs per nostril each morning and each evening Duration: 4 weeks Vehicle: pressured canisters mounted in a nasal applicator **Comparator group:** placebo (n = 13) **Use of additional interventions:** terfenadine as rescue medication if symptoms became intolerable.

Table continued

Outcomes	**Individual symptoms:** **Blocked nose** **Itchy nose** **Runny nose** **Sneezing** Measured on a scale of 0 to 3 daily. Mean change in symptom score from end of treatment to baseline reported. Data available for non-allergic rhinitis subgroup **Combined symptom score** Measured and reported as above Data available for non-allergic rhinitis subgroup **Global evaluation of efficacy** Measured by patient At final clinic visit Scale 0 (aggravated) to 4 (total control) Data not available for non-allergic rhinitis subgroup **Adverse events** Data not available for non-allergic rhinitis subgroup
Funding sources	None declared
Declarations of interest	None declared
Notes	—

Risk of bias

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

Ellegård 2001

Methods	Double-blind, parallel-group, randomised, placebo-controlled trial with 1-week run-in, 8 weeks treatment, 16 weeks follow-up, total 24 weeks
Participants	**Setting:** 28 maternity centres in the southern part of the County of Bohuslän (Bohuslandstinget) and in the city of Göteborg, Sweden **Sample size:** **Number randomised:** 60 patients randomised; 26 (of 31) reported in fluticasone group and 27 (of 29) reported in placebo group. **Number completed:** 53 **Participant (baseline) characteristics:** **Age:** 18 to 39 years **Gender:** all females (given pregnancy rhinitis) **Symptom duration:** at least 10 days **Severity:** at least moderate, given requirement to demand treatment Overall no difference with respect to age, number of children, weeks of nasal congestion, gestational week and number of cigarette smokers. **Inclusion criteria:** Pregnancy rhinitis: pregnant women 18 to 39 years of age with a treatment demanding nasal congestion for at least 10 days, without other signs of respiratory tract infection. **Exclusion criteria:** 1) corticosteroid treatment during the present pregnancy, or a contra-indication for corticosteroids; 2) sodium cromoglycate 1 month before entry; 3) medication with known influence on nasal mucosa, apart from local decongestants, that were allowed for continuous use up to 6 weeks before entry; 4) serious or unstable concurrent disease; 5) anatomical abnormalities affecting nasal breathing, nasal surgery during the present pregnancy or chronic nasal symptoms before pregnancy; 6) purulent respiratory infection within 1 month before entry; and 7) more than 1 fetus.
Interventions	**Intervention group:** fluticasone propionate (n = 31 randomised, 26 reported) Dose: 50 µg per actuation Frequency: 2 actuations to each nostril in the morning (200 µg daily dosage) Duration: 8 weeks treatment Vehicle: nasal spray **Comparator group: placebo** (vehicle of the active spray) (n = 29 randomised, 27 reported) **Use of additional interventions:** none

Table continued

Outcomes	**Nasal congestion** Measured on a scale of 0 to 4; 0 = better Reported for 8 weeks of treatment and 16 weeks of post-treatment follow-up In our analysis, we used data at the end of 8 weeks of treatment **Blockage index (BI)** Measured as BI=(PEF-nPEF)/PEF Reported for 8 weeks of treatment and 16 weeks of post-treatment follow-up In our analysis, we used data at the end of 8 weeks of treatment **Acoustic rhinometry** Reported as 3 separate parameters: volume (cm^3), MCA (cm^2), dip 2 (cm^2), however SDs could not be recalculated
Funding sources	Göteberg Medical Society and GlaxoWellcome
Declarations of interest	None declared
Notes	This is the only study of intranasal corticosteroids in pregnancy rhinitis. Even though it was industry sponsored, it found no effect of the studied medication. Outcomes not included here due to lack of summary data or clinical: acoustic rhinometry (full summary data not reported), anterior rhinoscopic assessment of nasal secretions.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised study: "The investigation was designed as a single-centre, placebo controlled, randomized, double-blind study with parallel groups." Random sequence generation is not further described.
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	Unclear risk	Double-blind study: "may be due to the fact that we made a blind, placebo-controlled study". "The investigation was designed as a single-centre, placebo controlled, randomized, double-blind study with parallel groups." However, blinding is not described in further detail. Both treatments consisted of nasal spray making adequate blinding possible. Subjective nasal scores could have been influenced by inadequate blinding of patients. For a small amount also reporting of nasal secretions and nasal crusts could have been influenced by inadequate blinding of investigators. Assessment of nPEF and PEF are less likely to be influenced by inadequate blinding.
Blinding of outcome assessment (detection bias)	Unclear risk	Not described, see above. Blinding of outcome assessment: patients are said to be blinded, but this is not further described. Blinding of the investigator is not further described, it is said to be "double blinded".
Incomplete outcome data (attrition bias)	Unclear risk	Not all results listed in 'Methods' are fully reported, however most clinically important results are presented.
Selective reporting (reporting bias)	High risk	5 patients withdrawn from treatment group, 2 from placebo group.
Other bias	Low risk	Even though this was an industry-sponsored trial, it did not show a beneficial effect of the studied medication.

Guo 2015

Methods	Parallel-group randomised controlled trial with 6 weeks duration of treatment
Participants	**Setting:** Eye Otolaryngology Department, Eye Otolaryngology Hospital Affiliated to Fudan University, China **Sample size:** **Number randomised:** 162 **Number completed:** 154 **Participant (baseline) characteristics:** **Age:** AZENS + FPNS (44.91 ± 6.77 years); FPNS only (42.43 ± 8.24 years) **Gender:** N/A, no difference stated in paper **Symptom duration:** AZENS + FPNS (2.70 ± 1.42 years); FPNS only (3.01 ± 1.41 years) **Severity:** AZENS + FPNS (nasal symptom score: 2.48 ± 0.40); FPNS only (nasal symptom score: 2.50 ± 0.37) Overall no difference for age, symptom duration and nasal symptom score **Inclusion criteria:** • Patients between 30 to 60 years of age. • Symptoms present for at least 9 months per year, with a history of at least 1 year. • Primary symptom of nasal congestion; may be accompanied by sticky or clear rhinorrhoea or sneezing. • The symptom of nasal mucosal hyperaemia and congestion is mainly caused by inferior turbinate enlargement. • The nasal symptom score ≥ 2, and the patients have strong willingness to improve the nasal symptom and have confidence in drug treatment. **Exclusion criteria:** • Nasal symptoms caused by allergy, typical symptoms of allergic rhinitis, in patients once suffered from asthma or eczema, and allergen testing is positive. • Another cause of rhinitis (e.g. infectious or rhinitis medicamentosa). • Anatomic abnormalities (e.g. deviated nasal septum or spur). • Acute or chronic sinusitis, nasal polyps or the other space-occupying nasal lesions. • Use of nasal corticosteroids, decongestants, antihistamines or cold medicine within one month. • History of nasal surgery.

Table continued

Interventions	**Intervention groups:** fluticasone propionate nasal spray (FPNS): same as in comparator group below; dosage unclear (n = 82 randomised, 78 treated, 5 lost to follow-up) Dose: no information provided Frequency: FPNS 2 sprays each nostril, once a day Duration: 6 weeks Vehicle: nasal spray **Comparator group:** azelastine nasal spray (AZENS) combined with FPNS (n = 79 randomised, 76 received treatment as allocated, 3 lost to follow-up) Dose: no information provided Frequency: AZENS 2 sprays in each nostril, twice a day; FPNS 2 sprays each nostril, once a day Duration: 6 weeks Vehicle: nasal spray **Use of additional interventions:** none
Outcomes	**1. Total nasal symptom scores (no breakdown)** Measured pre-intervention, at 2 weeks and at 6 weeks (in the meta-analysis reported at 6 weeks) **2. Satisfaction score** Binary outcome Comprising a composite of ease of medication use, adverse outcomes, cost, treatment efficacy
Funding sources	None
Declarations of interest	None declared
Notes	Funding source not provided. Total nasal symptom scores are measured at 2 weeks and at 6 weeks. Results at 6 weeks are reported in the meta-analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised controlled trial; however, there was not sufficient information on sequence generation.
Allocation concealment (selection bias)	Unclear risk	There was no information about allocation concealment.
Blinding of participants and personnel (performance bias)	Unclear risk	As the primary outcomes of nasal symptom scores and adverse events are both self-reported outcome measures, and the article had no information on blinding, there was not sufficient information to make a judgement.
Blinding of outcome assessment (detection bias)	Unclear risk	As the primary outcomes of nasal symptom scores and adverse events are both self-reported outcome measures, and the article had no information on blinding, there was not sufficient information to make a judgement.
Incomplete outcome data (attrition bias)	Low risk	8 of 161 patients lost to follow-up, likely not significant.
Selective reporting (reporting bias)	High risk	No protocol provided and all the reported outcomes were not prespecified in the methods section of the article. Total nasal symptom score calculation is not specified.
Other bias	Low risk	No other sources of bias were found in this study.

Hallén 1997

Methods	Double-blind, parallel-group, randomised, placebo-controlled trial with 14 days duration of treatment
Participants	**Setting:** outpatient department of the ENT clinic at Sodersjukhuset, Stockholm, Sweden **Sample size:** **Number randomised:** 20 patients randomised; 10 per treatment group, 19 patients reported **Number completed:** 20 (results for 1 patient were excluded because of a concurrent common cold during study period) **Participant (baseline) characteristics:** **Age:** mean age 33 years **Gender:** 12 female and 8 male **Symptom duration:** 2 years of topical decongestant use **Severity:** not described **Inclusion criteria:** patients with rhinitis medicamentosa, defined as overuse of topical decongestants for at least 2 years, using their spray 1 to 15 times a day. 5 patients with documented allergies were NOT excluded. **Exclusion criteria:** anatomic problems on rhinoscopy (not identified in any patient).
Interventions	**Intervention group:** fluticasone propionate (n = 10 randomised, 9 or 10 reported (1 patient excluded without identification of group)) Dose: 50 µg per spray (200 µg per day total) Frequency: 2 sprays into each nostril in the morning Duration: 2 weeks treatment Vehicle: aqueous nasal spray **Comparator group: placebo (**vehicle of the active spray) (n = 10 randomised, 9 or 10 reported (1 patient excluded without identification of group)) **Use of additional interventions:** none
Outcomes	**1. Nasal congestion** Measured on a VAS, 0 to 100 Reported for all days, 0 to 14 days **2. Rhinostereometry** Measure of nasal mucosal swelling: changes in the position of the mucosal surface of the medial side of the head of the inferior concha are registered in the plane of focus along the mm scale **3. Acoustic rhinometry (MCA 2 area)** Measured in cm^2 **4. PNIF** Measured in L/min
Funding sources	GlaxoWellcome
Declarations of interest	None declared

Table continued

Notes	5 patients with documented allergies were NOT excluded. No difference between AM (Figure4) and PM (Figure5) data, AM data included. 1 patient's results not reported, but it is not indicated which group they belonged to, so most likely both groups had 10 patients. The study was financially supported by Glaxo Wellcome AB, Molndal, Sweden.

Risk of bias

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

Havas 2002

Methods	Double-blind, parallel-group, quasi-randomised (on odds and even basis) controlled trial; 31 days total (3 days prior to treatment and 4 weeks of treatment)
Participants	**Setting:** Department of Otolaryngology Head and Neck Surgery, Prince of Wales Hospital, Sydney, Australia **Sample size:** **Number randomised:** 40 **Number completed:** 40 **Participant (baseline) characteristics:** **Age:** Budesonide group: males 40.3 years; females 37.0 years Capsaicin group: males 41.5 years; females 41.0 years **Gender:** 20 males, 20 females **Symptom duration:** perennial **Severity:** not reported No significant difference for main examined symptoms (based on figures) **Inclusion criteria:** patients with perennial non-allergic rhinitis (IgE < 100 and RAST negative) examined by the senior author. Nasal endoscopy used to confirm rhinitis. **Exclusion criteria:** any relevant antecedent history of rhinosinusitis or antecedent nasal or sinus surgery. Presence on nasoendoscopy of nasal septal deviation, nasal polyposis, rhinosinusitis and/or neoplasm. Smokers.
Interventions	**Intervention group:** budesonide (n = 20) Dose: 64 µg/dose), 2 puffs of the spray in each nostril, after administration of lignocaine/phenylephrine (co-phenylcaine) before the 1st treatment Frequency: each AM and PM Duration: 2 weeks Vehicle: nasal spray **Comparator group:** capsaicin (n = 20) Dose: 70 µL, delivering 0.654 µg of capsaicin (capsaicin 71%, dihydrocapsaicin 20.94% and nordihydrocapsaicin 4.94%), 2 puffs into each nostril. Co-phenylcaine spray 10 minutes prior to capsaicin first treatment. Frequency: once weekly self-administration of 2 puffs of capsaicin in each nostril weekly Duration: 4 weeks Vehicle: nasal spray **Use of additional interventions:** co-phenylcaine spray before both budesonide and capsaicin

Table continued

Outcomes	**Individual symptom scores (headache, post-nasal drip, rhinorrhoea, nasal blockage, sore throat, sneezing)** Assessed on a VAS (0 to 5; 0 = no symptoms), separately for each side, 3 days prior to treatment and during last 3 days of treatment. **Aggregate total relief** Decrease of symptom scores after treatment: sum of relief scores for all 6 symptoms. **Responders** (improved versus worse or unchanged)
Funding sources	None
Declarations of interest	None declared
Notes	Calculated a total nasal symptom score from means rhinorrhoea, blockage and sneezing and calculated a pooled SD. **Disclosures:** no financial interest with company supplying capsaicin.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Pseudo-randomisation: "they were pseudo-randomized in two groups based on odds and evens basis".
Allocation concealment (selection bias)	High risk	Sequence generation was on an odds and evens basis.
Blinding of participants and personnel (performance bias)	High risk	High risk due to pseudo-randomisation.
Blinding of outcome assessment (detection bias)	Unclear risk	Not described
Incomplete outcome data (attrition bias)	Low risk	All outcomes described in 'Methods' are reported in 'Results'.
Selective reporting (reporting bias)	Low risk	No selective outcome reporting identified.
Other bias	Low risk	No other sources of bias identified.

Hillas 1980

Methods	Double-blind, cross-over, randomised controlled trial with 4-week treatments, wash-out not described. Cross-over, in 4 sequences: 1) sodium cromoglycate/placebo/beclomethasone dipropionate/placebo; 2) beclomethasone dipropionate/placebo/sodium cromoglycate/placebo; 3) placebo/sodium cromoglycate/placebo/beclomethasone dipropionate; and 4) placebo/beclomethasone dipropionate/placebo/sodium cromoglycate)
Participants	**Setting:** Department of Medicine, University of Auckland School of Medicine, Auckland, and Auckland Hospital Board, Auckland, New Zealand **Sample size:** **Number randomised:** 58 patients randomised, 52 patients analysed, of which 21 were non-allergic rhinitis patients **Number completed:** 52 **Participant (baseline) characteristics:** **Age:** 13 to 58 years (mean age 29 years) for allergic and non-allergic rhinitis groups **Gender:** females: 29; males: 23 for allergic and non-allergic rhinitis groups **Symptom duration:** 1 to 45 years (mean 11 years) **Severity:** severe **Inclusion criteria:** only patients with severe chronic perennial rhinitis, usually without asthma, were admitted to the trial. Almost all patients had been treated previously either surgically or with drugs, or both. Patients who received no relief from the sprays and were severely debilitated by their symptoms were permitted to use antihistamine tablets, but were requested to record the number taken each day. Nasal infections, including those not clinically obvious but detected by the presence of increased numbers of neutrophils in nasal smears, were treated with a short course of antibiotics before the trial. **Exclusion criteria:** large polyps, mechanical obstruction, severe nasal infections, aspirin sensitivity, steroid dependence, use of continuous medication excepting oral contraceptives, pregnant women and children under the age of 12.

Table continued

Interventions	**Intervention group: sodium cromoglycate/Comparator group: beclomethasone dipropionate** **Beclomethasone dipropionate** (n = 21) Dose: 50 µg/puff; 1 puff into each nostril Frequency: 4 times per day (total daily dosage of 400 µg) Duration: 4 weeks Vehicle: aerosol **Beclomethasone dipropionate placebo** (n = 21) Dose: placebo Frequency: 4 times per day Duration: 4 weeks Vehicle: aerosol **Sodium cromoglycate** (n = 21) Dose: 2% Frequency: 6 times per day Duration: 4 weeks Vehicle: spray **Sodium cromoglycate placebo** (n = 21) Dose: placebo Frequency: 6 times per day Duration: 4 weeks Vehicle: spray **Use of additional interventions:** none
Outcomes	**Total nasal symptom score** Measured as a composite score of individual symptom scores of sneezing, rhinorrhoea, nasal pruritis, blocked nose, itchy eyes, watery eyes and red eyes Measured on a scale of 0 to 3, where 0 = nil, 1 = mild, 2 = moderate and 3 = severe Reported as a mean of 4-week treatment period Data not available for non-allergic rhinitis group separately **Individual symptom scores** Measured as above Data not available for non-allergic rhinitis group separately **Symptomatic relief (responders)** Patients were asked whether the drug relieved their symptoms partially or completely
Funding sources	Medical Research Council of New Zealand, Fisons (Australia) Ltd, Essex Laboratories, Australia and Schering Corporation
Declarations of interest	None declared

Table continued

Notes	Only data on responders versus no responders for non-allergic rhinitis subgroup. Wash-out period not described, potential spillover of treatment effect. Industry-sponsored trial by 2 companies providing 2 different drugs. The study shows no preference for one of the drugs, and therefore likely industry involvement was unbiased. Conclusion: Beclomethasone dipropionate was significantly more effective in relieving symptoms than sodium cromoglycate (76.9% and 50% of the patients improved respectively, P < 0.001). Both drugs were more active than placebos but while beclomethasone dipropionate was very clearly more effective (P < 0.0005), sodium cromoglycate was only marginally better than its placebo (P < 0.05). Beclomethasone dipropionate was selected by 56% of the patients as the best agent for continuing therapy.

Risk of bias

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

Incaudo 1980

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

Table continued

Outcomes	**Individual symptoms: sneezing, stuffy nose, runny nose, nose blowing, post-nasal drip, measured on a scale of 1 to 4** Only P values reported: no difference between flunisolide and placebo in non-allergic rhinitis subgroup Data available for non-allergic rhinitis subgroup **Overall severity of rhinitis** Recalculated from Figure 1 of the article Scale 1 (absent) to 4 (severe) **Disease control** Data reported as P values for allergic and non-allergic groups, or cumulatively for both groups. Missing summary data cannot be imputed. **Adverse events** Data available for non-allergic rhinitis subgroup **Significant benefit from flunisolide** Compares only those patients in the flunisolide group, therefore comparisons cannot be made with placebo
Funding sources	None
Declarations of interest	None declared
Notes	Individual symptoms: sneezing, stuffy nose, runny nose, nose blowing, post-nasal drip. For all individual symptoms, only P values are presented in Table III. All P values are negative for non-allergic rhinitis group, but actual data cannot be calculated from this table. Study of perennial rhinitis including both allergic and non-allergic rhinitis patients, but only males. Co-intervention in the form of usual symptomatic medication was allowed to be used by patients. Company involvement unclear manufacturer? Ethics approval not cited.

Risk of bias

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

Jacobs 2009

Methods	Double-blind, parallel-group, randomised, placebo-controlled trial with 7to 14-day screening; 4-week treatment; follow-up phone call 3 to 5 days after
Participants	**Setting:** 106 investigative centres in 6 countries (United States, Canada, Czech Republic, Germany, Norway and Romania) **Sample size:** **Number randomised:** 699 **Number completed:** 660 **Participant (baseline) characteristics:** **Age:** 12 to 18 years 33 (5%) 18 to 65 years 589 (84%) 65 to 75 years 59 (8%) 75 years 18 (3%) **Gender:** female 479 (69%), male 220 (31%) **Symptom duration:** symptomatic on the average of the last 8 recordings of rTNSS **Severity:** at least moderate (4.5 out of 9 on the average of the last 8 recordings of rTNSS and 2 out of 3 for average reflective congestion symptom) Pooled patient demographics and baseline characteristics were similar between the active and placebo groups **Inclusion criteria:** vasomotor rhinitis (VMR) eligibility requirements included a confirmed 2-year clinical history of perennial VMR, negative skin prick tests and no history of responses to seasonal or perennial allergens, a positive response to histamine skin testing, a normal sinus radiograph (to rule out infectious sinusitis), and negative nasal cytology for eosinophils, defined as the absence of eosinophils in nasal smears. In addition, a diagnosis of the VMR w/t (weather/temperature) subtype was required, which required confirmation of disease fluctuation with weather conditions by selection of weather/temperature change as the predominant trigger for worsened rhinitis on the Vasomotor Rhinitis Questionnaire. **Exclusion criteria:** participants with rhinitis principally caused by airborne irritant triggers (VMRir), allergic rhinitis, infectious disease or non-allergic rhinitis with eosinophilic syndrome were excluded; and participants were required to meet minimum symptom criteria and show persistence of their symptoms. Participants were excluded if they had evidence of significant concurrent disease, a clinically significant abnormal ECG, severe physical obstruction or septal perforation of the nose, moderate-to-severe asthma, rhinitis medicamentosa, upper respiratory tract infection, ocular disease (glaucoma, cataracts, or herpes simplex), nasal or oropharyngeal candidiasis, history of adrenal insufficiency or shingles, or a risk of developing chickenpox or measles during the study. Participants could not use tobacco products. Pregnant women or those planning to become pregnant were excluded.

Table continued

Interventions	**Intervention group:** fluticasone furoate (n = 353) Dose: 110 µg Frequency: once daily Duration: 4 weeks Vehicle: nasal spray **Comparator group:** placebo (vehicle of the active spray) (n = 346) **Use of additional interventions:** none
Outcomes	**1. Change in daily reflective total nasal symptom score (rTNSS)** Participants rated congestion, rhinorrhoea, and post-nasal drip twice daily on diary cards using a 4-point categorical scale ranging from 0 (symptom not present) to 3 (symptom hard to tolerate; interferes with daily activities or sleeping) Recorded as reflective symptom ratings (severity over the last 12 hours) and instantaneous symptom ratings (severity at the moment of the assessment) TNSS is the sum of the 3 symptom scores Measured over treatment period (week 1 to 4) **2. Change in morning instantaneous TNSS** Measured as above We chose to not report, as severity over 12 hours would be more relevant than instantaneous symptoms **3. Change in individual symptom scores for congestion, rhinorrhoea and post-nasal drip** Recorded as above **4. Overall response to therapy** For the entire treatment period 7-point categorical scale (significantly improved, moderately improved, mildly improved, no change, mildly worse, moderately worse, significantly worse) We converted the first 3 orders of the scale into 'responders' and the last 4 into 'non-responders' achieving a dichotomous outcome **5. Adverse events** Reported for headache, nasopharyngitis, epistaxis, pharyngo-laryngeal pain, diarrhoea, sinus headache, nausea, back pain, dysphonia and vomiting We decided to include any adverse events in the meta-analysis Individual results were not significantly different
Funding sources	GlaxoSmithKline
Declarations of interest	None declared

Table continued

Notes	Study sponsored by GlaxoSmithKline. Weather and temperature-sensitive vasomotor rhinitis. One of the biggest and most well known (frequently cited) studies. 5% belongs to age 12 to 18 years. Outcomes TNSS, individual symptoms, overall response and adverse events. No significant difference between allergic and non-allergic rhinitis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised study: "To evaluate the efficacy and safety of fluticasone furoate nasal spray in subjects with VMRw/t, two global, multicenter, randomized, double-blind, placebo-controlled studies were conducted". "Subjects were stratified at randomization by country to account for possible country-specific medical practice differences and effects on study outcome." Random sequence generation is not further described.
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	Unclear risk	"Double-blind study" but blinding is not further described. Both treatments consisted of nasal spray making adequate blinding possible. Outcomes were symptom scores and adverse events. These could have been influenced by inadequate blinding.
Blinding of outcome assessment (detection bias)	Unclear risk	Not described, see above
Incomplete outcome data (attrition bias)	Unclear risk	Data available for 95% of patients.
Selective reporting (reporting bias)	Low risk	All outcomes described in 'Methods' are fully reported in 'Results'.
Other bias	Unclear risk	Company-sponsored study, but results do not support the use of the medication. The Jacobs 2009 study reports a very unlikely standard deviation (SD) value that does not match with the presented means, n and P values. The data would make more sense if the standard deviation (SD) presented values were actually standard error of the mean (SEM), which was confirmed by a re-analysis.

Jessen 1990

Methods	Double-blind, double-dummy, cross-over, randomised controlled trial with 2 weeks treatment, 2 weeks wash-out, 2 weeks treatment; 3 weeks follow-up after treatment
Participants	**Setting:** Department of Otolaryngology, University of Lund, Sweden **Sample size:** **Number randomised:** 31 patients randomised, 24 patients reported **Number completed:** 24 **Participant (baseline) characteristics:** **Age:** 20 to 77 years (mean age 49 years) **Gender:** 14 female, 10 male **Symptom duration:** 0.5 to 30 years (mean 5.4 years) **Severity:** at least moderate degree **Inclusion criteria:** patients with the diagnosis of cholinergic non-allergic rhinitis, with excessive nasal secretion for 0.5 to 30 years, and negative skin prick test. **Exclusion criteria:** asthma or nasal polyps; pregnancy; negative response to ipratropium testing; negative skin prick testing; upper airway infection or use of other relevant medication 2 weeks before the trial.
Interventions	**Intervention group:** beclomethasone (n = 24) Dose: 400 µg per day Frequency: 2 puffs in the morning and evening to each nostril Duration: 2 weeks treatment, 2 weeks wash-out, 2 weeks treatment with comparator Vehicle: aerosol **Comparator group:** ipratropium (n = 24) Dose: 160 µg **Co-treatment:** 5 out of 24 patients were treated with 0.1% xylometazoline due to high nasal airway resistance on rhinomanometry. It is unclear which group these patients belonged to. **Use of additional interventions:** none
Outcomes	**1. Rhinomanometry** **2. Secretions** Measured by patient on a scale of 0 for no symptoms to "3 or 4 for severe symptoms" Reported as cumulative score for 2 weeks **3. Sneezing** As above **4. Blockage** As above **5. Number of tissues used** **6. Adverse events** no data
Funding sources	None
Declarations of interest	None declared

Table continued

Notes	Scale somewhat ambiguous ("0 for no symptoms to "3 or 4 for severe symptoms"). Symptom data presented for the period of 2 weeks. Given scale is up to 3-4, and given numbers presented are in range of 6.1 to 19.8, we assume that these are cumulative scores for 2 weeks (sum of scores). Five of 24 patients had co-treatment with 0.1% xylometazoline. It is unclear which group these patients belonged to. Rhinomanometry data was not reported. Patients report preference for drug; unclear how can they prefer if they are blinded.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Double blind double dummy randomized cross-over design". Random sequence generation not described.
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	Unclear risk	"Double-blind study"; however, blinding not described in further detail. Both treatments consisted of nasal spray making adequate blinding possible. Outcomes were symptom scores and preference of treatment that could be influenced by inadequate blinding. Assessment of eosinophilia in nasal smears is a little bit less likely to be influenced by inadequate blinding.
Blinding of outcome assessment (detection bias)	Unclear risk	Not described. See above.
Incomplete outcome data (attrition bias)	High risk	31 patients randomised, but only 24 patients included: 5 excluded due to no benefit from ipratropium and 2 found the trial regime too time-consuming. This violates the intention-to-treat protocol.
Selective reporting (reporting bias)	Unclear risk	Most clinically relevant outcomes fully reported, however reported as means for each outcome.
Other bias	High risk	The study comments on patient preference for medication and it is unclear how patients could comment unless blinding was compromised. Scale somewhat ambiguous (0 for no symptoms to "3 or 4 for severe symptoms"). Five of 24 patients had co-treatment with 0.1% xylometazoline. It is unclear which group these patients belonged to.

Kalpaklioglu 2010

Methods	Single-blind, parallel-group, randomised controlled trial with 2 weeks duration of treatment
Participants	**Setting:** tertiary care university hospital in Turkey **Sample size:** **Number randomised:** 63 patients with non-allergic rhinitis, additional 69 patients with allergic rhinitis, not considered in this analysis **Number completed:** 63 **Participant (baseline) characteristics:** **Age:** not reported separately for non-allergic rhinitis group **Gender:** more female in the triamcinolone acetone nasal spray group for both allergic and non-allergic rhinitis combined, however unclear if this holds true for non-allergic rhinitis group only. **Symptom duration:** not reported **Severity:** at least moderate, given requirement to demand treatment Overall no difference with respect to age, education, BMI, duration of rhinitis, nasal operation, sinusitis. As noted above, there were more females in the triamcinolone acetone nasal spray group for both allergic and non-allergic rhinitis combined, however unclear if this holds true for non-allergic rhinitis group only. **Inclusion criteria:** history of at least 2 of the following symptoms: nasal itching, sneezing, rhinorrhoea and/or nasal congestion, as described by the Allergic Rhinitis and Its Impact on Asthma guidelines. Allergic rhinitis was defined as nasal symptoms accompanied by SPT positivity with clinical relevance, whereas non-allergic rhinitis was defined as nasal symptoms with negative SPTs. **Exclusion criteria:** patients with nasal polyposis, infectious or occupational rhinitis, major structural nasal abnormalities, current sinusitis and those who were pregnant or lactating.
Interventions	**Intervention group:** triamcinolone acetonide (n = 32) Dose: 2 sprays/nostril (220 µg/day) Frequency: once daily Duration: 14 days Vehicle: nasal spray **Comparator group:** azelastine hydrochloride 0.1%, 2 sprays/nostril twice daily, 1.1 mg/day (n = 31) **Use of additional interventions:** none

Table continued

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

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised study: "randomized parallel-group trial", but random sequence generation not further described.
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	Unclear risk	Single-blind study, but likely participants blinded; not described in detail, however. Symptom scores can be influenced in case of inadequate blinding, assessment of nasal lavage is less likely to have high risk of bias.
Blinding of outcome assessment (detection bias)	Unclear risk	Single-blind study and likely assessors not blinded; not described in detail, however. See above.
Incomplete outcome data (attrition bias)	Low risk	All patients reported.
Selective reporting (reporting bias)	Low risk	Most outcomes reported, however individual symptom SDs not reported.
Other bias	Low risk	No other risks of bias can be distinguished.

Lin 2017

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

Table continued

Interventions	**Intervention group:** Group B (intranasal budesonide) (n = 25) Dose (per spray and per day if available): 2 sprays per nostril per day (64 µg per spray) = 256 µg/day Frequency: every morning Duration: 3 months (outcomes measured at 1 month, 2 months and 3 months) Vehicle: nasal spray Group D (nasal irrigation + intranasal budesonide) (n = 27) Dose (per spray and per day if available): nasal irrigation: 100 mL of 3% saline per nostril; intranasal budesonide: same as Group B Frequency: nasal irrigation: twice a day; intranasal budesonide: same as Group B Duration: outcomes are measured at 1 month and 3 months follow-up Vehicle: nasal irrigation: syringe; intranasal budesonide: nasal spray **Comparator group:** Group A (no treatment) (n = 20) Group C (saline irrigation using 3% saline) (n = 25) **Use of additional interventions:** none
Outcomes	**Primary outcomes:** Total nasal symptom scores in VAS Significant adverse event epistaxis: number is reported **Secondary outcomes:** Quality of life is reported in SF-12v2 Other adverse events (pharyngitis, nasal dryness/crusting): numbers are reported
Funding sources	National Natural Science Foundation of China.
Declarations of interest	None declared
Notes	Only vasomotor rhinitis patients. Unexpected data with disappearance of benefit of intranasal corticosteroids with longer follow-up. Results measured after 1 month, 2 months and after 3 months follow-up. Funded by National Natural Science Foundation of China.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation: "random sequence generated by software"
Allocation concealment (selection bias)	High risk	P448 (in Chinese): "The allocation was performed using random sequence generation software. 1~120 random sequence was generated and assigned to each patient according to their order of admission. Patients assigned to Number 1~30, 31~60, 61~90, 91~120 were respectively allocated to Group A, B, C, and D." There is non-random component: day/order of admission.
Blinding of participants and personnel (performance bias)	High risk	Allocation concealment has a high risk of bias.
Blinding of outcome assessment (detection bias)	High risk	Blinding of participants and personnel was not reported in this paper. However, considering that the outcomes were primarily patient-reported, blinding could not be achieved.
Incomplete outcome data (attrition bias)	Unclear risk	The dropout of participants was 11/101 = 10.89%.
Selective reporting (reporting bias)	Unclear risk	It is unknown whether there was selective reporting because the protocol for this trial is not available.
Other bias	Low risk	No other risks of bias can be distinguished.

Lundblad 2001

Methods	Double-blind, parallel-group, randomised, placebo-controlled trial with 2 weeks screening, 6 weeks of treatment, 3 weeks follow-up after treatment
Participants	**Setting:** Department of Otorhinolaryngology**,** 16 sites (7 in Sweden, 3 in Denmark, 3 in Finland and 3 in Norway) **Sample size:** **Number randomised:** 329 **Number completed:** 329 **Participant (baseline) characteristics:** **Age:** 18 to 82 years (mean 42.8 years) **Gender:** 167 males, 162 females **Symptom duration:** mean duration of 9 years **Severity:** at least moderate degree **Inclusion criteria:** patients with nonspecific rhinitis symptoms of at least moderate degree for at least 4 days per week during the month before entering the study; a negative skin prick test to a standard test panel; a score of ≥ 2 for rhinorrhoea or congestion and at least a moderate score during the month prior to the trial for at least 1 hour daily and for at least 4 days per week. **Exclusion criteria:** intolerance to aspirin or NSAIDs; significant septal deviations or other structural deformities, nasal polyps; use of prohibited medications (topical nasal, ocular or oral decongestants, nasal saline, shortor long-acting antihistamines (for 24 to 72 hours); nasal atropine or ipratropium bromide, ketotifen, azelastine and intranasal or ocular corticosteroids (for 1 to 2 weeks); investigational drugs, high potency dermatological corticosteroids group III--IV (Nordic classification), inhaled, oral, intravenous, rectal or intramuscular cortico-steroids (for 1 to 3 months).
Interven-tions	**Intervention group:** mometasone furoate (n = 167) Dose: 200 µg Frequency: once daily Duration: 6 weeks Vehicle: spray **Comparator group:** placebo (constituents not described) (n = 162) **Use of additional interventions:** as a rescue medication Clarityn (loratadine) 10 mg was dispensed by the physician at baseline and, if needed, at visits 3 and 4.

Table continued

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

Risk of bias

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

Löfkvist 1976

Methods	Double-blind, cross-over, placebo-controlled trial with 4 weeks treatment, 1 week wash-out, 4 weeks placebo or in reverse order. Randomisation is unclear
Participants	**Setting:** university hospital in Lund, Sweden **Sample size:** **Number randomised:** 39 **Number completed:** 39 **Participant (baseline) characteristics:** **Age:** 19 to 66 years (mean 39 years) **Gender:** 19 males, 20 females **Symptom duration:** half of the patients had had symptoms for more than 10 years **Severity:** not reported **Inclusion criteria:** patients with a history of vasomotor rhinitis for many years, who had perennial symptoms in the form of obstruction, nasal drip, sneezing and nasal itching in varying degrees, and had negative allergy testing. **Exclusion criteria:** nasal polyposis, obvious septum deviation, bronchial asthma, pregnancy, or influenza-like disease.
Interventions	**Intervention group:** beclomethasone dipropionate (n = 19) Dose: 50 µg (300 µg daily dose) Frequency: 3 times per day Duration: 4 weeks Vehicle: spray **Comparator group:** placebo (constituents not described) (n = 20) **Use of additional interventions:** none
Outcomes	**1. Total nasal symptom score** Reported as a mean values and SD, in Figure 1 of the publication Time points day 1, weeks 1 to 9 Assessed via 4 symptoms nasal catarrh, blockage, nasal itching and sneezing, each measured on a scale of 0 to 3 Possible scores from 0 to 12 **2. Individual nasal symptom scores** For nasal catarrh, blockage, nasal itching and sneezing, each measured on a scale of 0 to 3 Reported as a mean values and SD, in Figure 1 of the publication Time points day 1, weeks 1 to 9 **3. Patient's subjective evaluation of therapeutic effect** Patients rated improvement after beclomethasone or placebo periods Originally reported as "free of trouble", "improved", "unchanged" or "worsened" We converted this into "responder", to include "free of trouble", "improved" and "non-responder", to include "unchanged" or "worsened"
Funding sources	Glaxo Lakemedel AB, Sweden; Alfred Osterlund's Stiftelse, Malmo, Sweden

Table continued

Declarations of interest	None declared
Notes	Patients rated improvement after beclomethasone or placebo periods. Originally reported as "free of trouble", "improved", "unchanged" or "worsened", converted into "responder", to include "free of trouble", "improved", and "non-responder", to include "unchanged" or "worsened".

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Randomisation not described
Allocation concealment (selection bias)	High risk	Randomisation not described
Blinding of participants and personnel (performance bias)	Unclear risk	Double-blind study, not further described. Nasal sprays were in identical packages so blinding could have been possible. Symptom scores could have been influenced by inadequate blinding, cortisol levels not likely.
Blinding of outcome assessment (detection bias)	Unclear risk	See above
Incomplete outcome data (attrition bias)	Unclear risk	One patient withdrew due to influenza-simulating disease during beclomethasone treatment. It is unclear what happened with this patient's data. Plasma cortisol levels reported for 19 patients only.
Selective reporting (reporting bias)	Unclear risk	Medical examination results not reported numerically, however given this is not an important outcome, we judged the risk of bias as unclear.
Other bias	Unclear risk	Cross-over design with no clear signs of randomisation.

Malm 1976

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

Table continued

Notes	Cross-over trial. Only overall summary data available for each intervention. Randomisation unclear. Beclomethasone dipropionate 200 µg, 400 µg and 800 µg daily versus placebo. 2-week treatments each, no wash-out period. Patients assigned to 4 treatment sequences to go through all interventions in different orders. Dosage of 400 µg daily included in meta-analysis. Not clarified how many patients per treatment sequence. Calculated a total nasal symptom score from means rhinorrhoea, blockage and sneezing and calculated a pooled SD. Remarkable decrease in symptom scores from baseline in Malm 1976 (60% decrease from baseline) and Malm 1981 (75% decrease from baseline) studies.

Risk of bias

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

Malm 1981

Methods	Double-blind, cross-over, randomised controlled trial with 2 weeks run-in period; 2 weeks treatment; 1 week wash-out; 2 weeks treatment; 1 week wash-out; 2 weeks treatment; 1 week wash-out; 2 weeks treatment
Participants	**Setting:** university hospital in Lund, Sweden **Sample size:** **Number randomised:** 23 patients randomised **Number completed:** 22 **Participant (baseline) characteristics:** **Age:** 20 to 68 years (mean: 42 years) **Gender:** 5 males, 17 females **Symptom duration:** at least 1 year **Severity:** not reported **Inclusion criteria:** patients with perennial non-allergic rhinitis with 2 or more of the symptoms of nasal obstruction, nasal secretion, sneezing attacks for at least 1 year, and negative skin prick test. **Exclusion criteria:** bronchial asthma or nasal polyposis.
Interventions	**Intervention groups:** budesonide (n = 22) Doses: 50 µg daily, 200 µg daily and 800 µg per day (cross-over study design) Frequency: 1 puff in each nostril, twice a day (morning and evening) Duration: 2 weeks Vehicle: pressurised aerosol **Comparator group:** placebo (constituents not described) (n = 22) **Use of additional interventions:** phenylpropanolamine as rescue medication was allowed
Outcomes	**1. Nasal obstruction** Measured by patient Scale of 0 to 3 (0 is good) Reported as mean ± SEM of at least 3 days of the patient's symptom score in each treatment period **2. Nasal secretion** As above **3. Sneezing** Measured by patient Scale of 0 to 3 (0 is good: no sneezing = 0; 1 to 5 sneezes = 1 point; 6 to 15 = 2 points; more than 15 sneezes = 3 points) Reported as above **4. Nasal airway resistance** Measured via rhinomanometry: nasal resistance parameter v2 Measured once at the end of the first week of the run-in period and then on the day after each treatment period Reported in degrees, 0 to 360 theoretically, wider angles correspond to higher levels of resistance, low score is good **5. Treatment side effects**
Funding sources	AB Draco, a subsidiary of AB Astra

Table continued

Declarations of interest	None declared
Notes	This is a cross-over trial. Budesonide 50 µg, 200 µg and 800 µg daily versus placebo. 2-week run-in, 2-week treatment each, 1-week wash-out period. Dosage 200 µg daily included in the meta-analysis. 22 patients, however: 3 patients with no nasal obstruction and 1 patient with no sneezing attacks during the trial were excluded. Another patient from the originally randomised patients was excluded for social reasons. Outcomes: nasal obstruction, nasal secretion, sneezing; patient-reported, scale of 0 to 3, reported as mean ± SEM of at least 3 days of the patient's symptom score in each treatment period. Calculated a total nasal symptom score from means for rhinorrhoea, blockage and sneezing and calculated a pooled SD. Remarkable decrease in symptom scores from baseline in Malm 1976 (60% decrease from baseline) and Malm 1981 (75% decrease from baseline) studies. Involvement of AB Draco, a subsidiary of AB Astra, a pharmaceutical company, is unclear.

Risk of bias

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

Meltzer 1994

Methods	Double-blind, multi-centre, parallel-group, randomised, placebo-controlled trial with 4 weeks duration of treatment
Participants	**Setting:** Allergy and Asthma Research Centre, part of multi-centre trial **Sample size:** **Number randomised:** 286 non-allergic rhinitis patients **Number completed:** 286 non-allergic rhinitis patients **Participant (baseline) characteristics:** **Age:** not reported **Gender:** not reported **Symptom duration:** at least 4 of 7 days prior to receiving study drug **Severity:** nasal symptom scores of > 150 of 400 possible points for sneezing, rhinorrhoea, nasal obstruction and post-nasal drip and, on those 4 days the severity of at least 1 of the 4 symptoms must have been at least 50 of 100 points **Inclusion criteria:** 1) history of non-allergic rhinitis; 2) total serum immunoglobulin E (IgE) level < 250 IU-ml; 3) negative SPT; 4) normal sinus radiograph. **Exclusion criteria:** not defined, see inclusion criteria.
Interventions	**Intervention group:** FPANS (fluticasone propionate) 100 µg or 200 µg twice daily **Comparator group:** placebo **Use of additional interventions:** none
Outcomes	Reduction of nasal symptom scores, particularly obstruction, overall assessment of response to therapy: unclear definition, scale/range of nasal symptom scores.
Funding sources	None declared
Declarations of interest	None declared
Notes	No numerical data for non-allergic rhinitis group separately, only note that FPANS in non-allergic rhinitis reduces total symptoms, improves individual symptoms, mainly obstruction, and achieves significant overall improvement.

Risk of bias

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

Miller 1969

Methods	Double-blind, cross-over, quasi-randomised (serial assignment into 2 groups) controlled trial with 2 months total: 1 month on one treatment, then another month on another. No wash-out period described
Participants	**Setting:** unclear, likely private office, USA **Sample size:** **Number randomised:** 90 patients randomised, 88 reported **Number completed:** 88 **Participant (baseline) characteristics:** **Age:** nearly all were adults, except 4 boys (9 to 14 years of age), 1 girl of 17 years of age. Most patients were between 31 and 60 years of age **Gender:** 61 female, 27 male **Symptom duration:** not reported **Severity:** not reported **Inclusion criteria:** vasomotor rhinitis, as defined by physical examination (reactive non-allergic nasal membranes), skin testing where appropriate and absence of allergic history. **Exclusion criteria:** pregnancy, active tuberculosis, ocular herpes simplex, acute or chronic infection, or other contraindication to adrenocortical hormone therapy, use of medication for vasomotor rhinitis from 1 week before the trial until the end of the trial.

Table continued

Interventions	**Intervention groups:** dexamethasone (n = 88) Doses: 0.084 mg of dexamethasone per spray, 2 sprays in each nostril (672 µg to 1008 µg of dexamethasone per day) Frequency: 2 to 3 times per day Duration: 1 month (no wash-out period) Vehicle: aerosol container **Comparator group:** placebo (inactive ingredients) (n = 88) **Use of additional interventions:** none
Outcomes	**1. Response to therapy** Measured on a scale: 100% = excellent; 75% to 99% = good; 50% to 74% = fair; < 50% = poor Measured at 1 month after treatment Data could be used for numerical analysis **2. Nasal obstruction** Measured by patient at 2 and 4 weeks after treatment Scale 0 to 3, 0 is good Reported as mean; SD recalculated based on P value **3. Discharge** Same as above Data not included given P value not presented **4. Post-nasal drip** Same as above Data not included **5. Sneezing** Same as above Data not available **6. Anosmia** Same as above Data not available **7. Side effects** Headache: data available
Funding sources	None
Declarations of interest	None declared
Notes	No wash-out period in cross-over study. Vasomotor rhinitis patients. Only 1 patient had polyps, so decided that contamination was not an issue. 5 patients were below 18 years of age, but given that the majority appeared to be over 12 we decided to include all patients. Reported means for secretion, obstruction and post-nasal drip, however we were not able to calculate a SD for secretion and post-nasal drip as the P value was not reported, only the mean. So we can calculate a TNSS of obstruction, secretion and post-nasal drip, but we cannot calculate a pooled SD, making this outcome useless.

Risk of bias

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

O'Reilly 1991

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

Table continued

Outcomes	**1. Nasal obstruction** Measured on a scale of 0 to 5 Reported as P values only **2. Anterior rhinorrhoea** As above **3. Posterior rhinorrhoea** As above **4. Sneezing** As above **5. Facial pain** As above **6. Total nasal symptom score** Composite score for all 5 symptoms Reported only as P values **7. Rhinomanometry** Using Brom's method with the symptom scoring Not reported given too wide a variation between baseline and placebo values **8. Adverse reactions** Not specified
Funding sources	None
Declarations of interest	None declared
Notes	No wash-out period. 7 out of 23 dropout rate. Only P values reported, no means and SDs.

Risk of bias

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

Scadding 1995

Methods	Double-blind, parallel-group, randomised controlled trial with 2-week run-in period, 12 weeks of treatment
Participants	**Setting:** 36 centres in Western Europe **Sample size:** **Number randomised:** 516 patients with allergic and non-allergic rhinitis were randomised (106 withdrawals before randomisation). **Number completed:** 371 patients with allergic and non-allergic rhinitis were included in analysis, of which 188 were patients with non-allergic rhinitis reported (50 with fluticasone propionate once daily, 49 with fluticasone propionate twice daily, 43 with beclomethasone, 46 with placebo). **Participant (baseline) characteristics:** **Age:** not described separately for non-allergic rhinitis group, range 10 to 83 **Gender:** percentage of females in the overall groups ranged 50% to 57% in different arms **Symptom duration:** 5 or more of the 14-day period **Severity:** moderate to severe (score of 2 or 3 on a 0 to 3 scale) Not described for non-allergic rhinitis group separately, overall homogenous for combined allergic and non-allergic rhinitis **Inclusion criteria:** patients aged over 12 years with a history of moderate to severe perennial rhinitis were recruited. Skin prick tests to common inhaled perennial allergens (house dust, house dust mite, cat, dog, moulds) were performed. Patients with negative skin prick test were classified as non-allergic. **Exclusion criteria:** allergic rhinitis, invalid or insufficient diary record card data, fewer than 2 symptoms of rhinitis at visit 1, insufficient symptoms in run-in, disallowed concurrent medication, baseline nasal infection and non-compliance.
Interventions	**Intervention groups:** fluticasone propionate once daily (n = 50) Doses: 200 µg per dose Frequency: once per day Duration: 12 weeks Vehicle: aqueous nasal spray **Comparator group:** fluticasone propionate twice daily (n = 49) As above, but twice a day **Comparator group:** beclomethasone dipropionate (n = 43) Doses: 200 µg per dose Frequency: twice per day Duration: 12 weeks Vehicle: aqueous nasal spray **Comparator group:** placebo (n = 46) Frequency of treatment not described Otherwise same as above **Use of additional interventions:** none

Table continued

Outcomes	**1. Nasal blockage on waking** Measured by patient on a scale of 0 to 3 on a daily card, 3 is severe **2. Nasal blockage during the rest of the day** As above **3. Sneezing** As above **4. Rhinorrhoea** As above **5. Overall assessment of symptoms** As above **6. Overall assessment of symptoms at clinic visit** VAS, 0 to 10 cm, 10 = worst symptoms **7. Adverse events** No numerical data
Funding sources	Glaxo Group Research ltd
Declarations of interest	None declared
Notes	Data not reported separately for non-allergic rhinitis group, but authors suggest that tests for interaction between rhinitis category and treatment were carried out and no interaction was found. Conclusion: their analysis suggests no differences based on allergic sensitisation.

Risk of bias

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

Schulz 1978

Methods	Double-blind, parallel-group, randomised controlled trial with 2-week baseline, 6 weeks of treatment
Participants	**Setting:** Division of Clinical Immunology and Allergy, Montreal General Hospital, Montreal, Canada **Sample size:** **Number randomised:** 69 with allergic and non-allergic rhinitis (perennial rhinitis) randomised **Number completed:** 60 (9 patients terminated early and excluded from analysis) (32 non-allergic rhinitis) **Participant (baseline) characteristics:** **Age:** 15 to 71 years **Gender:** in the combined allergic and non-allergic rhinitis population: 29 males, 40 females. Distribution for non-allergic rhinitis group not reported **Symptom duration:** not reported **Severity:** not described for non-allergic rhinitis group separately. In the combined allergic and non-allergic rhinitis population, there were no significant demographic or historical differences between treatment groups. During the 2-week baseline period, however, patients in the flunisolide group reported a greater number of hours with the symptom "stuffy nose" than patients in the placebo group. **Inclusion criteria:** perennial rhinitis, seasonal allergic rhinitis, including non-allergic rhinitis. **Exclusion criteria:** allergic rhinitis.
Interventions	**Intervention groups:** flunisolide (n = 14) Doses: 25 µg per spray, 2 sprays per nostril, 300 µg per day total for both sides Frequency: 3 times per day Duration: 6 weeks Vehicle: aqueous solution, via metered dose pump spray **Comparator group:** placebo (n = 18) Identical vehicle, without the flunisolide Otherwise same as above **Use of additional interventions:** none

Table continued

Outcomes	**1. Sneezing** Measured by patient on daily record chart Duration (in hours) measured **2. Stuffy nose** As above **3. Runny nose** As above **4. Nose blowing** As above **5. Post-nasal drip** As above **6. TNSS** All 5 symptoms combined to determine overall duration of patients' symptoms Reported as percentage of days during which all 5 of the symptoms lasted 1 hour or less and the percentage of days during which at least 1 of the 5 symptoms lasted 4 hours or more. **7. Overall effect of the test drug** Evaluated by patient at the end of treatment Measured as total control, substantial but not complete control, minor but definite control, no benefit and aggravated nasal symptoms Only data available for non-allergic rhinitis group
Funding sources	None
Declarations of interest	None declared
Notes	Most outcomes not available for non-allergic rhinitis group separately. Only data for non-allergic rhinitis (Table 2) were overall effect of symptoms (responder data) and this was recalculated into responder and non-responder data.

Risk of bias

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

Singh 2017

Methods	Non-blinded, parallel-group, randomised clinical study with 2 weeks duration of treatment
Participants	**Setting:** the clinical EEC study and collection of biospecimens were conducted at Inflamax Research (Mississauga, ON, Canada) and the biospecimens were analysed at the University of Cincinnati **Sample size:** **Number randomised:** 30 **Number completed:** 30 **Participant (baseline) characteristics:** **Age:** AzeFlu (44.91 ± 6.77 years); placebo (42.43 ± 8.24 years) **Gender:** AzeFlu: female: 12, male: 8; placebo: female: 6, male **Symptom duration:** unclear **Severity:** unclear **Inclusion criteria:** NAVMR based on symptoms and triggers; nasal symptoms in response to a panel of non-allergic triggers, including CDA, in a NAVMR questionnaire. **Exclusion criteria:** positive test skin; mechanical obstruction; infection of the nasal cavity.

Table continued

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

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised trial. There was insufficient information on sequence generation.
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	High risk	As the primary outcomes of nasal symptom scores and adverse events are both self-reported outcomes and the study is not blinded, this has a high risk of bias.
Blinding of outcome assessment (detection bias)	High risk	See above
Incomplete outcome data (attrition bias)	Low risk	No loss to follow-up
Selective reporting (reporting bias)	High risk	For the most important outcome TNSS the outcomes are not reported; the authors only state: "The mean change in TNSS for the AzeFlu cohort (vs. placebo cohort) was reduced, but did not reach statistical significance. A similar numerical trend was observed, albeit to a lesser extent, for individual symptom scores of runny nose, post-nasal drip, and nasal congestion."
Other bias	Unclear risk	No other risks of bias could be distinguished.

Song 2018

Methods	Unclear blinded, parallel-group, randomised clinical study with 8 weeks treatment
Participants	**Setting:** Department of Otolaryngology, Head and Neck Surgery, Affiliated Hospital of Guizhou Medical Universtiy Guiyang, China **Sample size:** **Number randomised:** 120 (40 budesonide, 40 azelastine, 40 budesonide with azelastine) **Number completed:** 120 **Participant (baseline) characteristics:** **Age:** Group A (budesonide and azelastine) 42.4 ± 2.9 years; Group B (budesonide) 41.6 ± 2.7 years; Group C (azelastine) 43.8 ± 1.9 years **Gender:** general: male (M): 61, female (F): 59; Group A (budesonide and azelastine): M/F: 21/19; Group B (budesonide): M/F: 18/22; Group C (azelastine): M/F: 21/18 **Symptom duration:** not reported **Severity:** baseline VAS: **budesonide** (VAS: 6.81 ± 1.61); **azelastine** (VAS: 6.63 ± 1.85); **budesonide with azelastine** (VAS: 6.75 ± 1.48) **Inclusion criteria:** typical symptoms and characteristics of vasomotor rhinitis; negative skin prick test results; serum specific IgE (-); blood eosinophilia % < 5%; nasal secretion eosinophilia %< 5%. **Exclusion criteria:** allergic rhinitis, asthma, eczema, acute or chronic rhinosinusitis, nasal tumour, systemic or any disease that might influence the result of this study, usage of nasal, oral or systemic glucocorticoids, antihistamines, leukotriene receptor inhibitors, various blood decongestant or theophylline in last 3 months; involvement of any other clinical trials; allergy to glucocorticoid or antihistamine drugs; pregnancy or breastfeeding; healthcare workers for the study.
Interventions	**Intervention group: budesonide** (n = 40) Dose: 50 g/ puff, 2 puffs per nostril Frequency: 2 times per day: total dosage 400 µg Duration: 8 weeks Vehicle: spray **Comparator groups:** **Azelastine** (n = 40) Dose: 50g/ puff, 2 puffs per nostril Frequency: 2 times per day: total dosage 400 µg Duration: 8 weeks Vehicle: spray **Budesonide with azelastine** (n = 40) Dose: 50 g/puff, 2 puffs per nostril Frequency: 2 times per day: total dosage 400 µg Duration: 8 weeks Vehicle: spray **Use of additional interventions:** none

Table continued

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

Risk of bias

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

Spector 1980

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

Table continued

Outcomes	**1. Sneezing** Daily symptom diary Duration (in hours) measured per day **2. Stuffiness** Same as above **3. Runny nose** Same as above **4. Nose blowing** Same as above **5. Post-nasal drip** Same as above **6. Adverse effects** No data provided **TNSS:** patient evaluation, sum of 5 symptoms (sneezing, stuffiness, runny nose, nose blowing and post-nasal drip) numerically assessed as absent (1), mild (2), moderate (3) or severe (4) **7. Peak expiratory flow rate, nasal (PEFRn)** **8. Peak expiratory flow rate, mouth (PEFRm)** **9. Blockage index** (PEFRm-PEFRn)/PEFRm
Funding sources	Study funded in part by Syntex Corporation. The authors' relationship with the funder is unclear.
Declarations of interest	None declared
Notes	Women of childbearing potential excluded. Same study reported in Jones 1979, which however, did not provide numerical data on symptom scores (only Figure 1 in article with no SDs or P values). We have decided to include Spector 1980 and not Jones 1979. A PEFR was not obtained for all patients.

Risk of bias

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

Tantilipikorn 2010

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

Table continued

Outcomes	**1. Rhinorrhoea** Measured by patient on paper diary card, in AM and PM 4-point categorical scale of 0 to 3 (none, mild, moderate, severe) Measured as instantaneous (i) and over previous 12 hours (reflective) Instantaneous measured in AM, and reflective in both AM and PM Measured during screening and treatment periods **2. Nasal congestion** Same as above **3. Post-nasal drip** Same as above **4. Eye itching/burning** Same as above **5. Eye tearing/watering** Same as above **6. Eye redness** Same as above **7. rTNSS reflective total nasal symptom score** Combined 3 reflective individual nasal symptom scores Measured in AM and PM, which were averaged to arrive at the final daily value (daily rTNSS) Weekly data averaged **8. rTOSS reflective total ocular symptom score** Same as above, to derive daily rTOSS **9. AM iTOSS morning instantaneous predose TOSS** Obtained by summing of instantaneous pre-dose morning ocular scores **10. Adverse effects** Epistaxis and any other adverse events
Funding sources	GlaxoSmithKline
Declarations of interest	None declared
Notes	Some of the study authors were investigators for GlaxoSmithKline, while rest of the authors were its employees. However, the study shows negative outcomes and it is unlikely that the relationship with the company influenced the study results.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised study: "Subjects who fulfilled the randomization criteria were randomly assigned in a 1:1 ratio to receive either FFNS 110 mcg once daily or vehicle placebo nasal spray once daily with the first dose being administered in the clinic following device demonstration. Subjects were stratified into two groups based on nasal cytology: those with eosinophils constituting >5% or <5% of nasal white blood cells." The sequence generation is not described.
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	Unclear risk	Double-blind study, blinding is not further described.
Blinding of outcome assessment (detection bias)	Unclear risk	Double-blind study, blinding is not further described.
Incomplete outcome data (attrition bias)	Low risk	All patients reported
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	Some of the study authors were investigators for GlaxoSmithKline, while the rest of the authors were its employees. However, the study shows negative outcomes and it is unlikely that the relationship with the company influenced the study results.

Tarlo 1977

Methods	Double-blind, cross-over, randomised controlled trial with 6 weeks treatment, 6 months follow-up (BDA for 3 weeks and placebo for 3 weeks; the order of administration was randomised)
Participants	**Setting:** Chest Allergy Clinic of St. Joseph's Hospital in Hamilton **Sample size:** **Number randomised:** 26 patients with perennial rhinitis, 9 non-allergic rhinitis **Number completed:** 26 **Participant (baseline) characteristics:** **Age:** ranged from 15 to 61 years (mean 34 years) **Gender:** 16 male and 10 female **Symptom duration:** rhinitis had been present for 2 to 20 years (mean 8.6 years) **Severity:** not reported In the week prior to the start of the inhalers, the mean daily values for the symptom scores in the 26 patients was 4.5 for nasal congestion, 2.4 for rhinorrhoea, and 1.0 for sneezing (maximum 6 each). Both taste and smell were absent or impaired in 9, and smell alone was absent or impaired in 3. **Inclusion criteria:** unclear **Exclusion criteria:** not reported
Interventions	**Intervention group:** BDA (beclomethasone dipropionate aerosol (BDA), 50 µg 4 times daily sprayed into each nostril) (n = unclear) **Comparator group:** placebo: Freon propellant, same schedule (n = unclear) **Use of additional interventions:** none

Table continued

Outcomes	Recording of symptoms on dairy cards: the diary card was similar to that used by Norman and colleagues. Daily and nightly sneezing, nasal congestion and rhinorrhoea were each recorded as 0 if absent, 1 if they lasted less than 30 minutes, 2 if between 30 minutes and 2 hours, and 3 if longer than 2 hours. Taste and smell were recorded daily on the same card as normal, impaired or absent. NAIR (nasal airway resistance) was measured by a modification of the method of Taylor and Shivalkar. A tight-fitting skin diver's mask was applied over the patient's nose and eyes. This was connected to a pneumotachograph for measuring flow and to a pressure transducer for measuring the transnasal pressure between the inside of the mask and a mouthpiece held tightly between the teeth and lips. Flow and pressure were recorded on the y and x axes, respectively, of an x-y recorder, and NAIR was calculated from the slope of the tangent to the pressure-flow curve at a flow of 0.4 L/set. Before the use of the inhalers was started, NAIR was measured on 2 occasions. It was elevated (> 4 cm H,O/L/set) on one occasion in 6 and on both occasions in 10; borderline (3 to 4 cm H,O/L/sec) on one occasion in 4; normal (<b3 cm H,O/L/sec) on both occasions in 6. Total nasal symptoms: the sum of the nasal symptom scores (sneezing, congestion and rhinorrhoea, as well as the total) was measured during the third week of treatment Adverse events (no data for non-allergic rhinitis group separately), in general reported as mild
Funding sources	None
Declarations of interest	None declared
Notes	Limited numerical data for non-allergic rhinitis group separately. Polyps were present in 8 and asthma in 6 patients. 16 patients showed some evidence of increased IgE production. 9 patients had no signs of allergy and perennial rhinitis. Conclusions: After 6 months 6/9 were successfully treated with intranasal corticosteroids and 3/9 were unsuccessfully treated with intranasal corticosteroids. General conclusion: results in those in whom a possible allergic component could be identified were not different from those of the whole group.

Risk of bias

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

Turkeltaub 1982

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

Table continued

Funding sources	Syntex Corporation
Declarations of interest	None declared
Notes	Unconventional total nasal symptom score calculation. 15 patients excluded from perennial rhinitis group in efficacy assessment. Involvement of Syntex Corporation (a pharmaceutical company) is unclear.

Risk of bias

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

Varricchio 2011

Methods	Single-blind (patients not blinded), parallel-group, randomised, placebo-controlled trial with 8 weeks duration of treatment
Participants	**Setting:** 2 hospitals in Naples, Italy **Sample size:** **Number randomised:** 60 **Number completed:** 60 **Participant (baseline) characteristics:** **Age:** 21 to 63 years (mean 42.8 years) **Gender:** 39 male, 21 female **Symptom duration:** unclear **Severity:** unclear Not significant for age, gender, nasal score, turbinate hypertrophy, nasal cytology **Inclusion criteria:** patients with diagnosis of non-allergic rhinitis based on history of nasal symptoms (including sneezing, rhinorrhoea and nasal obstruction typically dependent on exposure to triggers such as odours, irritants, weather changes), presence of inflammatory cells on nasal smear, and negative SPT according to validated criteria. **Exclusion criteria:** acute or chronic upper respiratory infections, anatomic nasal defects, documented sensitisation (skin prick testing done to confirm), using intranasal or oral corticosteroids, nasal or oral decongestants, anti-leukotrienes, and intranasal or oral antihistamines during the previous 4 weeks, or had a history of chronic epistaxis, immunodeficiency, or hypersensitivity to flunisolide.
Interventions	**Intervention group:** flunisolide (n = 30) Dose: 0.5 mg/ml, 2 mL (1 mg) at each application, twice a day (total 2 mg per day) = 2000 µg/day Frequency: twice a day Duration: 8 weeks Vehicle: Rinowash nebuliser **Comparator group: placebo** (isotonic saline solution) (n = 30) **Use of additional interventions:** none
Outcomes	**1. Total symptom score**: 4 items (nasal itching, sneezing, rhinorrhoea and nasal obstruction) assessed on a scale of 0 to 3 Possible scores from 0 to 12 Lower score indicates better outcome Assessed on day 1 and 8 weeks **2. Adverse events** Unclear how assessed (only narrative results reported)
Funding sources	None
Declarations of interest	None declared
Notes	Comparisons made both between groups, as well as change of baseline. Very high dose of flunisolide 2 mg per day. Other studies used 200 µg to 400 µg per day.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomly assigned; random sequence generation was not described.
Allocation concealment (selection bias)	High risk	Allocation was not concealed from patients; single-blinded study.
Blinding of participants and personnel (performance bias)	High risk	Single-blind study: patients were not blinded.
Blinding of outcome assessment (detection bias)	Unclear risk	Assessing physicians were blinded, patients not; no more details on blinding of physicians. Symptom scoring by patients.
Incomplete outcome data (attrition bias)	Low risk	All patients enrolled in the study completed the 8-week trial.
Selective reporting (reporting bias)	Low risk	All data reported.
Other bias	Low risk	No others potential biases could be distinguished.

Warland 1982

Methods	Double-blind, cross-over, randomised, placebo-controlled trial with 4 weeks per treatment, 2-week interval between 2 treatment periods
Participants	**Setting:** University of Bergen, Norway **Sample size:** **Number randomised:** 34 patients suffering from perennial rhinitis, 22 allergic rhinitis patients, 12 vasomotor rhinitis patients **Number completed:** 12 vasomotor rhinitis patients reported **Participant (baseline) characteristics:** **Age:** mean 32.5 (range 16 to 76) **Gender:** 14 males, 20 females **Symptom duration:** mean 5.9 years **Severity:** 1 slight, 24 moderate, 9 severe **Inclusion criteria:** unclear. **Exclusion criteria:** patients who were pregnant, who were suffering from nasal obstruction due to nasal polyps, or who were taking corticosteroids were excluded from the trial.
Interventions	**Intervention groups:** flunisolide nasal solution: 200 µg per day (n = unclear) **Comparator group:** placebo (n = unclear) **Use of additional interventions:** none

Table continued

Outcomes	Daily record of overall severity of symptoms on a scale from 0 to 3 Sneezing, runny nose, nose blowing and post-nasal drip per individual nasal symptom on a scale from 0 to 4. Condition of nasal mucosa and quantity and aspect of nasal secretions. Conclusion: a statistically significant difference in favour of flunisolide nasal solution Vasomotor rhinitis: total effect: 0/12, substantial effect: 3/13, minor effect: 3/12
Funding sources	None
Declarations of interest	None declared
Notes	Flunisolide nasal solution seems to be effective in both allergic rhinitis as vasomotor rhinitis, although is seems to be more effective in an allergic state. Limited separate data for non-allergic rhinitis subgroup versus allergic rhinitis subgroup. No numerical data for non-allergic rhinitis subgroup for one of the outcomes from our protocol.

Risk of bias

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

Webb 2002

Methods	Double-blind, double-dummy, parallel-group, randomised, placebo-controlled trial with 7 days screening, 28 days treatment
Participants	**Setting:** clinic patients, Allergy and Asthma Research Associates, USA. Reported as integrated data from 2 multi-centre trials and 1 single-centre trial **Sample size:** **Number randomised:** 983 **Number completed:** 651 **Participant (baseline) characteristics:** **Age:** range 12 to 83 years; mean 41 to 43 years **Gender:** % males 34% to 39% in 3 treatment groups **Symptom duration:** more than 1 year **Severity:** as above **Ethnicity:** 93% to 96% Caucasian No differences between groups for age, gender, ethnicity, duration of symptoms, % NARES and baseline TNSS (overall, in NARES and in non-NARES) **Inclusion criteria:** perennial non-allergic rhinitis, negative skin tests to all geographically relevant allergens. Symptom severity 150 on TNSS on at least 4 of 7 days immediately preceding randomisation **Exclusion criteria:** other rhinitis medications (e.g. antihistamines)
Interventions	**Parallel-group study:** a. Fluticasone propionate 200 µg daily b. Fluticasone propionate 400 µg daily **Included in meta-analysis:** Fluticasone propionate 400 µg daily (n = 325) Doses: 400 µg daily Frequency: twice daily Duration: 28 days Vehicle: aqueous solution Device: aqueous nasal spray **Comparator group:** placebo (n = 326) Vehicle without active ingredient Otherwise same as above **Use of additional interventions:** none

Table continued

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

Risk of bias

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

AZENS: azelastine nasal spray
BDA: beclomethasone dipropionate aerosol
BMI: body mass index
ECG: electrocardiogram
FDA: (US) Food and Drug Administration
FFNS: fluticasone furoate nasal spray
FP: fluticasone propionate
FPANS: fluticasone propionate aqueous nasal spray
FPNS: fluticasone propionate nasal spray
MCA: minimal cross-sectional area
N/A: not available
NANIPER: non-allergic, non-infectious perennial rhinitis
NARES: non-allergic rhinitis with eosinophilia syndrome
NAVMR: non-allergic vasomotor rhinitis
NSAID: non-steroidal anti-inflammatory drug
PEF: peak expiratory flow
PEFR: peak expiratory flow rate
PNIF: peak nasal inspiratory flow
RAST: radioallergosorbent
RCT: randomised controlled trial
RQLQ: Rhinoconjunctivitis Quality of Life Questionnaire
rTNSS: reflective total nasal symptom score
rTOSS: reflective total ocular symptom score

SD: standard deviation
SEM: standard error of the mean
SNOT-22: Sinonasal Outcomes Test 22
SPT: skin prick test
TNSS: reflective total nasal symptom score
TOSS: total ocular symptom score
URTI: upper respiratory tract infection
VAS: visual analogue scale
VMR: vasomotor rhinitis

CHARACTERISTICS OF EXCLUDED STUDIES

Adamopoulos 1995

Reason for exclusion Neither numerical nor narrative data available for non-allergic rhinitis subgroup

Arbesman 1983

Reason for exclusion Neither numerical nor narrative data available for non-allergic rhinitis subgroup

Astafieva 2012

Reason for exclusion COMPARISON: this study compared 2 types of intranasal corticosteroids, brand versus generic. This was not included in our protocol.

Balle 1982

Reason for exclusion Neither numerical nor narrative data available for non-allergic rhinitis subgroup

Berger 2012

Reason for exclusion Neither numerical nor narrative data available for non-allergic rhinitis subgroup

Bernstein 1997

Reason for exclusion Neither numerical nor narrative data available for non-allergic rhinitis subgroup

Blair 1977

Reason for exclusion Neither numerical nor narrative data available for non-allergic rhinitis subgroup

Bunnag 1992

Reason for exclusion Neither numerical nor narrative data available for non-allergic rhinitis subgroup

Celiker 2011

Reason for exclusion COMPARISON: this study compared intranasal corticosteroids with radiofrequency ablation. This comparison was not included in our protocol.

Chatterjee 1974

Reason for exclusion Neither numerical nor narrative data available for non-allergic rhinitis subgroup

Dieges 1978

Reason for exclusion Neither numerical nor narrative data available for non-allergic rhinitis subgroup

Dockhorn 1999

Reason for exclusion Neither numerical nor narrative data available for non-allergic rhinitis subgroup

Gibson 1974

Reason for exclusion Neither numerical nor narrative data available for non-allergic rhinitis subgroup

Hansen 1974

Reason for exclusion Neither numerical nor narrative data available for non-allergic rhinitis subgroup

Harding 1976

Reason for exclusion Neither numerical nor narrative data available for non-allergic rhinitis subgroup

Hartley 1985

Reason for exclusion Neither numerical nor narrative data available for non-allergic rhinitis subgroup

Haye 1993

Reason for exclusion Neither numerical nor narrative data available for non-allergic rhinitis subgroup

Jones 1979

Reason for exclusion Neither numerical nor narrative data available for non-allergic rhinitis subgroup

Joubert 1983

Reason for exclusion Neither numerical nor narrative data available for non-allergic rhinitis subgroup

Juniper 1993

Reason for exclusion Neither numerical nor narrative data available for non-allergic rhinitis subgroup

Kakumanu 2003

Reason for exclusion Neither numerical nor narrative data available for non-allergic rhinitis subgroup

Kivisaari 1998

Reason for exclusion Neither numerical nor narrative data available for non-allergic rhinitis subgroup

Kohan 1989

Reason for exclusion Neither numerical nor narrative data available for non-allergic rhinitis subgroup

Lahdensuo 1977

Reason for exclusion Neither numerical nor narrative data available for non-allergic rhinitis subgroup

Lau 1990

Reason for exclusion Neither numerical nor narrative data available for non-allergic rhinitis subgroup

Lebowitz 1993

Reason for exclusion Neither numerical nor narrative data available for non-allergic rhinitis subgroup

Malmberg 1988

Reason for exclusion Neither numerical nor narrative data available for non-allergic rhinitis subgroup

McAllen 1969

Reason for exclusion Neither numerical nor narrative data available for non-allergic rhinitis subgroup

McAllen 1980

Reason for exclusion Neither numerical nor narrative data available for non-allergic rhinitis subgroup

Negreiros 1975

Reason for exclusion Neither numerical nor narrative data available for non-allergic rhinitis subgroup

Price 2013

Reason for exclusion The authors were contacted, but suggested "the subpopulation studied with NAR is too small from which to draw any meaningful conclusions

Rusnak 1981

Reason for exclusion Neither numerical nor narrative data available for non-allergic rhinitis subgroup

Scadding 1991

Reason for exclusion Neither numerical nor narrative data available for non-allergic rhinitis subgroup

Shaw 1979

Reason for exclusion Neither numerical nor narrative data available for non-allergic rhinitis subgroup

Small 1982

Reason for exclusion No data were provided in the results for the placebo group

Svendsen 1989

Reason for exclusion Neither numerical nor narrative data available for non-allergic rhinitis subgroup

Sy 1979

Reason for exclusion Neither numerical nor narrative data available for non-allergic rhinitis subgroup

Synnerstad 1996

Reason for exclusion This was a parallel-group, open-label (non-blinded) randomised study of budesonide versus beclomethasone dipropionate nasal sprays. In addition to obvious high risk of bias for allocation concealment, blinding of participants and personnel, and blinding of outcome assessors, the study had issues with incomplete outcome data, and some issues with selective outcome reporting (individual nasal symptoms measured but not thoroughly reported, total nasal symptoms reported but not included in methods). This study was supported by a grant from Astra Draco AB, Lund, Sweden, and the second author worked for the company. The company provided budesonide (Rhinocort). The study suggested that budesonide was better than beclomethasone. There are significant grounds to suspect high risk of bias. Based on these observations combined with incomplete and selective outcome data reporting little to no valuable numerical or descriptive outcome data, we decided to exclude this study.

Turner Warwick 1980

Reason for exclusion Neither numerical nor narrative data available for non-allergic rhinitis subgroup

Webb 1977

Reason for exclusion Neither numerical nor narrative data available for non-allergic rhinitis subgroup

Weckx 2001

Reason for exclusion Neither numerical nor narrative data available for non-allergic rhinitis subgroup

Wight 1992

Reason for exclusion Neither numerical nor narrative data available for non-allergic rhinitis subgroup

Zucker 2019

Reason for exclusion Meta-analysis with the only relevant study already included in our review

Characteristics of ongoing studies

NCT04002349

Methods	Randomised, parallel-group clinical trial
Participants	Non-allergic rhinitis patients
Interventions	Placebo (0.9% natural saline spray), budesonide nasal spray (Rhinocort), levocabastine nasal spray, combined treatment
Outcomes	Unclear
Starting date	1 July 2019
Contact information	Principal investigators: Luo Zhang MD; Yifan Meng, PhD Beijing Tongren Hospital, Beijing, China Email: dr.luozhang@gmail.com; mengyifan1015@126.com
Notes	**Estimated study completion date: 31 March 2020**

DATA AND ANALYSES

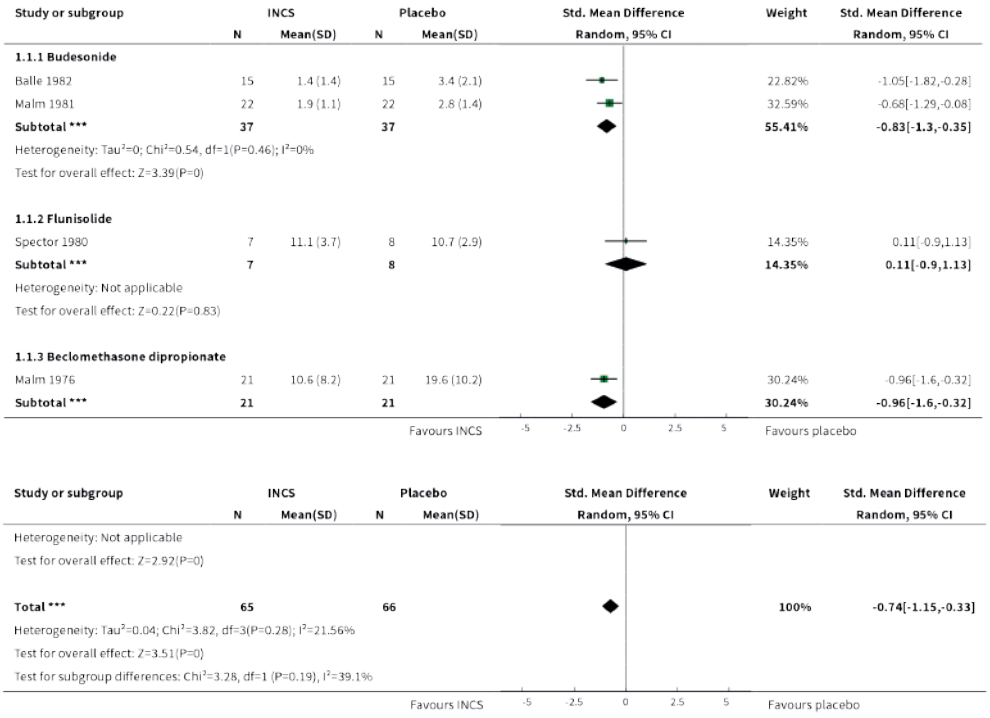
Comparison 1. Intranasal corticosteroids versus placebo

Outcome or Subgroup	Studies	Partic-ipants	Statistical Method	Effect Estimate
1.1 Total nasal symptom score, follow-up ≤ 4 weeks	4	131	Std. Mean Difference (IV, Random, 95% CI)	-0.74 [-1.15, -0.33]
1.1.1 Budesonide	2	74	Std. Mean Difference (IV, Random, 95% CI)	-0.83 [-1.30, -0.35]
1.1.2 Flunisolide	1	15	Std. Mean Difference (IV, Random, 95% CI)	0.11 [-0.90, 1.13]
1.1.3 Beclomethasone dipropionate	1	42	Std. Mean Difference (IV, Random, 95% CI)	-0.96 [-1.60, -0.32]
1.2 Total nasal symptom score, follow-up > 4 weeks	3	85	Std. Mean Difference (IV, Random, 95% CI)	-0.24 [-0.67, 0.20]
1.2.1 Fluticasone propi-onate	1	31	Std. Mean Difference (IV, Random, 95% CI)	-0.17 [-0.87, 0.54]
1.2.2 Flunisolide	2	54	Std. Mean Difference (IV, Random, 95% CI)	-0.28 [-0.84, 0.27]
1.3 Total nasal symptom score (change from base-line), follow-up ≤ 4 weeks	4	1465	Std. Mean Difference (IV, Random, 95% CI)	-0.54 [-1.18, 0.10]
1.3.1 Fluticasone furoate (110 µg fluticasone furoate equals around 200 µg FP, BUD or BDP)	2	794	Std. Mean Difference (IV, Random, 95% CI)	-0.62 [-1.72, 0.47]
1.3.2 Budesonide	1	20	Std. Mean Difference (IV, Random, 95% CI)	-0.74 [-1.65, 0.17]
1.3.3 Fluticasone propi-onate	1	651	Std. Mean Difference (IV, Random, 95% CI)	-0.24 [-0.40, -0.09]
1.4 Significant adverse event: epistaxis	4	1174	Risk Difference (M-H, Fixed, 95% CI)	0.04 [0.01, 0.06]
1.4.1 Fluticasone furoate (110 µg fluticasone furoate equals around 200 µg FP, BUD or BDP)	2	801	Risk Difference (M-H, Fixed, 95% CI)	0.02 [-0.00, 0.05]
1.4.2 Budesonide	1	44	Risk Difference (M-H, Fixed, 95% CI)	0.05 [-0.07, 0.16]
1.4.3 Mometasone furoate	1	329	Risk Difference (M-H, Fixed, 95% CI)	0.07 [0.01, 0.13]
1.5 Objective measure-ment of airflow: peak flow rate (expiratory)	1	11	Std. Mean Difference (IV, Random, 95% CI)	0.78 [-0.47, 2.03]

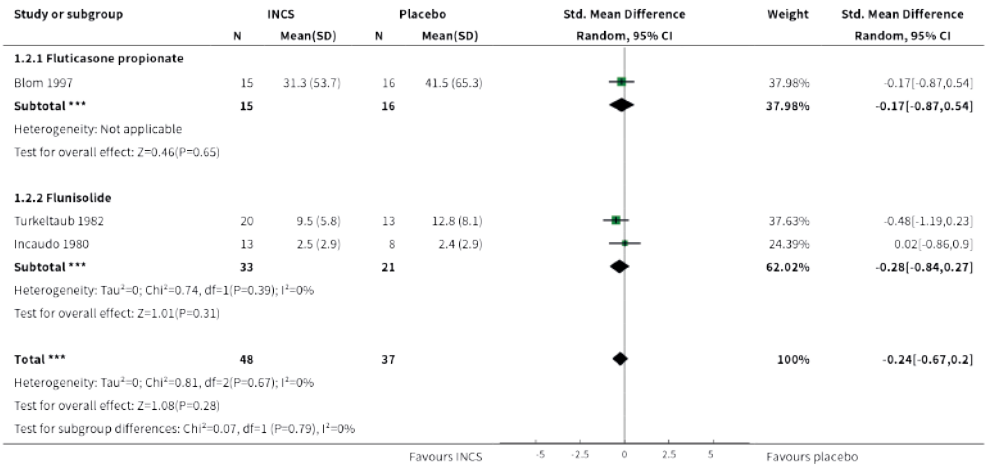
Table continued

1.6 Objective measurement of airflow: rhinomanometry	1	44	Std. Mean Difference (IV, Fixed, 95% CI)	-0.46 [-1.06, 0.14]
1.7 Other adverse events	3	1130	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.87, 1.12]
1.7.1 Fluticasone furoate (110 µg fluticasone furoate equals around 200 µg FP, BUD or BDP)	2	801	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.81, 1.16]
1.7.2 Mometasone furoate	1	329	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.87, 1.19]

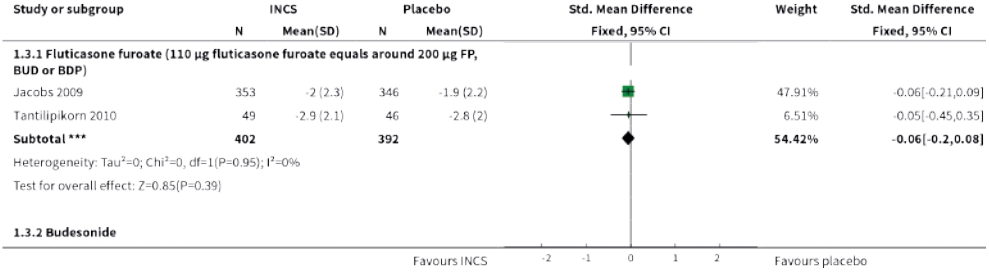
Analysis 1.1. Comparison 1 Intranasal corticosteroids versus placebo, Outcome 1 Total nasal symptom score, follow-up ≤ 4 weeks.

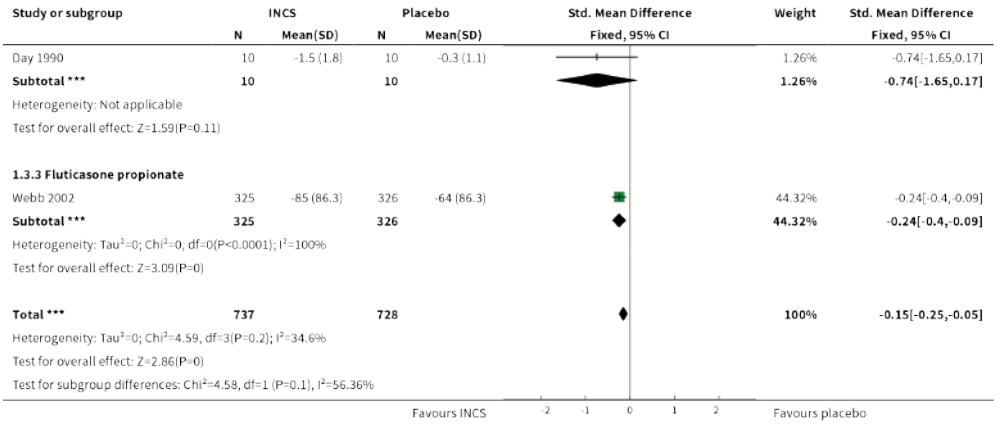


Analysis 1.2. Comparison 1 Intranasal corticosteroids versus placebo, Outcome 2 Total nasal symptom score, follow-up > 4 weeks.

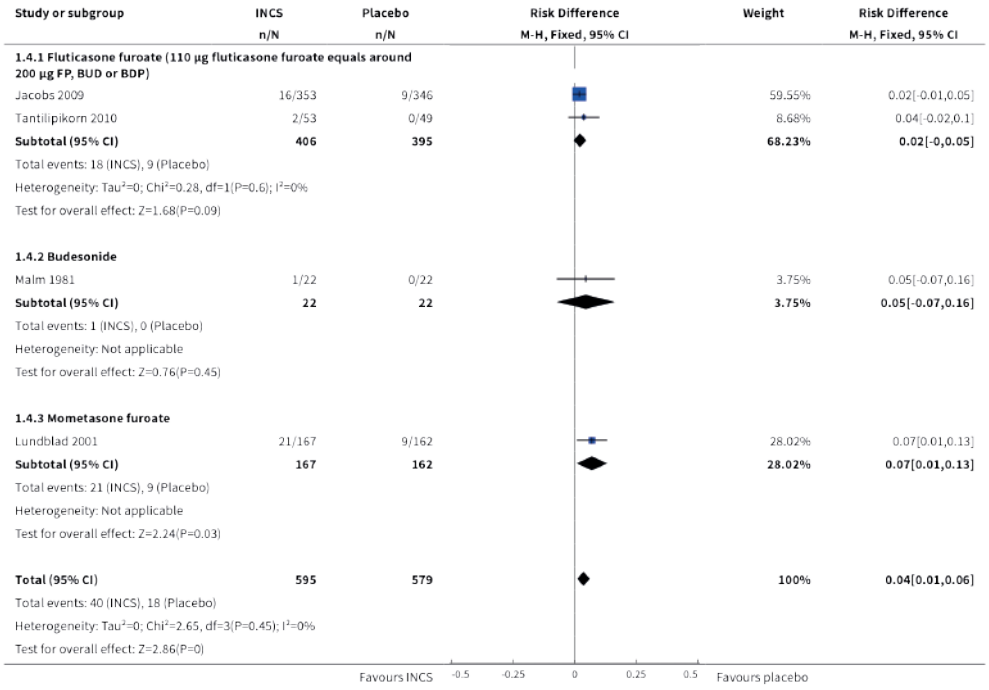


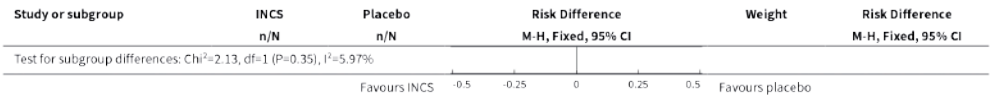
Analysis 1.3. Comparison 1 Intranasal corticosteroids versus placebo, Outcome 3 Total nasal symptom score (change from baseline), follow-up ≤ 4 weeks.



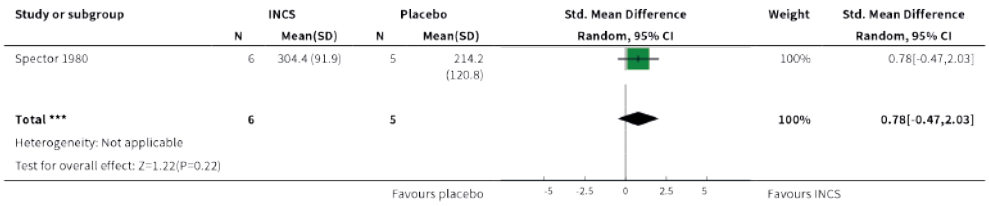


Analysis 1.4. Comparison 1 Intranasal corticosteroids versus placebo, Outcome 4 Significant adverse event: epistaxis.

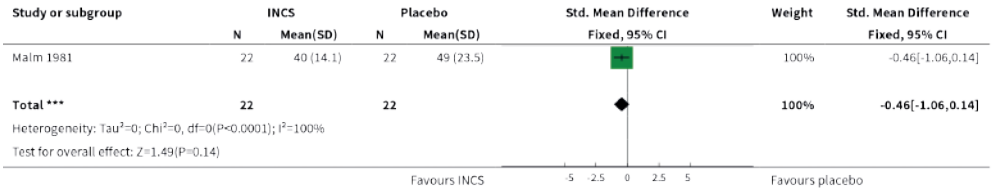




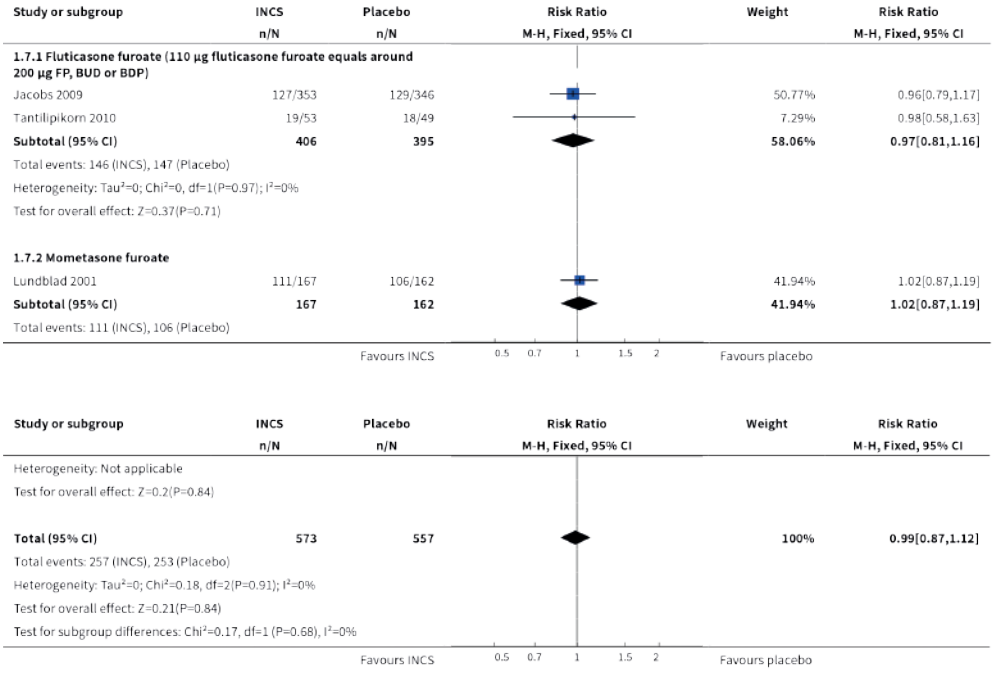
Analysis 1.5. Comparison 1 Intranasal corticosteroids versus placebo, Outcome 5 Objective measurement of airflow: peak flow rate (expiratory).



Analysis 1.6. Comparison 1 Intranasal corticosteroids versus placebo, Outcome 6 Objective measurement of airflow: rhinomanometry.



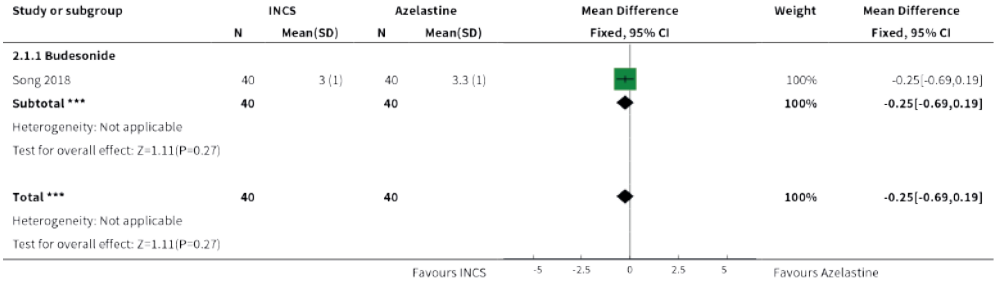
Analysis 1.7. Comparison 1 Intranasal corticosteroids versus placebo, Outcome 7 Other adverse events.



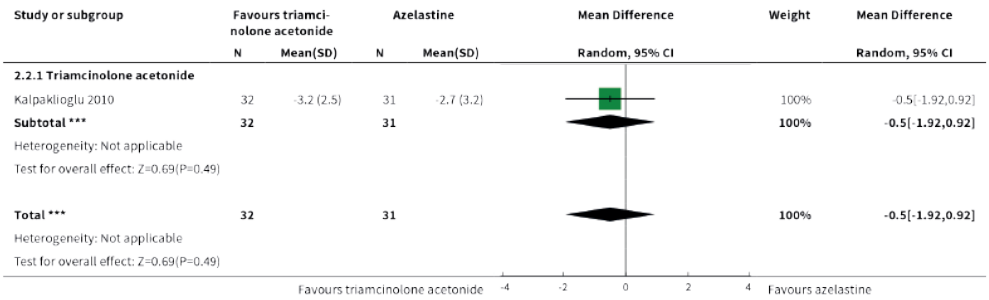
Comparison 2. Intranasal corticosteroids versus intranasal antihistamine

Outcome or Subgroup	Studies	Partic-ipants	Statistical Method	Effect Estimate
2.1 Total nasal symptom score, follow-up > 4 weeks	1	80	Mean Difference (IV, Fixed, 95% CI)	-0.25 [-0.69, 0.19]
2.1.1 Budesonide	1	80	Mean Difference (IV, Fixed, 95% CI)	-0.25 [-0.69, 0.19]
2.2 Total nasal symptom score (change from base-line), follow-up ≤ 4 weeks	1	63	Mean Difference (IV, Random, 95% CI)	-0.50 [-1.92, 0.92]
2.2.1 Triamcinolone acetonide	1	63	Mean Difference (IV, Random, 95% CI)	-0.50 [-1.92, 0.92]
2.3 Quality of life (SF-12v2)	1	80	Mean Difference (IV, Fixed, 95% CI)	-1.30 [-3.60, 1.00]
2.3.1 Budesonide	1	80	Mean Difference (IV, Fixed, 95% CI)	-1.30 [-3.60, 1.00]
2.4 Objective measure-ment of airflow: inspi-ratory peak flow rate (change from baseline)	1	63	Mean Difference (IV, Random, 95% CI)	-6.17 [-15.25, 2.91]
2.4.1 Triamcinolone acetonide	1	63	Mean Difference (IV, Random, 95% CI)	-6.17 [-15.25, 2.91]
2.5 Other adverse events	1	80	Risk Ratio (M-H, Fixed, 95% CI)	2.00 [0.19, 21.18]
2.5.1 Budesonide	1	80	Risk Ratio (M-H, Fixed, 95% CI)	2.00 [0.19, 21.18]

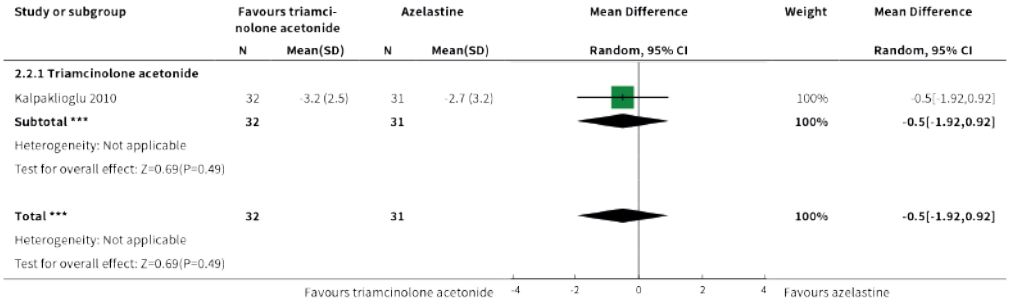
Analysis 2.1. Comparison 2 Intranasal corticosteroids versus intranasal antihistamine, Outcome 1 Total nasal symptom score, follow-up > 4 weeks.



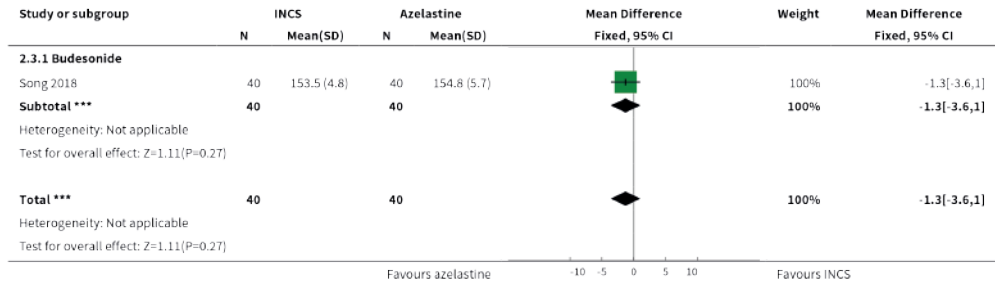
Analysis 2.2. Comparison 2 Intranasal corticosteroids versus intranasal antihistamine, Outcome 2 Total nasal symptom score (change from baseline), follow-up ≤ 4 weeks.



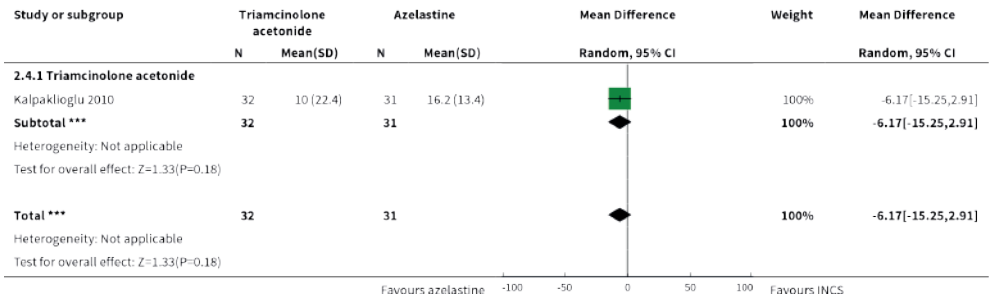
Analysis 2.2. Comparison 2 Intranasal corticosteroids versus intranasal antihistamine, Outcome 2 Total nasal symptom score (change from baseline), follow-up ≤ 4 weeks.



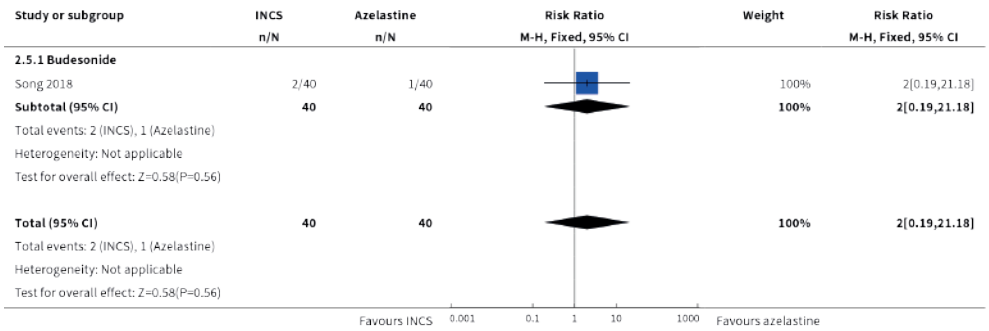
Analysis 2.3. Comparison 2 Intranasal corticosteroids versus intranasal antihistamine, Outcome 3 Quality of life (SF-12v2).



Analysis 2.4. Comparison 2 Intranasal corticosteroids versus intranasal antihistamine, Outcome 4 Objective measurement of airflow: inspiratory peak flow rate (change from baseline).



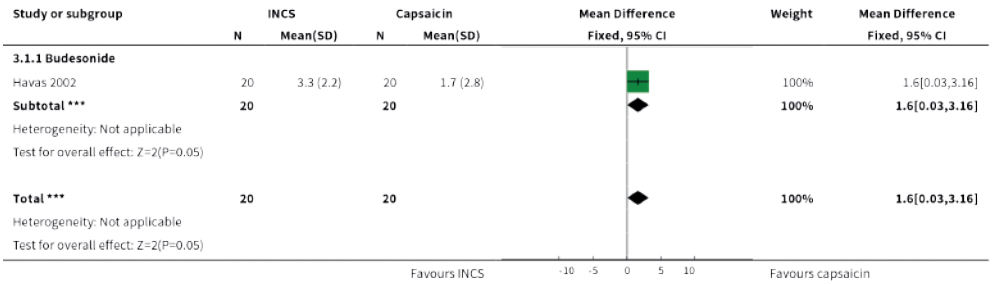
Analysis 2.5. Comparison 2 Intranasal corticosteroids versus intranasal antihistamine, Outcome 5 Other adverse events.



Comparison 3. Intranasal corticosteroids versus capsaicin

Outcome or Subgroup	Studies	Partic-ipants	Statistical Method	Effect Estimate
3.1 Total nasal symptom score, follow-up ≤ 4 weeks	1	40	Mean Difference (IV, Fixed, 95% CI)	1.60 [0.03, 3.16]
3.1.1 Budesonide	1	40	Mean Difference (IV, Fixed, 95% CI)	1.60 [0.03, 3.16]

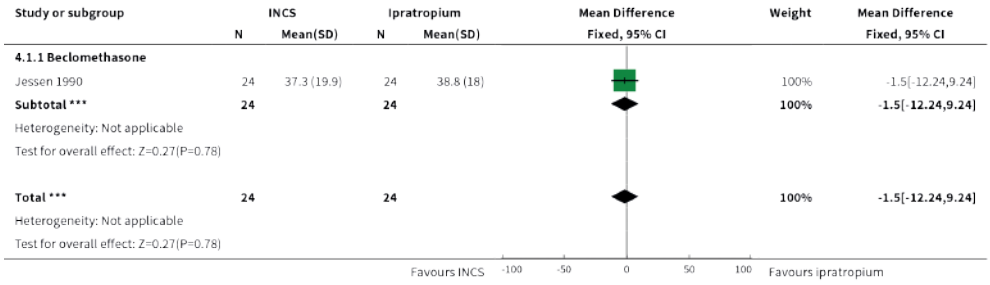
Analysis 3.1. Comparison 3 Intranasal corticosteroids versus capsaicin, Outcome 1 Total nasal symptom score, follow-up ≤ 4 weeks.



Comparison 4. Intranasal corticosteroids versus ipratropium bromide

Outcome or Subgroup	Studies	Partic-ipants	Statistical Method	Effect Estimate
4.1 Total nasal symptom score, follow-up ≤ 4 weeks	1	48	Mean Difference (IV, Fixed, 95% CI)	-1.50 [-12.24, 9.24]
4.1.1 Beclomethasone	1	48	Mean Difference (IV, Fixed, 95% CI)	-1.50 [-12.24, 9.24]

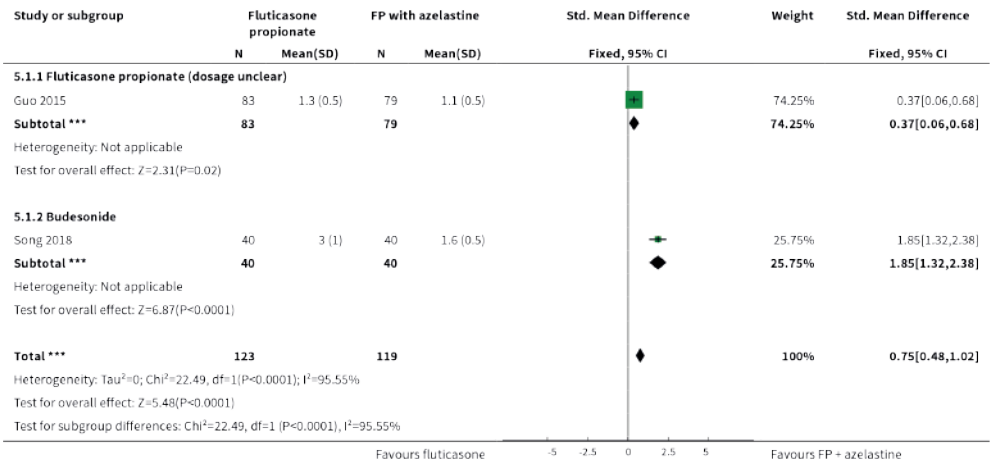
Analysis 4.1. Comparison 4 Intranasal corticosteroids versus ipratropium bromide, Outcome 1 Total nasal symptom score, follow-up ≤ 4 weeks.



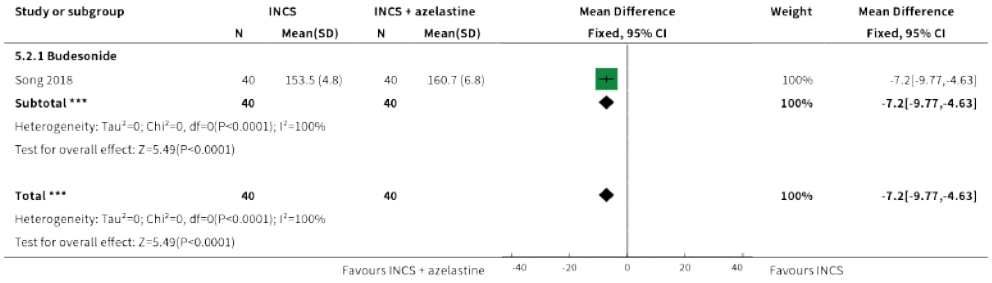
Comparison 5. Intranasal corticosteroids (INCS) versus INCS + intranasal antihistamine

Outcome or Subgroup	Studies	Partic-ipants	Statistical Method	Effect Estimate
5.1 Total nasal symptom score, follow-up > 4 weeks	2	242	Std. Mean Difference (IV, Fixed, 95% CI)	0.75 [0.48, 1.02]
5.1.1 Fluticasone propio-nate (dosage unclear)	1	162	Std. Mean Difference (IV, Fixed, 95% CI)	0.37 [0.06, 0.68]
5.1.2 Budesonide	1	80	Std. Mean Difference (IV, Fixed, 95% CI)	1.85 [1.32, 2.38]
5.2 Quality of life (SF12-v2)	1	80	Mean Difference (IV, Fixed, 95% CI)	-7.20 [-9.77, -4.63]
5.2.1 Budesonide	1	80	Mean Difference (IV, Fixed, 95% CI)	-7.20 [-9.77, -4.63]
5.3 Other adverse events	2	242	Risk Ratio (M-H, Fixed, 95% CI)	0.26 [0.07, 1.01]
5.3.1 Fluticasone propio-nate (dosage unclear)	1	162	Risk Ratio (M-H, Fixed, 95% CI)	0.09 [0.00, 1.54]
5.3.2 Budesonide	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.10, 2.58]

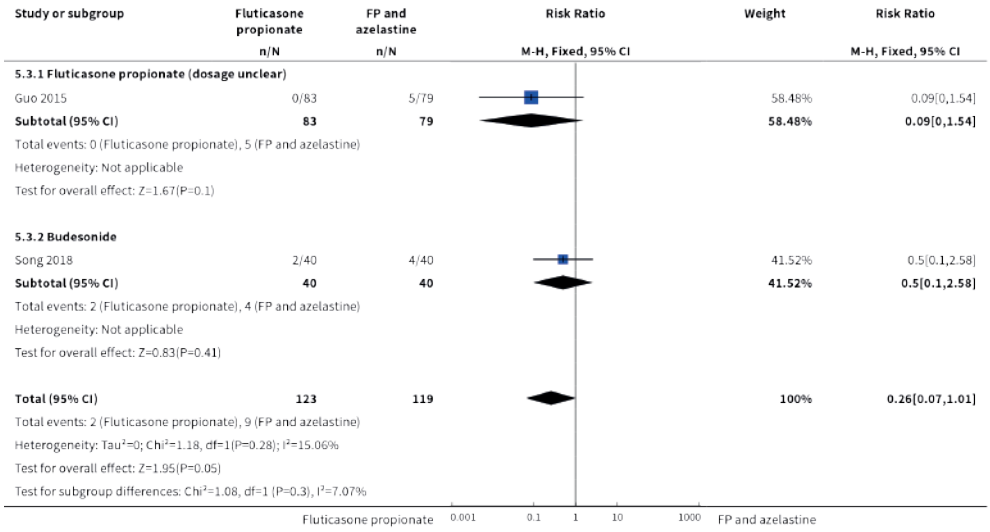
Analysis 5.1. Comparison 5 Intranasal corticosteroids (INCS) versus INCS + intranasal antihistamine, Outcome 1 Total nasal symptom score, follow-up > 4 weeks.



Analysis 5.2. Comparison 5 Intranasal corticosteroids (INCS) versus INCS + intranasal antihistamine, Outcome 2 Quality of life (SF12-v2).



Analysis 5.3. Comparison 5 Intranasal corticosteroids (INCS) versus INCS + intranasal antihistamine, Outcome 3 Other adverse events.

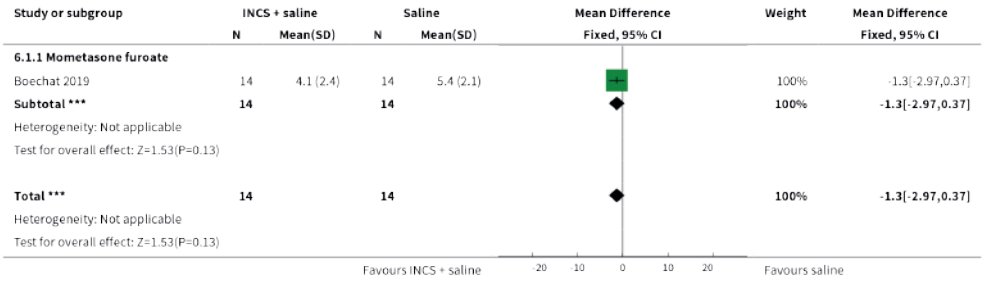


5

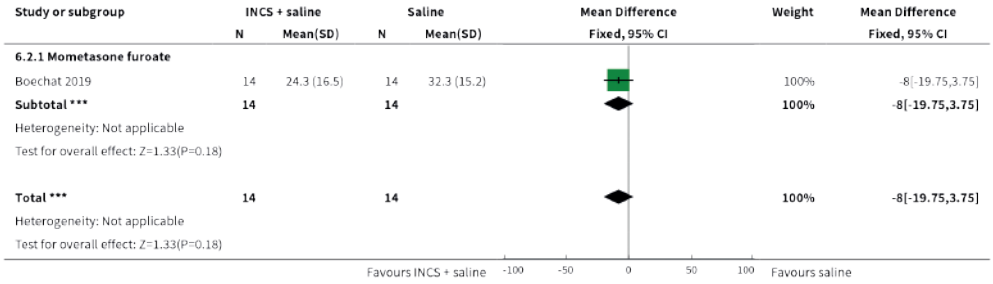
Comparison 6. Intranasal corticosteroids + saline versus saline

Outcome or Subgroup	Studies	Partic-ipants	Statistical Method	Effect Estimate
6.1 Total nasal symptom score, follow-up ≤ 4 weeks	1	28	Mean Difference (IV, Fixed, 95% CI)	-1.30 [-2.97, 0.37]
6.1.1 Mometasone furoate	1	28	Mean Difference (IV, Fixed, 95% CI)	-1.30 [-2.97, 0.37]
6.2 Quality of life (SNOT-22)	1	28	Mean Difference (IV, Fixed, 95% CI)	-8.00 [-19.75, 3.75]
6.2.1 Mometasone furoate	1	28	Mean Difference (IV, Fixed, 95% CI)	-8.00 [-19.75, 3.75]
6.3 Objective measure-ment of airflow: peak nasal inspiratory flow	1	28	Mean Difference (IV, Fixed, 95% CI)	-9.20 [-33.96, 15.56]
6.3.1 Mometasone furoate	1	28	Mean Difference (IV, Fixed, 95% CI)	-9.20 [-33.96, 15.56]

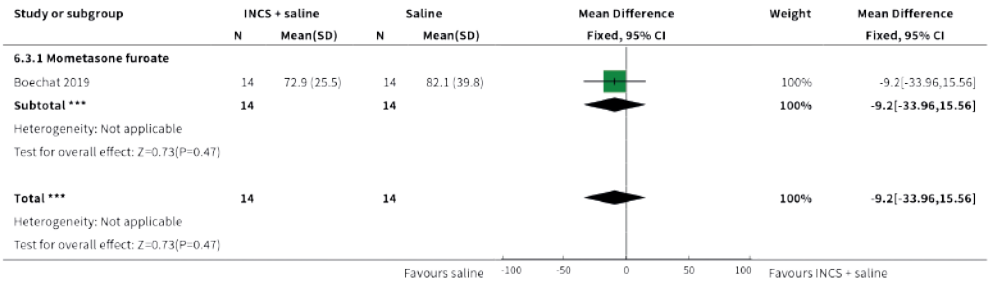
Analysis 6.1. Comparison 6 Intranasal corticosteroids + saline versus saline, Outcome 1 Total nasal symptom score, follow-up ≤ 4 weeks.



Analysis 6.2. Comparison 6 Intranasal corticosteroids + saline versus saline, Outcome 2 Quality of life (SNOT-22).



Analysis 6.3. Comparison 6 Intranasal corticosteroids + saline versus saline, Outcome 3 Objective measurement of airflow: peak nasal inspiratory flow.



ADDITIONAL TABLES

Table 1. Summary of patient-reported disease severity scores

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

Table continued

Study ID	Symptoms measured	Score for each symptom	Summation (total range)	Notes
Boechat 2019	Combined nasal symptom score (after emailing author): 1. Nasal blockage 2. Sneezing 3. Nasal itching 4. Rhinorrhoea	Measured on a VAS scale of 0 to 10 (10 is worse)	Measured pre-intervention and at 2 weeks	—
Behncke 2006	Total nasal symptom score, unclear definition	Unclear	Unclear	—
Day 1990	1. Blocked nose 2. Itchy nose 3. Runny nose 4. Sneezing	Measured on a scale of 0 to 3 (0 is better)	Mean change in total combined symptom score (range 0 to 3) from end of treatment to baseline (week 4 versus week 0)	—
Ellegård 2001	Congestion	Measured on a scale of 0 to 4 (0 is better)	Reported after 8 weeks of treatment and 16 weeks of post-treatment follow-up (range 0 to 4); as only one symptom no summation needed	We evaluated the data at the end of 8 weeks of treatment as this was the most common method of measurement among other studies
Guo 2015	Total nasal symptom score; no breakdown in individual symptoms	Scale unclear	Measured pre-intervention and at 2 weeks; range and summation unclear	—

Table continued

Study ID	Symptoms measured	Score for each symptom	Summation (total range)	Notes
Hallén 1997	Nasal congestion	Measured on a VAS of 0 to 100 (0 is better)	Reported for all days, 0 to 14 days, in the morning and in the evening (range 0 to 100); as only one symptom no summation needed	No differences between morning and evening data. Reported morning data at day 13.
Havas 2002	1. Rhinorrhoea 2. Nasal blockage 3. Sneezing 4. Headache 5. Post-nasal drip 6. Sore throat	Measured on a VAS of 0 to 5 (0 = no symptoms), separately for each side	Sum of mean values of rhinorrhoea, nasal blockage and sneezing (range 0 to 30); measurement at end of treatment	We did not use the reported aggregate relief score, but instead calculated a total nasal symptom score out of rhinorrhoea, nasal blockage and sneezing (mean values and SDs per symptom were provided)
Hillas 1980	Total nasal symptom score 1. Sneezing 2. Rhinorrhoea 3. Nasal pruritis 4. Blocked nose 5. Itchy eyes 6. Watery eyes 7. Red eyes	Both measured on a scale of 0 to 3 (0 = nil, 1 = mild, 2 = moderate and 3 = severe)	Total nasal symptom score: reported as a mean of 4-week treatment period	No separate data reported for non-allergic rhinitis, only responder/non-responder data
Incaudo 1980	Overall severity of rhinitis	Measured daily on a scale of 1 to 4 (0 is better)	Reported mean at end of week 2, 4, 6 and 8 (range 0 to 4)	We did not use the reported individual rhinitis symptoms to calculate a total nasal symptom score, as only P values were reported

Table continued

Study ID	Symptoms measured	Score for each symptom	Summation (total range)	Notes
Jacobs 2009	1. Congestion 2. Rhinorrhoea 3. Post-nasal drip	Measured twice daily on diary cards using a 4-point categorical scale ranging from 0 (symptom not present) to 3 (symptom hard to tolerate; interferes with daily activities or sleeping)	TNSS is sum of the 3 symptom scores (range 0 to 9). Change in TNSS (range 0 to 9) from end of treatment (week 4) to baseline.	We used daily reflective TNSS and not morning instantaneous TNSS
Jessen 1990	1. Nasal secretion 2. Sneezing 3. Nasal blockage	All 3 symptoms were measured daily on a scale of 0 to 3/4 (0 is better)	Reported as sum score of 2-week treatment period (range 0 to 126/168)	Unclear whether maximum scale was 3 or 4
Kalpaklioglu 2010	1. Rhinorrhoea 2. Congestion 3. Itching 4. Sneezing 5. Anosmia 6. Conjunctivitis	Scale of 0 to 4 (0 is better)	Most likely although not explicitly cited sum of all individual symptoms. Reported for 2 weeks after treatment. Reported as mean change from baseline.	—
Lin 2017	1. Nasal obstruction 2. Nasal itch 3. Rhinorrhoea 4. Sneezing	Unclear scale	Unclear total range of symptoms	—

Table continued

Study ID	Symptoms measured	Score for each symptom	Summation (total range)	Notes
Lundblad 2001	1. Rhinorrhoea 2. Nasal stuffiness/ congestion 3. Nasal itching 4. Sneezing	Measured on a scale of 0 to 3 (0 is better)	Range 0 to 12; reported most likely as sum at the end of treatment	Converted into dichotomous outcome: improved versus unimproved. Improvement defined as a reduction of at least 1 point in the overall symptom score. No numerical data on original TNSS, so not included in meta-analysis for this outcome
Löfkvist 1976	1. Nasal catarrh 2. Blockage 3. Nasal itching 4. Sneezing	Measured on a scale of 0 to 3 (0 is better)	Range 0 to 12	No numerical data on original TNSS, therefore not included in meta-analysis. There are data on 'non-responder/ improvement/ responder'
Malm 1976	1. Nasal obstruction 2. Rhinorrhoea 3. Sneezing 4. Eye irritation	Measured on a scale of 0 to 3 (0 is better)	TNSS not reported, but calculated for meta-analysis: sum of mean values of nasal obstruction, rhinorrhoea and sneezing (range 0 to 9); measurement at end of treatment)	We calculated a total nasal symptom score out of rhinorrhoea, nasal blockage and sneezing (mean values and SDs per symptom were provided) for the dosages 200 µg, 400 µg and 800 µg

Table continued

Study ID	Symptoms measured	Score for each symptom	Summation (total range)	Notes
Malm 1981	1. Nasal obstruction 2. Nasal secretion 3. Sneezing	Measured on a scale of 0 to 3 (0 is better) Reported as mean ± SEM of at last 3 days of the patients symptom score in each treatment period for nasal obstruction and secretion. For sneezing: scale of 0 to 3 (0 is good: no sneezing = 0; 1 to 5 sneezes = 1 point; 6 to 15 = 2 points; more than 15 sneezes = 3 points)	TNSS not reported, but calculated for meta-analysis: sum of mean values of nasal obstruction, rhinorrhoea and sneezing (range 0 to 9)	We calculated a total nasal symptom score out of rhinorrhoea, nasal blockage and sneezing (mean values and SDs per symptom were provided) for the dosages 50 µg, 200 µg and 800 µg
Meltzer 1994	Nasal symptom score, unclear definition	Unclear	Unclear	Unclear
Miller 1969	1. Nasal obstruction 2. Discharge 3. Post-nasal drip 4. Sneezing	Measured by patient at 2 and 4 weeks after treatment on a scale of 0 to 3 (0 is better)	Not reported	We were unable to calculate a SD for rhinorrhoea (secretion) and post-nasal drip as the P values for these symptoms were not reported, therefore not included in meta-analysis for this outcome
O'Reilly 1991	1. Nasal obstruction 2. Anterior rhinorrhoea 3. Posterior rhinorrhoea 4. Sneezing 5. Facial pain	Measured on a scale of 0 to 5 (0 is better)	Composite score for all 5 symptoms, range 0 to 25	Only P values reported, therefore not included in meta-analysis for this outcome

Table continued

Study ID	Symptoms measured	Score for each symptom	Summation (total range)	Notes
Scadding 1995	A. 1. Nasal blockage on waking 2. Nasal blockage during the rest of the day 3. Sneezing 4. Rhinorrhoea B. 1. Overall assessment of symptoms by patient 2. Overall assessment of symptoms at clinic visit	A. Measured by patient on a scale of 0 to 3 on a daily card (0 is better) B. 1. Measured by patient on a scale of 0 to 3 on a daily card (0 is better) 2. VAS, 0 to 10 cm (10 = worst symptoms)	A. Range 0 to 12 B.1. Range 0 to 3 B.2. Range 0 to 10	No data reported for non-allergic rhinitis subgroup separately, therefore not included in meta-analysis. The study states that there were no differences between allergic and non-allergic rhinitis patients
Schulz 1978	1. Sneezing 2. Stuffy nose 3. Runny nose 4. Nose blowing 5. Post-nasal drip	Duration in hours per symptom measured	All 5 symptoms combined to determine overall duration of patients' symptoms. Reported as percentage of days during which all 5 of the symptoms lasted 1 hour or less and the percentage of days during which at least one of the 5 symptoms lasted 4 hours or more	No data reported for non-allergic rhinitis subgroup separately for this outcome, therefore not included in meta-analysis. There are data on 'responder/non-responder'.
Singh 2017	—	—	—	Not included in meta-analysis as TNSS data are reported in relationship to cold dry air provocation

Table continued

Study ID	Symptoms measured	Score for each symptom	Summation (total range)	Notes
Song 2018	A. Overall VAS B. Individual symptom VAS: 1. Congestion 2. Sneezing 3. Itching 4. Rhinorrhoea	Measured on a VAS: 0 to 10, 0 is better	Range (0 to 10), measurement at week 8	—
Spector 1980	1. Sneezing 2. Stuffiness 3. Runny nose 4. Nose blowing 5. Post-nasal drip	Patient evaluation, sum of 5 symptoms numerically assessed as absent (1), mild (2), moderate (3), or severe (4); range 1 to 4	Range (5 to 20), measurement at week 4	—
Tantilipikorn 2010	1. Rhinorrhoea 2. Nasal congestion 3. Post-nasal drip 4. Eye itching/ burning 5. Eye tearing/ watering 6. Eye redness	4-point categorical scale of 0 to 3 (none, mild, moderate, severe), measured by patient on paper diary card, in AM and PM, as instantaneous (i) and over previous 12 hours (reflective). Instantaneous score measured in AM, and reflective in both AM and PM measured during screening and treatment periods	Combined 3 reflective individual nasal symptom scores (range 0 to 9) Measured in AM and PM, which were averaged to arrive at the final daily value (daily rTNSS)	Compared data from week 4 to baseline to arrive at change from baseline TNSS. We included the reflective TNSS (rTNSS) in the meta-analysis, not the instantaneous TNSS (iTNSS).
Tarlo 1977	Individual rhinitis symptoms: 1. Daily and nightly sneezing 2. Nasal congestion 3. Rhinorrhoea Total nasal symptoms	0 if absent, 1 if they lasted less than 30 minutes, 2 if between 30 minutes and 2 hours, and 3 if longer than 2 hours	Total nasal symptoms: the sum of the nasal symptom scores (sneezing, congestion, and rhinorrhoea, as well as the total)	No separate data for non-allergic rhinitis subgroups

Table continued

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

Table continued

Study ID	Symptoms measured	Score for each symptom	Summation (total range)	Notes
Webb 2002	1. Nasal obstruction 2. Post-nasal drip 3. Rhinorrhoea	Measured on a VAS, 0 to 100 (0 is better)	Range 0 to 300, measured at both 2 weeks and 4 weeks	TNSS reported as change from baseline. Combination of 3 studies

TNSS: total nasal symptom score
iTNSS: instantaneous total nasal symptom score
rTNSS: reflective total nasal symptom score
SD: standard deviation

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

Study	Findings
Arikan 2006	Concluded that treatment with fluticasone propionate provided significantly greater relief from the symptom of nasal obstruction compared with placebo over the entire 3-month treatment period. Patients' subjective assessments of nasal obstruction after medical treatment correlated with the results of objective testing.
Lin 2017	This study was not included in the meta-analysis because of lack of quality of the study data. Firstly, the study presents unexpected data, with disappearance of the benefit of intranasal corticosteroids with longer follow-up. Secondly, including the study in the meta-analysis resulted in a high level of heterogeneity. The SD values that are presented in the study do not match with the presented means, n and P values. The data make more sense if the as-presented SD values should actually be standard error of the mean (SEM), which was confirmed by a re-analysis. As the authors did not reply to our question regarding the above, we decided to not include this study in the meta-analysis. The study did show a beneficial effect of intranasal corticosteroids over placebo, however this effect disappeared with longer follow-up.
Meltzer 1994	This study was not included in the meta-analysis for this outcome as it did not report numerical data for the non-allergic rhinitis subgroup. They did conclude that fluticasone propionate reduces total symptoms, improves individual symptoms (mainly obstruction) and achieves a significant overall improvement in non-allergic rhinitis compared to placebo.
Miller 1969	Reported a statistically significant difference in symptoms in favour of intranasal corticosteroids (it did not report P values for rhinorrhoea and post-nasal drip so we were not able to calculate a SD).
Lundblad 2001	Reported no numerical data on original TNSS, so it could not be included in the meta-analysis for this outcome. It did report data that could be translated into proportions of 'responders/non-responders'. The study did not find significant differences between intranasal corticosteroids and placebo. The study converted TNSS into a dichotomous outcome: improved versus unimproved. Improvement was defined as a reduction of at least 1 point in the overall symptom score. No numerical data on original TNSS was provided, therefore this study was not included in the meta-analysis for this outcome.

Table continued

Löfkvist 1976	This study was not included in the meta-analysis as no data on TNSS were reported. The study did report data on 'responders/non-responders' with 29/39 responders in the intranasal corticosteroids group and 12/39 responders in the placebo group, favouring intranasal corticosteroids with an odds ratio (OR) of 0.44 (95% confidence interval (CI) 0.24 to 0.64).
O'Reilly 1991	This study was not included in the meta-analysis as only P values were reported. Patients reported subjective symptom scores on a scale of 0 to 5 for nasal obstruction, anterior rhinorrhoea, posterior rhinorrhoea, sneezing and facial pain. When the composite scores for all 5 symptoms were compared, there was a significant difference between beclomethasone dipropionate and baseline (P = 0.01) and beclomethasone dipropionate and placebo (P = 0.02) in favour of beclomethasone dipropionate.
Scadding 1995	This study on 2 types of intranasal corticosteroids versus placebo in perennial rhinitis patients (allergic and non-allergic rhinitis) reported a number of individual rhinitis symptoms and an overall assessment of symptoms, but no separate data on non-allergic rhinitis patients were presented. However, the study does state that there were no differences between allergic and non-allergic rhinitis. This study reported a significant improvement with intranasal corticosteroids versus placebo in perennial allergic rhinitis, with fluticasone propionate aqueous nasal spray (200 µg) as effective as beclomethasone dipropionate µg twice daily.
Schulz 1978	This study was not included in the meta-analysis as no data on TNSS were reported. The study did report data on responders/non-responders with 6 of 14 responders in the intranasal corticosteroids group and 8 of 18 responders in the placebo group with an OR of 0.02 (95% CI 0.33 to 0.36), therefore not a significant difference.
Tarlo 1977	This study was not included in the meta-analysis for this outcome as it did not report enough numerical data for the non-allergic rhinitis subgroup. They concluded that after 6 months 6 of 9 non-allergic rhinitis patients were successfully treated with intranasal corticosteroids and 3 of 9 non-allergic rhinitis patients were unsuccessfully treated with intranasal corticosteroids. They concluded that their results (in favour of intranasal corticosteroids over placebo) in those in whom a possible allergic component could be identified were not different from those of the whole group.
Varricchio 2011	This study was not included in the meta-analysis because we decided to only include studies with an intranasal corticosteroid dosage of 200 µg to 400 µg. This study uses an intranasal corticosteroid dosage of 2000 µg. The study did report a significant improvement in nasal symptoms in non-allergic rhinitis after an 8-week treatment period with intranasal flunisolide.
Warland 1982	This study was not included in the meta-analysis for this outcome because it did not report numerical data for the non-allergic rhinitis subgroup. They concluded that flunisolide nasal solution seems to be effective in both allergic rhinitis and vasomotor rhinitis patients, although it seems to be more effective in an allergic state.

SD: standard deviation
TNSS: total nasal symptom score

APPENDICES

Appendix 1. Search strategies

CENTRAL	PubMed	EMBASE (Ovid)
1 MESH DESCRIPTOR Rhinitis EXPLODE ALL AND CENTRAL:TARGET 2 (rhinit*):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 3 NARES or NAR or LAR or NANIPER AND CENTRAL:TARGET 4 #1 OR #2 OR #3 5 MESH DESCRIPTOR Steroids EXPLODE ALL AND CENTRAL:TARGET 6 MESH DESCRIPTOR Glucocorticoids EXPLODE ALL AND CENTRAL:TARGET 7 MESH DESCRIPTOR Hydroxycorticosteroids EXPLODE ALL AND CENTRAL:TARGET 8 MESH DESCRIPTOR Anti-Inflammatory Agents EXPLODE ALL AND CENTRAL:TARGET 9 MESH DESCRIPTOR Anti-Inflammatory Agents, Non-Steroidal EXPLODE ALL AND CENTRAL:TARGET 10 #8 NOT #9 11 (STEROID* or CORTICOSTEROID* or GLUCOCORTICOID* or CORTICOID* or BECLOMETHASONE or BECLAMET or BECLOCORT or BECOLMETASONE or BETAMETHASONE or BETAMETASONE or BETADEXAMETHASONE or FLUBENISOLONE or CELESTO or BECOTIDE or BECONASE or VANCENASE or ALANASE or NASALIDE or NASAREL):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 12 (FLUNISOLIDE or NASALIDE or NASAREL or RHI	#1 “Rhinitis”[Mesh] #2 rhinit* #3 (NARES or NAR or LAR or NANIPER) #4 (#1 OR #2 OR #3) #5 “Anti-Inflammatory Agents”[Mesh] #6 “Anti-Inflammatory Agents, Non-Steroidal”[Mesh] #7 (#5 NOT #6) #8 (STEROID* or CORTICOSTEROID* or GLUCOCORTICOID* or CORTICOID* or BECLOMETHASONE or BECLAMET or BECLOCORT or BECOLMETASONE or BETAMETHASONE or BETAMETASONE or BETADEXAMETHASONE or FLUBENISOLONE or CELESTO or BECOTIDE or BECONASE or VANCENASE or ALANASE or NASALIDE or NASAREL) #9 “Hydroxycorticosteroids”[Mesh] #10 “Glucocorticoids”[Mesh] #11 “Steroids”[Mesh] #12 (FLUNISOLIDE or NASALIDE or NASAREL or RHINALAR or FLUTICASONE or FLONASE or FLOUNCE or FLIXONASE or MOMETASONE or NASONEX or TRIAMCINOLONE or	1 exp rhinitis/ 2 rhinit*.tw. 3 (NARES or NAR or LAR or NANIPER).tw. 4 1 or 2 or 3 5 exp steroid/ 6 exp glucocorticoid/ 7 exp hydroxycorticosteroid/ 8 exp antiinflammatory agent/ 9 exp nonsteroid antiinflammatory agent/ 10 (STEROID* or CORTICOSTEROID* or GLUCOCORTICOID* or CORTICOID* or BECLOMETHASONE or BECLAMET or BECLOCORT or BECOLMETASONE or BETAMETHASONE or BETAMETASONE or BETADEXAMETHASONE or FLUBENISOLONE or CELESTO or BECOTIDE or BECONASE or VANCENASE or ALANASE or NASALIDE or NASAREL).tw. 11 (FLUNISOLIDE or NASALIDE or NASAREL or RHINALAR or FLUTICASONE or FLONASE or FLOUNCE or FLIXONASE or MOMETASONE or NASONEX or TRIAMCINOLONE or NASACORT or “TRI NASAL” or ARISTOCORT or VOLON or AVAMYS).tw. 12 (HYDROCORTISONE or CORTISOL or DEXAMETHASONE or DEXAMETASONE or HEXADECADROL or DECADRON or DEXACORT or DEXASONE or HEXADROL or METHYLFLUORPREDNISOLONE or MILLICORTEN or ORADEXON or BUDESONIDE or HORACORT or PULMICORT or RHINOCORT).tw. 13 8 not 9

NALAR or FLUTICASONE or FLONASE or FLOUNCE or FLIXONASE or MOMETASONE or NASONEX or TRIAMCINOLONE or NASACORT or "TRI NASAL" or ARISTOCORT or VOLON or AVAMYS):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 13 (HYDROCORTISONE or CORTISOL or DEXAMETHASONE or DEXAMETASONE or HEXADECADROL or DECADRON or DEXACORT or DEXASONE or HEXADROL or METHYLFLUORPREDNISOLONE or MILLICORTEN or ORADEXON or BUDESONIDE or HORACORT or PULMICORT or RHINOCORT):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 14 #5 or #6 or #7 or #10 or #11 or #12 or #13 15 #4 and #14 16 MESH DESCRIPTOR Administration, Topical EXPLODE ALL AND CENTRAL:TARGET 17 MESH DESCRIPTOR Nebulizers and Vaporizers EXPLODE ALL AND CENTRAL:TARGET 18 MESH DESCRIPTOR Administration, Intranasal EXPLODE ALL AND CENTRAL:TARGET 19 (spray or aerosol or powder or inhal* or solution or turbuhaler or intranasal* or intra next nasal or topical* or drops):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 20 #16 OR #17 OR #18 OR #19 21 #15 AND #20	NASACORT or "TRI NASAL" or ARISTOCORT or VOLON or AVAMYS) #13 (HYDROCORTISONE or CORTISOL or DEXAMETHASONE or DEXAMETASONE or HEXADECADROL or DECADRON or DEXACORT or DEXASONE or HEXADROL or METHYLFLUORPREDNISOLONE or MILLICORTEN or ORADEXON or BUDESONIDE or HORACORT or PULMICORT or RHINOCORT) #14 (#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13) #15 (spray or aerosol or powder or inhal* or solution or turbuhaler or intranasal* or intra next nasal or topical* or drops) #16 "Administration, Intranasal"[Mesh] #17 "Nebulizers and Vaporizers"[Mesh] #18 "Administration, Topical"[Mesh] #19 (#15 OR #16 OR #17 OR #18) #20 (#4 AND #14 AND #19)	14 5 or 6 or 7 or 10 or 11 or 12 or 13 15 4 and 14 16 exp topical drug administration/ 17 exp nebulizer/ 18 exp vaporizer/ 19 exp intranasal drug administration/ 20 (spray or aerosol or powder or inhal* or solution or turbuhaler or intranasal* or intra next nasal or topical* or drops).tw. 21 16 or 17 or 18 or 19 or 20 22 15 and 21
Web of Science (Web of Knowledge)	**CINAHL (EBSCO)**	**Trial registers**

Table continued

#1 TS=rhinit* #2 TS=(NARES or NAR or LAR or NANIPER) #3 #2 OR #1 #4 TS=(STEROID* or CORTICOSTEROID* or GLUCOCORTICOID* or CORTICOID* or BECLOMETHASONE or BECLAMET or BECLOCORT or BECOLMETASONE or BETAMETHASONE or BETAMETASONE or BETADEXAMETHASONE or FLUBENISOLONE or CELESTO or BECOTIDE or BECONASE or VANCENASE or ALANASE or NASALIDE or NASAREL) #5 TS=(FLUNISOLIDE or NASALIDE or NASAREL or RHINALAR or FLUTICASONE or FLONASE or FLOUNCE or FLIXONASE or MOMETASONE or NASONEX or TRIAMCINOLONE or NASACORT or "TRI NASAL" or ARISTOCORT or VOLON or AVAMYS) #6 TS=(HYDROCORTISONE or CORTISOL or DEXAMETHASONE or DEXAMETASONE or HEXADECADROL or DECADRON or DEXACORT or DEXASONE or HEXADROL or METHYLFLUORPREDNISOLONE or MILLICORTEN or ORADEXON or BUDESONIDE or HORACORT or PULMICORT or RHINOCORT) #7 #6 OR #5 OR #4 #8 TS=(spray or aerosol or powder or inhal* or solution or turbuhaler or intranasal* or intra next nasal or topical* or drops) #9 #8 AND #7 AND #3	S20 S14 AND S19 S19 S15 OR S16 OR S17 OR S18 S18 TX spray or aerosol or powder or inhal* or solution or turbuhaler or intranasal* or intra next nasal or topical* or drops S17 (MH "Administration, Intranasal") S16 (MH "Nebulizers and Vaporizers") S15 (MH "Administration, Topical+") S14 S4 AND S13 S13 S5 OR S6 OR S9 OR S10 OR S11 OR S12 S12 HYDROCORTISONE or CORTISOL or DEXAMETHASONE or DEXAMETASONE or HEXADECADROL or DECADRON or DEXACORT or DEXASONE or HEXADROL or METHYLFLUORPREDNISOLONE or MILLICORTEN or ORADEXON or BUDESONIDE or HORACORT or PULMICORT or RHINOCORT S11 FLUNISOLIDE or NASALIDE or NASAREL or RHINALAR or FLUTICASONE or FLONASE or FLOUNCE or FLIXONASE or MOMETASONE or NASONEX or TRIAMCINOLONE or NASACORT or "TRI NASAL" or ARISTOCORT or VOLON or AVAMYS S10 STEROID* or CORTICOSTEROID* or GLUCOCORTICOID* or	**ICTRP** rhinitis AND steroids OR rhinitis AND corticosteroid OR rhinitis AND corticoid OR rhinitis AND glucocorticoid OR rhinitis AND fluticasone **ClinicalTrials.gov** (rhinitis) AND (steroids OR CORTICOSTEROID OR GLUCOCORTICOID OR CORTICOID OR FLUTICASONE OR hydrofluoroalkane OR ciclesonide OR butorphanol OR beclomethasone) **ClinicalTrials.gov (via CRS)** 1 ((rhinit* or NARES or NAR or LAR or NANIPER)):AB,EH,KW,KY,MC,MH,TI,TO AND INSEGMENT 2 (STEROID* or CORTICOSTEROID* or GLUCOCORTICOID* or CORTICOID* or BECLOMETHASONE or BECLAMET or BECLOCORT or BECOLMETASONE or BETAMETHASONE or BETAMETASONE or BETADEXAMETHASONE or FLUBENISOLONE or CELESTO or BECOTIDE or BECONASE or VANCENASE or ALANASE or NASALIDE or NASAREL):AB,EH,KW,KY,MC,MH,TI,TO AND INSEGMENT 3 (FLUNISOLIDE or NASALIDE or NASAREL or RHINALAR or FLUTICASONE or FLONASE or FLOUNCE or FLIXONASE or MOMETASONE or NASONEX or TRIAMCINOLONE or NASACORT or "TRI NASAL" or ARISTOCORT or VOLON or AVAMYS):AB,EH,KW,KY,MC,MH,TI,TO AND INSEGMENT 4 (HYDROCORTISONE or CORTISOL or DEXAMETHASONE or DEXAMETASONE or HEXADECADROL or DECADRON or DEXACORT or DEXASONE or HEXADROL or METHYLFLUORPREDNISOLONE or MILLICORTEN or ORADEXON or BUDESONIDE or HORACORT or PULMICORT or RHINOCORT):AB,EH,KW,KY,MC,MH,TI,TO AND INSEGMENT

	CORTICOID* or BECLOMETHASONE or BECLAMET or BECLOCORT or BECOLMETASONE or BETAMETHASONE or BETAMETASONE or BETADEXAMETHASONE or FLUBENISOLONE or CELESTO or BECOTIDE or BECONASE or VANCENASE or ALANASE or NASALIDE or NASAREL S9 S7 not S8 S8 (MH "Antiinflammatory Agents, Non-Steroidal+") S7 (MH "Antiinflammatory Agents+") S6 (MH "Glucocorticoids") S5 (MH "Steroids+") S4 S1 OR S2 OR S3 S3 TX NARES or NAR or LAR or NANIPER S2 TX rhinit* S1 (MH "Rhinitis+")	5 #2 OR #3 OR #4 6 #1 AND #5 7 nct:AU AND INSEGMENT 8 #7 AND #6

Appendix 2. Summary of the data collection form

We extracted the following characteristics using a data collection form.

- General information: publication type, year, country, author contact details.
- Study eligibility: type of study, participants, types of interventions, comparisons and outcomes.
- Study methods: design, unit of allocation, start and end dates, duration of participation, ethical approval, funding, possible conflicts of interest.
- Participants: population description, setting, inclusion and exclusion criteria, method of recruitment, informed consent, total number randomised, clusters (if applicable), baseline imbalances, withdrawals and exclusions, age, sex, race/ethnicity, severity of illness, comorbidities, previous nasal and sinus surgery, other relevant socio-demographics, measured and reported subgroups.
- Intervention and comparison groups: intranasal corticosteroids and comparison type, number randomised to group, duration of treatment, timing, delivery, providers, co-interventions, economic information, resource requirements, integrity of delivery, compliance.
- Outcomes: type of outcome, time points measured, time points reported, unit of measurement, scale, assumed risk estimate, power.
- 'Risk of bias' assessment: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, other bias.
- Data and analysis: comparison, outcome, subgroup, time points, results, number of missing participants, reason missing, number of participants moved from another group, reason for move, unit of analysis, statistical method.
- Other information: key conclusions of the study, references to other relevant studies.

CONTRIBUTIONS OF AUTHORS

Christine Segboer (CS), Artur Gevorgyan (AG), Klementina Avdeeva (KA), Supinda Chusakul (SC), Jesada Kanjanaumporn (JK), Songklot Aeumjaturapat (SA), Laurens Reeskamp (LR), Wytske Fokkens (WJF), Kornkiat Snidvongs (KS).

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

DECLARATIONS OF INTEREST

- Christine Segboer: none known.
- Artur Gevorgyan: Artur Gevorgyan has received speaker fees in 2017 from Takeda Canada, Abbott, Meda Pharmaceuticals and Mylan. Meda and Mylan are related to Dymista nasal spray. Takeda is related to Omnaris.
- Klementina Avdeeva: none known.
- Supinda Chusakul: none known.
- Jesada Kanjanaumporn: none known.
- Songklot Aeumjaturapat: none known.
- Laurens Reeskamp: none known.
- Wytske Fokkens: WJ Fokkens has received private sector support for research and/or clinical trials related to the treatment of allergic and non-allergic rhinitis from Chordate (2018/19), as well as public sector research support from the EU, and for studies not related to allergic and non-allergic rhinitis from GSK (2017-19), Sanofi (2016-19) and Novartis (2018-19). WJ Fokkens has also received a speaker fee from Sanofi (2018-19).
- Kornkiat Snidvongs: none known.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National Institute for Health Research, UK. Infrastructure funding for Cochrane ENT

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

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

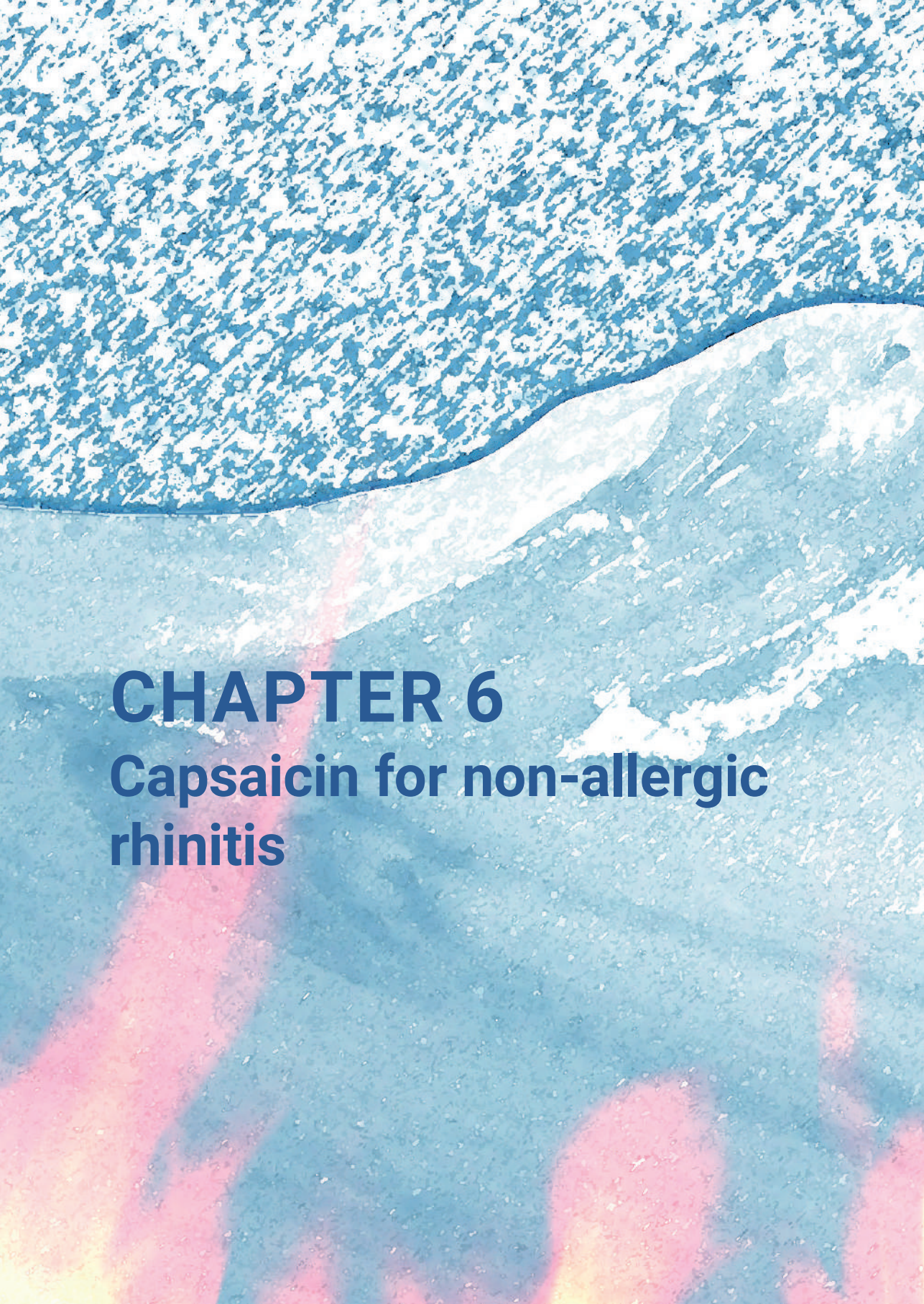
Although we did not plan to perform a meta-analysis if heterogeneity was considered substantial (50% to 90%) or considerable (75% to 100%), we made one exception. We carried out pooling in the presence of very high heterogeneity in the case of the comparison 'Total nasal symptom score (change from baseline)' as result of the study Jacobs 2009. The problems with Jacobs 2009 that are responsible for the high heterogeneity are described in detail above. This study is, however, one of the largest of the studies on this topic and very well known. For that reason we decided to retain it in the meta-analysis.

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

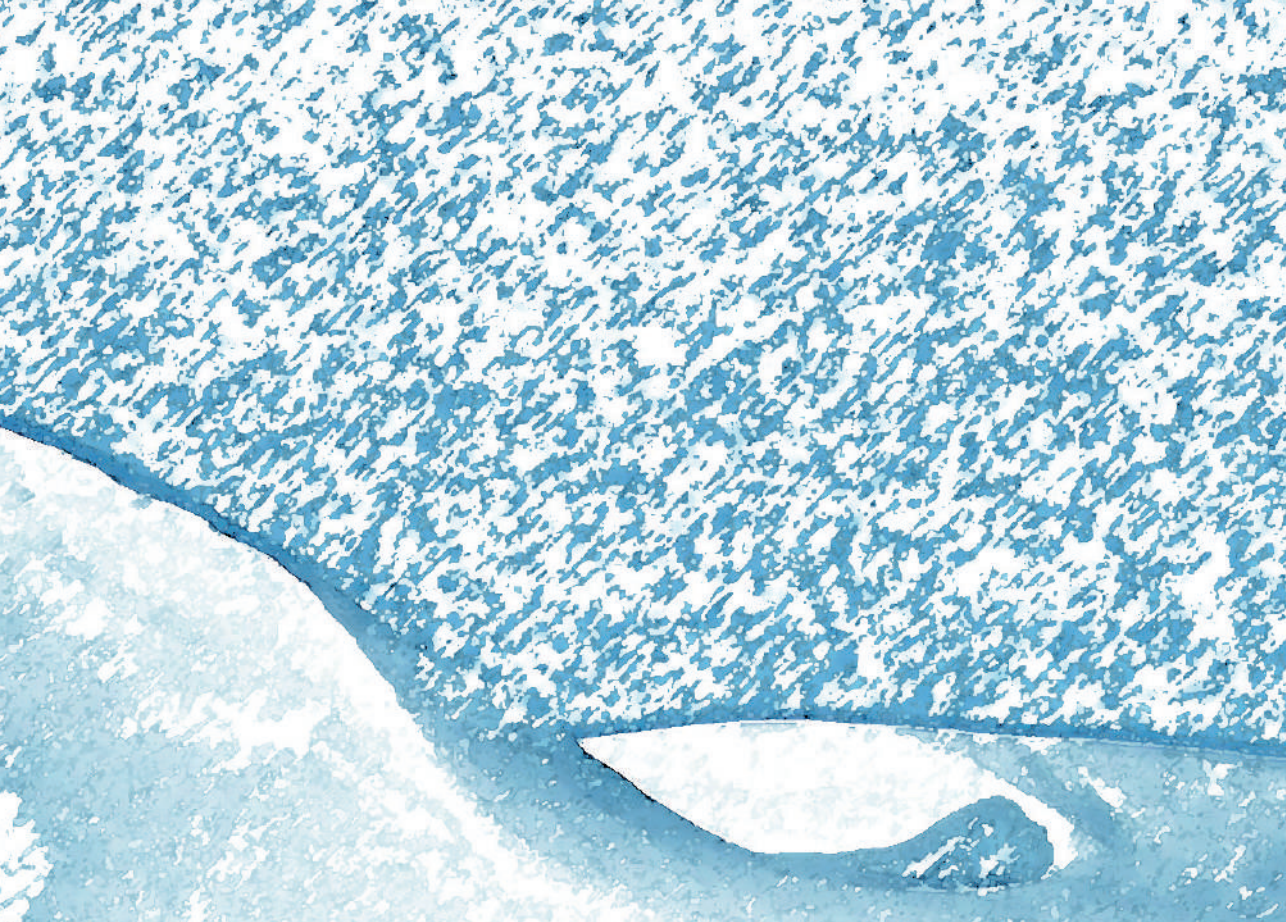
Among studies treatment daily dosage varied from 50 µg to 2000 µg. Most of the studies that compared different dosages of intranasal corticosteroids used a cross-over study design with the exception of Blom 1997 and Webb 2002, which used a parallel-group study design. In the cross-over studies the same participants were treated with different dosages of intranasal corticosteroids, with short (one-week) or no washout, complicating a clear comparison between these dosage subgroups (Balle 1982; Malm 1976; Malm 1981). Only Balle 1982 showed a dosage effect for two nasal symptom score outcomes. Malm 1976 and Malm 1981 showed no significant difference between the dosage subgroups. The two parallel-group studies both concluded that there were no statistically significant differences between the different

intranasal corticosteroid dosage subgroups (Blom 1997; Webb 2002). In the parallel-group studies the different dosage subgroups contained different participants but were compared with the same control group. To prevent counting the same participants or controls more than once, we decided to include one intranasal corticosteroid dosage in the meta-analysis. The most common intranasal corticosteroid dosage was 200 µg. A test for subgroup differences showed no significant difference ('no dosage effect') between 200 µg and 400 µg of intranasal corticosteroids. We therefore included studies in the meta-analysis with an intranasal corticosteroid dosage range of 200 µg to 400 µg.

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



CHAPTER 6
Capsaicin for non-allergic rhinitis



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Cochrane Database Syst Rev. 2015 Jul; 14(7)

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

Table 1 Capsaicin compared to placebo for non-allergic rhinitis

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

Table continued

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.

[1]Small sample size (40 patients total).
[2]Single study.
[3]Pseudo-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 disregulation 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 2012). 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 hyper-reactivity 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 aetiologic 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 (TRPV-1) 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 nonspecific 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, TRIPdatabase, *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 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.

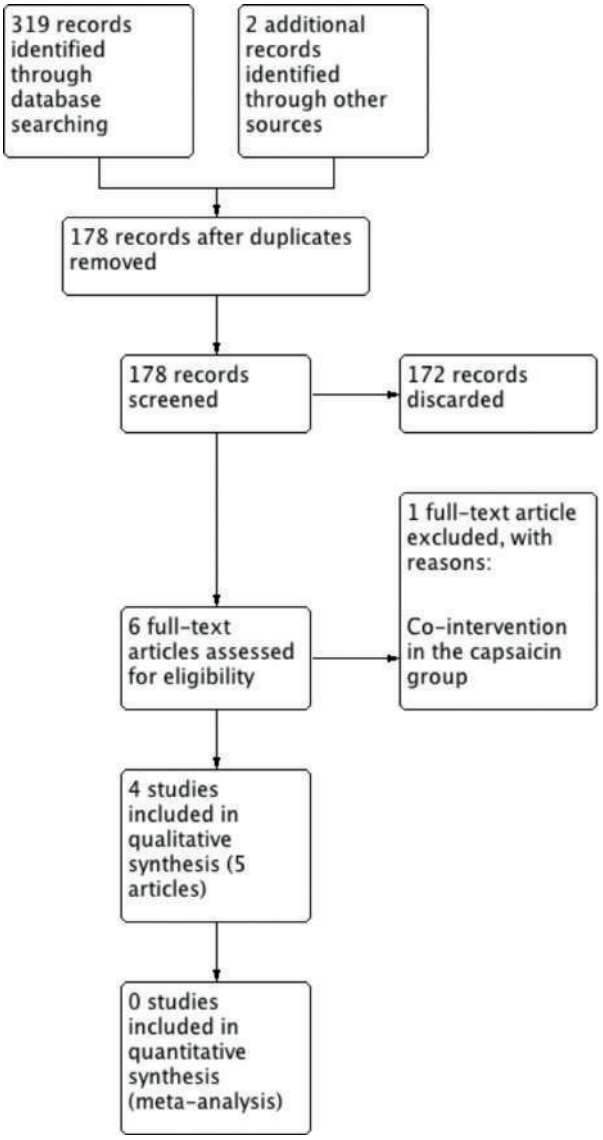

Figure 1. Process for sifting search results and selecting studies for inclusion

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 $C_4/D_4/E_4$, prostaglandin D_2 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 ≥ 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).

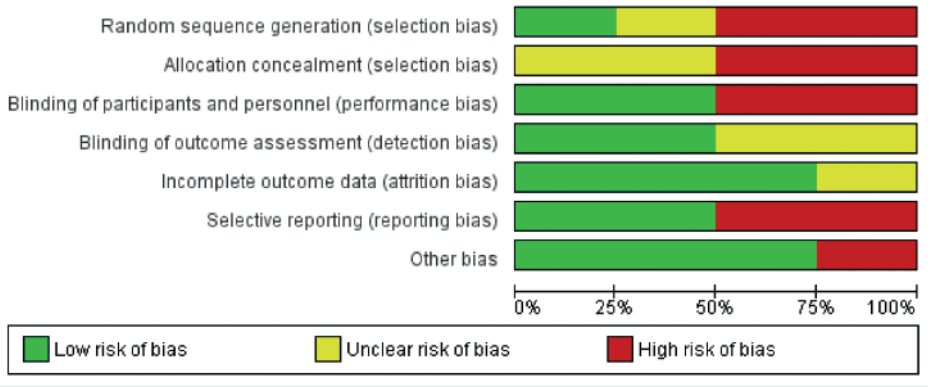

Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

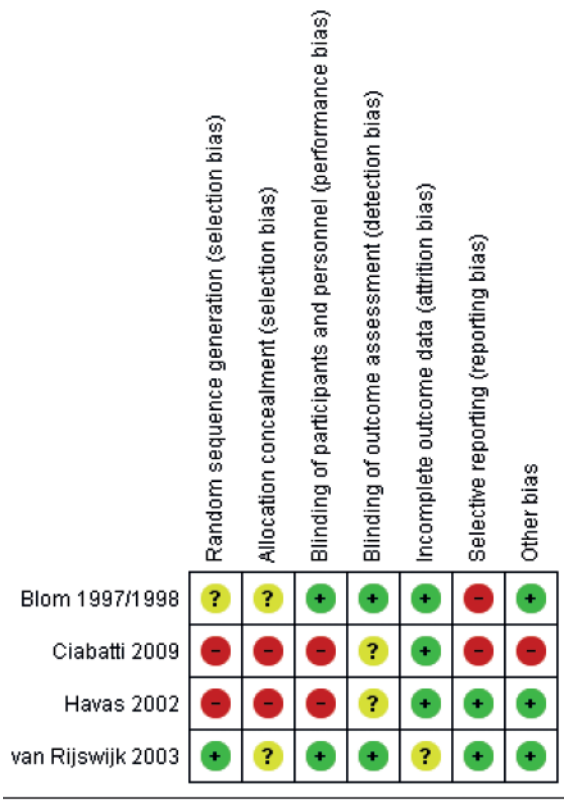

Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study

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 table 1.

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 $C_4/D_4/E_4$, prostaglandin D_2 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 table 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 table 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 hyper-reactivity, 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

Capsaicin compared to budesonide for non-allergic rhinitis

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						

Table continued

Capsaicin compared to budesonide for non-allergic rhinitis
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.

[1]Pseudo-randomisation was performed on an odds and evens basis.
[2]Small sample size (40 patients total).
[3]Single study.

Five capsaicin treatments in one day compared to daily capsaicin treatment for five days for non-allergic rhinitis

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

Table continued

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.

[1]Small sample size (30 total).

DISCUSSION

6

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 C_4/D_4/E_4, prostaglandin D_2 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) are 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 table 1; Summary of findings table 2; Summary of findings table 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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REFERENCES

References to studies included in this review

Blom 1997/1998

Blom HM, Rijswijk JB, Garrelds IM, Mulder PG, Timmermans T, Gerth van Wijk R. Intranasal capsaicin is efficacious in non-allergic, non-infectious perennial rhinitis. A placebo-controlled study. Clinical and Experimental Allergy 1997;27(7):796-801.

Blom HM, Severijnen LA, Rijswijk JB, Mulder PG, Wijk RG, Fokkens WJ. The long-term effects of capsaicin aqueous spray on the nasal mucosa. Clinical and Experimental Allergy 1998;28(11):1351-8.

Ciabatti 2009

Ciabatti PG, D'Ascanio L. Intranasal capsicum spray in idiopathic rhinitis: a randomized prospective application regimen trial. Acta Oto-Laryngologica 2009;129(4):367-71.

Havas 2002

Havas TE, Taplin MA. Intranasal neuropeptide depletion using topical capsaicin for the control of symptoms in non-allergic, non-infectious perennial rhinitis (NANIPER). Australian Journal of Otolaryngology 2002;5(2):107-13.

van Rijswijk 2003

van Rijswijk JB, Boeke EL, Keizer JM, Mulder PG, Blom HM, Fokkens WJ. Intranasal capsaicin reduces nasal hyper-reactivity in idiopathic rhinitis: a double-blind randomized application regimen study. Allergy 2003;58(8):754-61.

Excluded studies

Bernstein 2011

Bernstein J. A randomized, double-blind, parallel trial comparing capsaicin nasal spray with placebo in subjects with a significant component of non-allergic rhinitis. Annals of Allergy, Asthma, and Immunology 2011 Jun 29 [Epub ahead of print].

Ongoing studies

NCT02288156

Hellings P. Elaboration of patient-friendly treatment strategy with capsaicin nasal spray in patients with idiopathic rhinitis. https://clinicaltrials.gov/show/NCT02288156 2014. [NCT02288156]

Additional references

Ameille 2013

Ameille J, Hamelin K, Andujar P, Bensefa-Colas L, Bonneterre V, Dupas D, et al. Occupational asthma and occupational rhinitis: the united airways disease model revisited. Occupational and Environmental Medicine 2013 Feb 6 [Epub ahead of print].

Behrendt 2004

Behrendt HJ, Germann T, Gillen C, Hatt H, Jostock R. Characterization of the mouse cold-menthol receptor TRPM8 and vanilloid receptor type-1 VR1 using a fluorometric imaging plate reader (FLIPR) assay. British Journal of Pharmacology 2004;141(4):737-45.

Bousquet 2008

Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). Allergy 2008;63 Suppl 86:8-160.

Burns 2012

Burns P, Powe DG, Jones NS. Idiopathic rhinitis. Current Opinion in Otolaryngology & Head and Neck Surgery 2012;20(1):1-8.

Cheng 2006

Cheng J, Yang XN, Liu X, Zhang SP. Capsaicin for allergic rhinitis in adults. Cochrane Database of Systematic Reviews 2006, Issue 2. Art. No.: CD004460. DOI: 10.1002/14651858.CD004460.pub2.

Cuilty-Siller 1996

Cuilty-Siller C, Navaro C, Cruz-Ponce J, Kuhn F. Comparative clinical and rhinomanometric response to capsaicin and ipratropium bromide in vasomotor rhinitis. In: Otolaryngology Head and Neck Surgery. Vol. 115. 1996:P110.

Desrosiers 2011

Desrosiers M, Evans GA, Keith PK, Wright ED, Kaplan A, Bouchard J, et al. Canadian clinical practice guidelines for acute and chronic rhinosinusitis. Journal of Otolaryngology Head & Neck Surgery 2011;40 Suppl 2:S99-193.

Ellis 2007

Ellis AK, Keith PK. Non-allergic rhinitis with eosinophilia syndrome and related disorders. Clinical Allergy and Immunology 2007;19:87-100.

EPOS 2012

Fokkens WJ, Lund VJ, Mullol J, Bachert C, Alobid I, Baroody F, et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2012. Rhinology. Supplement 2012;50(23):1-298.

Fokkens 2002

Fokkens WJ. Thoughts on the pathophysiology of non-allergic rhinitis. Current Allergy and Asthma Reports 2002;2(3):203-9.

Garzaro 2012

Garzaro M, Pezzoli M, Landolfo V, Defilippi S, Giordano C, Pecorari G. Radiofrequency inferior turbinate reduction: long-term olfactory and functional outcomes. Otolaryngology Head and Neck Surgery 2012;146(1):146-50.

Gelardi 2008

Gelardi M, Maselli Del Giudice A, Fiorella ML, Soleti P, Di Gioacchino M, Conti CM, et al. Quality of life in non-allergic rhinitis depends on the predominant inflammatory cell type. Journal of Biological Regulators and Homeostatic Agents 2008;22(1):73-81.

Georgalas 2012

Georgalas C, Jovancevic L. Gustatory rhinitis. Current Opinion in Otolaryngology & Head and Neck Surgery 2012;20(1):9-14.

Groger 2012

Groger M, Klemens C, Wendt S, Becker S, Canis M, Havel M, et al. Mediators and cytokines in persistent allergic rhinitis and non-allergic rhinitis with eosinophilia syndrome. International Archives of Allergy and Applied Immunology 2012;159(2):171-8.

Handbook 2011
Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Higgins 2011
Higgins JPT, Deeks JJ (editors). Chapter 7: Selecting studies and collecting data. In: Higgins JPT, Green S (editors), Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Knudsen 2009
Knudsen TB, Thomsen SF, Nolte H, Backer V. A population-based clinical study of allergic and non-allergic asthma. Journal of Asthma 2009;46(1):91-4.

Lacroix 1991
Lacroix JS, Buvelot JM, Polla BS, Lundberg JM. Improvement of symptoms of non-allergic chronic rhinitis by local treatment with capsaicin. Clinical and Experimental Allergy 1991;21(5):595-600.

Marabini 1991
Marabini S, Ciabatti PG, Polli G, Fusco BM, Geppetti P. Beneficial effects of intranasal applications of capsaicin in patients with vasomotor rhinitis. European Archives of Oto-Rhino-Laryngology 1991;248(4):191-4.

Meltzer 1999
Meltzer EO, Grant JA. Impact of cetirizine on the burden of allergic rhinitis. Annals of Allergy, Asthma, and Immunology 1999;83(5):455-63.

Molgaard 2007
Molgaard E, Thomsen SF, Lund T, Pedersen L, Nolte H, Backer V. Differences between allergic and non-allergic rhinitis in a large sample of adolescents and adults. Allergy 2007;62(9):1033-7.

RevMan 2014
Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Robinson 2006
Robinson SR, Wormald PJ. Endoscopic vidian neurectomy. American Journal of Rhinology 2006;20(2):197-202.

Rondon 2012
Rondon C, Campo P, Togias A, Fokkens WJ, Durham SR, Powe DG, et al. Local allergic rhinitis: concept, pathophysiology, and management. Journal of Allergy and Clinical Immunology 2012;129(6):1460-7.

Rondon 2012a

Rondon C, Campo P, Galindo L, Blanca-Lopez N, Cassinello MS, Rodriguez-Bada JL, et al. Prevalence and clinical relevance of local allergic rhinitis. Allergy 2012;67(10):1282-8.

Rosenfeld 2007

Rosenfeld RM, Andes D, Bhattacharyya N, Cheung D, Eisenberg S, Ganiats TG, et al. Clinical practice guideline: adult sinusitis. Otolaryngology Head and Neck Surgery 2007;137(3 Suppl):S1-31.

Sanico 1998

Sanico AM, Philip G, Proud D, Naclerio RM, Togias A. Comparison of nasal mucosal responsiveness to neuronal stimulation in non-allergic and allergic rhinitis: effects of capsaicin nasal challenge. Clinical and Experimental Allergy 1998;28(1):92-100.

Schroer 2012

Schroer B, Pien LC. Non-allergic rhinitis: common problem, chronic symptoms. Cleveland Clinic Journal of Medicine 2012;79(4):285-93.

Stjarne 1989

Stjarne P, Lundblad L, Anggard A, Hokfelt T, Lundberg JM. Tachykinins and calcitonin gene-related peptide: co-existence in sensory nerves of the nasal mucosa and effects on blood flow. Cell and Tissue Research 1989;256(3):439-46.

Van Gerven 2012

Van Gerven L, Boeckxstaens G, Hellings P. Up-date on neuro-immune mechanisms involved in allergic and non-allergic rhinitis. Rhinology 2012;50(3):227-35.

van Rijswijk 2005

van Rijswijk JB, Blom HM, Fokkens WJ. Idiopathic rhinitis, the ongoing quest. Allergy 2005;60(12):1471-81.

Varghese 2010

Varghese M, Glaum MC, Lockey RF. Drug-induced rhinitis. Clinical and Experimental Allergy 2010;40(3):381-4.

CHARACTERISTICS OF STUDIES

Characteristics of included studies

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

Table continued

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.**

Risk of bias

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)	Low risk	Quote: "This study was performed in a double-blind placebo-controlled fashion."
Blinding of outcome assessment (detection bias)	Low risk	Quote: "This study was performed in a double-blind placebo-controlled fashion."
Incomplete outcome data (attrition bias)	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

Ciabatti 2009

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 µg/puff n = 52 **Intervention group B:** capsaicin 2 µg/puff n = 52 **Intervention group C:** capsaicin 4 µg/puff n = 52 **Intervention group D:** placebo 0 µg/puff n = 52 Capsicum oleous nasal spray 1 µg/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

Table continued

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.
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

Risk of bias

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)	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)	Unclear risk	Not described
Incomplete outcome data (attrition bias)	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

Risk of bias

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)	High risk	High risk due to pseudo-randomisation.
Blinding of outcome assessment (detection bias)	Unclear risk	Not described
Incomplete outcome data (attrition bias)	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

Table continued

Methods	**Allocation:** randomised, double-blind, double-dummy; 310 days (38 weeks post-treatment) **Design:** parallel-group study
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 hyper-reactivity 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

Risk of bias

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)	Low risk	Quote: "This study was performed in a double-blind randomized fashion."
Blinding of outcome assessment (detection bias)	Low risk	Quote: "This study was performed in a double-blind randomized fashion."
Incomplete outcome data (attrition bias)	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.

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

Bernstein 2011

Reason for exclusion	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

NCT02288156

Study name	'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

Table continued

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 hyper-reactivity 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	Studies	Partic-ipants	Statistical Method	Effect Estimate
1.1 Overall nasal symptoms 2 weeks post-treatment [VAS, 0-10]	1	24	Mean Difference (IV, Fixed, 95% CI [VAS, 0-10])	-3.34 [-5.24,-1.44]
1.2 Overall nasal symptoms 12 weeks post-treatment [VAS, 0-10]	1	24	Mean Difference (IV, Fixed, 95% CI [VAS, 0-10])	-3.73 [-5.45,-2.01]
1.3 Overall nasal symptoms 36 weeks post-treatment [VAS, 0-10]	1	24	Mean Difference (IV, Fixed, 95% CI [VAS, 0-10])	-3.52 [-5.55,-1.48]
1.4 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)	1.50 [0.58, 3.91]
1.5 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)	2.00 [0.81, 4.93]
1.6 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]

Analysis 1.1. Comparison 1 Capsaicin versus placebo, Outcome 1 Overall nasal symptoms 2 weeks post-treatment.

Review: Capsaicin for non-allergic rhinitis

Comparison: 1 Capsaicin versus placebo

Outcome: 1 Overall nasal symptoms 2 weeks post-treatment

Study or subgroup	Capsaicin N	Capsaicin Mean(SD)[VAS, 0-10]	Placebo N	Placebo Mean(SD)[VAS, 0-10]	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Blom 1997/1998	13	2.578 (2.059)	11	5.92 (2.594)		100.0 %	-3.34 [-5.24, -1.44]
Total (95% CI)	**13**		**11**			**100.0 %**	**-3.34 [-5.24, -1.44]**

Heterogeneity: not applicable

Test for overall effect: Z = 3.45 (P = 0.00056)

Test for subgroup differences: Not applicable

Analysis 1.2. Comparison 1 Capsaicin versus placebo, Outcome 2 Overall nasal symptoms 12 weeks post-treatment.

Review: Capsaicin for non-allergic rhinitis

Comparison: 1 Capsaicin versus placebo

Outcome: 2 Overall nasal symptoms 12 weeks post-treatment

Study or subgroup	Capsaicin N	Capsaicin Mean(SD)[VAS, 0-10]	Placebo N	Placebo Mean(SD)[VAS, 0-10]	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Blom 1997/1998	13	2.548 (2.436)	11	6.28 (1.846)		100.0 %	-3.73 [-5.45, -2.01]
Total (95% CI)	**13**		**11**			**100.0 %**	**-3.73 [-5.45, -2.01]**

Heterogeneity: not applicable

Test for overall effect: Z = 4.26 (P = 0.000020)

Test for subgroup differences: Not applicable

Analysis 1.3. Comparison 1 Capsaicin versus placebo, Outcome 3 Overall nasal symptoms 36 weeks post-treatment.

Review: Capsaicin for non-allergic rhinitis

Comparison: 1 Capsaicin versus placebo

Outcome: 3 Overall nasal symptoms 36 weeks post-treatment

Study or subgroup	Capsaicin N	Capsaicin Mean(SD)[VAS, 0-10]	Placebo N	Placebo Mean(SD)[VAS, 0-10]	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Blom 1997/1998	13	3.26 (3.132)	11	6.78 (1.886)		100.0 %	-3.52 [-5.55, -1.48]
Total (95% CI)	**13**		**11**			**100.0 %**	**-3.52 [-5.55, -1.48]**

Heterogeneity: not applicable

Test for overall effect: Z = 3.39 (P = 0.00070)

Test for subgroup differences: Not applicable

Analysis 1.4. Comparison 1 Capsaicin versus placebo, Outcome 4 Daily record chart symptom resolution at 4 weeks post-treatment (capsaicin 1 μg/puff versus placebo).

Review: Capsaicin for non-allergic rhinitis

Comparison: 1 Capsaicin versus placebo

Outcome: 4 Daily record chart symptom resolution at 4 weeks post-treatment (capsaicin 1 μg/puff versus placebo)

Study or subgroup	Capsaicin 1 μg/puff n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Ciabatti 2009	9/52	6/52		100.0 %	1.50 [0.58, 3.91]
Total (95% CI)	**52**	**52**		**100.0 %**	**1.50 [0.58, 3.91]**

Total events: 9 (Capsaicin 1 μg/puff), 6 (Placebo)
Heterogeneity: not applicable
Test for overall effect: Z = 0.83 (P = 0.41)
Test for subgroup differences: Not applicable

Analysis 1.5. Comparison 1 Capsaicin versus placebo, Outcome 5 Daily record chart symptom resolution at 4 weeks post-treatment (capsaicin 2 μg/puff versus placebo).

Review: Capsaicin for non-allergic rhinitis

Comparison: 1 Capsaicin versus placebo

Outcome: 5 Daily record chart symptom resolution at 4 weeks post-treatment (capsaicin 2 μg/puff versus placebo)

Study or subgroup	Capsaicin 2 μg/puff n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Ciabatti 2009	12/52	6/52		100.0 %	2.00 [0.81, 4.93]
Total (95% CI)	**52**	**52**		**100.0 %**	**2.00 [0.81, 4.93]**

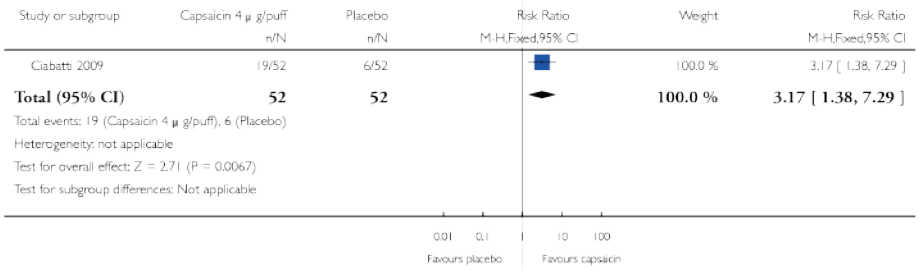
Total events: 12 (Capsaicin 2 μg/puff), 6 (Placebo)
Heterogeneity: not applicable
Test for overall effect: Z = 1.51 (P = 0.13)
Test for subgroup differences: Not applicable

Analysis 1.6. Comparison 1 Capsaicin versus placebo, Outcome 6 Daily record chart symptom resolution at 4 weeks post-treatment (capsaicin 4 μg/puff versus placebo).

Review: Capsaicin for non-allergic rhinitis

Comparison: 1 Capsaicin versus placebo

Outcome: 6 Daily record chart symptom resolution at 4 weeks post-treatment (capsaicin 4 μ g/puff versus placebo)



Comparison 2 Capsaicin versus budesonide

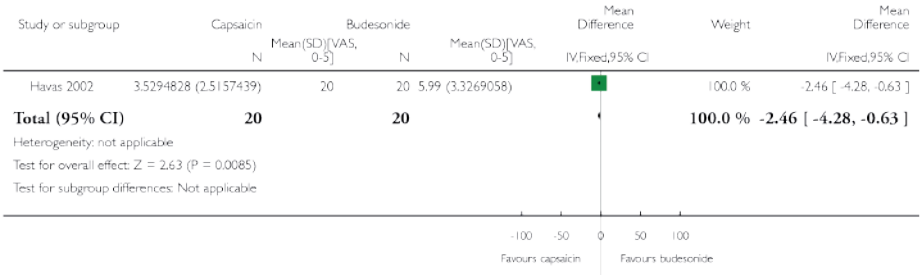
Outcome or Subgroup	Studies	Partic-ipants	Statistical Method	Effect Estimate
2.1 Aggregate score during the 4th week of treatment [VAS, 0-5]	1	40	Mean Difference (IV, Fixed, 95% CI [VAS, 0-5])	-2.46 [-4.28, -0.63]
2.2 Aggregate relief score during the 4th week of treatment	1	40	Mean Difference (IV, Fixed, 95% CI)	2.50 [1.06, 3.94]
2.1 Aggregate score during the 4th week of treatment [VAS, 0-5]	1	40	Mean Difference (IV, Fixed, 95% CI [VAS, 0-5])	-2.46 [-4.28, -0.63]
2.2 Aggregate relief score during the 4th week of treatment	1	40	Mean Difference (IV, Fixed, 95% CI)	2.50 [1.06, 3.94]
2.5 Postnasal drip during the 4th week of treatment [VAS, 0-5]	1	40	Mean Difference (IV, Fixed, 95% CI [VAS, 0-5])	-0.50 [-1.32, 0.33]
2.6 Rhinorrhoea during the 4th week of treatment [VAS, 0-5]	1	40	Mean Difference (IV, Fixed, 95% CI [VAS, 0-5])	-0.25 [-0.99, 0.48]
2.7 Nasal blockage during the 4th week of treatment [VAS, 0-5]	1	40	Mean Difference (IV, Fixed, 95% CI [VAS, 0-5])	-1.19 [-2.45, 0.06]
2.8 Sneezing during the 4th week of treatment [VAS, 0-5]	1	40	Mean Difference (IV, Fixed, 95% CI [VAS, 0-5])	-0.15 [-0.74, 0.43]
2.9 Sore throat during the 4th week of treatment [VAS, 0-5]	1	40	Mean Difference (IV, Fixed, 95% CI [VAS, 0-5])	-0.44 [-1.04, 0.15]

Analysis 2.1. Comparison 2 Capsaicin versus budesonide, Outcome 1 Aggregate score during the 4th week of treatment.

Review: Capsaicin for non-allergic rhinitis

Comparison: 2 Capsaicin versus budesonide

Outcome: 1 Aggregate score during the 4th week of treatment

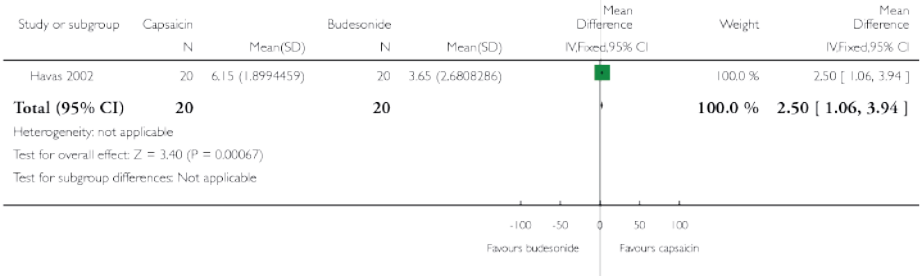


Analysis 2.2. Comparison 2 Capsaicin versus budesonide, Outcome 2 Aggregate relief score during the 4th week of treatment.

Review: Capsaicin for non-allergic rhinitis

Comparison: 2 Capsaicin versus budesonide

Outcome: 2 Aggregate relief score during the 4th week of treatment

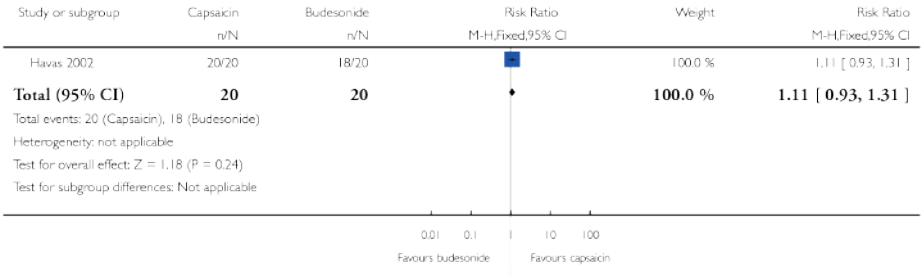


Analysis 2.3. Comparison 2 Capsaicin versus budesonide, Outcome 3 Nasal obstruction (responder/non-responder analysis) during the 4th week of treatment.

Review: Capsaicin for non-allergic rhinitis

Comparison: 2 Capsaicin versus budesonide

Outcome: 3 Nasal obstruction (responder/non-responder analysis) during the 4th week of treatment

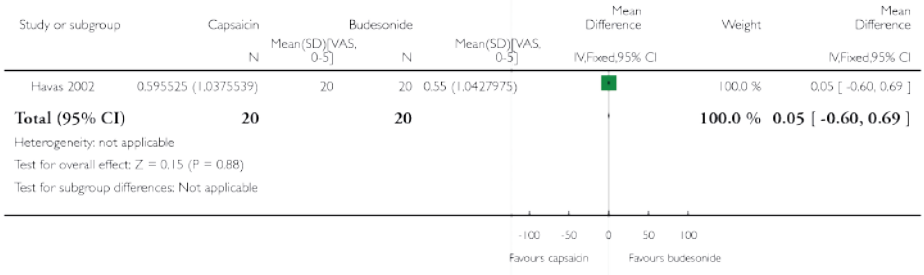


Analysis 2.4. Comparison 2 Capsaicin versus budesonide, Outcome 4 Headache during the 4th week of treatment.

Review: Capsaicin for non-allergic rhinitis

Comparison: 2 Capsaicin versus budesonide

Outcome: 4 Headache during the 4th week of treatment

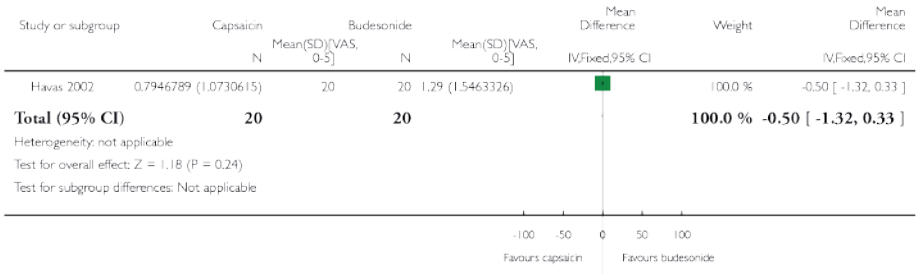


Analysis 2.5. Comparison 2 Capsaicin versus budesonide, Outcome 5 Postnasal drip during the 4th week of treatment.

Review: Capsaicin for non-allergic rhinitis

Comparison: 2 Capsaicin versus budesonide

Outcome: 5 Postnasal drip during the 4th week of treatment

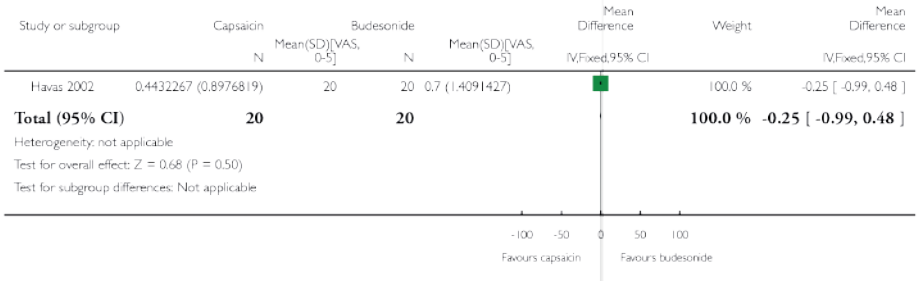


Analysis 2.6. Comparison 2 Capsaicin versus budesonide, Outcome 6 Rhinorrhoea during the 4th week of treatment.

Review: Capsaicin for non-allergic rhinitis

Comparison: 2 Capsaicin versus budesonide

Outcome: 6 Rhinorrhoea during the 4th week of treatment

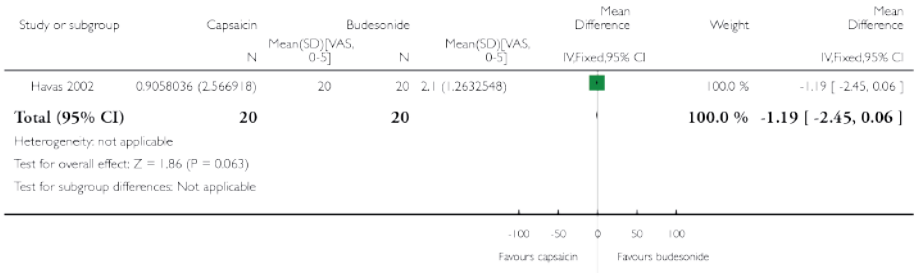


Analysis 2.7. Comparison 2 Capsaicin versus budesonide, Outcome 7 Nasal blockage during the 4th week of treatment.

Review: Capsaicin for non-allergic rhinitis

Comparison: 2 Capsaicin versus budesonide

Outcome: 7 Nasal blockage during the 4th week of treatment

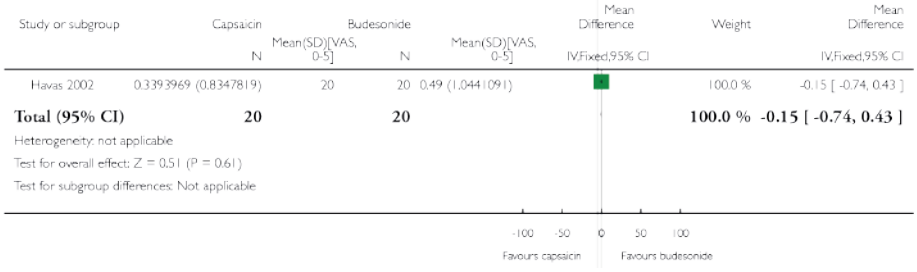


Analysis 2.8. Comparison 2 Capsaicin versus budesonide, Outcome 8 Sneezing during the 4th week of treatment.

Review: Capsaicin for non-allergic rhinitis

Comparison: 2 Capsaicin versus budesonide

Outcome: 8 Sneezing during the 4th week of treatment

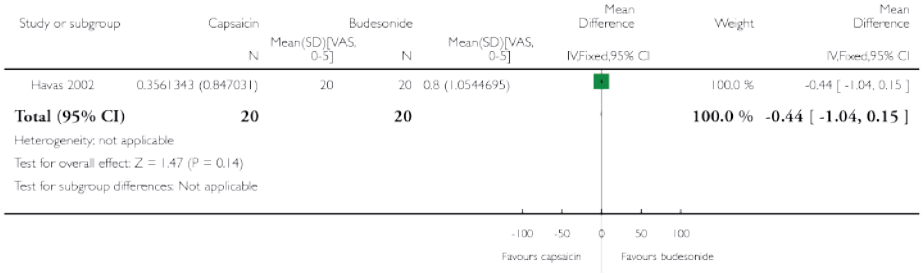


Analysis 2.9. Comparison 2 Capsaicin versus budesonide, Outcome 9 Sore throat during the 4th week of treatment.

Review: Capsaicin for non-allergic rhinitis

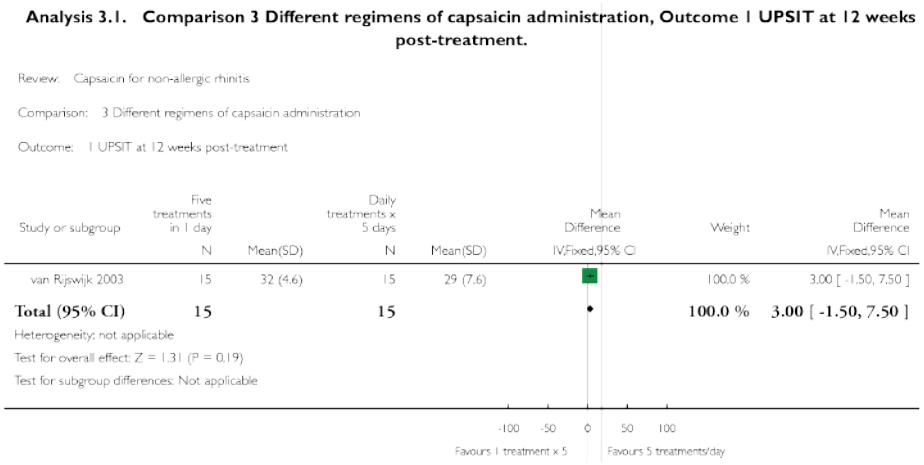
Comparison: 2 Capsaicin versus budesonide

Outcome: 9 Sore throat during the 4th week of treatment



Comparison 3 Different regimens of capsaicin administration

Outcome or Subgroup	Studies	Partici-pants	Statistical Method	Effect Estimate
3.1 UPSIT at 12 weeks post-treatment	1	30	Mean Difference (IV, Fixed, 95% CI)	3.00 [-1.50, 7.50]



Comparison 4 Different doses of capsaicin

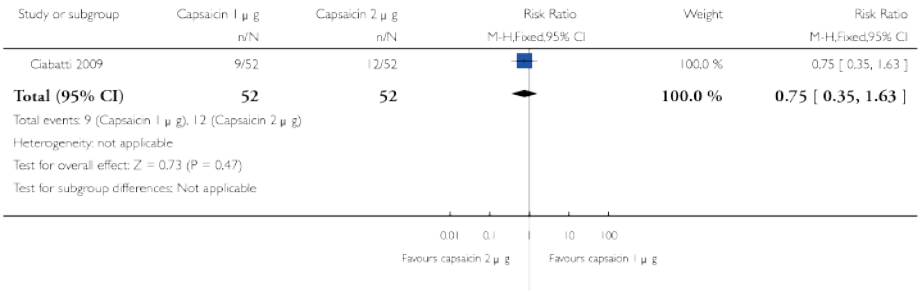
Outcome or Subgroup	Studies	Partici-pants	Statistical Method	Effect Estimate
4.1 Daily record chart symptom resolution at 4 weeks post-treatment (capsaicin 1 µg versus 2 µg/puff)	1	104	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.35, 1.63]
4.2 Daily record chart symptom resolution at 4 weeks post-treatment (capsaicin 1 µg versus 4 µg/puff)	1	104	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.24, 0.95]
4.3 Daily record chart symptom resolution at 4 weeks post-treatment (capsaicin 2 µg versus 4 µg/puff)	1	104	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.34, 1.16]

Analysis 4.1. Comparison 4 Different doses of capsaicin, Outcome 1 Daily record chart symptom resolution at 4 weeks post-treatment (capsaicin 1 μg versus 2 μg/puff).

Review: Capsaicin for non-allergic rhinitis

Comparison: 4 Different doses of capsaicin

Outcome: 1 Daily record chart symptom resolution at 4 weeks post-treatment (capsaicin 1 μ g versus 2 μ g/puff)

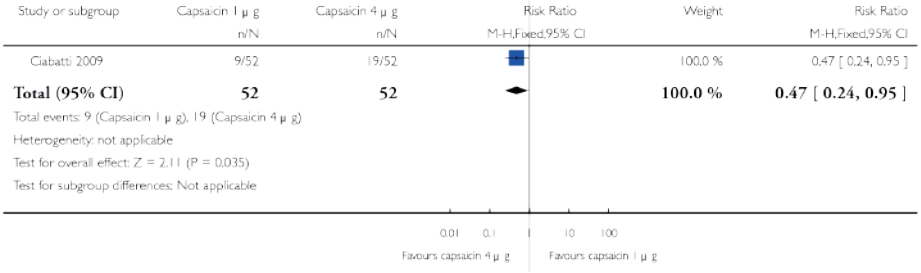


Analysis 4.2. Comparison 4 Different doses of capsaicin, Outcome 2 Daily record chart symptom resolution at 4 weeks post-treatment (capsaicin 1 μg versus 4 μg/puff).

Review: Capsaicin for non-allergic rhinitis

Comparison: 4 Different doses of capsaicin

Outcome: 2 Daily record chart symptom resolution at 4 weeks post-treatment (capsaicin 1 μ g versus 4 μ g/puff)

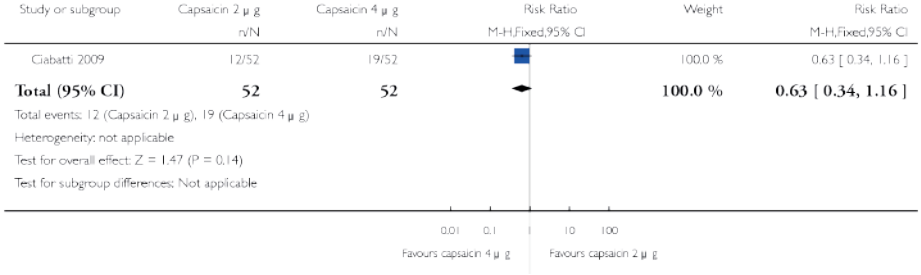


Analysis 4.3. Comparison 4 Different doses of capsaicin, Outcome 3 Daily record chart symptom resolution at 4 weeks post-treatment (capsaicin 2 μg versus 4 μg/puff).

Review: Capsaicin for non-allergic rhinitis

Comparison: 4 Different doses of capsaicin

Outcome: 3 Daily record chart symptom resolution at 4 weeks post-treatment (capsaicin 2 μ g versus 4 μ g/puff)



APPENDICES

Appendix 1 Search strategies

CENTRAL	PubMed	EMBASE (Ovid)	CINAHL (EBSCO)
#1 MeSH descriptor: [Rhinitis] explode all trees #2 rhinit* #3 NARES or NAR or LAR or NANIPER #4 #1 OR #2 OR #3 #5 MeSH descriptor: [Capsaicin] explode all trees #6 (Capsaicin* or Pepper or Axsain or Zacin or Capsicum or Capsidol or Zostrix or Capzasin or Gelcen or Katrum or Capsin or Capsacinoid* or sinus next buster) #7 #5 or #6 #8 #4 and #7	#1 "Rhinitis"[Mesh] #2 rhinit*[Title/Abstract] #3 (NARES or NAR or LAR or NANIPER[Title/Abstract]) #4 (#1 OR #2 OR #3) #5 "Capsaicin"[Mesh] #6 (Capsaicin* or Pepper or Axsain or Zacin or Capsicum or Capsidol or Zostrix or Capzasin or Gelcen or Katrum or Capsin or Capsacinoid*[Title/Abstract]) #7 (sinus[Title/Abstract]) AND buster[Title/Abstract] #8 (#5 OR #6 OR #7 OR #8) #9 (#4 AND #8)	1 exp rhinitis/ 2 "rhinit*".tw. 3 (NARES or NAR or LAR or NANIPER).tw. 4 (Capsaicin* or Pepper or Axsain or Zacin or Capsicum or Capsidol or Zostrix or Capzasin or Gelcen or Katrum or Capsin or Capsacinoid*).tw. 5 exp capsaicin/ 6 (sinus adj6 buster).tw. 7 1 or 2 or 3 8 4 or 5 or 6 9 7 and 8	S1 (MH "Rhinitis+") S2 TX rhinit* S3 TX NARES or NAR or LAR or NANIPER S4 S1 OR S2 OR S3 S5 (MH "Capsaicin") S6 TX Capsaicin* or Pepper or Axsain or Zacin or Capsicum or Capsidol or Zostrix or Capzasin or Gelcen or Katrum or Capsin or Capsacinoid* S7 TX sinus and buster S8 S5 OR S6 OR S7 S9 S4 AND S8
Clinicaltrials.gov (via the Cochrane Register of Studies)	**Web of Science**	**AMED (Ovid)**	**ICTRP**

Table continued

rhinitis AND (Capsaicin* OR Pepper OR Axsain OR Zacin OR Capsicum OR Capsidol OR Zostrix OR Capzasin OR Gelcen OR Katrum OR Capsin OR Capsacinoid*)	#1 TS=rhinit* #2 TS=(NARES or NAR or LAR or NANIPER) #3 #2 OR #1 #4 TS=(Capsaicin* or Pepper or Axsain or Zacin or Capsicum or Capsidol or Zostrix or Capzasin or Gelcen or Katrum or Capsin or Capsacinoid*) #5 TS=(sinus AND buster) #6 #5 OR #4 #7 #6 AND #3	1 exp rhinitis/ 2 "rhinit*".tw. 3 (NARES or NAR or LAR or NANIPER).tw. 4 (Capsaicin* or Pepper or Axsain or Zacin or Capsicum or Capsidol or Zostrix or Capzasin or Gelcen or Katrum or Capsin or Capsacinoid*).tw. 5 exp capsaicin/ 6 (sinus adj6 buster).tw. 7 1 or 2 or 3 8 4 or 5 or 6 9 7 and 8	rhinitis and Capsaicin or rhinitis and pepper or rhinitis and axsain or rhinitis and capsicum or rhinitis and capsidol or rhinitis and zostrix or rhinitis and capzasin or rhinitis and gelcen or rhinitis and katrum or rhinitis and capsin or rhinitis and capsacinoid

Appendix 2 Summary of the data collection form

We extracted the following characteristics using the data collection form.

- General information: publication type, year, country, author contact details.
- Study eligibility: type of study, participants, types of interventions, comparisons and outcomes.
- Study methods: design, unit of allocation, start and end dates, duration of participation, ethical approval, funding, possible conflicts of interest.
- Participants: population description, setting, inclusion and exclusion criteria, method of recruitment, informed consent, total number randomised, clusters (if applicable), baseline imbalances, withdrawals and exclusions, age, sex, race/ethnicity, severity of illness, comorbidities, other relevant socio-demographics, measured and reported subgroups.
- Intervention and comparison groups: capsaicin and comparison type, number randomised to group, duration of treatment, timing, delivery, providers, co-interventions, economic information, resource requirements, integrity of delivery, compliance.
- Outcomes: type of outcome, time points measured, time points reported, unit of measurement, scale, assumed risk estimate, power.

- 'Risk of bias' assessment: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, other bias.
- Data and analysis: comparison, outcome, subgroup, time points, results, number of missing participants, reason missing, number of participants moved from another group, reason for move, unit of analysis, statistical method.
- Other information: key conclusions of the study, references to other relevant studies.

CONTRIBUTIONS OF AUTHORS

AG, CG and RG 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 Bioinpsire, 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.

Cornelis M van Drunen has received grants form GSK, ALK, Allergopharma, the European Union (GA2LEN, BM4SIT) and the Dutch (NWO) and Flemish Government (FMO) in the field of (non)-allergic rhinitis and chronic rhinosinusitis.

Artur Gevorgyan was supported by the 2013 Clinical Fellowship of the European Academy of Allergy and Clinical Immunology.

Christine Segboer: no potential conflict of interest.

Rob Gorissen: no potential conflict of interest.

No funds have been received by the authors of the review that relate directly to capsaicin.

SOURCES OF SUPPORT

Internal sources

- None, Other.

The authors received no specific support for this study

External sources

- National Institute for Health Research, UK.

Infrastructure funding for the Cochrane ENT Group

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).

Index Terms

Medical Subject Headings (MeSH)

Anti-Inflammatory Agents [*therapeutic use]; Budesonide [therapeutic use]; Capsaicin [administration & dosage; *therapeutic use];

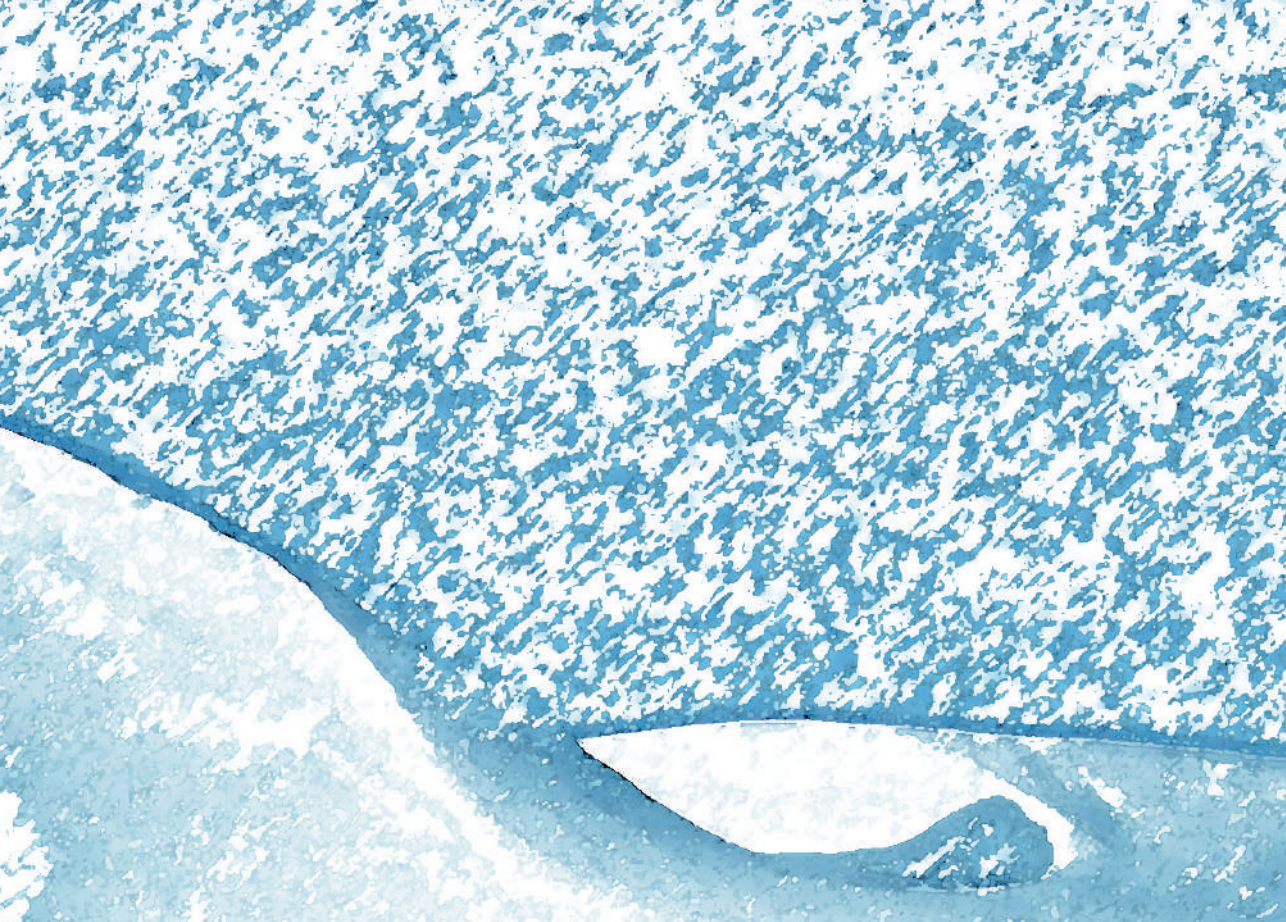
Randomized Controlled Trials as Topic; Rhinitis [*drug therapy]

MeSH check words

Adolescent; Adult; Aged; Humans; Middle Aged

CHAPTER 7

Inhibition of capsaicin-driven nasal hyper-reactivity by SB-705498, a TRPV-1 antagonist



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ABSTRACT

Aims

To assess the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of intranasal SB-705498, a selective TRPV-1 antagonist.

Methods

Two randomized, double-blind, placebo-controlled, clinical studies were performed: (i) an intranasal SB-705498 first time in human study to examine the safety and PK of five single escalating doses from 0.5 to 12 mg and of repeat dosing with 6 mg and 12 mg twice daily for 14 days and (ii) a PD efficacy study in subjects with non-allergic rhinitis (NAR) to evaluate the effect of 12 mg intranasal SB-705498 against nasal capsaicin challenge.

Results

Single and repeat dosing with intranasal SB-705498 was safe and well tolerated. The overall frequency of adverse events was similar for SB-705498 and placebo and no dose-dependent increase was observed. Administration of SB-705498 resulted in less than dose proportional AUC (0,12 h) and C_{max}, while repeat dosing from day 1 to day 14 led to its accumulation. SB-705498 receptor occupancy in nasal tissue was estimated to be high (>80%). Administration of 12 mg SB-705498 to patients with NAR induced a marked reduction in total symptom scores triggered by nasal capsaicin challenge. Inhibition of rhinorrhoea, nasal congestion and burning sensation was associated with 2- to 4-fold shift in capsaicin potency.

Conclusions

Intranasal SB-705498 has an appropriate safety and PK profile for development in humans and achieves clinically relevant attenuation of capsaicin-provoked rhinitis symptoms in patients with NAR. The potential impact intranasal SB-705498 may have in rhinitis treatment deserves further evaluation.

What is already known about this subject

- Transient receptor potential vanilloid 1 (TRPV-1) is an ion channel expressed on peripheral nerves, activated by several physical, chemical and biological factors.
- In the nose, overstimulation of TRPV-1-expressing sensory nerves may lead to nasal hyper-reactivity and development of rhinitis symptoms in sensitive individuals.
- Targeting TRPV-1 may offer the potential to control medical conditions characterized by sensory neuronal hyper-responsiveness, including the nasal hyper-reactivity that underlies non-allergic rhinitis (NAR).

What this study adds

- This study provides an insight on the early clinical evaluation of SB-705498, a selective TRPV-1 antagonist, as a potential intranasal therapeutic modality for NAR.
- The safety and pharmacokinetic (PK) profile of intranasal SB-705498 was established in humans and an agonist-antagonist intranasal dose–response capsaicin challenge was initiated to provide evidence of pharmacology in the target patient population.
- Intranasal SB-705498 could be developed as a potential new blocker of nasal hyper-reactivity in rhinitis patients.

INTRODUCTION

Rhinitis is a common condition that affects up to 30% of adults and 40% of children and poses a significant economic burden to the world population (1-3). A regular patho-physiological feature of rhinitis is nasal hyper-responsiveness. Nasal hyper-responsiveness is characterized by exaggerated nasal sensory and reflexogenic responses to environmental factors, such as weather changes, household chemicals, pollution or strong odours, that result in generation of symptoms of rhinorrhoea, nasal congestion, sneezing and itch (4, 5). Nasal hyper-responsiveness is often a consequence of allergic inflammation, as allergic mediators affect directly the sensory nasal nerves and reduce their threshold potential for activation (4). Nasal hyper-responsiveness is also the cardinal feature of non-allergic rhinitis (NAR), a disease entity thought to be driven by over-reactivity of nasal sensory nerves or over-interpretation of normally transmitted signals by the CNS response centres (6). Blocking the sensory neuronal pathways involved in nasal hyper-responsiveness has been proposed as a novel form of treatment for difficult to treat rhinitis patients. This concept is supported by clinical data demonstrating that cold dry air or hypertonic saline triggered nasal hyper-responsiveness is inhibited after anaesthetization or desensitization of the nasal sensory fibres (4, 7).

TRPV-1 (also known as VR1, vanilloid/capsaicin receptor, OTRPC1) (8) is a sensory nerve receptor, a member of a super-family of structurally related transmembrane ion channels, known to serve a multitude of cellular roles, including many facets of sensory transduction (9, 10). TRPV-1 is activated by several physiological stimuli including capsaicin, heat, low pH, osmotic stress and by endogenous inflammatory mediators, such as histamine, prostaglandins and lipoxygenases (9, 11). TRPV-1 is expressed on afferent sensory nerves, particularly on non-myelinated C-fibre nociceptors, and is present in the airways. In the upper airways expression of TRPV-1 has been confirmed on the trigeminal sensory neurones that innervate the epithelium and subepithelium of nasal mucosa (12). The expression of TRPV-1 has been found enhanced in chronic

inflammation (13). Several lines of experimental evidence indicate that TRPV-1 is a key player in the excitability of airway sensory neurons and TRPV-1 sensitive nerves have been shown to contribute in the development of lower and upper airway hyper-responsiveness, bronchoconstriction and cough (14, 15). This suggests that TRPV-1 may be a primary target for pharmacological intervention for a range of respiratory disorders.

To assess if TRPV-1 antagonism can prevent nasal hyper-responsiveness and therefore become a promising therapeutic modality for NAR, SB-705498, a potent and selective TRPV-1 antagonist (16, 17), has been developed for intranasal administration. SB-705498 is a known inhibitor of the multiple modes of TRPV-1 activation. Treatment with oral SB-705498 has been applied successfully in models of neuropathic and inflammatory pain (18). In a pre-clinical rhinitis model, intranasal as well as oral administration of SB-705498 has been shown to block the capsaicin-evoked nasal secretions (19). In this rhinitis model 10-fold lower doses of intranasal SB-705498 were required to achieve the same efficacy as the orally dosed compound. Furthermore, intranasal SB-705498 has a good safety and pre-clinical toxicology profile that allowed initiation of clinical studies.

In this article we describe a first time in human (FTIH) study to characterize the safety and PK profiles of intranasal SB-705498 in healthy volunteers and a pharmacodynamics (PD) study to evaluate its effects against capsaicin-provoked nasal reactivity in subjects with NAR.

METHODS

The FTIH study to determine the safety, tolerability and PK of single and repeat dosing with intranasal SB-705498 in healthy volunteers was conducted at Hammersmith Medicines Research, London, UK (GlaxoSmithKline protocol: VR1111610; clintrials.gov: NCT00907933). The PD study to evaluate the effect of intranasal SB-705498 on capsaicin-evoked nasal reactivity in patients with NAR was conducted at Academisch Medisch Centrum, Amsterdam, the Netherlands (GlaxoSmithKline protocol: VR1111925; clintrials.gov: NCT01439308).

Clinical study populations

FTIH study

Non-smoking male and female healthy volunteers aged 18–60 years with no previous history of nasal disorders were included in the study. A total of 14 and 30 healthy volunteers participated in the single and repeat dose arm of the study respectively.

PD study

Forty-one male and female, non-smoking NAR patients aged 18–55 years with no other concomitant disorders participated in the study. All patients had a diagnosis of NAR >1 year, as determined by the presence of perennial rhinitis symptoms triggered by environmental provocateurs (i.e. weather changes, irritants, air pollution etc.) for at least 9 months of the year. All NAR patients were required to have normal levels of total plasma IgE and negative allergen-specific skin or serum IgE tests.

All study participants provided written, informed consent to participate in the studies. Local Ethics Committees provided formal approval for the studies which were conducted in accordance with all known regulatory requirements and the guiding principles of the Declaration of Helsinki (20).

Clinical study designs

FTIH study

This study had two-arms. First the safety, tolerability and PK of five single ascending doses of intranasal SB-705498 (0.5, 1.5, 3, 6, and 12 mg) were evaluated in healthy volunteers following a randomized, double-blind, placebo-controlled, five period, incomplete block crossover design. The incomplete block design was intended to make the study more manageable for participants and more time efficient. Successfully screened subjects were randomized to receive a single intranasal dose of either SB-705498 or placebo in each treatment period, and over the course of the study each subject received five out of the six possible treatments, each once only. In each treatment period subjects attended the unit approximately 24 h before dosing and remained resident for 24 h post-dosing. A follow-up phone call was made 7 to 10 days later. At the end of each treatment period all available blinded safety and PK data were reviewed to allow dose escalation. Treatment periods were separated by a 7 day washout.

After the safety of single dosing was established a randomized, double-blind, placebo-controlled, parallel group study was initiated to evaluate the safety, tolerability and PK of 6 and 12 mg of intranasal SB-705498 administered twice daily for 14 days. New healthy volunteers were recruited for this arm of the study. Eligible subjects attended the study 24 h before the first dosing (day −1) and remained resident for approximately 36 h post-dosing. Subjects left the unit with a diary card and sufficient study medication to continue self-administration until day 7, when they returned to the unit for review of diary information and adherence and to get new medication supplies to continue self-administration until day 13. On day 13 subjects returned to the unit again and remained resident for approximately 48 h after their last dosing for assessments and collection of PK samples. A follow-up phone call was made 7–10 days after the final dose.

PD study

This was a randomized, double-blind, placebo-controlled, parallel group study to evaluate the effect of a single intranasal administration of 12 mg SB-705498 on capsaicin-evoked nasal reactivity in patients with NAR. PK and safety were also assessed. Subjects with NAR went through an initial screening to assess their eligibility for enrolment in the study and confirm their responsiveness to a single, unilateral, intranasal challenge with 50 µg capsaicin. Only subjects who developed a total symptom score (TSS) ≥3 in response to the capsaicin challenge entered the treatment phase of the study. On the dosing day 1 h after administration of SB-705498 or placebo, all patients underwent a baseline unilateral, intranasal vehicle control challenge and subsequently received three unilateral, intranasal challenges with incremental doses of capsaicin (2.5 µg, 12.5 µg and 50 µg). Clinical symptoms were assessed and nasal secretions were collected after each challenge. Patients were followed-up by telephone 48 h after treatment.

Justification of dose selection

The selection of doses for the FTIH and PD studies was based on the estimated SB-705498 dose–response from a guinea pig rhinitis PD model over the oral dose range 3 to 30 mg kg^{-1} (19). The estimated ED_{50} parameter (10 mg kg^{-1}) in the guinea pig was converted to the corresponding drug levels of 1.4 µg ml^{-1} (EC_{50}) in the nasal turbinates using clearance data obtained in guinea pigs after intravenous and intranasal dosing and blood to nasal tissue partition (in house data). The EC_{50} value in the guinea pig turbinates was then scaled to corresponding equivalent drug levels (EC_{50}) in human turbinates based on the known human clearance parameter of the drug and free drug fraction and assuming similar blood to nasal tissue partition as in the guinea pig. As described below, an estimation of a total intranasal dose of 12 mg (6 mg/nostril) would be required in humans to achieve intranasal concentrations corresponding to those found to be effective in the guinea pig. It was predicted that the intranasal dose of SB-705498 12 mg (6 mg in each nostril) would lead to high receptor occupancy (~ >80%) at the target nasal tissues. This estimate took into account the binding affinity of SB-705498 at the human TRPV-1 receptor (pKb = 7.5 in house data), an assumed volume of human nasal tissue of 20 ml (21) and an intranasal bioavailability of the drug of approximately 20% after intranasal dosing. The intranasal bioavailability in humans was approximated from preclinical data in the dog where the drug was given intranasally with and without charcoal (unpublished data on file, GlaxoSmithKline, Stevenage, UK). The charcoal block test is a standard and useful method to estimate the tissue bioavailability following topical administration (such as inhaled or intranasal route) of the drug compared with oral administration. Co-administration of charcoal with the drug prevents its oral absorption resulting in minimal systemic availability of the administered drug. The predicted nasal tissue and systemic exposure in humans with doses of intranasal SB-705498 up to 12 mg were within the safety margins derived from preclinical safety studies.

Safety assessments

Adverse events were recorded throughout the FTIH and PD studies. The investigator graded adverse event intensity (mild, moderate or severe) and relationship with study drug. Body temperature, vital signs, 12-lead electrocardiogram (ECG), nasal tolerability (nasal symptom scoring by visual analogue scale [VAS], nasal endoscopy (performed in the FTIH only) and visual nasal examination were evaluated at several time points post-dosing. Furthermore, there was repeat assessment of laboratory safety parameters, including plasma progesterone, adrenocorticotrophic hormone and cortisol concentrations (because administration of SB-705498 to rat or dog at high doses above the no adverse effect level (NOAEL) has been associated with vacuolation and hypertrophy of some hormone producing organs, most notably the adrenal cortex, but also the ovaries and testes).

PK assessment

In the FTIH, blood samples were collected for PK analysis pre-dose, 15 and 30 min and 1, 2, 4, 8, 12 and 24 h post each single dosing. In the 14 days repeat dosing arm, samples were taken at the same times relative to dosing on day 1 and day 14, and additional samples were taken 36 and 48 h after the last dose received on day 14. In the PD study blood samples were collected pre-dose, 30 min and 1, 2, 3 and 4 h post-dosing. Plasma was analyzed for parent drug by high performance liquid chromatography/tandem mass spectrometry using a Turbolonspray interface and multiple reaction monitoring (22, 23). The method had a lower limit of quantification (LLQ) of 2.5 ng ml^{-1} using a 50 µl aliquot of human plasma over a linear calibration range of 2.5 to 2000 ng ml^{-1}. Quality control (QC) samples, prepared at three different analyte concentrations and stored with study samples, were analyzed with each batch of samples against separately prepared calibration standards. For the analysis to be acceptable, no more than one-third of the QC results were to deviate from the nominal concentration by more than 15% and at least 50% of the results from each QC concentration were to be within 15% of nominal. All applicable analytical runs met all predefined run acceptance criteria.

SB-705498 PK parameters were derived from the initial time–concentration data by standard non-compartmental analysis using WinNonLin Pro (Version 4.1; Pharsight Products, Cary, NC, USA). The following parameters were assessed: AUC(0,*t*), AUC from time 0 to 4 h, from time 0 to 12 h and from time 0 to 24 h post-dose (AUC(0,4 h), AUC(0,12 h), AUC(0,24 h)), maximum observed plasma concentration (C_{max}) and time to maximum observed plasma concentration (t_{max}).

PD assessments

Intranasal capsaicin challenge

In the PD study the nasal response to unilateral, intranasal capsaicin challenge was assessed and the effect of prior treatment with intranasal SB-705498 *vs.* placebo

analyzed. In brief, patients blew their nose to clear any secretions and both nostrils were then washed 20 times in 1 min with 0.9% saline (10 ml). The lavage fluid was discarded and the nostrils were dried. Initially, a baseline assessment of the response to a unilateral intranasal vehicle control challenge was made by spraying saline into the right nostril using a metered pump device (25 µl or 50 µl per actuation). Subsequently the response to capsaicin challenge was evaluated by spraying a single (at screening) or incremental capsaicin doses (2.5 µg, 12.5 µg and 50 µg) into the right nostril using a metered pump device. The number of actuations was determined by the dose of capsaicin required. Challenges with saline or each dose of capsaicin were separated by an interval of 20 min during which a series of assessments were made.

At 1, 5, and 9 min after each challenge, patients were asked to grade the intensity of symptoms of burning sensation, rhinorrhoea, lacrimation and nasal congestion as follows: 0 = none; 1 = mild; 2 = moderate and 3 = severe. The individual scores were summed to produce a TSS. Patients also completed a 10 cm long VAS for nasal congestion, rhinorrhoea, lacrimation and burning sensation.

Peak nasal inspiratory flow (PNIF) was measured using an InCheck PNIF meter (Clement Clarke International Ltd, Harlow, United Kingdom) 15 min after each challenge. Three inspiratory efforts were made and the highest measure was recorded.

Statistical analysis

FTIH study

Sample sizes were based on logistic feasibility. In the single dose arm dose proportionality using C_{max} and AUC was assessed using a power model and analysis of variance (anova). In the repeat dose arm, a statistical analysis was performed on AUC(0,12 h) and C_{max} (after morning dosing) to evaluate the accumulation ratio. A mixed effect model was fitted with dose (categorical variable), day and dose by day interaction as fixed effects and repeated measures analysis was carried out on day using subject as a blocking effect. Day 14 was compared with day 1 in order to estimate the accumulation ratio for each treatment group.

PD study

An unblinded adaptive sample size re-estimation was planned for when 20 patients had completed the study to determine whether to terminate the study for futility or efficacy. Due to a high rate of recruitment, it was conducted after 37 patients had been dosed but the analysis used data from only 20 patients. Following the interim analysis the planned number of patients (n = 40) were subsequently recruited. Treatment differences and ratios (SB-705498 12 mg *vs.* placebo) of adjusted means were analyzed for TSS and nasal secretion weights using a repeated measures anova. A Bayesian analysis was conducted to derive the posterior probability distributions for total nasal secretion weights, mean TSS and average VAS measures for nasal

congestion, rhinorrhoea, lacrimation and burning sensation. The probabilities were derived using a mixed effects model (fitted for the frequentist analysis). However, a Student's *t* cumulative distribution function was used to obtain the probabilistic statements, assuming a non-informative prior. The difference between SB-705498 12 mg and placebo for change from baseline in PNIF was analyzed using a repeated measures anova.

Dose ratio analysis

A quantitative approach was performed in the PD study to evaluate the effect of single dose SB-705498 (antagonist) in the presence of incremental challenge with capsaicin (agonist) to estimate the shift in dose–response. Clinical endpoints corrected for saline baseline were evaluated including average TSS, components of TSS (nasal congestion, lacrimation, burning sensation, and rhinorrhoea), VAS scores for individual components (nasal congestion, lacrimation, burning sensation, rhinorrhoea) and PNIF. The standard parallel line assay method was applied to each of the clinical endpoints (24). With this method, an overall anovais carried out and tests of significance performed on the regression slope, linearity of dose–response and evidence of parallelism. For each clinical endpoint, the dose–response was compared only for the agonist and in the presence of the drug (antagonist). This comparison was done by estimation of the potency ratio (with associated 95% confidence intervals [CIs]), which corresponds to the inverse of the ratio for the doses that produce equivalent responses in the two treatment groups for each endpoint. This analysis was performed using PLA Version 2.0 software (Stegmann Systems, Rodgan, Germany) for parallel line and parallel logistics assays. This software includes a suite of transformation functions for the response variables to account for any heteroscedasticity. Individual datasets for each clinical endpoint for both studies were fitted to the appropriate model with a detailed statistical output of the overall dose ratio analysis. Dose ratio estimates for each clinical endpoint and associated 95% CIs are graphically presented.

Results

Participants

FTIH study

Fourteen healthy volunteers (HVT) with mean age 32.9 (23–52) years and thirty HVT with mean age 28.5 (21–48) years were randomized in the single and repeat dose arms of the study respectively. All subjects completed the study. The populations were predominantly Caucasian (11 subjects [79%] in the single dose arm and 24 subjects [80%] in the repeat dose arm) and male (11 subjects [79%] and 22 subjects [73%], respectively).

PD study

Forty-one patients (26 females and 15 males) were randomized (SB-705498 12 mg: 19 patients; placebo: 22 patients). All completed, except one patient who received SB-705498 12 mg and withdrew because of an adverse event (intermittent hypertension). Mean (range) ages were 40.1 (19–57) years in the SB-705498 group and 34.0 (18–55) years in the placebo group.

Safety and tolerability results

FTIH study

Single and repeat dosing with intranasal SB-705498 was well tolerated at all dose levels tested. No serious adverse events were reported in the study and no dose relationship in the incidence of adverse events was observed. Subjects who received single administration of 1.5 mg intranasal SB-705498 presented a slightly greater incidence of drug-related adverse events. However, this finding was not repeated at higher doses and therefore it was not considered clinically relevant. All adverse events were transient and of mild/moderate intensity. The most frequently reported adverse events were headache and oropharyngeal pain (Table 1). Clinically significant changes for vital signs, cardiac monitoring, body temperature, and standard haematology and biochemistry tests (including plasma progesterone, adrenocorticotrophic hormone and cortisol concentrations) were not detected. Furthermore, there were no consistent or dose dependent signs of nasal irritancy with clinical significance, as assessed by individual scoring of nasal symptoms, nasal endoscopy and visual nasal examination, after either single or repeat intranasal SB-705498 administration.

Table 1. Summary of adverse events reported by more than one subject in the FTIH study

Adverse event	Part 1						Part 2		
	Placebo	SB-705498					Placebo	SB-705498	
		0.5 mg	1.5 mg	3 mg	6 mg	12 mg		6 mg	12 mg
	n = 11	*n* = 12	*n* = 12	*n* = 11	*n* = 12	*n* = 12	*n* = 10	*n* = 10	*n* = 10
	n (%)	*n* (%)	*n* (%)	*n*(%)	*n*(%)	*n* (%)	*n* (%)	*n*(%)	*n*(%)
Any event	2 (18)	1 (8)	5 (42)	5 (45)	4 (33)	2 (17)	5 (50)	4 (40)	3 (30)
Any event judged drug-related*	1 (9)	0	2 (17)	1 (9)	0	1 (8)	5 (50)	4 (40)	3 (30)
Headache	2 (18)	1 (8)	1 (8)	2 (18)	0	0	3 (30)	1 (10)	2 (20)
Oropharyngeal pain	0	0	3 (25)	0	0	1 (8)	1 (10)	1 (10)	1 (10)
Upper respiratory tract infection	0	0	0	2 (18)	1 (8)	0	0	1 (10)	2 (20)
Abdominal pain	0	1 (8)	0	1 (9)	0	0	0	0	0
Nasal congestion	0	0	0	1 (9)	1 (8)	0	0	0	0

*Assesments of relationship were made prior to unblinding and, therefore, events could be judged related to placebo.

PD study

Administration of intranasal SB-705498 was well tolerated by NAR patients. Twenty-two patients reported adverse events: 11 (58%) had received SB-705498 and 11 (50%) had received placebo (Table 2). The most frequently reported event was cough, which was reported by five (26%) patients who received SB-705498 compared with two (9%) patients who received placebo. No serious adverse events were reported. One patient was withdrawn from the study because of intermittent hypertension of mild intensity that occurred 26 min after dosing with SB-705498 12 mg. The hypertension resolved approximately 2 h later. No clinically significant abnormalities in vital signs, 12-lead ECG, body temperature, nasal examination or clinical laboratory tests were observed. Nasal capsaicin challenge did not appear to cause other events than the expected nasal reactivity.

Table 2. Adverse events reported by more than one patient in the PD study

Adverse event	Placebo *n* = 22 *n* (%)	SB-705498 12 mg *n* = 19 *n* (%)
Any event	11 (50)	11 (58)
Cough	2 (9)	5 (26)
Headache	3 (14)	3 (16)
Fatigue	3 (14)	2 (11)
Sneezing	3 (14)	1 (5)
Throat irritation	2 (9)	1 (5)
Feeling cold	0	2 (11)
Lacrimation increased	1 (5)	1 (5)
Nausea	2 (9)	0
Upper airway obstruction	2 (9)	0

Pharmacokinetic results

FTIH study

Following intranasal administration, SB-705498 was fairly rapidly absorbed in HVT achieving maximum plasma concentration at 1–2 h post-dose (Table 3) and had slow distribution and elimination. This rate of absorption remained largely unaffected after repeat administration (Table 4) with plasma concentrations of SB-705498 declining slowly (Figure 1). Repeat administration led to higher plasma concentrations of SB-705498 compared with those achieved after single intranasal dosing (Figure 1). Generally, SB-705498 systemic exposure increased with dose escalation from 0.5 mg to 12 mg. However, the results of the power model suggest that the increase in systemic exposure was less than dose proportional in terms of AUC(0,12 h) (slope: 0.753 ng ml^{-1} h mg^{-1}, 90% CI 0.644, 0.862) and C_{max} (slope: 0.826 ng ml^{-1} mg^{-1}, 90% CI 0.730, 0.921). Repeat intranasal administration of 6 and 12 mg SB-705498 for 14 days was associated with systemic drug accumulation. Values of AUC(0,24 h) and C_{max} increased 2–3-fold on day 14 compared with day 1.

Table 3. Derived PK parameters [geometric mean (95% confidence interval)] after single dosing in the FTIH study

	Part 1				
	SB-705498 dose				
	0.5 mg	1.5 mg	3 mg	6 mg	12 mg
	n = 12	*n* = 12	*n* = 11	*n* = 12	*n* = 12
AUC(0,*t*) (ng ml^{-1} h)	NC	152.8 (121.0, 193.0)	249.8 (100.7, 619.4)	440.6 (346.2, 560.9)	903.6 (617.8, 321.7)
C_{max} (ng ml^{-1})	4.7 (3.3, 6.6)	22.2 (18.2, 27.1)	33.1 (20.1, 54.7)	43.0 (33.5, 55.2)	86.4 (64.4, 115.9)
t_{max} (h)*	1.0 [0.5, 2.0]	1.0 [1.0, 8.0]	2.0 (0.25, 4.02)	2.0 (1.00, 4.00)	2.0 (1.00, 8.00)

*Presented as median [range]. AUC(0,*t*), area under the plasma concentration–time curve from-time zero to time t; C_{max}, maximum plasma concentration; NC, Non-calculable due to non-quantifiable concentrations; t_{max}, time to C_{max}.

Table 4. Derived PK parameters [geometric mean (95% confidence interval)] after repeat dosing in the FTIH study

	Part 2			
	SB-705498 6 mg		SB-705498 12 mg	
	Day 1 a.m.	Day 14 a.m.	Day 1 a.m.	Day 14 a.m.
	n = 10	*n* = 10	*n* = 10	*n* = 10
AUC(0,24 h) (ng ml^{-1} h)	634.5 (307.8, 1308.0)	1522.1 (628.3. 3687.4)	1601.3 (1296.7, 1977.5)	3416.3 (2280.0, 5118.8)
C_{max} (ng ml^{-1})	38.2 (15.6, 93.4)	90.3 (39.5, 206.4)	102.1 (76.1, 137.0)	196.3 (125.3, 307.7)
t_{max} (h)[a]	2.0 (NC, 4.1)	2.0 (0.5, 4.0)	2.0 (0.5, 4.03)	3.0 (0.3, 12.0)

[a] Presented as median (range) AUC(0,24 h), area under the plasma concentration–time curve from time zero to 24 h; C_{max}, maximum plasma concentration; NC, Non-calculable due to non-quantifiable concentrations; t_{max}, time to C_{max}.

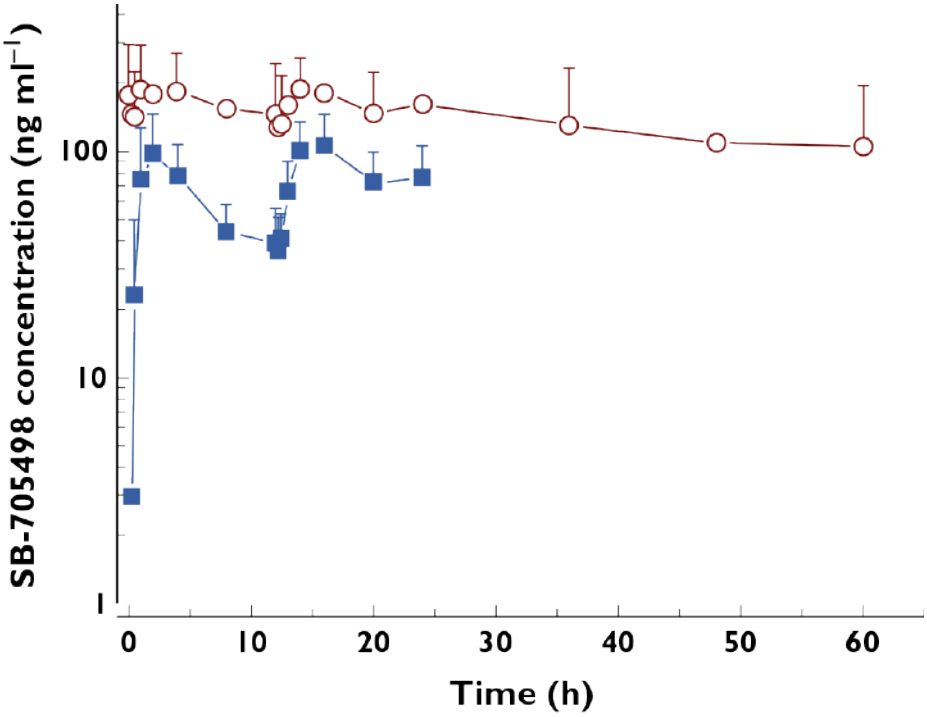


Figure 1. Mean (SD) plasma concentrations of SB-705498 after twice daily intranasal dosing on day 1 and day 14.
■ day 1 12 mg twice daily;
○ day 14 12 mg twice daily

PD study

PK analysis of blood samples from NAR patients confirmed that maximum plasma concentrations were achieved at 3 h post-dose. Geometric mean C_{max} was 77.7 ng ml^{-1} (95% CI 54.1, 111.5) and AUC(0,*t*) was 140.5 ng ml^{-1} h (95% CI 91.5, 215.9).

Pharmacodynamic results

PD study

Administration of a single dose of 12 mg intranasal SB-705498 to patients with NAR prior to intranasal challenge with capsaicin resulted in a decrease of the capsaicin-provoked symptoms, including burning sensation, rhinorrhoea, nasal congestion and lacrimation (Figure 2A). At baseline, following challenge with saline control, both SB-705498 and placebo groups reported similar symptoms. The TSS adjusted mean (95% CI) values were 1.45 (1.03, 1.86) for the placebo and 1.21 (0.75, 1.68) for the SB-705498 group. However, the TSS induced by all doses of capsaicin were markedly reduced in the SB-705498 treated group compared with placebo. Specifically, after challenge with 2.5 µg capsaicin, the adjusted mean (95% CI) values of TSS were 4.16

(3.35, 4.97) in the placebo and 2.97 (2.08, 3.87) in the SB-705498 group. After challenge with 12.5 µg capsaicin, the TSS values were 6.01 (5.10, 6.93) and 4.76 (3.74, 5.78), respectively, and after challenge with 50 µg capsaicin, the TSS values were 7.14 (6.04, 8.24) and 5.90 (4.969, 7.12) respectively. Bayesian analyses of mean TSS concluded that the probability that SB-705498 treatment led to some inhibition of challenge response (>0%) compared with placebo was $P > 0.9$ for all capsaicin doses.

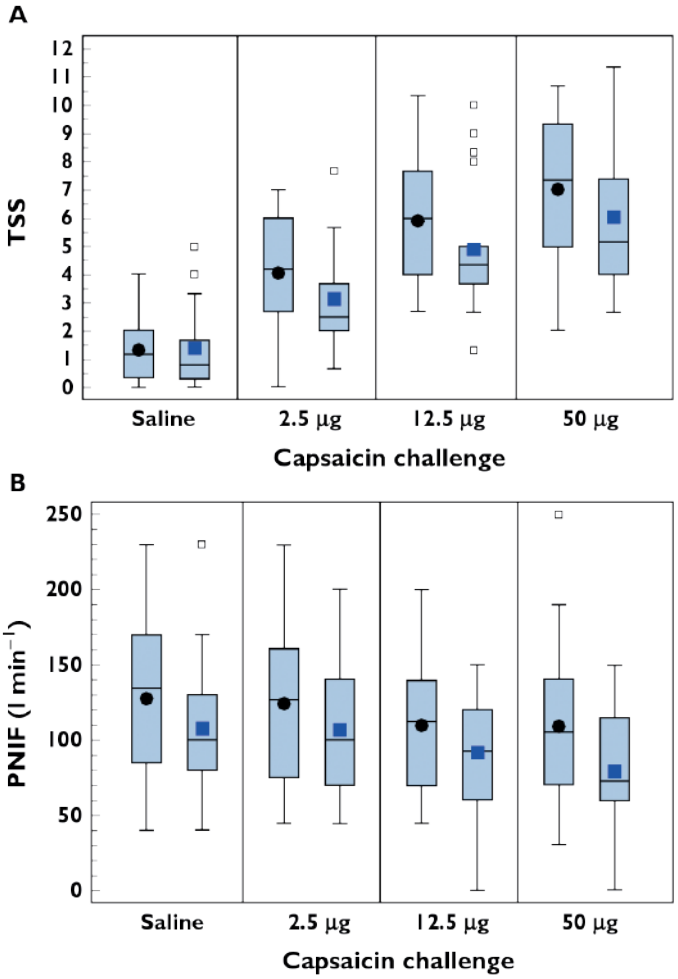


Figure 2. (A) Boxplots showing the effect of treatment with intranasal SB-705498 or placebo on total symptom scores (TSS) in patients with NAR. Square and circle symbols represent mean, horizontal line within the box represents median, lower and upper edges of box represent the 25th and 75th values percentiles, respectively. The 5th and 95th percentiles, not shown graphically, were, respectively,: ▫SB-705498 12 mg: saline 0 and 5; 2.5 µg capsaicin dose 0.67 and 7.67; 12.5 µg capsaicin dose 1.33 and 10.00; 50 µg capsaicin dose 2.67 and 11.30. Placebo: saline 0 and 3.67; 2.5 µg capsaicin dose 1.33 and 6.3; 12.5 µg capsaicin dose 2.67 and 8.67; 50 µg capsaicin dose 4.0 and 10.3.
(B) Boxplots showing the effect of treatment with intranasal SB-705498 or placebo and peak nasal inspiratory flow (PNIF) in patients with NAR. Square and circle symbols represent mean; horizontal line within the box represents median; lower and upper edges of box represent the 25th and 75th values percentiles respectively. The 5th and 95th percentiles, not shown graphically, were respectively:
▫SB-705498 12 mg: saline 40 and 230; 2.5 µg capsaicin dose 45 and 200; 12.5 µg capsaicin dose 0 and 150; 50 µg capsaicin dose 0 and 150. Placebo: saline 45 and 200; 2.5 µg capsaicin dose 50 and 200; 12.5 µg capsaicin dose 50 and 190; 50 µg capsaicin dose 40 and 190.
●●, placebo
■■■, SB-705498 12 mg

Assessment of VAS scores for individual symptoms triggered by capsaicin indicated that all recorded symptoms were affected by treatment with SB-705498. Figure 3 illustrates the effect of treatment with SB-705498 compared with placebo on burning sensation provoked by incremental capsaicin challenge. Burning sensation was of particular PD importance for the development of intranasal SB-705498, as capsaicin-induced burning sensation is mediated directly by TRPV-1 engagement in sensory neurones (25) and therefore evaluation of its inhibition is a direct measure related to target TRPV-1 inhibition.

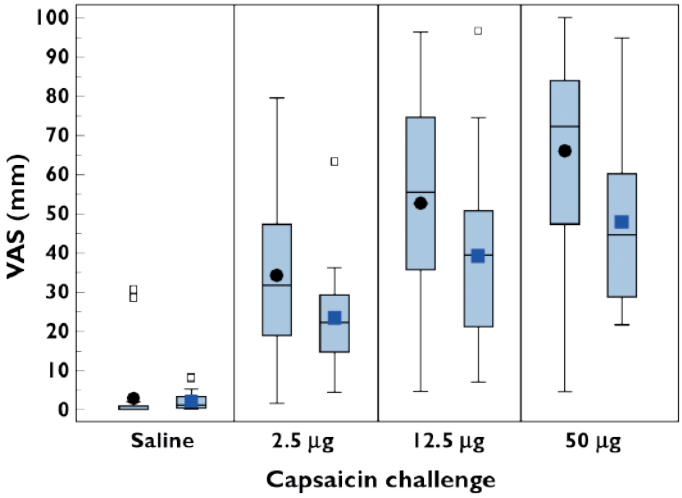


Figure 3. Boxplots showing the effect of treatment with intranasal SB-705498 or placebo on burning sensation, assessed by visual analogue scale (VAS). Square and circle symbols represent mean, horizontal line within the box represents median, lower and upper edges of box represent the 25th and 75th values percentiles, respectively. The 5th and 95th percentiles, not shown graphically, were, respectively,: SB-705498 12 mg: saline 0 and 8.3; 2.5 µg capsaicin dose 4.33 and 63.3; 12.5 µg capsaicin dose 7 and 96.67; 50 µg capsaicin dose 21.67 and 95. Placebo: saline 0 and 28.67; 2.5 µg capsaicin dose 3.3 and 73.0; 12.5 µg capsaicin dose 9 and 90; 50 µg capsaicin dose 9.67 and 99.3.
●●, placebo
■■■, SB-705498 12 mg

The dose ratio analyses carried out on the TSS and VAS scores (nasal congestion, rhinorrhoea and burning sensation) confirmed that the shifts in the relative potency between placebo and SB-705498 treated subjects were parallel. The parallel shift in the dose–response is consistent with the competitive mechanism of inhibition of TRPV-1 activation by the drug, which has also been demonstrated previously in *in vitro* cellular assays (17). Detailed evaluation of the shift in the capsaicin-induced TSS dose–response following SB-705498 administration showed a mean change of 2.8-fold in relative potency (Figure 4). For individual VAS scores a 2- to 4-fold change in relative potency was observed on average (Figure 4).

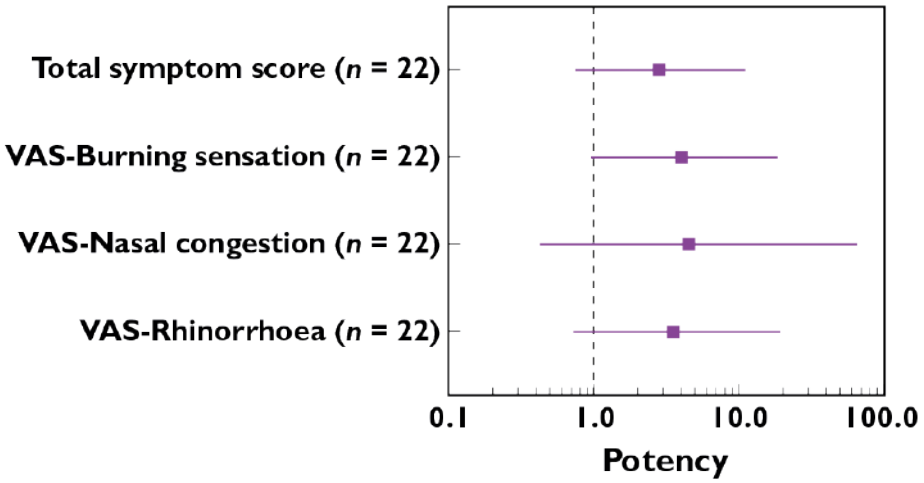


Figure 4. Forest plot depicting relative dose potency (mean and 95% CI) for clinical symptoms in patients with NAR. A ratio greater than 1 signifies a positive clinical endpoint response signal

Before administration of treatment, PNIF values were slightly greater in the placebo group than in the SB-705498 group; these differences were maintained after dosing with capsaicin (Figure 2B). A statistical analysis of the change from baseline indicated that challenge with increasing capsaicin dose resulted in some decrease (worsening) in PNIF values in both treatment arms. Treatment with SB-705498 compared with placebo, resulted in a minimal effect on PNIF values (mean change from baseline) which was more obvious after challenge with the lower doses of capsaicin.

DISCUSSION

The results of this study support the concept that selective blockade of TRPV-1 stimulation in the nose can reduce nasal hyper-responsiveness and development of rhinitis symptoms triggered by exogenous agents provoking sensory nerve excitability. This is the first study to explore and describe the safety, PK and PD efficacy of a novel intranasal formulation of SB-705498 in healthy volunteers and patients with NAR. Single and twice daily repeat intranasal administration of SB-705498, at doses up to 12 mg, was found to be safe overall and well tolerated. Treatment with intranasal SB-705498 showed target-specific local PD activity against nasal hyper-reactivity provoked by capsaicin challenge.

Because of the central role of TRPV-1 in multi-modal activation of sensory nerves, TRPV-1 antagonism has attracted significant interest as a target for the treatment of a wide range of disorders characterized by enhanced neural excitability, including

neurological, gastrointestinal, urinary and respiratory conditions. However, to date the foremost application of TRPV-1 antagonists has been in the treatment of pain. At least 11 TRPV-1 antagonists have been identified and assessed for safety and tolerability following systemic or oral administration (17). From these, five compounds have already progressed into 'proof of concept' studies to provide early efficacy readouts in patients with neuropathic or inflammatory pain. The GSK TRPV-1 antagonist SB-705498 was initially developed as a novel oral analgesic. SB705498 blocked effectively *in vitro* the activation of TRPV-1 by capsaicin, low pH and temperature (16, 17). In healthy volunteers single dosing with oral SB-705498 up to levels within the safety margin set by preclinical toxicology, was well tolerated and associated with a significant reduction of capsaicin-evoked skin flare and a lesser effect on thermal pain sensation (22). Furthermore in the same study, oral SB-705498 produced a marked decrease on the flare and hyperalgesia elicited by UVB-irradiation of skin, implying that TRPV-1 antagonism may exert an effect on neurogenic inflammation. The degree of SB-705498 PD efficacy on skin symptoms was correlated with the levels of systemic drug exposure which suggested that high oral SB-705498 doses would be necessary to achieve adequate restriction of nociceptive activity (22). Single oral administration of SB-705498 in healthy volunteers (22) up to 400 mg, resulted in t_{max} of 2 h (0.75–4 h) and terminal phase elimination half-life of 54 h (35–93 h) that corresponded with a low oral clearance of approximately 9 l h^{-1}.

The clinical development of oral TRPV-1 antagonists has been recently confounded by the finding that their administration carries the risk of eliciting hyperthermia. Significant, acute increase in body temperature has been observed in preclinical species, as well as in humans and has already led to discontinuation of the development of several potent TRPV-1 inhibitor compounds (26-29). Oral SB-705498 administration to guinea pigs has been shown to result in mild body temperature increase at 30 mg kg^{-1} (0.6°C), and 100 mg kg^{-1} (0.8°C) but not at 10 mg kg^{-1}, a dose which elicits an analgesic activity in the guinea pig (unpublished, in house data). Also, in a GSK clinical trial in subjects with dental pain single administration of oral SB-705498, at doses of 400–1000 mg (1.18–6.55 µg ml^{-1} (C_{max})), led to a potential trend towards a slight transient increase in body temperature 2 h after dosing (ClinicalTrials.gov Identifier: NCT00281684). The mechanisms underlying the effect of TRPV-1 antagonists on body temperature are not entirely clear, but they appear to arise from inhibition of TRPV-1 signalling on afferents innervating the viscera (30, 31). In most studies the induced hyperthermia seems to be dependent on the levels of systemic exposure. In the context of rhinitis treatment, it was thought that local application of a TRPV-1 inhibitor in the nose could achieve effective local TRPV-1 blockade with doses much lower than those needed to achieve the same effect following oral drug administration. This would reduce decisively the likelihood of treatment-related systemic adverse effects, including hyperthermia. It was therefore of interest to explore an intranasal formulation of SB-705498, as this would allow topical delivery at the site of action and thereby minimize the systemic exposure.

The challenge was to select a dose of SB-705498 that would maximize its pharmacology in the nasal tissue when administered topically. In addition, direct correlation of systemic drug concentrations with the corresponding pharmacodynamics in target nasal tissues would not be appropriate mainly due to uncertainty in the kinetics of the drug effect in the nasal turbinates. However, as described earlier in this manuscript, based on translation of findings from a PD guinea pig rhinitis model a maximum intranasal dose of 12 mg SB-705498 was selected for evaluation in the clinic. This dose was expected to achieve a high level of receptor occupancy after taking into account the human systemic exposure and the assumption of nasal bioavailability of the drug based on preclinical data. The charcoal block test in the dog has been shown to be a good predictor for assessing local drug deposition in humans (32, 33). Following intranasal administration about 20% of the SB-705498 dose is estimated to be available in the nasal tissues and absorbed across the nasal mucosa, while the remainder is expected to be swallowed and absorbed across the gastrointestinal tract. If complete drug absorption occurred in the nasal tissues, then 20% of the 12 mg of SB-705498 (e.g. approximately 2 mg) administered in this PD study could be anticipated in the nasal tissues and fluid in a maximum aqueous volume of approximately 20 ml (SB-705498 tissue concentration of 2 mg 20 ml^{-1}) (21). If nasal ciliary clearance ($t_{1/2}$ of 15 min) is taken into consideration (34), even one tenth of the estimated nasal tissue concentration would still be associated with high receptor occupancy.

The SB-705498 PK findings in the intranasal FTIH study were consistent with the predictions based on the PK data from the FTIH study with oral SB-705498 (22) and the nasal deposition values described above. The marked increase in plasma concentrations of SB-705498 after repeat intranasal dosing compared with single dosing was predictable based on the long terminal phase elimination half-life of approximately 54 h observed in a previous study where the drug was administered orally (22). As expected from the predicted systemic exposure, single and repeat administration of intranasal SB-705498 up to 12 mg was not associated with increase in body temperature in any of the study participants or with any other significant treatment-emergent AEs. In terms of PD efficacy, the results of our study indicated that the reduction of capsaicin-evoked rhinitis symptoms following administration of intranasal SB-705498 in patients with NAR is consistent with effective local TRPV-1 antagonism. The differences in capsaicin-induced TSS between the SB-705498 12 mg and placebo group remained similar across all capsaicin doses used and were in the range of 1.19–1.25, suggesting a uniform response by the antagonist SB-705498 to all capsaicin challenges conducted in the study. Some outlier TSS points were observed in the group of patients treated with SB-705498, but the most conservative approach was taken and these data were included in the statistical analysis. From a clinical perspective, it is difficult to comment at this stage if there are patients with particular characteristics who may not respond adequately to SB-705498, because the total number of participants per arm in the study was limited. Most likely, the data reflect the normal spectrum of variability in

the response to capsaicin, as well as to drug, as outliers with high TSS were noted following saline challenge, and an outlier with a much lower TSS was seen in the SB-705498 treated group after challenge with 12.5 µg capsaicin. An improvement in TSS of at least 1 unit represents a shift from one assessment grade to a lower grade, (e.g. from moderate to mild) and therefore, a change >1 unit is considered to be of clinical relevance. As shown in Figure 4, there was a consistent trend in the SB-705498 treatment effect on the clinical endpoints with their dose ratios greater than unity. It was estimated that a receptor occupancy at the TRPV-1 target of about 66% was achieved based on the dose ratio of 2.8 computed for TSS endpoint using the equation for competitive antagonism (fractional occupancy = dose ratio – 1/dose ratio) (35). Although treatment with SB-705498 reduced all individual symptoms assessed in the study, the magnitude of the treatment effect on each of them was different. Burning sensation was more profoundly affected (a 4-fold shift in dose–response relative to placebo) compared with the other rhinitis-like symptoms suggesting this endpoint is most directly coupled to TRPV-1 activity. Thus, the 4-fold shift in dose–response for the burning sensation endpoint would be associated with a high receptor occupancy at the TRPV-1 target of 75% and is consistent with that predicted as discussed before.

Although the effect of treatment with intranasal SB-705498 on capsaicin-evoked symptoms was marked, the results from the assessment of PNIF do not fully support the same conclusion. After challenge with the lowest dose of capsaicin (2.5 µg), patients treated with SB-705498 presented an improvement in PNIF compared with those who received placebo. However, this difference did not achieve statistical significance, while no significant effect was observed between SB-705498 and placebo after the challenges with higher doses of capsaicin. PNIF assessment is a simple objective tool to evaluate changes in nasal patency by both inflammatory and obstructive causes (36). It is known that application of low doses of capsaicin in the nose induces changes in the nasal mucosa that lead to vasodilation, increased vascular permeability and glandular exudation that underlie the development of rhinitis-like symptoms (37). Capsaicin, is a potent and selective activator of the TRPV-1 receptor at concentrations up to 1 µm, but may engage other targets at higher concentrations (38). Capsaicin can exert direct effects on vascular tone (39, 40), smooth muscle tension (41), ion fluxes (41), nitric oxide synthesis and COX2 gene expression (42). In the context of the nasal mucosa it was recently shown, using *ex vivo* functional experiments with human nasal tissue, that capsaicin induces TRPV-1-independent vasodilation of the nasal vascular bed (38). This vasodilatory effect was mediated by modulation of COX-2 enzymatic activity associated with reduced prostaglandin E_2 production and could be suppressed by sulprostone, an agonist of prostaglandin E receptors (38). Therefore, we could speculate that antagonism of the TRPV-1 receptor by the administration of intranasal SB-705498 may lead to effective attenuation of the direct TRPV-1-mediated effects, as reflected by the marked reduction of the burning sensation, but have a lesser effect on capsaicin-induced responses via other signalling

pathways that are engaged with high local concentrations of capsaicin. This may explain why we observed variability in the degree of reduction on the PD parameters assessed in this study.

The results of a topical, low dose of SB-705498 on symptoms of allergic rhinitis in a 7 days repeat allergen challenge study were recently reported (5). In this study 15 ml of a 30 µmsolution of SB-705498 (equivalent to approximately 0.2 mg) was delivered via nasal lavage to patients with seasonal allergic rhinitis 2 min prior to allergen challenge and the effect on allergen challenge driven symptoms was measured following the allergen challenge. The selected dose of SB-705498, although it was found previously adequate to inhibit symptoms induced by a 5 µm capsaicin nasal spray, was shown to be ineffective in attenuating symptoms induced by allergen. Whilst these results may suggest that TRPV-1 is not a key driver of allergen evoked symptoms, it is possible that the formulation used in this study did not have the necessary duration of action to inhibit TRPV-1 beyond the 2 min explored for the capsaicin challenge (allergen symptoms were recorded at 10 min post-challenge). Hence, it is uncertain as to whether the effect of this formulation was still sufficient to block TRPV-1 at the point where allergen symptoms were recorded. Duration of action studies are required to evaluate fully the effect of novel SB-705498 formulations before conclusions can be drawn about the role of TRPV-1 in rhinitis symptoms. Furthermore, it is expected that TRPV-1 may play a more prominent role in nasal hyper-responsiveness where the primary defect is directly linked to sensory over-sensitivity, as in many cases of NAR, than in conditions with a major immunopathology involvement, as in allergy.

In conclusion, TRPV-1 antagonists offer a new mechanism of action for the potential treatment of nasal hyper-responsiveness. The results of these studies indicate that intranasal SB-705498, at a clinically safe and well-tolerated dose, has target specific PD activity in humans. The data provide the first clinical evidence that local application of a TRPV-1 antagonist in the nose may alleviate symptoms triggered by stimulation of capsaicin sensitive nasal nerves. This suggests that SB-705498 could be further developed as a novel form of treatment for rhinitis patients with difficult to treat nasal hyper-responsiveness.

Competing Interests

All authors have completed the Unified Competing Interest form at **http://www.icmje.org/coi_disclosure.pdf** and declare CH, CvD, CS, IT and WF are employees of the Department of Otorhinolaryngology, Academic Medical Center, Amsterdam, the Netherlands and this institution received funding from GSK for the conduct of the study. CvD has received research grants from GSK, Allergopharma and ALK-Abello A/S. JD, KS, AN, MB and D are all employees of GSK and hold GSK shares.

REFERENCES

1 Varjonen E et al. Prevalence of atopic disorders among adolescents in Turku, Finland. Allergy 1992; 47: 243– 248

2 Druce H. Allergic and nonallergic rhinitis. In: Allergy Principles and Practice, 5th edn. MO: Mosby-Year Book, 1998; 1005– 1016

3 Settipane RA. Rhinitis: a dose of epidemiological reality. Allergy Asthma Proc 2003; 24: 147– 154

4 Sarin S et al. The role of the nervous system in rhinitis. J Allerg Clin Immunol 2006; 118: 999– 1014

5 Alenmyr L et al. Effect of mucosal TRPV-1 inhibition in allergic rhinitis. Basic Clin Pharmacol Toxicol 2012; 110: 264– 268

6 Van Rijswijk JB et al. Idiopathic rhinitis, the ongoing quest. Allergy 2005; 60: 1471– 1481

7 Van Rijswijk JB et al. Intranasal capsaicin reduces nasal hyper-reactivity in idiopathic rhinitis: a double-blind randomized application regimen study. Allergy 2003; 58: 754– 761

8 Alexander SPH et al. Guide to Receptors and Channels (GRAC), 5th edition. Br J Pharmacol 2011; 164 (Suppl. 1): S1– S324

9 Caterina MJ et al. The vanilloid receptor: a molecular gateway to the pain pathway. Annu Rev Neurosci 2001; 24: 487– 517

10 Gunthorpe MJ et al. The diversity in the vanilloid (TRPV) receptor family of ion channels. Trends Pharmacol Sci 2002; 23: 183– 191

11 Hwang SW et al. Direct activation of capsaicin receptors by products of lipoxygenases: endogenous capsaicin-like substances. Proc Natl Acad Sci USA 2000; 97: 6155– 6160

12 Seki N et al. Expression and localization of TRPV-1 in human nasal mucosa. Rhinology 2006; 44: 128– 134

13 O'Hanlon S et al. Neuronal markers in allergic rhinitis: expression and correlation with sensory testing. Laryngoscope 2007; 117: 1519– 1527

14 Geppetti P et al. The transient receptor potential vanilloid 1: role in airway inflammation and disease. Eur J Pharmacol 2006; 533: 207– 214

15 Lee LY et al. Role of TRPV-1 in inflammation-induced airway hypersensitivity. Cur Opin Pharmacol 2009; 9: 243– 249

16 Rami HK et al. Discovery of SB-705498: a potent, selective and orally bioavailable TRPV-1 antagonist suitable for clinical development. Bioorg Med Chem Lett 2006; 16: 3287– 3291

17 Gunthorpe MJ et al. Characterization of SB-705498, a potent and selective vanilloid receptor-1 (VR1/TRPV-1) antagonist that inhibits the capsaicin-, acid-, and hear-mediated activation of the receptor. J Pharmacol Exp Ther 2007; 321: 1183– 1192

18 Gunthorpe MJ et al. Clinical development of TRPV-1 antagonists: targeting a pivotal point in the pain pathway. Drug Discov Today 2009; 14: 56– 67

19 Changani K et al. Efficacy of the TRPV-1 antagonist SB-705498 in an MRI guinea pig model of rhinitis. ERS Annual Congress, Amsterdam, 2011

20 World Medical Association. Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects. Available at http://www.wma.net/en/30publications/10policies/b3/(last accessed 31 October 2011)

21 Tarhan E. Acoustic rhinometry in humans: accuracy of nasal passage area estimates, and ability to quantify paranasal sinus volume and ostium size. J Appl Physiol 2005; 99: 616– 623

22 Chizh BA et al The effects of the TRPV-1 antagonist SB-705498 on TRPV-1 receptor-mediated activity and inflammatory hyperalgesia in humans. Pain 2007; 132: 132– 141

23 Lambert GA et al. The effects of the TRPV-1 receptor antagonist SB-705498 on trigeminovascular sensitisation and neurotransmission. Naunyn Schmiedebergs Arch Pharmacol 2009; 380: 311– 325

24 Finney DJ. A computer program for parallel line bioassays. J Pharmacol Exp Ther 1976; 198: 497– 506

25 Caterina MJ et al. The capsaicin receptor: a heat-activated ion channel in the pain pathway. Nature 1997; 389: 816– 824

26 Gavva NR et al. The vanilloid receptor TRPV-1 is tonically activated in vivo and involved in body temperature regulation. J Neurosci 2007; 27: 3366– 3374

27 Wong GY et al. Therapeutic potential of vanilloid receptor TRPV-1 agonists and antagonists as analgesics: recent advances and setbacks. Brain Res Rev 2009; 60: 267– 277

28 Krarup AL et al. Randomised clinical trial; the efficacy of a transient receptor potential vanilloid 1 antagonist AZD1386 in human oesophageal pain. Aliment Pharmacol Ther 2011; 33: 1113– 1122

29 Round P et al. An investigation of the safety and pharmacokinetics of the novel TRPV-1 antagonist XEN-D0501 in healthy subjects. Br J Clin Pharmacol 2011; 72: 921– 931

30 Steiner AA et al. Nonthermal activation of transient receptor potential vanilloid-1 channels in abdominal viscera tonically inhibits autonomic cold-defense effectors. J Neurosci 2007; 27: 7459– 7468

31 Romanovsky AA et al. The transient receptor potential vanilloid-1 channel in thermoregulation: a thermosensor it is not. Pharmacol Rev 2009; 61: 228– 261

32 Borgstrom L et al. Pharm Res 1990; 7: 1068– 1070

33 McDowell JE et al. Pharmacokinetics and bioavailability of intranasal fluticasone in humans. Clin Drug Invest 1997; 1: 44– 52

34 Squillante E. Measurement of nasal residence time by microdialysis. Curr Sep 2002; 19: 127– 130

35 Rang HP et al. A new kind of drug antagonism: evidence that agonists cause a molecular change in acetylcholine receptors. Mol Pharmacol 1969; 5: 394– 411

36 Teixeira RU et al. Peak nasal inspiratory flow evaluation as an objective method of measuring nasal airflow. Braz J Otorhinolaryngol 2011; 77: 473– 480

37 Sanico AM et al. Comparison of nasal mucosal responsiveness to neuronal stimulation in non-allergic and allergic rhinitis: effects of capsaicin nasal challenge. Clin Exp Allergy 1998; 28: 92– 100

38 Van Crombruggen K et al. Capsaicin-induced vasodilatation in human nasal vasculature is mediated by modulation of cyclooxygenase-2 activity and abrogated by sulprostone. Naunyn Schmiedebergs Arch Pharmacol 2011; 383: 613– 626

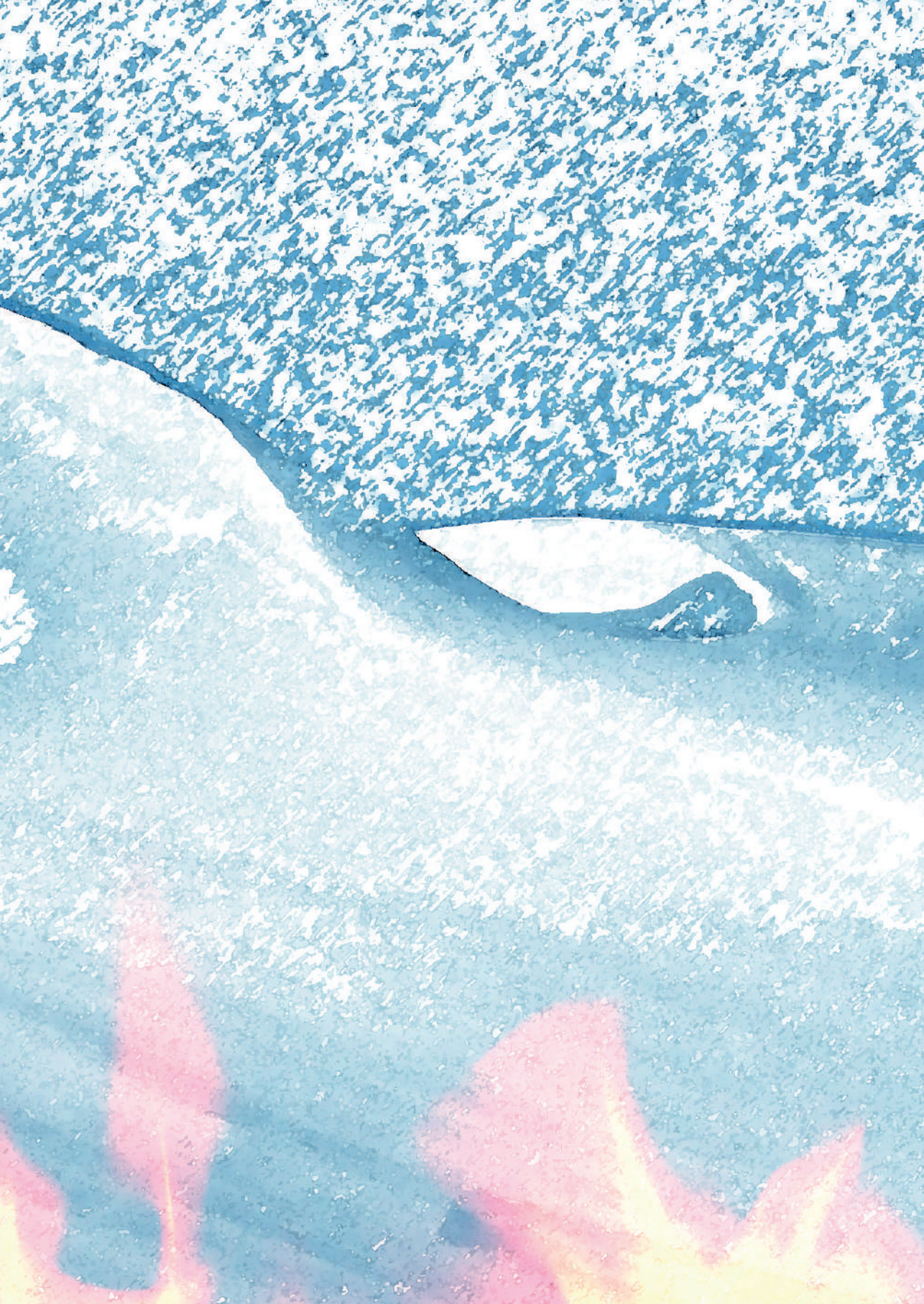
39 Yeon D et al. Capsaicin-induced relaxation in rabbit coronary artery. J Vet Med Sci 2001; 63: 499– 503

40 Gupta S et al. Pharmacological characterisation of capsaicin-induced relaxations in human and porcine isolated arteries. Naunyn Schmiedebergs Arch Pharmacol 2007; 375: 29– 38

41 Fujimoto S et al. Characterization of capsaicin-induced, capsazepine-insensitive relaxation of ileal smooth muscle of rats. Eur J Pharmacol 2004; 487: 175– 182

42 Chen CW et al. Signal transduction for inhibition of inducible nitric oxide synthase and cyclooxygenase-2 induction by capsaicin and related analogs in macrophages. Br J Pharmacol 2003; 140: 1077– 1087

CHAPTER 8
General discussion and future perspectives



GENERAL DISCUSSION AND FUTURE PERSPECTIVES

Epidemiology

The prevalence rate of NAR is estimated to be around 200 million people worldwide (1). This estimation is not very reliable as literature on the prevalence of NAR is limited and mainly consists of patient groups visiting in first or mostly even second or third line of health care. To reliably differentiate NAR from chronic rhinosinusitis (CRS) and allergic rhinitis (AR) one needs accurate tests for allergen sensitization, nasal endoscopy and/or CT-sinus. Not all these diagnostic tools are available in first line health care. Thereby, within NAR one has to differentiate between the different phenotypes, which can be difficult because of overlap and lack of strict definitions. All this makes a reliable estimation of prevalence rate of NAR and its different phenotypes in first line health care complicated. To assess the prevalence rate of NAR in the second or third line of healthcare embarks the problem of population bias, as NAR patients who were successfully treated with intranasal corticosteroids (INCS) and/or anti-histamines by their general practitioner (GP) will likely not be referred to secondary care. Because of these disadvantages related to patient selection, we did not perform a study on prevalence rate in NAR in our university setting. However, this question, preferably addressed internationally on population level, does represent one of the most important future needs. As we show in **chapter 4**, NAR patients have a significant impairment of quality of life (QoL). Together with a risk to develop asthma later on in life and the estimated high prevalence rate, NAR is likely to represent a disease with a significant burden of disease with high socio-economic costs and consequences that needs awareness (2).

To improve the accuracy of an estimated prevalence rate of NAR, there is a need for population-based (questionnaire) studies in Europe and worldwide, to assess the prevalence rate of NAR and its phenotypes and endotypes, in both children and adults. Also other demographic features, like distribution of gender and age and the prevalence rate/risk of (developing) associated conditions like asthma or chronic rhinosinusitis in different phenotypes and endotypes of NAR, are unknown.

Diagnosis and pheno- and endotyping

For long, non-allergic rhinitis was seen as an undefined and ununderstood diagnosis, wrongly interpreted as *diagnosis per exclusionem*. This resulted in a trial and error approach of treatment, which is not only very frustrating for both doctor and patient but also far from cost-effective. There is a need for a cost-effective diagnostic flow-scheme in NAR like there is for patients with chronic rhinosinusitis with or without nasal polyposis. The increasing knowledge on phenotypes and endotypes already results in a more structured process of diagnosis and endotype-specific treatment in NAR patients. However, optimal control of symptoms for all NAR patients -despite the above described approach of phenotyping and endotype-specific treatment- is far from an achieved goal, as QoL and treatment satisfaction questionnaire results

show (**chapter 4**). Phenotyping can be complicated because of overlap and lack of diagnostic tools. Besides from cold dry air provocation -mainly used for research purposes-, the diagnostic tools in NAR are very limited.

There is a need for an international consensus on a flow-scheme for the diagnosis of NAR, ranging from proper phenotyping, the use of questionnaires, allergen sensitization testing, to performing nasal endoscopy and diagnostic tools like CT sinus.

Moreover, there is a need for more detailed and uniform definitions of some of the phenotypes in NAR. For example, in smoke induced, occupational rhinitis and hormonal rhinitis, the knowledge on the underlying endotype is based on scarce literature and definitions are copied from one paper to the other. Also, the different types of medication-induced rhinitis -besides from the knowledge on xylometazoline or aspirin and NSAIDS- deserve a better understanding and definition, also because this might give us better insights in (sub)-endotyping of NAR in general.

Most of all the problem of better definition of phenotypes holds true for the idiopathic phenotype that likely also consists of further subphenotypes. In mixed rhinitis patients, with a perennial allergen sensitization, the clinical differentiation between allergic and non-allergic symptoms can be very complicated. The idiopathic rhinitis phenotype is often described with the symptom of nasal hyper-reactivity. It is not completely clear whether all idiopathic rhinitis patients have nasal hyper-reactivity. And on the other hand, a significant part of the patients with AR have nasal hyper-reactivity as well (3).

The phenotype of local allergic rhinitis (LAR) gained renewed attention during the last few years. Prevalence studies in different countries have not been able to level the prevalence rates in Malaga of 50-60% (4) (5). Explanations for this variation in prevalence rate range from demographic differences, different selection of patient groups (patients in first- versus second- or third- line of healthcare), variation in diagnosis of patient groups and differences in nasal-allergen provocation procedures. Multi-center trials assessing prevalence rates of LAR with the same selection and definition of patient groups and identical materials and methods to perform nasal allergen provocation tests, will help us answer this question in the best way possible. Moreover, the recently published EAACI guidelines on nasal provocation will limit methodological differences (6).

As phenotyping is limited, the future of knowledge on NAR lies in gaining knowledge on endotyping.

On an endotype-level, the increasing knowledge regarding neurogenic inflammation results in both development of new treatment options (TRPV-1-antagonist) and better understanding of the working mechanisms of previously 'found-to-be-effective'

treatment options (capsaicin, azelastine) in NAR. However, there is still a lot unknown when it comes to the neurogenic endotype, including the involved receptors, nerve fibers, (action of) individual mediators and interaction between the autonomic nervous system and local neurogenic inflammation. A lot of what is written on the neurogenic endotype is not stated by firm evidence and is based on in vitro studies or hypotheses. Further one, it is possible that the neurogenic inflammatory endotype needs to be further differentiated into subendotypes.

The symptom of nasal hyper-reactivity seems to be a nonspecific symptom of chronic rhinitis patients (**chapter 2)**. However, TRPV-1 desensitization by means of capsaicin has not proven itself to be effective in all patients with nasal hyper-reactivity. It seems to be not or less effective in AR or other NAR phenotypes like smoking rhinitis, suggesting a different endotype of neurogenic inflammation, although the effectiveness of capsaicin in different pheno- and endotypes of AR and NAR needs further investigation (**chapter 6**). But also, within idiopathic rhinitis with nasal hyper-reactivity not all patients are effectively treated with capsaicin suggesting different (sub-) pheno- and endotypes that are not yet elucidated within this patient group. The goals of more effective endotype-specific treatment options and more knowledge on phenotyping and endotyping are therefore intertwined.

Thinking about endotypes, probably also should include thinking about (defective) epithelial barrier function. In the lower airways and in chronic rhinosinusitis this concept–and its interaction with known infectious and inflammatory processes–has gained growing attention during the last years. Disruption of epithelial barrier function –being part of the innate immune system–in AR is responsible for increased passage of antigens and exposure of underlying tissue to these stimuli, thereby resulting in progression of allergic disease. Allergen antigen proteolytic activity and breakdown of tight junctions by inflammatory mediators like histamine and other cytokines in nasal secretions of AR patients are responsible for epithelial disruption (7). It is very likely that also in NAR there is a role for epithelial barrier dysfunction although no studies on this topic are available until now.

Proteomic endotyping so far has not resulted in differentiating idiopathic rhinitis from other forms of rhinitis like AR, mixed rhinitis and even healthy controls. However, also a conclusion what idiopathic rhinitis is *not* about is of importance. Key-players in inflammation like growth factors, eosinophils, neutrophils, several chemokines and mediators of Th1/Th2-inflammation and mast cells of neurogenic inflammation do not seem to be involved in idiopathic rhinitis (**chapter 3**). Limitations of this study are that we did not assess neurogenic inflammatory mediators like CGRP or SP and that the quantity of mediators was still limited which may have resulted in false negative outcomes.

The novel transcriptomic approach of endotyping by means of micro-array analysis assessing differences on a RNA-level is a promising new tool (8). This approach has several advantages compared to a proteomic approach. Micro-array analysis enables us to assess thousands of genes at once, unbiased and with a 'helicopter view'. Comparison of gene-expression profiles, not only with healthy controls but also patients with allergic rhinitis and chronic rhinosinusitis with and without polyposis and with or without asthma, will give us new insights in the underlying endotypes.

Finally, with optimal knowledge on phenotypes and endotypes, obtaining international consensus on a *phenotype* to *endotype* and *endotype-specific* treatment flowchart like in table 1 of the introduction, would be highly recommendable as it is very usable in clinical practice.

Treatment

A meta-analysis of the randomized controlled trials that were performed on the effectiveness of INCS in NAR gives no real recommendation for this treatment in NAR in general (**chapter 5)**. There is still a need for studies with INCS in distinct NAR pheno- and endotypes. One can think of a higher effectiveness of INCS in NAR patients with inflammatory endotypes like NARES, LAR, smoke induced rhinitis or pregnancy rhinitis.

Two, relatively old, randomized controlled trials showed effectiveness of azelastine in NAR patients (9, 10). The effectiveness of antihistamine therapy in NAR remained an intriguing and unanswered question for a long time, as one would not expect anti-histamine therapy to be effective in a disease in which there is no (known) role for histamine. A recent (*in vitro*) study suggested that azelastine could be effective in treating symptoms of nasal hyper-reactivity in idiopathic rhinitis by inducing TRPV-1 desensitization by means of influencing intraneuronal calcium flows (11). Future trials with azelastine in better-defined pheno- and endotypes are recommended. Other questions relate to the recommended dose and ways of delivery of azelastine (oral versus intranasal) in NAR. The positive results of a novel treatment that combines INCS with azelastine in AR raises the question of effectiveness of this combination treatment in NAR (12). In clinical practice this combined therapy is sometimes already used in both AR and NAR patients with positive results, however we are in need for more clinical studies assessing this question. As mentioned above, INCS in NAR cannot be strongly recommended based on the current literature (**chapter 5)**. This raises the question whether in (specific phenotypes of) NAR combined therapy of INCS and azelastine will have a benefit above treatment with azelastine only.

Capsaicin is one of the few evidence-based treatment options in non-allergic rhinitis with minor and limited side-effects (**chapter 6**). The effectiveness is under condition of a high enough dose of capsaicin (120 ug) and the correct patient selection (likely to be idiopathic rhinitis patients with nasal hyper-reactivity and gustatory rhinitis) (13).

Different ways of delivery, when and how often treatment can be repeated, explanation of effectiveness of capsaicin in different (sub-) phenotypes and in different types and grade of severity of symptoms are all topics that need to be further investigated (**chapter 6**).

As both capsaicin and azelastine seem to be effective in treating symptoms of neurogenic inflammation, this raises the question whether either capsaicin or azelastine (individual, successive or combined use) should be considered in an individual idiopathic rhinitis patient with symptoms of nasal hyper-reactivity. Capsaicin has been studied and proven to be effective in several clinical trials, while the effectiveness of azelastine in NAR is limited to two trials and the suggestive working mechanism is only reviewed in one *in vitro* study. On the other hand, treatment with capsaicin can induce (although limited and very well treatable) symptoms of a burning sensation and mild pain or discomfort that might discourage patients, while the use of a nasal spray like azelastine might seem more comfortable to a patient. Azelastine has the disadvantage that it (likely) has to be used chronically to remain its effectiveness, in contrast to the longer-term effects of capsaicin after single or only limited repetitive use.

The TRPV-1 and TRPA-1 receptors are of interest when it comes to treating neurogenic inflammation. A recently developed TRPV-1 antagonist has shown moderate results (**chapter 7**). Other new treatment options could focus on different TRP-receptors, sensory C-fibers and neuro-inflammatory mediators.

Novel treatment modalities like antibodies targeted at specific mediators or cells ('biologicals') that have gained an important place in asthma and CRS might also deserve a future role in NAR.

There also seems to be a role for either overactivity of the parasympathetic nervous system or underactivity of the sympathetic nervous system, representing possible goals for novel treatment options.

As both neurogenic inflammation and neurogenic dysbalance seem to interact, it would be of interest to evaluate whether treatment like iptratroprium bromide acting on the cholinergic receptor could be combined with azelastine acting on the TRPV-1 receptor.

Studies on the effectiveness of vidian neurectomy are mostly limited to case-control studies. The results of these studies are promising and show limited side effects. Unfortunately, most of these studies were (non-randomized) retrospective studies, with both AR and NAR patients and in many there were no patient-reported outcomes both pre- and post-operative. Therefore, the evidence for vidian neurectomy remains controversial (14, 15). It would be of great interest to perform a cohort trial with a

long follow-up period and uniform patient selection criteria for selection of NAR and its phenotypes.

Finally, it is unknown whether there is role for inferior turbinate reduction in non-allergic rhinitis patients. When the underlying endotype is unknown and/or all available treatments have failed, turbinate reduction is sometimes considered in both AR and NAR patients with symptoms of nasal congestion. However, when inferior turbinate hypertrophy mainly consists of bone, the nowadays popular therapy of radiofrequency coblation reduction will likely not be effective and surgical reduction (with higher post-operative risk of bleeding) is indicated. Thereby, in these cases of bony hypertrophy we are rather talking about treating anatomy (in the same way as when we treat a septal deviation) than about treating symptoms of mucosa, i.e. rhinitis. In case of mucosal hypertrophy as result of rhinitis in either NAR or AR, reduction therapy will bear the risk of only having temporary effectiveness, as the underlying disease mechanism responsible for mucosal hypertrophy is not treated and regrowth of mucosa is to be expected.

Therefore, to reliably assess effectiveness of turbinate reduction therapy, a pre-operative CT scan to assess either bony or mucosal hypertrophy could be indicated, together with an accurate selection of distinct pheno- and endotypes and a long-term follow-up.

Lower and upper airways

Non-allergic rhinitis seems to be a risk to develop non-allergic asthma later on in life (2) The risk of developing asthma is independent on IgE-sensitization as rhinitis and asthma were found to be comorbidities independent of the atopic state (16). Ipratroprium bromide known as treatment in both the upper airways as the lower airways both act on the muscarinic cholinergic receptor. In the lower airways there seems to be an interaction between the muscarinic cholinergic receptor and the TRP-receptor, indicating an interaction between neurogenic dysbalance and neurogenic inflammation. Neurogenic inflammation and overexpression over TRPV-1 receptors as part of lower airway hyper-reactivity seem to play an important role in the development of non-atopic asthma (17). However, the exact mechanism of the development of non-allergic rhinitis to non-atopic asthma remains unknown and further research on this topic will reveal more knowledge on the underlying endotypes and possible treatment options.

A question that needs to be answered is whether desensitization of TRPV-1 receptors in non-allergic rhinitis will also desensitize these TRP receptors in the lower airways, resulting in inhibition of development to non-allergic asthma. Can ipratroprium bromide nasal spray also be used to modulate TRP-receptors in the upper airways, as it seems to be able to do in the lower airways? Can a combination of intranasal steroid with

ipratroprium bromide -as in asthma- have a beneficial effect in non-allergic rhinitis patients as well?

NAR versus AR and CRS

Nasal hyper-reactivity is a common symptom (prevalence 63-65%) in both allergic rhinitis and non-allergic rhinitis patients (**chapter 2**). Does that mean that neurogenic inflammation is part of allergic rhinitis patients as it is in non-allergic rhinitis? Capsaicin as TRPV-1 agonist does not seem to be effective in treating hyper-reactivity in allergic rhinitis, however fluticasone combined with azelastine does seem to have a beneficial effect on nasal hyper-reactivity in AR (3). Sensory C fibers seem to be also present in the nasal mucosa of AR patients and are thought to be able to release similar neurotransmitters in both AR and NAR patients after provocation/stimulation (18). In AR patients treating the IgE-mediated inflammation seems to down-regulate the neurogenic inflammation (3). In other words, the sequence of events resulting in neurogenic inflammation is likely to be different in AR compared to NAR. Assessment of these differences is of interest as it can give us insights in the differences between neurogenic inflammation in different patients and better treatment options.

Preliminary results of micro-array analysis of epithelial cells in different diseases of the upper airways show that there might also be a role for neurogenic inflammation in chronic rhinosinusitis (CRS). As hyper-responsiveness of the lower airways is a nonspecific symptom not related to a specific disease or phenotype, it is very likely that nasal hyper-reactivity is a nonspecific symptom of diseased upper airway mucosa in CRS with or without nasal polyposis. This raises the question for a possible role of treatment options of neurogenic inflammation like azelastine in CRS.

CONCLUDING REMARKS

Non-allergic rhinitis has been ignored and put aside as a *diagnosis per exclusionem* with different names and explanations for too long, frustrating both doctor and patient.

The diagnosis of NAR deserves at least the same -and preferably more- attention the coming years as allergic rhinitis. In allergic rhinitis the detailed understanding of the underlying disease mechanism has resulted in public attention, awareness and understanding, resulting in elegant treatment options ranging from commercially available tablets or nasal sprays to immunotherapy. The socio-economic burden of NAR is comparable -and likely even higher- compared to AR, as prevalence rate of both diseases are competitive and their rhinitis symptoms very comparable. In contrast to the proportion of AR patients with seasonal symptoms only, most NAR patients suffer from their symptoms whole year round. However, in NAR patients the amount of available and effective treatment options are limited when compared to AR. Thereby NAR

patients often lack compassion from doctors and their surroundings, as their diagnosis is unknown and ununderstood. At home or in the work-environment of these patients, a sniffing nose without explanation is often put aside as minor or even existing only in the mind of the patient. It was not even long ago, that non-allergic rhinitis was considered more to be a psychogenic than a physical disorder. The now known significant quality of life impairment of these patients and the growing knowledge on the underlying disease mechanisms should make doctors humble and aware on how much these patients are suffering. When it comes to rhinitis symptoms and irritability or tiredness this suffering seems to be significantly more than patients with allergic rhinitis.

As in CRS and in the lower airways, international studies like GA2LEN with consensus on definition and diagnostic criteria are desperately needed, addressing demographic and social features of NAR and increasing public awareness and future research investments.

Spreading the today available knowledge on NAR phenotypes and endotype-specific treatments will help change the attitude of doctors and change NAR from an unknown and unpopular *diagnosis per excusionem* with a trial and error approach of treatment, to a more structured diagnosis and treatment strategy, improving satisfaction of both doctor and patient.

The latest promising developments in the field of understanding nasal hyper-reactivity and neurogenic inflammation resulting in development of novel effective treatment options, encourages us to continue our studies on the neurogenic endotype and its subendotypes, in different phenotypes of NAR and AR patients. A helicopter view -enabling us to compare not only different diseases of the upper airways but also to learn from the lower airways- will gain the fastest results. Micro-array analysis is a promising new tool for endotyping and deserves a prominent position in novel research. Neurogenic inflammation and the role of neurogenic dysbalance, is not limited to the upper airways or lower airways only. Also, in other diseases like migraine there is a growing attention for this disease mechanism, encouraging the development of novel treatment options.

NAR has been left in the cold for too long. It deserves a position as hot topic in the exciting research field of neurogenic inflammation and endotyping. This will improve not only its status but also -most importantly- the quality of life of these patients that deserve a better understanding and treatment after all these years.

REFERENCES

1. Bousquet, J. et al. *Important research questions in allergy and related diseases: non-allergic rhinitis: a GA2LEN paper.* Allergy, 2008. 63(7): p. 842-53.

2. Shaaban, R. et al. *Rhinitis and onset of asthma: a longitudinal population-based study.* Lancet, 2008. 372(9643): p. 1049-57.

3. Kortekaas Krohn, I. et al. *MP29-02 reduces nasal hyper-reactivity and nasal mediators in patients with house dust mite-allergic rhinitis.* Allergy, 2018. 73(5): p. 1084-1093.

4. Rondon, C. G. Canto, and M. Blanca, *Local allergic rhinitis: a new entity, characterization and further studies.* Curr Opin Allergy Clin Immunol, 2010. 10(1): p. 1-7.

5. Rondon, C. et al. *Prevalence and clinical relevance of local allergic rhinitis.* Allergy, 2012. 67(10): p. 1282-8.

6. Auge, J. et al. *EAACI Position paper on the standardization of nasal allergen challenges.* Allergy, 2018. 73(8): p. 1597-1608.

7. Toppila-Salmi, S. et al. *Molecular mechanisms of nasal epithelium in rhinitis and rhinosinusitis.* Curr Allergy Asthma Rep, 2015. 15(2): p. 495.

8. van Drunen, C.M. et al. *Considerations on the application of microarray analysis in rhinology.* Rhinology, 2008. 46(4): p. 259-66.

9. Banov, C.H. P. Lieberman, and G. Vasomotor Rhinitis Study, *Efficacy of azelastine nasal spray in the treatment of vasomotor (perennial non-allergic) rhinitis.* Ann Allergy Asthma Immunol, 2001. 86(1): p. 28-35.

10. Gehanno, P. et al. *Vasomotor rhinitis: clinical efficacy of azelastine nasal spray in comparison with placebo.* ORL J Otorhinolaryngol Relat Spec, 2001. 63(2): p. 76-81.

11. Singh, U. et al. *Azelastine desensitization of transient receptor potential vanilloid 1: a potential mechanism explaining its therapeutic effect in non-allergic rhinitis.* Am J Rhinol Allergy, 2014. 28(3): p. 215-24.

12. Guo, L. et al. *Clinical study of the combination therapy with intranasal antihistamine and nasal corticosteroids in the treatment of nasal obstruction of persistent non-allergic rhinitis.* Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi, 2015. 29(3): p. 243-5, 251.

13. Blom, H.M. et al. *Intranasal capsaicin is efficacious in non-allergic, non-infectious perennial rhinitis. A placebo-controlled study.* Clin Exp Allergy, 1997. 27(7): p. 796-801.

14. Harvey, R. *From legacy to novel: vidian neurectomy and eustachian tube balloon dilatation in modern ENT practice.* J Laryngol Otol, 2016. 130 Suppl 4: p. S1.

15. Robinson, S.R. and P.J. Wormald, *Endoscopic vidian neurectomy.* Am J Rhinol, 2006. 20(2): p. 197-202.

16. Leynaert, B. et al. *Epidemiologic evidence for asthma and rhinitis comorbidity.* J Allergy Clin Immunol, 2000. 106(5 Suppl): p. S201-5.

17. Bernstein, J.A. and U. Singh, *Neural Abnormalities in Non-allergic Rhinitis.* Curr Allergy Asthma Rep, 2015. 15(4): p. 18.

18. Baraniuk, J.N. and S.J. Merck, *Neuroregulation of human nasal mucosa.* Ann N Y Acad Sci, 2009. 1170: p. 604-9.

APPENDICES

Summary

Samenvatting

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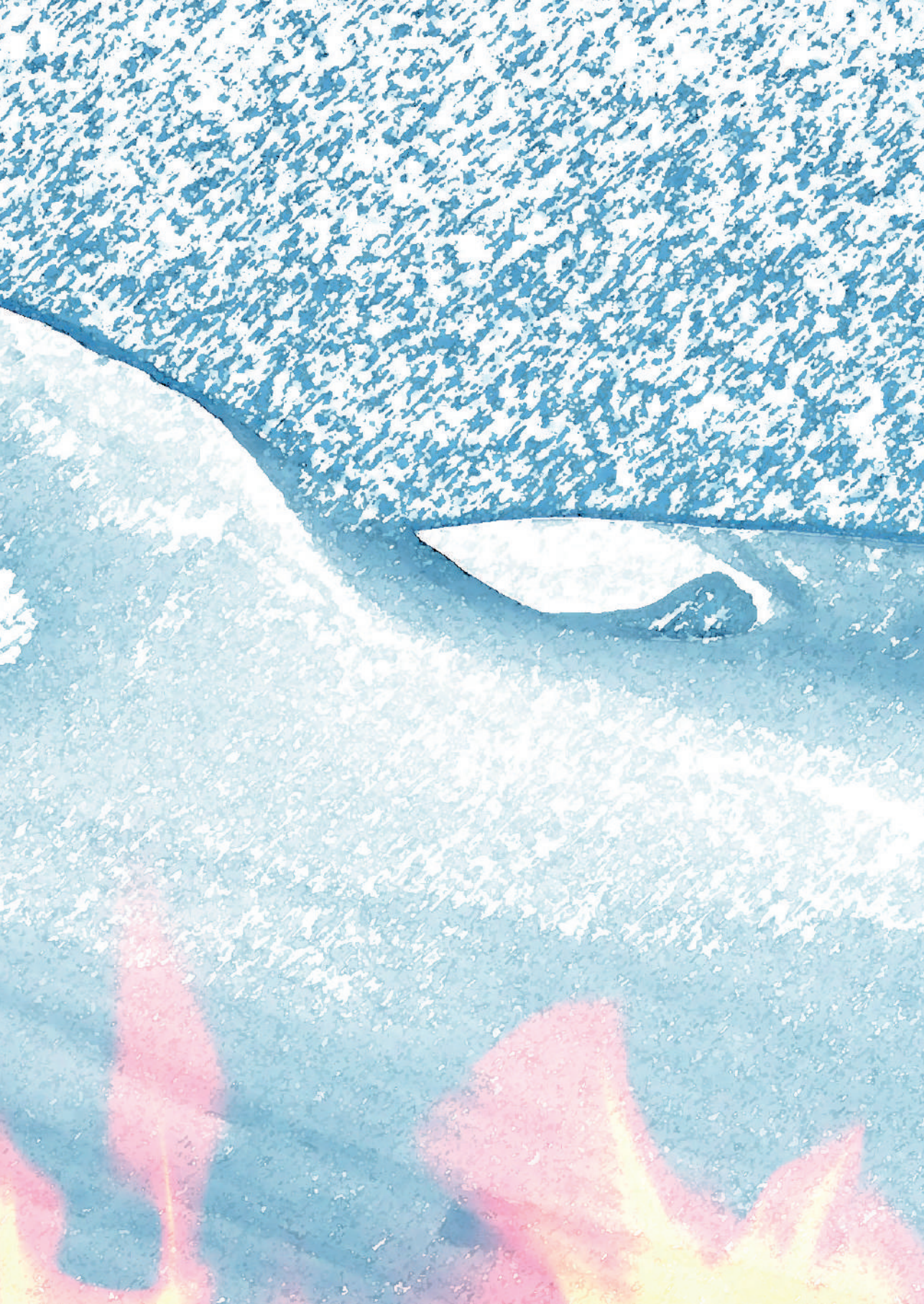
Portfolio

List of publications

About the author

Dankwoord



SUMMARY

Non-allergic rhinitis (NAR) is a chronic disease with a high prevalence rate and a significant burden of disease. For long it was considered a *diagnosis per exclusionem* and was characterized by several changing names and definitions and a lack of knowledge regarding the underlying disease mechanism(s). As a result, treatment of patients with non-allergic rhinitis was often characterized by an unsuccessful *trial and error* approach without evidence-based treatment strategies.

Of all the upper respiratory tract diseases, perhaps NAR is most in need of a phenotype and endotype-driven diagnostic approach and endotype-specific treatment strategies.

This thesis focused on optimizing the diagnostic process and phenotyping in NAR and improving evidence-based treatment strategies.

In **chapter 2** we describe a prospectively collected database study to assess patient-reported symptoms of hyper-reactivity in non-allergic (NAR) and allergic rhinitis (AR) patients. In the second part, cold dry air provocation (CDA) was performed as an objective hyper-reactivity measure in NAR and AR patients and healthy controls. Symptoms scores, nasal secretions and peak nasal inspiratory flow (PNIF) were measured. Comparisons were made between NAR and AR patients in both studies.

For long, nasal hyper-reactivity was considered a defining symptom of NAR patients only and triggered by either physical or chemical stimuli.

This study demonstrated a similar hyper-reactivity prevalence rate in AR of 63.4% and in NAR of 66.9%. There were no differences between AR and NAR in terms of the number or type of hyper-reactivity stimuli. Hyper-reactivity to physical stimuli did not exclude a response to chemical stimuli, or vice versa.

In **chapter 3** we assessed a wide panel of inflammatory mediators in nasal secretions of NAR, AR en mixed patients and healthy controls. Until now it has been proven difficult to endotype NAR patients, in contrast to AR patients. Whether NAR patients have an inflammatory endotype is a relevant question as this will predict therapeutic effectiveness of intranasal corticosteroids in this patient group. After performing a multiplex ELISA with 29 inflammatory mediators no Th1/Th2-inflammatory endotype in NAR or mixed rhinitis patients could be found. This confirms that in most NAR patients there is a non-inflammatory endotype that is in need of other treatments than the conventional treatments like intranasal corticosteroids.

In **chapter 4** we present the results of an observational cohort study in 287 AR and 160 NAR patients assessing quality of life (QoL) and use of medication and treatment

satisfaction. Until now, no validated QoL questionnaire was available for NAR patients. After performing a validation for the mini-Rhinoconjunctivitis Quality of Life (mini-RQLQ) in NAR patients, a significantly impaired QoL in NAR patients was shown. Impairment of QoL in NAR patients was comparable to AR patients, with an exception for the mini-RQLQ subdomains 'nasal complaints' and 'other complaints' (i.e. tiredness etc.) for which NAR scored significantly higher (lower quality of life) compared to AR. More than half of NAR and AR patients were unsatisfied with their current treatment.

In **chapter 5** the results of a Cochrane Review on intranasal steroids in 4452 NAR patients are presented. The overall quality of the evidence in this review is low to very low. Intranasal corticosteroids are compared to placebo (2045 patients) but also to other treatment modalities. It is unclear whether intranasal corticosteroids reduce patient-reported disease severity in non-allergic rhinitis patients compared with placebo when measured at up to three months follow-up.

In **chapter 6** the results of a Cochrane Review on intranasal capsaicin in 302 idiopathic NAR patients are presented. There is low to moderate quality level of evidence of the effectiveness of capsaicin in NAR. Capsaicin seems to work better than intranasal steroids in NAR patients. The recommended treatment strategy is to give 5 treatments in one day with at least 4 ug capsaicin per puff. Given that many other options do not work well in non-allergic rhinitis, capsaicin is a reasonable option to try under physician supervision.

In **chapter 7** the results of two randomized controlled trials (RCT's) are presented, showing that a TRPV-antagonist has an appropiate safety profile and is capable of achieving a clinically relevant attenuation of capsaicin-provoked rhinitis symptoms in patients with NAR.

Chapter 8 comprises the general discussion, overall conclusions and future perspectives of this research.

SAMENVATTING

Niet-allergische rhinitis (NAR) is een chronische ziekte met een hoog prevalentiecijfer en een significant hoge ziektelast. Voorheen werd NAR beschouwd als een *diagnosis per exclusionem* en had verschillende benamingen en definities door een tekort aan kennis omtrent het onderliggende ziektemechanisme. Het gevolg hiervan was dat NAR patiënten vaak onsuccesvol werden behandeld op een 'trial en error' wijze. Er was een gebrek aan evidence-based behandelstrategieën.

Van alle ziektebeelden van de bovenste luchtweg heeft NAR misschien wel het meest behoefte aan een fenotype- en endotype-gerichte diagnostische benadering en aan endotype-specifieke behandelingen.

Dit proefschrift is erop gericht de diagnostiek en fenotypering van NAR te optimaliseren en evidence-based behandelstrategieën voor NAR patiënten te definiëren.

In **hoofdstuk 2** beschrijven we in het eerste deel een prospectieve database studie naar symptomen van nasale hyper-reactiviteit gerapporteerd door niet-allergische rhinitis (NAR) en allergische rhinitis (AR) patiënten.

In het tweede deel werd een koude droge lucht provocatie uitgevoerd als objectieve maat voor het bepalen van nasale hyper-reactiviteit in NAR patiënten, AR patiënten en gezonde controles. Nasale symptomen, nasaal secreet en nasale passage (peak nasal inspiratory flow (PNIF)) werden na deze provocatie in kaart gebracht. In zowel het eerste als in het tweede deel van de studie werden NAR en AR patiënten met elkaar vergeleken.

Voor een lange periode was het een algemene aanname dat nasale hyper-reactiviteit alleen toebehoort aan NAR patiënten en dat deze patiëntengroep zich met dit symptoom onderscheidt van andere chronische rhinitis patiëntengroepen. Tevens werd gedacht dat nasale hyper-reactiviteit kon worden onderscheiden in twee groepen; nasale hyper-reactiviteit uitgelokt door fysische stimuli en nasale hyper-reactiviteit uitgelokt door chemische stimuli.

Deze studie liet echter een vergelijkbaar prevalentiecijfer van nasale hyper-reactiviteit zien in zowel AR (63.4%) als NAR (66.9%) patiënten. Er was niet alleen geen significant verschil in het prevalentiecijfer, er konden ook geen verschillen worden aangetoond tussen AR en NAR wat betreft het aantal of type stimuli die hyper-reactiviteit kunnen uitlokken. Hyper-reactiviteit voor fysische stimuli sloot een hyper-reactiviteit voor chemische stimuli niet uit en vice versa.

In **hoofdstuk 3** onderzochten we een breed aantal inflammatoire mediatoren in het nasaal secreet van NAR, AR en mixed rhinitis (mengvorm van NAR en AR) patiënten en gezonde controles. Het is tot nu toe altijd moeilijk gebleken om het endotype van NAR patiënten te bepalen in tegenstelling tot dat van AR patiënten. Het is van belang om te bepalen of NAR patiënten een inflammatoir endotype hebben aangezien dit kan voorspellen of intranasale corticosteroïden effectief zullen zijn in deze patiëntengroep. Na het uitvoeren van een multiplex ELISA (Enzyme-Linked Immuno Sorbent Assay) met 29 inflammatoire mediatoren kon er in deze studie noch een Th1 noch een Th2 inflammatoir endotype worden aangetoond in de NAR en mixed rhinitis patiënten. Dit bevestigt dat er bij de meeste NAR patienten sprake is van een niet-inflammatoir endotype en dat een andere behandeling dan de gebruikelijke behandeling (intranasale corticosteroïden) voor deze patiëntengroep in veel gevallen noodzakelijk is.

In **hoofdstuk 4** worden de resultaten getoond van een observationele cohort studie in 287 AR en 160 NAR patiënten naar de kwaliteit van leven, het gebruik van medicatie en tevredenheid met de huidige behandeling. Tot nu toe was er geen gevalideerde 'kwaliteit van leven' vragenlijst beschikbaar voor NAR patiënten. Na het uitvoeren van een validatie van de mini-Rhinoconjunctivitis Quality of Life Questionnaire (mini-RQLQ) voor het gebruik bij NAR patiënten, kon na het gebruik van deze vragenlijst in de NAR patiëntenpopulatie, een significante beperking in kwaliteit van leven van NAR patiënten worden aangetoond. Deze beperking in kwaliteit van leven van NAR patiënten was vergelijkbaar met AR patiënten, met de uitzondering dat voor de subdomeinen 'neussymptomen' en 'andere klachten' (bv. vermoeidheid) NAR patiënten zelfs significant slechter (i.e. een lagere kwaliteit van leven) scoorden dan AR patiënten. Meer dan de helft van de NAR en AR patiënten waren ontevreden met hun huidige behandeling.

In **hoofdstuk 5** worden de resultaten getoond van een Cochrane Review naar het effect van intranasale corticosteroïden in 4452 NAR patiënten. De kwaliteit van de evidence is in het algemeen laag tot zeer laag. Intranasale corticosteroïden werden vergeleken met placebo (2045 patiënten) maar ook met andere behandelopties. Het is onduidelijk of bij een follow-up duur tot 3 maanden, intranasale corticosteroïden de door NAR patiënten gerapporteerde ziekte-ernst verlaagt.

In **hoofdstuk 6** worden de resultaten getoond van een Cochrane Review naar het effect van intranasaal capsaïcine in 302 idiopatische NAR patiënten. De kwaliteit van de evidence is laag tot matig. Capsaicine lijkt beter te werken dan intranasale corticosteroïden in NAR patiënten. De aanbevolen behandelstrategie is om intranasaal capsaïcine 5 maal op een dag te geven in een dosis van minimaal 4 ug capsaïcine per spray. Aangezien veel andere behandelopties in niet-allergische rhinitis niet goed

werken, kan redelijkerwijs een behandeling met intranasaal capsaïcine onder supervisie van een arts worden overwogen.

In **hoofdstuk 7** worden de resultaten van twee randomized controlled trials (RCT's) gepresenteerd die laten zien dat een TRVP-antagonist een geschikt veiligheidsprofiel heeft en daarnaast in staat is om een klinisch relevante afname te bewerkstelligen van door capsaïcine uitgelokte rhinitis symptomen in NAR patiënten.

In **hoofdstuk 8** worden de conclusies van het onderzoek besproken, gevolgd door een algemene discussie en perspectieven voor de toekomst.

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Dr. I. Terreehorst

Courses

- 2011: Good Clinical Practice (GlaxoSmithKline) (ECTS 1.00)
- 2011: Advanced Immunology (ECTS 1.00)
- 2011: Clinical Data Management (ECTS 0.30)
- 2012: Pubmed (ECTS 0.10)
- 2012: Reference Manager Basic (ECTS 0.50)
- 2012: Practical Biostatistics (ECTS 1.00)
- 2012: Evidence Based Medicine (ECTS 1.00)
- 2012: Basiscursus Regelgeving en Organisatie voor Klinisch onderzoek (ETCS 0.50)
- 2012: Mini-Endoscopie course, UMCG, Groningen (ECTS 0.50)
- 2013: Mini-FESS course, LUMC, Leiden (ECTS 0.50)
- 2014: Teach the Teacher course, AMC, Amsterdam (ECTS 0.25)
- 2014: KNO-Radiologie 'KNOR' course, Zaandam (ECTS 0.50)
- 2014: Mini-OSAS, OLVG, Amsterdam (ECTS 0.50)
- 2015: Mini-Oren course, Radboud UMC, Nijmegen (ECTS 0.50)
- 2015: Mini-around the nose, Radboud UMC, Nijmegen (ECTS 0.50)
- 2016: Mondpathologie course, Breukelen (ECTS 0.25)
- 2017: Nascholingscursus Kliniek van Duizeligheid en Evenwichtsstoornissen (ECTS 0.50)
- 2018: European Rhinoplasty Course, Leuven (ECTS 0.50)

Presentations

- 2019 'Lokale allergische rhinitis: feit of fabel.' *Oral presentation, Symposium Kinderallergologie.* April 2019, Maarssen (The Netherlands) (ECTS 0.50)
- 2019: 'Liefde voor de Neus', *oral symposium at several locations in the Netherlands during 2019'.* February-November 2019, The Netherlands (ECTS 0.50)
- 2018 'Innovatieve Behandelingsstrategieën binnen KNO-luchtwegpathologie'. *Oral presentation, regionale refereeravond Zeeland en Brabant (ZEEBRA).* September 2018, Bergen op Zoom (The Netherlands) (ECTS 0.50)
- 2018 'Rhinitis en rhinosinusitis'. *Oral presentation, Amsterdams Geneeskundig Genootschap* (*AGG*). October 2018, Amsterdam (The Netherlands) (ECTS 0.50)
- 2017 'Biologicals in rhinosinusitis'. *Oral presentation, European Academy of Allergy and Clinical Immunology (EAACI).* May 2018, München (Germany) (ECTS 0.50)
- 2017 'Neurogenic inflammation in NAR and AR'. *Oral presentation, ORL-HNS congress.* October 2017, Barcelona (Spain) (ECTS 0.50)
- 2017 *'Oral presentation, refereeravond Academic Medical Center Amsterdam (AMC).* September 2017, Amsterdam (The Netherlands) (ECTS 0.50)
- 2017 'Niet-allergische rhinitis: diagnostiek en nieuwe behandelopties'. *Oral presentation, regionale refereeravond AMC.* June 2017, Amsterdam (The Netherlands) (ECTS 0.50)
- 2017 'Innovatieve behandelstrategieën binnen KNO-luchtwegpathologie'. *Oral presentation,* VinK (Vrouwen in de KNO). May 2017, Vlieland (The Netherlands) (ECTS 0.50)
- 2016 'Quality of life in allergic and non-allergic rhinitis patients. *Poster presentation*, *European Forum for Research and Education in Allergy and Airway Disease (EUFOREA).* November 2016, Brussels (Belgium) (ECTS 0.50)
- 2016 'Local nasal allergy – clinical relevance?' *Oral presentation, European Rhinologic Society (ERS) congress.* July 2016, Stockholm (Sweden) (ECTS 0.50)
- 2016 'Uncontrolled upper-airway disease. Non-allergic rhinitis'. *Oral presentation, EAACI congress.* June 2016, Vienna (Austria) (ECTS 0.50)

- 2016 'Lokale allergische rhinitis: fact or fiction'. *Oral presentation, symposium van Nederlandse Vereniging voor Allergologie (NVvA).* September 2016, Breukelen (The Netherlands) (ECTS 0.50)
- 2015 'Lokale allergische rhinitis: feit of fictie'. *Oral presentation, regionale allergie refereermiddag AMC.* September 2015, Zaandam (The Netherlands) (ECTS 0.50)
- 2015 'Molecular cellular pathogenesis of non-allergic and allergic rhinitis'. *Oral presentation, EAACI congress.* June 2015, Barcelona (Spain) (ECTS 0.50)
- 'New Insights into The Pathogenesis Of Non-allergic Rhinitis'. *Poster presentation* ***(poster award)****, Symposium on Experimental Rhinology and Immunology of the Nose (SERIN) congress.* March 2015, Stockholm (Sweden) (ECTS 0.50)
- 2015 'Breek me de bek niet open'. *Oral presentation, KNO Vergadering.* April 2015, Nieuwegein (The Netherlands) (ECTS 0.50)
- 2014 'Differentiating groups of rhinitis patients based on molecular markers in nasal secretions'. ***(oral presentation award)****, ERS congress.* June 2014, Amsterdam (The Netherlands) (ECTS 0.50)
- 2014 'Nasal hyper-reactivity in non-allergic and allergic rhinitis patients'. *Symposium, ERS congress.* June 2014, Amsterdam (The Netherlands) (ECTS 0.50)
- 2014 'Nasal hyper-reactivitity in non-allergic and allergic rhinitis patients'. *Oral presentation, EAACI congress.* June 2014, Copenhagen (Denmark) (ECTS 0.50)
- 2014 'Nasale hyper-reactiviteit in niet-allergische en allergische rhinitis patiënten'. *Oral presentation, KNO Vergadering.* April 2014, Nieuwegein (The Netherlands) (ECTS 0.50)
- 2013 'Kwaliteit van leven in niet-allergische rhinitis patienten'. *Oral presentation, KNO Vergadering.* November 2013, Nieuwegein (The Netherlands) (ECTS 0.50)
- 2013 'Quality of life in allergic and non-allergic rhinitis patients'. *Oral presentation, SERIN.* March 2013, Leuven (Belgium) (ECTS 0.50)
- 2011 'Nasal hyper-reactivity in allergic and non-allergic rhinitis patients'. *Poster presentation, EAACI congress.* June 2011, Istanbul (Turkey) (ECTS 0.50)
- 2010 'Nasal hyper-reactivity in allergic and non-allergic rhinitis patients'. *Oral presentation, SERIN congress.* November 2010, Brussels (Belgium) (ECTS 0.50)

National and international conferences

- 2019 European Academy of Allergy and Clinical Immunology, Istanbul, Portugal (ECTS 0.50)
- 2018 European Rhinoplasty Course, Brussels, Belgium (ECTS 0.50)
- 2018 European Academy of Allergy and Clinical Immunology, München, Germany (ECTS 0.75)
- 2017 Otorhinolaryngology Head and Surgery (ORL-HNS congress), Barcelona, Spain (ECTS 0.50)
- 2017 Rhinology World Congress, Hong Kong (ECTS 0.75)
- 2016 European Rhinology Research Forum (EUFOREA), Brussels, Belgium (ECTS 0.50)
- 2016 European Academy of Allergy and Clinical Immunology, Vienna, Austria (ECTS 0.75)
- 2016 Congress of the European Rhinologic Society, Stockholm, Sweden (ECTS 0.75)
- 2015 Symposium on Experimental Rhinology and Immunology of the Nose, Stockholm, Sweden (ECTS 0.50)
- 2014 Congress of the European Rhinologic Society, Amsterdam, The Netherlands (ECTS 0.75)
- 2014 European Academy of Allergy and Clinical Immunology, Copenhagen, Denmark (ECTS 0.75)
- 2013 Symposium on Experimental Rhinology and Immunology of the Nose, Leuven, Belgium (ECTS 0.50)
- 2011 European Academy of Allergy and Clinical Immunology, Istanbul, Turkey (ECTS 0.50)
- 2010 Symposium on Experimental Rhinology and Immunology of the nose, Brussels, Belgium (ECTS 0.50)

Others

- 2014-until now Member of Junior European Rhinologic Society

Awards

- 2014 ERS, Oral Presentation Prize
- 2015 SERIN, Poster Prize

LIST OF PUBLICATIONS

- **Segboer C,** Gevorgyan A, Avdeeva K, Chusakul S, Kanjanaumporn J, Aeumjaturapat, S, Reeskamp LF, Snidvongs K, Wytske F. **Intranasal corticosteroids in non-allergic rhinitis.** *Cochrane Database Syst Rev*: *2019;* **2**(11)
- Seys S, Bousquet J, Bachert C, Fokkens W, Agache I, Bernal-Sprekelsen M, Callebaut I, Cardel L, Carrie S, Castelnuovo P, Cathcart R, Constantinidis J, Cools L, Cornet M, Clement G, de Sousa JC, Cox T, Doulaptsi M, Gevaert P, Hopkins C, Hox V, Hummel T, Hosemann W, Jacobs R, Jorissen M, Landis B, Leunig A, Lund VJ, Mullol J, Onerci M, Palkonen S, Proano I, Prokopakis E, Ryan D, Riechelmann H, Saevels J, **Segboer C**, Speleman K, Steinsvik EA, Surda P, Tomazic PV, Vanderveken O, Van Gerven L, Van Zele T, Verhaeghe B, Vierstraete K, Vlaminck S, Wilkinson J, Williams S, Pugin B, Hellings P. **mySinusitisCoach: patient empowerment in chronic rhinosinusitis using mobile technology.** *Rhinology 2018;* **56**(3)*:209-215*
- **Segboer C,** Terreehorst I, Gevorgyan A, Hellings P, van Drunen CM, Fokkens W. **Quality of life is significantly impaired in non-allergic rhinitis patients.** *Allergy* 2018; **73**(5):1094-1100
- **Segboer C**, Fokkens W, Terreehorst I, van Drunen C. **Endotyping of non-allergic, allergic and mixed rhinitis patients using a broad panel of biomarkers in nasal secretions.** *PLoS One.* 2018; **26**;13(7)
- Hellings P, Akdis CA, Bachert C, Bousquet J, Pugin B, Adriaensen G, Advani R, Agache I, Anjo C, Anmolsingh R, Annoni E, Bieber T, Bizaki A, Braverman I, Callebaut I, Castillo Vizuete J, Chalermwatanachai T, Chmielewski R, Cingi C, Cools L, Coppije C, Cornet M, De Boeck I, De Corso E, De Greve G, Doulaptsi M, Edmiston R, Erskine S, Gevaert E, Gevaert P, Golebski K, Hopkins C, Hox V, Jaeggi C, Joos G, Khwaja S, Kjeldsen A, Klimek L, Koennecke M, Kortekaas Krohn I, Krysko O, Kumar BN, Langdon C, Lange B, Lekakis G, Levie P, Lourijsen E, Lund VJ, Martens K, Mő Sges R, Mullol J, Nyembue T, Palkonen S, Philpott C, Pimentel J, Poirrier A, Pratas A, Prokopakis E, Pujols L, Rombaux P, Schmidt-Weber C, **Segboer C**, Spacova I, Staikuniene J, Steelant B, Steinsvik E, Teufelberger A, Van Gerven L, Van Gool K, Verbrugge R, Verhaeghe B, Virkkula P, Vlaminck S, Vries-Uss E, Wagenmann M, Zuberbier T, Seys S, Fokkens WJ. **EUFOREA Rhinology Research Forum 2016: report of the brainstorming sessions on needs and priorities in rhinitis and rhinosinusitis.** *Rhinology* 2017; **55**(3):202-210
- Fokkens W, Hellings P, **Segboer C. Capsaicin for Rhinitis.** *Curr Allergy Asthma Rep* 2016; **16**(8):60
- Gevorgyan A[1], **Segboer C[1] ([1]:shared first authorship),** Gorissen R, van Drunen CM, Fokkens W. **Capsaicin for non-allergic rhinitis.** *Cochrane Database Syst Rev* 2015; **14**(7)
- **Segboer C**, Holland C, Reinartz S, Terreehorst I, Gevorgyan A, Hellings P, van Drunen C, Fokkens W. **Nasal hyper-reactivity is a common feature in both allergic and non-allergic rhinitis.** *Allergy* 2013; **68**(11): 1427-34

- Holland C, van Drunen C, Denyer J, Smart K, **Segboer C,** Terreehorst I, Newlands A, Beerahee M, Fokkens W, Tsitoura D. **Inhibition of capsaicin-driven nasal hyper-reactivity by SB-705498, a TRPV-1 antagonist.** *Br J Clin Pharmacol* 2014; **77**(5):777-88
- Dietz de Loos D, **Segboer C,** Gevorgyan A, Fokkens W. **Disease-specific quality-of-life questionnaires in rhinitis and rhinosinusitis: review and evaluation.** *Curr Allergy Asthma Rep*. 2013; **13**(2):162-70
- van Drunen C, Mjösberg J, **Segboer C,** Cornet M, Fokkens W. **Role of innate immunity in the pathogenesis of chronic rhinosinusitis: progress and new avenues.** *Curr Allergy Asthma Rep.* 2012; **12**(2):120-6
- **Segboer C**, Rijntjes E. **'Schizispatiënt geboren met tanden'.** *Nederlands Tijdschrift voor Keel-Neus-Oorheelkunde* (NTvKNO); 2009

ABOUT THE AUTHOR

Christine Louise Segboer was born on the 25th of May in 1985 in The Hague, The Netherlands. After graduation at the Maerlant Lyceum in The Hague (2003, *summa cum laude*), she started her medical training at the University of Leiden. During her study she participated in several scientific research projects, including at the Otorhinolaryngology department of the Leids Universitair Medisch Centrum (LUMC), Leiden. In 2009 she completed her medicine studies (*cum laude*) with a scientific research project at the Otorhinolaryngology department of the Academic Medical Center in Amsterdam (prof. dr. W.J. Fokkens).

As of 2010 she started her PhD project (prof. dr. W.J. Fokkens, Dr. C.M. van Drunen) combined with clinical work at the department of Otorhinolaryngology. In 2012 she continued her fulltime specialist training in Otorhinolaryngology at the Academic Medical Center in Amsterdam (prof. dr. W J. Fokkens, prof. dr. S. van der Baan, dr. S.M. Reinartz, dr. A.M. König). After finishing her specialist training in 2017 she worked for one year as an ENT surgeon both at the Academic Medical Center in Amsterdam as at the Alrijne Hospital in Leiden/Leiderdorp.

From the beginning of 2018 she obtained a position as an ENT surgeon at the Dijklander Hospital in Hoorn, subspecialized in Rhinology.

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Marein, jij weet heel goed hoe heerlijk het voelt als een promotietraject tot een einde komt en hebt dan ook erg met mij meegeleefd. Met Jip, al springend voor mijn laptopscherm, was het soms een uitdaging om te schrijven, maar nu is het eindelijk af. Dank je wel voor je betrokkenheid, toegankelijkheid en alles wat je aan regelzaken op je neemt. Dit heeft ook bijgedragen aan het kunnen afronden van mijn proefschrift. Je bent een heel fijne collega en ik kan altijd bij je terecht.

Jiska, als 'maatje' is het superfijn om met jou alles te kunnen bespreken en zo veel van elkaar te begrijpen. Samen kunnen we het allemaal weer wat relativeren - zelfs de diesel - en met elkaar lachen. Ik ben benieuwd of we nu gezellig naast elkaar naar Hoorn zullen rijden nu ik je niet meer kan inhalen straks met een maximumsnelheid van 100 km per uur. Ik bof met jou als collega.

Lieve **Paranimfen,** lieve Marjolein en Dirk. Het lag met onze appgroep 'Paranimfen' al vele jaren vast dat jullie mijn paranimfen zouden zijn en met jullie heb ik dan ook de beste paranimfen die ik me kan wensen.

Lieve **Marjolein,** na onze vele gemeenschappelijke jaren 'in hetzelfde schuitje' is een mooie vriendschap ontstaan. Ik zie nog levendig jouw eerst dagen voor me in het AMC

en de eerste persoonlijke gesprekken die we voerden. Ik heb veel te danken aan jouw altijd luisterend oor, je vrolijkheid en heldere en eerlijke blik. Met niemand kan ik zo goed lachen als met jou. We hebben elkaar er op meerdere momenten doorheen gesleept en met resultaat. Nu is het eindelijk af. Maar gelukkig komt daarbij geen einde aan de vele momenten van koffie drinken, etentjes en congressen in het buitenland. Want ik ken niemand die zo van het leven kan genieten als jij. Ik kan me er nu al op verheugen dat er in dit opzicht nog vele jaren voor ons liggen.

Lieve **Dirk,** met jouw komst was ons drietal compleet en we hebben een lange periode als laatste 'AGIKO's' onze stempel gedrukt op de KNO-research. Onze gemeenschappelijke 'Leidsche' tongval waarmee we het niveau van de ochtendoverdracht hoog hebben gehouden, schiep natuurlijk meteen een band. Als geen ander ben jij altijd gelijkmatig, nauwkeurig, behulpzaam en collegiaal. Waar zal ik ooit een collega vinden die zoveel deuren voor mij opendoet en op zoveel momenten mijn ski's draagt als jij, Dirk? Gelukkig kennen we ook een andere kant van jou. Maar die hoort niet in dit boekje thuis. Nu jij nog Dirk, we veranderen de naam van onze appgroep pas als jij ook klaar bent met je promotie. Gelukkig heeft Marjolein zich al opgeworpen als jouw copromotor. Zo is ze.

Lieve schoonfamilie, lieve **Harry** en **Carola**, lieve **Sophie, Alexander** en **Pieter,** Jullie zijn de liefste en meest betrokken schoonfamilie die ik mij ooit had kunnen wensen. Met het missen van mijn eigen ouders, had dit gemis niet beter kunnen worden opgevuld.

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Lieve **Pieter,** altijd vroeg je hoe het ging met de promotie en luisterde je belangstellend naar de vorderingen of hobbels op de weg. Je bent een gezellige zwager en we delen veel interesses waardoor we over allerlei onderwerpen kunnen kletsen onder het genot van een speciaal biertje. Laten we dit altijd blijven doen. Dank je wel voor je steun en vriendschap.

Lieve **Harry** en **Carola,** ik weet nog goed de middag dat ik jullie voor het eerst ontmoette in café Lazy Louis in Amersfoort. Daar vertelde ik dat ik bezig was met mijn promotieonderzoek, en in de afrondende fase was. Die afrondende fase heeft nog wat jaren voortgeduurd maar nu kunnen jullie dan eindelijk het resultaat met mij vieren. Jullie warmte, gezelligheid en jullie aanwezigheid en steun op alle momenten in de breedste zin van het woord, zijn in geen woorden uit te drukken. Waar tref je schoonouders die precies weten wanneer je dienst hebt, een belangrijke vergadering of wanneer er extra brood of yoghurt moet worden meegegeven? Ik bof enorm met jullie, jullie zijn heel waardevol voor mij en het is dan ook een feit dat dit boekje er niet was geweest zonder jullie. Dank jullie wel.

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