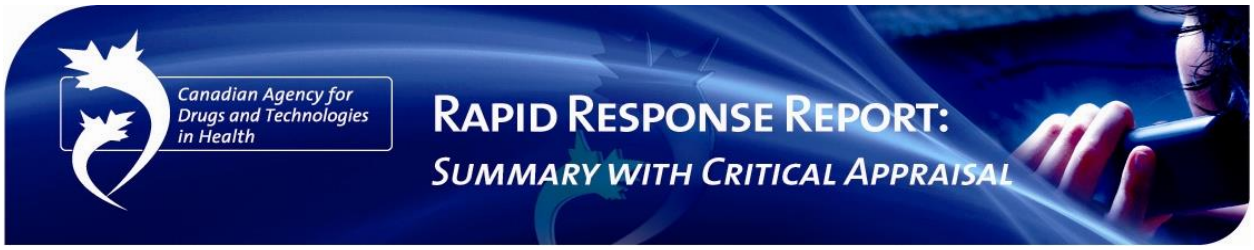

TITLE: Over-the-counter Nasal Products for Sinus Congestion: A Review of the Clinical Effectiveness

DATE: 11 May 2016

CONTEXT AND POLICY ISSUES

Sinonasal disease, which includes conditions such as chronic rhinosinusitis, allergic rhinitis, non-allergic rhinitis and upper respiratory tract infections or common cold, can result in significant morbidity.[1] It can impact the individuals daily activities and quality of life.[2] Allergic rhinitis is a global health problem and is estimated to affect 10% to 40% of the world's population.[3] In Canada, it is estimated that allergic rhinitis affects approximately 20% to 25% of the population.[2] The prevalence of chronic rhinosinusitis in Canada is estimated as 5%.[4] Rhinosinusitis is estimated to affect more than 31 million people in the United States each year.[5] Common cold infections are widespread and it is estimated that adults suffer from two to four episodes per year.[6] Treatment for sinonasal disease includes pharmacological therapies such as antihistamines, corticosteroids and decongestants as well as non-pharmacological therapies such as saline sprays, saline irrigation, and microemulsions.[5,7,8] The non-pharmacological treatments generally act by mucous clearance, removal of allergens and inflammatory mediators or reduction in the interaction between allergen and mucosa.[8-10] There is some uncertainty around optimal treatment strategies.

The purpose of this report is to review the clinical efficacy of over-the-counter non-pharmacological nasal products used to relieve sinus congestion associated with colds and allergies

RESEARCH QUESTION

What is the clinical effectiveness of over-the-counter nasal products to relieve sinus congestion associated with colds and allergies?

KEY FINDINGS

Evidence from two systematic reviews suggests that saline treatment is effective for patients with chronic rhinosinusitis. Evidence from one RCT and one observational study suggests that saline treatment is effective for patients with allergic rhinitis.

Saline treatment was compared with other non-pharmacological treatments (such as microemulsion, xylitol, carrageenan, and thermal water) in a variety of conditions (such as allergic rhinitis, non-allergic chronic rhinitis, and common cold) and generally findings suggested greater improvement with these other non-pharmacological treatments. However, for each comparison findings were derived from a single RCT, hence results need to be interpreted in the light of this.

METHODS

Literature Search Methods

A limited literature search was conducted on key resources including Ovid Medline, PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2011 and April 13, 2016.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adults with sinus congestion
Intervention	Over-the-counter nasal sprays, irrigation products, or lubricants (e.g. sodium chloride spray or rinse, polyethylene glycol gel, propylene glycol gel, sesame oil spray)
Comparator	No treatment Over-the counter nasal products compared with each other
Outcomes	Clinical effectiveness (e.g. reduced congestion), safety
Study Designs	Health technology assessments (HTA), systematic reviews (SR), meta-analyses (MA), randomized controlled trials (RCT), non-randomized studies, economic studies and evidence-based guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2011. Studies on patients undergoing or had undergone sinus surgery were excluded. Studies on pharmacological therapies, such decongestants, antihistamines or corticosteroids, were excluded. Studies on pediatric

populations or mixed populations (i.e. including both adult and pediatric population, with results not presented separately) were excluded. Studies on prior treatment followed by allergen challenge were excluded. Systematic reviews with all studies included in a more comprehensive systematic review were excluded. Systematic reviews included in an included systematic review were excluded.

Critical Appraisal of Individual Studies

The included systematic reviews were critically appraised using the AMSTAR checklist,[11] and randomized controlled studies and observational studies were critically appraised using the Downs and Black checklist,[12] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

SUMMARY OF EVIDENCE

Quantity of Research Available

A total of 545 citations were identified in the literature search. Following screening of titles and abstracts, 520 citations were excluded and 25 potentially relevant reports from the electronic search were retrieved for full-text review. No potentially relevant publications were retrieved from the grey literature search. Of these 25 potentially relevant articles, 14 publications were excluded for various reasons, while 11 publications met the inclusion criteria and were included in this report. These were comprised of three systematic reviews,[9,13,14] seven RCTs[5,7,8,10,15-17] and one observational study.[3] Appendix 1 describes the PRISMA flowchart of the study selection.

Summary of Study Characteristics

Characteristics of the included systematic review, RCTs and observational study are summarized below and details are available in Appendix 2, Table A1 and A2.

Systematic Reviews

Three systematic reviews[9,13,14] were identified. One systematic review[13] was published by Rudmik et al. in 2015 from Canada, one systematic review[9] was published by Wei et al. in 2013 from the United States of America (USA), and one systematic review[14] was published by Arroll in 2011 from New Zealand. All three systematic reviews examined various treatments; only information on those treatments relevant for this report were extracted and presented. Considering this, one systematic review[13] included three relevant systematic reviews published in 2007, 2013 and 2014; one systematic review[9] included seven relevant RCTs published between 2000 and 2007; and one systematic review[14] included one relevant systematic review published in 2009. Two systematic reviews[9,13] were on patients with chronic rhinosinusitis, and one systematic review[14] was on patients with the common cold. As already mentioned, all three systematic reviews examined various treatments and only those treatments satisfying the inclusion criteria are presented in this report. Two systematic reviews[9,13] included treatments with saline and one systematic review[14] included treatment with zinc gel. Treatment duration was reported in one systematic review[9] and varied between seven days and six months. Outcomes reported included symptom assessment,[9,13,14] quality of life assessment,[9,13] radiologic and endoscopic findings,[9] and adverse effects.[9,13,14]

Randomized controlled trials (RCTs)

Seven relevant double-blind RCTs[5,7,8,10,15-17] on adult patients were identified. Of these seven RCTs, two RCTs[8,10] were crossover studies. One RCT[7] by Valerieva et al. was published in 2015 from Bulgaria; one RCT[15] by Cingi et al. was published in 2014 from Turkey; one RCT[17] by Ludwig et al. was published in 2013 from Austria; two RCTs were published in 2012, one each by Chusakul et al.[10] from Thailand. and by Ottaviano et al.[16] from Italy; and two RCTs were published in 2011, one each by Ottaviano et al.[5] from Italy and by Andersson et al.[8] from Sweden.

Of these seven RCTs, three RCTs[7,8,10] were on allergic rhinitis, two RCTs[5,16] were on non-allergic chronic rhinitis, one RCT[17] was on the common cold and one RCT[15] was on nasal obstruction. The number of patients in the six RCTs[5,7,8,10,15-17] varied between 20 and 80, and in one RCT[17] it was 211. The proportion of females varied between 25% and 78% in six RCTs and was not reported in one RCT.[5] The mean or median ages were reported in four RCTs[7,10,15,17] and varied between 30 years and 37 years, and only age ranges were reported in three RCTs (19 years to 48 years in one RCT[8] and 18 years to 65 years in two RCTs[5,16]).

One RCT[10] compared irrigation with saline preparations of three different pH ranges, each performed twice daily for 10 days. One RCT[5] compared sulfurous, salty, bromic, iodic thermal water (SSBI) irrigation with saline (isotonic sodium chloride solution [ISCS]) irrigation, each performed four times a day for one month. One RCT[16] compared sulfurous-arsenical-ferruginos thermal water irrigation with saline irrigation, each performed once daily for one month. One RCT[17] compared carrageenan spray with saline spray, each administered thrice a day for seven days. One RCT[15] compared xylitol spray with saline spray, each administered twice daily for five days. One RCT[8] compared microemulsion spray with saline spray, each was administered twice daily for six days. One RCT[7] compared hydroxypropyl methylcellulose puff with lactose puff, each administered twice daily for seven days. Outcomes reported included symptom relief,[8,10] peak nasal inspiratory flow (PNIF),[7] quality of life (QoL),[7,15] cytologic findings,[5,16] endoscopic findings,[5,16] nasal patency,[5,16] disease duration,[17] and adverse effects.[5,7,8,10,15-17]

Observational study

One relevant prospective, before and after study[3] on allergic rhinitis was identified. It was published by Nguyen et al.[3] in 2014 from the USA. The study included 40 patients with a mean age of 38 years; the proportion of females was 73%. The patients were treated with low pressure saline irrigation performed twice a day for eight weeks. Outcomes reported included PNIF, QoL and adverse effects.

Summary of Critical Appraisal

Critical appraisal of the included systematic review, RCTs and observational studies is summarized below and details are available in Appendix 3, Tables A3 and A4.

Systematic Reviews

In all three included systematic reviews[9,13,14] the objectives were clearly stated, the inclusion criteria were stated, multiple databases were searched, and a list of included studies was provided. Lists of excluded studies were not provided in any of the three included systematic reviews. Details of the individual included studies were provided in one systematic review[9] but

were lacking in two systematic reviews[13,14] It should be noted that both these systematic reviews summarized the results of previous systematic reviews, hence did not include details of individual studies. The quality of evidence was graded in all three systematic reviews; in two systematic reviews[9,13] (on saline treatment), levels of evidence were assigned to the studies (details in Appendix 3, Table A3 and Appendix 4, Table A5) and in one systematic review[14] (on zinc gel) the evidence was stated as low quality. Article selection and data extraction appear to have been conducted in duplicate in one systematic review[13] but was unclear in two systematic reviews.[9,14] Publication bias does not appear to have been explored. Conflict of interest disclosures were provided in all three systematic reviews and potential for bias seemed unlikely in the two systematic reviews,[9,13] which included saline treatments and was difficult to judge for the one systematic review[14] which included treatment with zinc gel.

Randomized controlled trial

In all seven RCTs[5,7,8,10,15-17] objectives were clearly stated, the inclusion and exclusion criteria were provided and patient characteristics, interventions and outcomes were described. However, details of patient characteristics were generally sparse. All the RCTs were double blinded. In six RCTs[5,7,10,15-17] the patients and investigators were blinded and in one RCT[8] details of blinding were not stated. Randomization details were provided in four RCTs[5,7,16,17] and appeared to be appropriate. Details were not provided in three RCTs.[8,10,15] There were no drop-outs in one RCT[10] comparing different saline preparations, and low dropout rates in two RCTs,[15,17] comparing saline with either xylitol or carrageenan. The dropout rate was 26% in one RCT[16] and it was unclear if the dropout rates were similar in the two treatment groups (thermal water or saline). In one RCT[5] the drop-out rate was dissimilar in the two groups (12% in the SSBI group and 22% in the ISCS group). It was unclear if there were any dropouts in one RCT[8] comparing saline with microemulsion. In one RCT[7] the drop-out rate was 10% and similar in both HPMC and lactose groups. Sample size determinations were mentioned in three RCTs[7,15,17] and not in four RCTs.[5,8,10,16] Generalizability of the findings was limited as the RCTs had strict inclusion and exclusion criteria, were conducted or appeared to be conducted at single centers and sample size was generally small (patient numbers mostly ranging between 20 and 80). In two RCTs[8,15] conflict of interest was not mentioned, in two RCTs[7,10] the authors stated there was no conflict of interest, in two RCTs[5,16] one of the investigators was associated with the product manufacturer, and in one RCT[17] the potential for bias was difficult to judge from the conflict of interest disclosure.

Observational study

In this observational study[3] objectives were clearly stated, inclusion and exclusion criteria, patient characteristics, interventions and outcomes were described. It was a prospective study and there were no dropouts. A sample size calculation was not conducted as it was a pilot study. There was no comparator arm. Generalizability was limited to the study population at a single center.

Summary of Findings

<u>*What is the clinical effectiveness* of over-the-counter nasal products to relieve sinus congestion associated with colds and allergies*?*</u>

Findings are summarized below and details are provided in Appendix 4, Tables A5 and A6.

Systematic Review

Three relevant systematic reviews[9,13,14] were identified. Of these three systematic reviews, two systematic reviews[9,13] had information on treatments with saline and one systematic review[14] contained information on treatment with zinc gel

Saline:
The systematic review by Rudmik et al.[13] on the management of patients with chronic rhinosinusitis included three systematic reviews; of which one systematic review included eight studies, one systematic review included seven studies and one systematic review included one study. It reported that, compared with no treatment, saline irrigation statistically significantly improved symptom scores (standardized mean difference [SMD] was 1.42 and 95% confidence interval [CI] 1.01 to 1.84; a positive SMD indicates improvement). Further it reported that high volume (> 240 mL) saline irrigation resulted in better effects than low volume saline irrigation. Potential adverse effects included nasal burning, ear plugging, nausea, and bacterial contamination from the irrigation bottle, but the frequency of these events was not described. It concluded that the benefits associated with saline irrigation outweighed the associated cost and potential harms.

The systematic review by Wei et al.[9] on the management of patients with chronic rhinosinusitis included seven RCTs that were relevant for our report. It reported results narratively for each individual RCT. One RCT found that compared to no irrigation, saline irrigation resulted in statistically significant improvement in rhinosinusitis disability index (RSDI) scores. However, there was no statistically significant improvement in short form 12 (SF-12) scores between the two groups. One RCT showed that compared to cetirizine (anti-histamine) alone, cetirizine plus saline spray resulted in statistically significant reduction in rhinasthma score. One RCT showed that hypertonic saline resulted in statistically significant reduction in quality of life as assessed by the rhinoconjunctivitis quality of life questionnaire (RQLQ) but no statistically significant reduction was observed with normal saline. One RCT showed that normal saline improved nasal airway patency and hypertonic saline did not and that both hypertonic saline and normal saline improved saccharine clearance times. Also, compared to normal saline, hypertonic saline resulted in statistically significant increased nasal burning. One RCT showed that compared to saline spray, large volume isotonic saline irrigation resulted in statistically significant improvement in sino-nasal outcome test 20 (SNOT-20) scores. One RCT found that for treatments with normal saline irrigation using either bulb syringe or pot, there were significant reductions in rhinosinusitis outcome measure 31 (RSOM31). There was no significant difference between the two treatment modalities. One RCT showed that both Ems salt solution and normal saline significantly improved symptom, endoscopic and radiologic scores and there was no significant difference between the two treatments. The methods of administering saline treatments and the types of outcomes reported, varied across the studies; overall this systematic review suggested that saline treatment was beneficial.

Zinc gel:
One systematic review by Arroll et al.[14] on the management of patients with the common cold included one systematic review with three RCTs, that was relevant for our report. It found that with zinc gel treatment fewer patients had symptoms persisting on day 3, compared to placebo treatment (relative risk [RR] 0.63, 95% CI 0.56 to 0.70). The RCTs included in the systematic review were heterogeneous, I^2 = 99.2%. This systematic review presented harms data from 10 case reports. These 10 patients who had been treated with intranasal zinc had severe nose burning followed by severe hypsomia with parosomia or anosomia.

Randomized controlled trials (RCTs)

Seven relevant RCTs[5,7,8,10,15-17] on adult patients were identified. Of these seven RCTs, three RCTs[7,8,10] were on allergic rhinitis, two RCTs[5,16] were on non-allergic chronic rhinitis, one RCT[17] was on common cold and one RCT[15] was on nasal obstruction and hypertrophied turbinate mucosa.

Comparison of different saline preparations:

One crossover RCT[10] by Chusakul et al. showed that there was a decrease in overall nasal symptoms for treatment by irrigation with each of the three saline preparations used (saline [pH 6.2 to 6.4], saline [pH 7.2 to 7.4] and saline [pH 8.2 to 8.4]) but this was only statistically significant for saline (pH 7.2 to 7.4). There was no statistically significant difference in outcomes between the different types. Patient preference was significantly greater with buffered saline (pH 7.2 to 7.4) compared to the other two saline preparations, (P = 0.02). There was no significant difference in adverse effects between the three treatments.

Comparison of thermal water and saline:

Two RCTs[5,16] compared nasal irrigation with either thermal water or saline. One RCT[16] by Ottaviano et al. compared sulfurous-arsenical-ferruginous thermal water (T) with saline (C) in smokers with non-allergic chronic rhinitis. It showed that the T group had statistically greater reduction in nasal resistance at both the 1 and 3 months follow up compared to the C group (P = 0.001 and 0.0003 respectively). Also, nasal endoscopic findings showed statistically significantly greater improvement in the clinical picture in the T group compared to the C group (P = 0.03). Endoscopic finding were categorized into four classes: 0 for no anatomical alterations or acute inflammation; 1 for septal deviation; 2 for hypertrophic inferior turbinates; and 3 for acute rhinosinusitis. No local side effects attributable to the use of the thermal water were recorded. The other RCT[5] by Ottaviano et al. SSBI with (ISCS in patients with non-allergic chronic rhinosinusitis. It showed that compared to baseline, there was a statistically significant improvement in endoscopic clinical features with both the SSBI and ISCS treatments (P = 0.005 for SSBI and 0.01 with ISCS). Nasal resistance, as assessed by active anterior rhinomanometry, appeared to improve in both the treatment groups compared to baseline values and the difference was statistically significant in the SSBI group (P = 0.01) but did not achieve statistical significance in the ISCS group (P = 0.25). Adverse events that may be related to the nasal irrigation treatment were recorded only in the SSBI treatment group; six patients reported mild nasal irritation and local burning sensation and five patients reported extremely limited epistaxis.

Comparison of saline and carrageenan:

One RCT[17] by Ludwig et al. demonstrated that in patients with the common cold, the improvement in symptoms was 2.1 days faster in the carrageenan treated group compared to the saline (placebo) treated group (P = 0.037). The viral titre was statistically significantly reduced with carrageenan treatment compared with the saline treatment (P = 0.024). It was stated that both treatments were well tolerated and that there were no statistically significant differences in number or distribution of AEs between the treatment groups.

Comparison of saline and xylitol:

One RCT[15] by Cingi et al. on adults with nasal obstruction and hypertrophied turbinate mucosa, found greater improvement in congestion with xylitol treatment compared to saline treatment but the difference was not statistically significant ($P > 0.05$). Quality of life as assessed using the visual analog scale (VAS) did not appear to be statistically significantly different between pre-treatment and post-treatment for both treatments ($P = 0.098$ for xylitol and 0.447 for saline). Improvement in quality of life as assessed using the RQLQ was statistically significant post-treatment compared to pre-treatment for xylitol ($P = 0.001$) but did not achieve statistical significance for saline ($P > 0.05$). No serious adverse effects were reported in any of the treatment groups.

Comparison of saline and microemulsion:

One crossover RCT[8] by Andersson et al. showed that in patients with perennial allergic rhinitis to house dust mites, there was a statistically significant improvement in nasal scores for treatment with microemulsion (comprised of polyethylene glycol, sesame oil and other substances) compared with treatment with saline ($P < 0.01$). No side effects were reported during the study period.

Comparison of HPMC and lactose (placebo):

One RCT[7] by Valerieva et al. showed that in patients with a history of persistent, moderate-to-severe allergic rhinitis, there was no statistically significant difference in PNIF between the HPMC and placebo groups on days 1 and 8, however the PNIF was 26% greater with HPMC compared with placebo on day 15 ($P = 0.014$). Total symptoms, as assessed by VAS, were statistically significantly reduced in both groups compared to baseline (38% [$P = 0.002$] with HPMC and 42% [$P < 0.001$] with placebo) however there was no statistically significant difference between the two groups. The median number of times the patients had to resort to rescue medication during days 8 to 15, when the study products were no longer used were numerically lower in the HPMC group than in the placebo group, but the difference between the groups was not statistically significant (8.5 for HPMC and 16 for placebo, $P = 0.076$). Adverse events were mild and infrequent and were not considered to be related to the products.

Observational study

One prospective, before and after, observational study[3] by Nguyen et al. showed that in patients with allergic rhinitis, treatment with saline irrigation resulted in statistically significant reduction mRQLQ scores, indicating improvement, (mean ± standard deviation: 36.7 ± 20.48 at baseline and 10.1 ± 10.6 at 8 weeks post treatment, $P < 0.001$). However, PNIF values at baseline and post treatment were not statistically significantly different. No adverse events were reported.

Limitations

The systematic reviews examined a broad range of treatments (many of which were not relevant for our report), hence the information on individual treatments were not detailed.

Comparison across studies was difficult as the disease condition of the patients varied, and also interventions and comparators varied. Also, not all studies reported the same outcomes. Furthermore, different methods were used to assess symptom improvement and QoL.

Many of the RCTs included in the systematic review by Wei et al.[9] were also included in one of the systematic reviews included in the systematic review by Rudmik et al.[13] As there was overlap in the studies included in the two systematic reviews, hence the findings of these two systematic reviews are not mutually exclusive. There were some inconsistencies in levels of evidence assigned to individual RCTs in these two systematic reviews. As sufficient details of the appraisals were not reported, it was not possible to determine the reason for these discrepancies.

Saline treatment was compared with a variety of different non-pharmacological treatments (such as microemulsion, xylitol, carrageenan, and thermal water). However, for each comparison findings were derived from a single RCT, hence results need to be interpreted in the light of this.

Though adverse effects generally appear to be similar in the various treatment groups compared, it should be noted that the incidence of adverse events was generally low with the treatments reviewed in this report and the studies did not have sufficient power to detect such small differences in adverse effects between the treatments.

None of the included RCTs and observational study was conducted in Canada. The included systematic reviews did not have details on the settings of the included studies so it was unclear if any of the studies were conducted in Canada. As such it is unclear to what extent the findings may be generalized to the Canadian context.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Eleven relevant articles were identified. These were comprised of three systematic reviews,[9,13,14] seven RCTs[5,7,8,10,15-17] and one prospective, before and after observational study.[3]

Two systematic reviews found that compared with no treatment, saline irrigation treatments resulted in improvement in patients with chronic rhinosinusitis. One RCT and one observational study also found saline irrigation treatments to be effective for patients with allergic rhinitis. Saline treatment was also compared with other non-pharmacological treatments (such as microemulsion, xylitol, carrageenan, and thermal water) in a variety of conditions (such as allergic rhinitis, non-allergic chronic rhinitis, and common cold) and generally findings suggest that these non-pharmacological treatments may be more effective than saline. However, findings for each comparison were from single RCTs, and the majority of the RCTs were of short term (5 to 7 days) or small sample size (20 to 80 patients). Hence results need to be interpreted with caution. Generalizability of these findings is limited as these were single center studies pertaining to a specific patient condition.

After the literature search was completed and during the preparation of this report, a systematic review, by Chong et al.[18] on saline irrigation for chronic rhinosinusitis, was published and hence is not included in this report. This recent systematic review included two studies of which one study (Rabago et al.) was relevant for our report. This recent systematic review found that irrigation with large volume hypertonic saline had some benefit compared with placebo, but the quality of evidence was judged to be low for three months and very low for six months of treatment. The findings are not inconsistent with our findings. This study (Rabago et al.) was included in the included systematic review in our report but this recent systematic review by Chong et al.[18] contains some additional details about the study.

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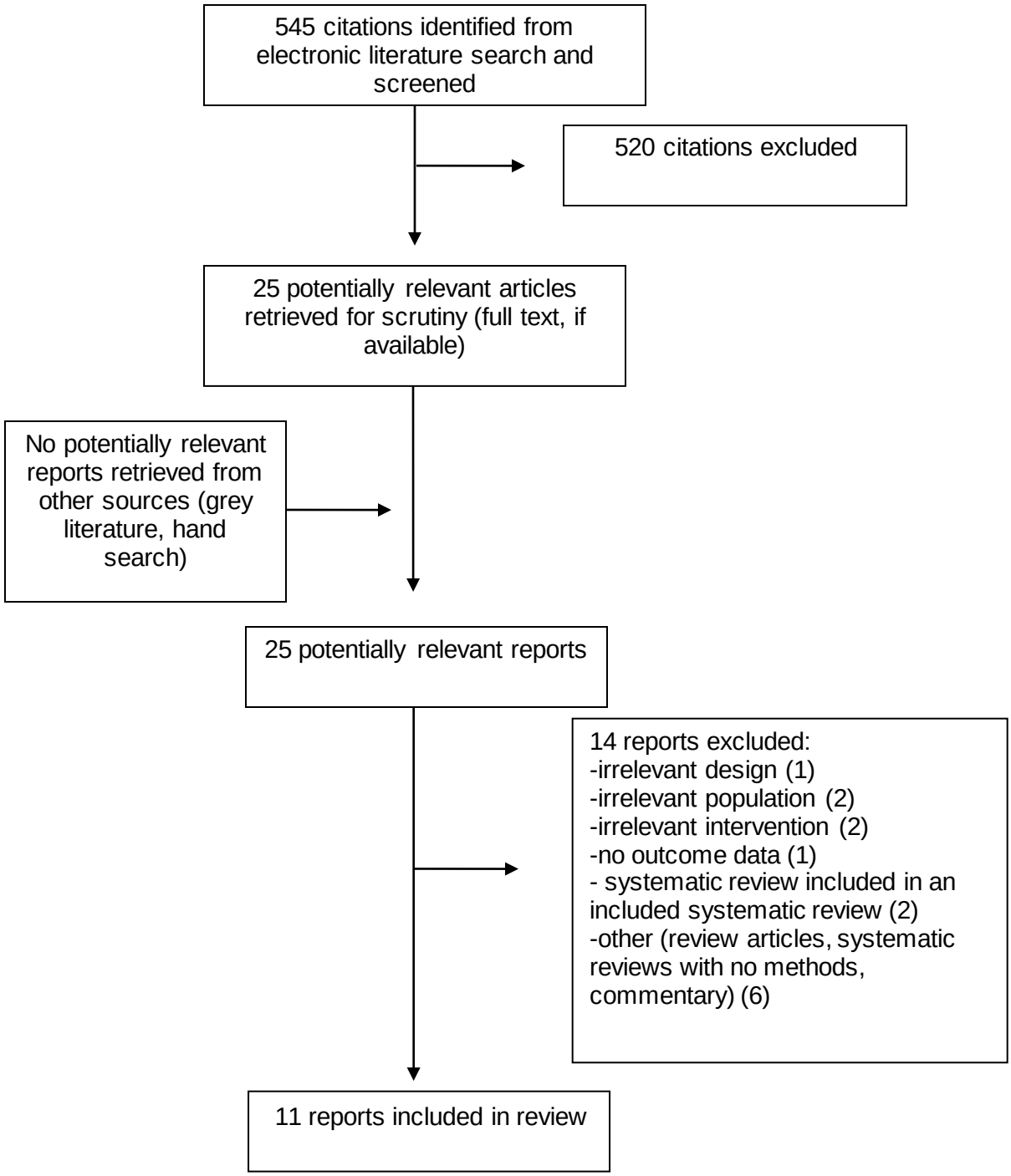
ABBREVIATIONS

4 PR	4-phase rhinomanometry
AAR	active anterior rhinomanometry
AE	adverse events
CI	confidence interval
cm	centimeter
DB	double-blind
g	gram
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HPMC	hydroxypropyl-methylcllulose
HSS	hyperchromatic supranuclear stria
ISCS	isotonic sodium chloride solution
L	liter
MA	meta-analysis
MCA	minimal cross section area
MCCT	mucociliary clearance time
mRQLQ	mini rhinoconjunctivitis quality of life questionnaire
NA	not applicable
NPIF	nasal peak inspiratory flow (same as PNIF = peak nasal inspiratory flow)
NR	not reported
NS	not significant
Pa	Pascal (unit for measuring pressure)
QoL	quality of life
RCT	randomized controlled trial
RQLQ	rhinoconjunctivitis quality of life questionnaire
RR	relative risk
RSDI	rhinosinusitis disability index
RSOM31	rhinosinusitis outcome measure 31
SB	single blind
SD	standard deviation
SE	standard error
SF-12	mMedical outcome survey short form (general health assessment)
SMD	standardized mean difference
SNOT-20	sino-nasal outcome test 20
SR	systematic review
SSBI	sulfurous, salty, bromic, iodic thermal water
TNSS	total nasal symptom score
USA	United States of America
VAS	visual analog scale
vs	versus

APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Publications

Table A1: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Types and numbers of primary studies included[a]	Population Characteristics[a]	Comparisons[a]	Clinical Outcomes
Arroll,[14] 2011, New Zealand	1 SR with 3 RCTs including 451 patients. Objective: To determine the effects of treatments for common cold	Adults with common cold	Zinc gel vs placebo	Symptoms
Rudmik,[13] 2015, Canada	2 SRs and 1 MA (1 SR with 7 RCTs, 1 SR with 1 RCT and 1 MA with 8 RCTs including 399 patients) for saline irrigation Objective: To determine the effect of therapies for adult chronic sinusitis	Adult with chronic rhinosinusitis	Saline vs placebo or no treatment; Isotonic saline vs hypertonic saline; High volume vs low volume saline irrigations	Symptom, QoL; AE
Wei,[9] 2013, USA	10 RCTs (7 on adults, 2 on children and 1 unclear if adults) for topical nasal saline treatment Objective: To determine the effect of topical nasal therapies for chronic rhinosinusitis	Chronic rhinosinusitis (majority of RCTs were on adults)	Saline vs control or no treatment; Isotonic saline vs hypertonic saline; Saline irrigation using different administration methods (bulb syringe vs pot)	Symptom, QoL, radiologic and endoscopic findings; AE

[a]It should be noted that the systematic reviews had a broad objective and included various treatments or populations, and only information relevant for this report is presented here.
AE = adverse events, MA = meta-analysis, QoL = quality of life, RCT = randomized controlled trial, SR = systematic review , vs = versus

Table A2: Characteristics of Included Clinical Studies

First Author, Publication Year, Country, Study Name	Study Design	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes
Randomized controlled trials					
Andersson,[8] 2011, Sweden	RCT (DB, 3-arm, cross-over, 1 week washout period, treatment period 6 days) (on-going treatment for allergic rhinitis was withdrawn 2 weeks prior to initiation of present study)	Adults with perennial allergic rhinitis (with respect to house dust mite) N = 20 Age (range) (years): 19 to 48 Female: 5	Microemulsion spray (a mixture of glycerol-monooleate, propylene-glycol, polyethylene-glycol 400, sesame oil, polysorbate-80 and isotonic saline) (50 µL per actuation, twice daily for 6 days)	Saline spray (50 µL per actuation, twice daily for 6 days)	Symptom score (TNSS), side effects
Chusakul,[10] 2012, Thailand	RCT (DB, 3-arm, cross-over, 5 days washout period, treatment period 10 days)	Adults with allergic rhinitis N = 36, (no drop outs) Age (median, [range]) (years): 37 [18 to 59] Female = 28	Irrigation with non-buffered saline (pH 6.2 to 6.4 (240 mL , twice daily for 10 days)	Irrigation with two types of buffered saline (pH 7.2 to 7.4) and (pH 8.2 to 8.4) (240 mL , twice daily for 10 days)	Symptom changes, patients' preference. AE
Cingi,[15] 2014, Turkey	RCT (DB, 3 arm study but only 2 arms relevant for this review; study period was 5 days)	Adults with nasal obstruction and hypertrophied turbinate mucosa that was refractory to medical treatment N = 42 (14 in each group; had initially started with 15 in each group)	Xylitol (twice daily for 5 days)	Physiological saline (twice daily for 5 days)	VAS, 4 PR, RQLQ. AE

Table A2: Characteristics of Included Clinical Studies

First Author, Publication Year, Country, Study Name	Study Design	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes
		Age: (mean [range]) (years); 30.25 [18 to 42] Female/ male: 24/ 18			
Ludwig,[17] 2013, Austria	RCT (single center, DB, treatment period 7 days, follow up till 28 days)	Adults with common cold N = 211 Age (mean ± SD) (years): 33.7 ± 12.9 in C, 33.3 ± 12.9 in S Female/Male: 50%/50% in C, 51%/49% in S	Carrageenan nasal spray (Coldamaris: containing 0.12% carrageenan) (Group C) 3 times daily into each nostril for 7 days	Saline (9.0 g/L sodium chloride) nasal spray (placebo) (Group S) 3 times daily into each nostril for 7 days	Disease duration, viral titre; AE
Ottaviano,[16] 2012, Italy	RCT (single center, DB, treatment period of 1 month, total follow-up = 3 month i.e. 2 additional month after treatment was stopped)	Adult smokers with non-allergic chronic rhinitis (cigarette smoking habit ≥5 years) N = 70 consecutive patients (35 in each group) (62 attended first FU at 1 month and 52 attended second FU at 2 months) Age(range) (years): 18 to 65 Female/ male: 24/ 11 in treatment group and in control group	Irrigaqtion with sulfurous-arsenical-ferruginos thermal water from Levico Spa, Italy (Study group: T) (20 mL per day for 1 month)	Irrigation with isotonic saline (Control group: C) (20 mL per day for 1 month)	Nasal cytology, nasal patency, endoscopic findings; AE

Table A2: Characteristics of Included Clinical Studies

First Author, Publication Year, Country, Study Name	Study Design	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes
Ottaviano,[5] 2011, Italy	RCT (DB, treatment period of 1 month)	Adults with nonallergic chronic rhinosinusitis N = 80 consecutive patients (40 in each group) Age(range) (years): 18 to 65 Female/ male: NR	Irrigation with sulfurous, salty, bromic, iodic thermal water (SSBI) (from Sirmione Spa, Italy) (5 mL , 4 times a day for 1 month)	Irrigation with isotonic sodium chloride solution (ISCS) (5 mL , 4 times a day for 1 month)	Endoscopic, cytological and microbiologcal findings, nasal patency or resistance; AE
Valerieva,[7] 2015, Bulgaria	RCT (single center, DB, treatment period 7 days, follow up till 15 days) The study was conducted outside the pollen season	Adults with clinical history of persistent moderate-to-severe allergic rhinitis N = 40 (20 in each treatment group) Age (mean [range]) (years): 35 (18 to 49) Female/Male: 23/17	Hydroxypropyl-methylcellulose (HPMC) puff Oxymetazoline puff is administered prior to HPMC. Twice daily for 7 days Oxymetazoline puffs were allowed as rescue medication between day 8 and 15	Lactose powder (placebo) puff Oxymetazoline puff is administered prior to lactose. Twice daily for 7 days Oxymetazoline puffs were allowed as rescue medication between day 8 and 15	PNIF (also known as NPIF), QoL (VAS); AE
Observational study					
Nguyen,[3] 2014, USA	Observational study (Prospective, unblended, single arm, before and after study)	Adults with allergic rhinitis N= 40 Age (mean [range]) (years): 38 (21 to 71) Female/ Male: 29/11	Low pressure nasal irrigation with isotonic saline. Performed twice a day for 8 weeks (Patients had received nasal steroids for 1 month and had	No comparator	QoL (mRQLQ), NPIF (also known as PNIF); AE

Table A2: Characteristics of Included Clinical Studies					
First Author, Publication Year, Country, Study Name	**Study Design**	**Patient Characteristics**	**Intervention(s)**	**Comparator(s)**	**Clinical Outcomes**
			remained symptomatic. Patients continued on the nasal steroids during the study		

4 PR = 4-phase rhinomanometry, AE = adverse effects, DB = double-blind, ISCS = isotonic sodium chloride solution, NR = not reported, mRQLQ = mini RQLQ, NPIF = nasal peak inspiratory flow (also called PNIF = peak nasal inspiratory flow), RCT = randomized controlled trial, RQLQ = Rhinoconjunctivitis quality of life questionnaire, SSBI = sulfurous, salty, bromic, iodic thermal water, TNSS = total nasal symptom score, VAS = visual analog scale

APPENDIX 3: Critical Appraisal of Included Publications

Table A3: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR checklist[11]

Strengths	Limitations
Arroll,[14] 2011, New Zealand	
• The objective was clearly stated. • The inclusion and exclusion criteria were stated. • Multiple databases were searched, 1966 to January 2010. Harm alerts from organizations such as US FDA and UK MHRA were examined. • List of included studies was provided • Evidence was graded using the GRADE evaluation system; quality of evidence was stated to be low, details of the grading were not provided. • The author declared conflict of interest. He is associated with Pharmac (government organization), and an educational foundation (funded by industry), and is author of some of the included studies	• List of excluded studies was not provided • Study selection description lacked details and no flow chart was presented • Details of the included studies in the included systematic reviews were lacking. • Unclear if article selection and data extraction was conducted in duplicate • Publication bias does not appear to have been explored
Rudmik,[13] 2015, Canada	
• The objective was clearly stated. • The inclusion and exclusion criteria were stated. • Multiple databases were searched, 1947 to November 2015. Also reference list of the relevant articles were manually searched. • Study selection was described but no flow chart was presented • List of included studies was provided • Evidence was graded using the American Heart Association grading system. The overall evidence was graded as A-1, "which indicates there is evidence and/or general agreement that a given treatment is useful and effective; data derived from multiple randomized clinical trials (RCTs)" Page 930. However, the level of evidence of each included study varied. It was determined using the evidence scale from the Oxford Centre for Evidence-based Medicine[19] and varied between 1a and 2b (details in Appendix 4 Table A5) • Two reviewers independently reviewed the studies, examined bias and graded the evidence. • The authors provided disclosures and conflict of interest appears unlikely	• List of excluded studies was not provided • Details of the included studies in the included systematic reviews were lacking. • Details of the meta-analyses were lacking • Publication bias does not appear to have been explored

Table A3: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR checklist[11]

Strengths	Limitations
Wei,[9] 2013, USA	
• The objective was clearly stated. • The inclusion criteria were stated. • Multiple databases were searched, 1966 to May 2012 • List of included studies was provided • Characteristics of the individual studies were provided. • Individual study outcomes were described narratively • Quality of evidence was assessed based on the Oxford Center for Evidence-Based Medicine levels. The evidence was judged to be of level 1b (details in Appendix 4 Table A5) • Conflict of interest was declared. One of the three authors was associated with industry. It was stated that the authors had no other funding, financial relationships, or conflicts of interest to declare	• The exclusion criteria were not explicitly stated. • List of excluded studies was not provided • Study selection description lacked details and no flow chart was presented • List of excluded studies was not provided • Unclear if article selection and data extraction was conducted in duplicate • Publication bias does not appear to have been explored

Table A4: Strengths and Limitations of Randomized Controlled Trials and Observational Studies using Downs and Black Checklist[12]

Strengths	Limitations
Randomized controlled trials (RCTs)	
Andersson,[8] 2011, Sweden	
• Objectives were clearly stated. • Inclusion and exclusion criteria were stated • Patient characteristics were described though not in detail. Interventions and outcomes were described. Crossover trial so patient variation between groups was eliminated. • Randomized and double-blinded (details not provided). • *P*-values were provided • Conflict of interest disclosures were not provided	• Unclear if 1 week washout period is sufficient. • Sample size calculation was not provided. • Unclear if there were any dropouts • Generalizability limited to the study population (N = 20 patients with perennial allergic rhinitis with respect to house dust mites in Sweden
Chusakul,[10] 2012, Thailand	
• Objectives were clearly stated. • Inclusion and exclusion criteria were stated • Patient characteristics were described though not in detail. Interventions and outcomes were described. Crossover trial so patient variation between groups was eliminated. • Randomized (details not provided). Double-blind, both patient and investigators were blinded • There were no dropouts	• Unclear if 5 days washout period is sufficient. • Sample size calculation was not provided • Generalizability limited to the study population (N = 36 patients with allergic rhinitis in Thailand

Table A4: Strengths and Limitations of Randomized Controlled Trials and Observational Studies using Downs and Black Checklist[12]	
• *P*-values were provided • The authors stated that there was no conflict of interest.	
Cingi,[15] 2014, Turkey	
• Objectives were clearly stated. • Inclusion and exclusion criteria were stated • Sample size calculation was conducted • Patient characteristics were described but not separately for the individual treatment groups. Interventions and outcomes were described. • Randomized (details not provided). Both patient and investigators were blinded • In each group 1 of the 15 patients did not complete the study as had stopped taking the medication; 14 in each group completed the study. • *P*-values were provided • Conflict of interest disclosures were not provided	• Generalizability limited to the study population (N = 42 patients with nonallergic rhinitis and with inferior turbinate hypertrophy in Turkey
Ludwig,[17] 2013, Bulgaria	
• Objectives were clearly stated. • Inclusion and exclusion criteria were stated • Sample size calculation was conducted • Patient characteristic, interventions and outcomes were described • Randomized (schedule using random permuted blocks, prepared by a third party). Both patient and investigators were blinded. Both sprays were indistinguishable. • Lost to flow up was low (about 2% in group) • *P*-values were provided • Conflict of interest was disclosed and investigators were associated with industry. The association, if any, between this industry and the manufacturer of the treatment modality was unclear	• Generalizability limited to the study population (N = 211 patients with common cold; study conducted at a single center in Austria
Ottaviano,[16] 2012, Italy	
• Objectives were clearly stated. • Inclusion and exclusion criteria were stated • Patient characteristics were described but not always separately for the individual treatment groups. Interventions and outcomes were described. • Randomized (schedule computer generated). Stated to be double blind, both treatments were indistinguishable by patients and investigators. • Completion rates for both groups together were	• Sample size calculation was not provided • Generalizability limited to the study population (N = 70 smokers with non-allergic chronic rhinitis; study conducted at a tertiary academic referral center in Italy

Table A4: Strengths and Limitations of Randomized Controlled Trials and Observational Studies using Downs and Black Checklist[12]

reported but not for the each group separately. First follow up attended by 89% and second follow up attended by 74% • *P*-values were provided • Conflict of interest was disclosed. Of the seven authors one author was a member of the scientific committee of Levico Spa (from where the thermal water was obtained)	
Ottaviano,[5] 2011, Italy	
• Objectives were clearly stated. • Inclusion and exclusion criteria were stated • Patient characteristics were sparsely described and not separately for the individual treatment groups. Interventions and outcomes were described. • Randomized (schedule computer generated). Stated to be double blind; the containers containing the two treatments were identical and indistinguishable by patients and investigators • Completion rates were reported. The number and percentage of patients completing the study were 35 (88%) in the SSBI group and 31 (78%) in the ISCS group. • *P*-values were provided • Conflict of interest was disclosed. Of the seven authors one author was a member of the scientific committee of Sirmione Spa (from where the thermal water was obtained)	• Sample size calculation was not provided • Generalizability limited to the study population (N = 80 patients with non-allergic chronic rhinosinusitis in Italy
Valerieva,[7] 2015, Bulgaria	
• Objectives were clearly stated. • Inclusion and exclusion criteria were stated • Sample size calculation was conducted • Patient characteristics were described but not always separately for the individual treatment groups. Interventions and outcomes were described. • Randomized (sequence computer generated). Stated to be double blind; the containers containing the two treatments were identical and indistinguishable by patients and investigators • Drop-out rates were similar in both groups (10%) • *P*-values were provided • The authors stated there was no conflict of interest to declare	• Generalizability limited to the study population (N = 40 patients with allergic rhinitis; study conducted at a single center in Bulgaria)

Table A4: Strengths and Limitations of Randomized Controlled Trials and Observational Studies using Downs and Black Checklist[12]	
Observational study	
Nguyen,[3] 2014, USA	
• Objectives were clearly stated. • Inclusion and exclusion criteria were stated • Patient characteristic, interventions and outcomes were described. • Prospective study but not randomized • No drop-outs • *P*-values were provided • The authors stated that there was no conflict of interest to declare.	• Sample size calculation was not conducted as it was a pilot study. • Non-randomized and no comparator arm. • Generalizability limited to the study population (N = 40 patients with allergic chronic rhiniitis at aa Medical University Sinus Clinic in USA

APPENDIX 4: Main Study Findings and Author's Conclusions

Table A5: Summary of Findings of the Systematic Review

Main Study Findings and Author's Conclusions
Arroll,[14] 2011, New Zealand
Main Findings: Findings of the SR ***Efficacy*** Analyses of 3 included RCTs with 451 patients on zinc gel compared to placebo: Percentage of patients with symptoms persisting on day 3: 60% of patients treated with zinc intranasal gel and 95% of patients treated with placebo RR 0.63, 95% CI 0.56 to 0.70 (statistically significantly better effect with zinc gel compared with placebo). Heterogeneity, I^2 = 99.2% Of the 3 RCTs, 2 RCTs had used high dose zinc whereas 1 RCT used low dose zinc. Of the 3 RCTs, 2 RCTs only included patients with symptoms for <24 hours, whereas 1 RCT included only patients with symptoms for 24 to 48 hours. ***Adverse effects*** In the SR, 1 included RCT with 78 patients reported on adverse effects. Overall adverse effects were 23% with zinc and 8% with placebo. Stinging or burning sensations were reported by 13% in the zinc group compared with 5% in the placebo group. The SR also mentioned 10 case reports of permanent anosmia with intranasal zinc gluconate. These 10 adult patients had immediate severe burning of the nose followed by severe hyposomia with parosmia or anosmia. **Authors' Conclusions:** "We don't know whether zinc gel or lozenges, Echinacea, steam inhalation, or analgesics or anti-inflammatory drugs reduce the duration of symptoms of colds." Page 1
Rudmik,[13] 2015, Canada
Main Findings: Findings were derived from 2 SRs and 1 SR with MA: I SR (published by Rudmik et al. in 2013) included 7 studies (level of evidence: 1a in one study, 1b in one study and 2b in five studies). It found that in patients with chronic sinusitis the benefits associated with saline irrigation outweighed the associated cost and potential harms. It recommended the use of saline irrigation as an adjunct to treatment with intranasal steroid. I SR (published by van den Berg et al. in 2014) included 1 RCT (level of evidence: 1b). It found that high volume (> 240 mL) saline irrigation was better than low volume saline irrigation, for patients with chronic sinusitis I SR (published by Harvey et al. in 2007) included 8 RCTs (level of evidence: 1b) and conducted MA. It found that for patients with chronic sinusitis, the symptom scores improved statistically significantly with saline irrigation compared with no treatment. SMD = 1.42, 95% CI = 1.01 to 1.84; a positive SMD indicates improvement. Compared to intranasal steroid treatment, saline irrigation was statistically significantly less effective, SMD = -3.29 and 95% CI = -5.51 to -1.06; a negative SMD indicates less efficacy. (Levels of evidence scale was from the Oxford Centre for Evidence-based Medicine. 1a indicates evidence from systematic review (with homogeneity) of RCTs 1b indicates evidence from individual RCT with narrow confidence interval 2b indicates evidence from individual cohort study including low quality RCT)[19]

Table A5: Summary of Findings of the Systematic Review

Authors' Conclusions:

"In summary, an A-I grade and recommendation supports using sinonasal saline irrigation as an adjunctive therapy to intranasal corticosteroids for patients with and without nasal polyps. Isotonic and hypertonic saline irrigations provide similar symptom improvement. High-volume (>100 mL) saline irrigation is superior to low volume nasal saline spray techniques." Page 928

Wei,[9] 2013, USA

Main Findings:

Findings from the SR on chronic rhinosinusitis which included 7 RCTs for topical nasal saline treatment in adults (relevant for our report)

Study; first author, publication year	No. of patients	Treatment duration	Level of evidence[a]	Conclusion
RCT, DB; Bachmann, 2000	40	7 days	1b	Compared to baseline values, both isotonic Ems salt solution and normal saline significantly improved symptom, endoscopic and radiologic scores. No significant difference between the two groups.
RCT; Heatley, 2001	150	2 weeks	1b	Both groups treated with normal saline irrigation using either bulb syringe or pot, showed significant reduction in RSOM31. There was no significant difference between the two treatment methods.
RCT; Rabago, 2002	76	6 months	1b	Compared to no irrigation, saline irrigation resulted in statistically significant improvement in RSDI scores. There was no statistically significant improvement in SF-12 scores
RCT, SB; Codray, 2005	15	7 days	1b	Hypertonic saline resulted in statistically significant reductions in RQLQ. No statistically significant reductions were observed with normal saline.
RCT; Rogkakou, 2005	14	4 weeks	1b	Compared to cetirizine alone, cetirizine with saline spray resulted in statistically significant reduction in rhinasthma score.
RCT; Pynnonen, 2007	127	8 weeks	1b	Compared to saline spray, large volume isotonic saline irrigation resulted in statistically significant improvement in SNOT-20 scores at time points 2, 4 and 8 weeks

Table A5: Summary of Findings of the Systematic Review

RCT DB; Hauptman, 2007	80	NR	1b	Both hypertonic saline and normal saline improved saccharine clearance times. Normal saline improved nasal airway patency but hypertonic saline did not. Compared to normal saline, hypertonic saline resulted in statistically significant increased nasal burning

[a]Level evidence was 1b based on RCT results with narrow confidence interval; using the levels of evidence scale from the Oxford Centre for Evidence-based Medicine[19]
DB = double blind, NR = not reported, RSDI = rhinosinusitis disability index, RQLQ = rhinoconjunctivitis quality of life questionnaire, RSOM31 = rhinosinusitis outcomes measure 31, SB = single blind, SF-12 =mMedical outcome survey short form (general health assessment), SNOT-20 = sino-nasal outcome test 20

Authors' Conclusions:

"A high aggregate quality of evidence supports the effectiveness of saline irrigations in treating CRS……" Page 2347
(CRS = chronic rhinosinusitis)

Table A6: Summary of Findings of Included Clinical Studies

Main Study Findings and Author's Conclusions

Randomized controlled trials

Andersson,[9] 2011, Sweden

Main Findings

Findings from the crossover RCT on comparison of microemulsion spray with saline sprayfor patients with perennial allergic rhinitis (with respect to house dust mites).

Efficacy

Total nasal symptom scores were reduced by intervention with microemulsion. There was a statistically significant difference in nasal scores between treatment with microemulsion and saline, favoring microemulsion ($P < 0.01$)

Adverse effects

No side effects occurred during the study period

Authors' Conclusions

"We conclude that intervention with a microemulsion may reduce symptoms of house dust mite allergic rhinitis at natural allergen exposure. Our findings suggest the possibility that topical microemulsions can be a useful option to reduce nasal mucosal exposure to allergen in perennial allergic rhinitis. Page 146

Chusakul,[10] 2012, Thailand

Main Findings:

Findings from the crossover RCT on comparison of irrigation with 3 types of saline for patients with allergic rhinitis.

Efficacy

Changes in symptoms, MCCT and nasal patency

Outcome	Saline (pH 6.2 to 6.4)		Saline (pH 7.2 to 7.4)		Saline (pH 8.2 to 8.4)	
	Change post treatment	*P* value	Change post treatment	*P* value	Change post treatment	*P* value
Nasal blockage	-0.65	0.36	0.05	0.42	-0.85	0.14
Rhinorrhea	-0.35	0.11	-0.5	0.46	0.35	0.49
Sneezing	-0.5	0.19	-0.4	0.21	-1.25	**0.03**
Itchiy nose	-1.15	0.07	-0.65	0.07	-0.7	0.14
Overall nasal symptoms	-1.05	0.06	-0.4	**0.03**	-0.15	0.29
MCCT (s)	15	0.55	10	0.81	-5	0.31
MCA1 (cm^2)	0.02	0.20	0.02	0.76	-0.02	0.62
MCA2 (cm2)	0.003	0.44	-0.02	0.81	-0.01	0.93
Nasal flow (Pa s/ cm2)	-0.16	0.86	0.03	0.36	-0.2	0.72

MCA = minimal cross sectional area, MCCT = mucociliary clearance time

There was no difference found with respect to any of the above outcomes after treatment, when the 3 saline irrigation types were compared with each other.

Patient preference was significantly greater with buffered saline (pH 7.2 to 7.4) compared to the other two saline preparations, ($P = 0.02$)

Table A6: Summary of Findings of Included Clinical Studies

Adverse effects

Adverse effect	Percentage of patients with adverse effects		
	Saline (pH 6.2 to 6.4)	Saline (pH 7.2 to 7.4)	Saline (pH 8.2 to 8.4)
Nasal burning	36.1	19.4	25
Ear fullness/ pain	30.6	33.3	25
There was no significant difference in adverse effects between the three treatments			

Authors' Conclusions:

"Buffered isotonic saline with some degree of alkalinity may improve nasal symptoms. Isotonic saline irrigations, regardless of alkalinity, may not improve mocociliary function and nasal patency. Buffered isotonic saline with mild alkalinity is the most preferred." Page 53

Cingi,[15] 2014, Turkey

Main Findings

Findings from the RCT comparing xylitol with saline in patients with nasal obstruction and hypertrophied turbinate mucosa (patients with inferior turbinate hypertrophy secondary to nonallergic rhinitis).

Efficacy

There appeared to be greater improvement in congestion with xylitol treatment compared to saline treatment but the difference was not statistically significant ($P < 0.05$)

Visual analogue scale (VAS) scores

Treatment	VAS score (mean ± SD)		*P* value
	Pretreatment	Post treatment	
Saline	7.6 ± 1.23	6.8 ± 1.55	0.447
Xylitol (XlearR nasal spray)	7.5 ± 1.04	5.9 ± 1.97	0.098

RQLQ scores

Treatment	Overall quality of life score		*P* value
	Pretreatment	Change after treatment	
Saline	2.75 ± 1.03	-0.26 ± 0.084	> 0.05
Xylitol (XlearR nasal spray)	2.76 ± 1.09	-0.93 ± 0.084	0.001

4-phase rhinomanometry

There was no statistically significant difference between pretreatment and posttreatment rhinomanometry results both for saline and xylitol ($P > 0.05$ in both treatments)

Adverse effects

No serious adverse effects were reported in any of the treatment groups

Authors' Conclusions

"This study demonstrates that XlearR is an effective modality in the treatment of nasal congestion and has positive effect on the QoL of patients. Further studies are needed in order to plan an ongoing treatment of XlearR at certain intervals for continuous relief of symptoms and a better and longstanding QoL." Page 479

Ludwig,[17] 2013, Bulgaria

Main Findings

Findings from the RCT comparing treatments with carrageenan nasal spray with saline nasal spray for common cold

Efficacy

Improvement in symptoms was 2.1 days faster in the carrageenan group compared to the saline (placebo) group ($P = 0.037$)

Table A6: Summary of Findings of Included Clinical Studies

(Note: The pre-specified primary end-point was duration of disease, defined as the time until the last day with symptoms and all other days in the study period without symptoms. It was not met and was changed before unblinding)
The viral titre was statistically significantly reduced with carrageenan treatment compared with the saline treatment (P = 0.024).

Adverse effects
The investigators stated that both treatments were well tolerated and that there were no statistically significant differences in number or distribution of AEs between the treatment groups. In total, 43 AEs (treatment related or not related) were reported in 38 patients (i.e.19 patients in each treatment group). Majority of AEs were observed only once or twice per system organ class category corresponding to frequencies ranging between 0.94% and 1.92%. None of the patients discontinued treatment due to AEs.

Authors' Conclusions
"In adults with common cold virus infections, direct local administration of carrageenan with nasal sprays reduced the duration of cold symptoms." Page 124

Ottaviano,[16] 2012, Italy

Main Findings
Findings from the RCT comparing treatments with sulfurous-arsenical-ferruginous thermal water (T) with control saline (C) in smokers with chronic rhinitis

Efficacy
At one month post treatment, compared to baseline value, the thermal water treatment group (T) had a statistically significantly higher number of ciliated cells (P =0.003) but the increase in the saline group (C) was not statistically significant (P = 0.46). At one month post treatment, there were no statistically significant changes from baseline values with respect to AAR, neutrophils or olfactory threshold in any of the treatment groups.

The T group had statistically greater reduction in nasal resistance at both the 1 and 3 months follow up compared to the C group (P = 0.001 and 0.0003 respectively). The T group had statistically greater neutrophil count at 1 month follow up compared to the C group (P = 0.02) The olfactory threshold was statistically significantly higher at both the 1 and 3 months follow up in the C group compared to the T group (P =0.0007 and 0.01 respectively).

Table: Comparison between the two treatment groups (thermal water [T] and control saline [C])

Time point	*P* values for T group compared to C group with respect to the different parameters			
	Nasal patency using AAR (Pa s/ mL)	Ciliated cells	Neutrophils	Olfactory threshold
At baseline	0.86	0.23	0.27	0.46
At 1 month (after completing 1 month of treatment)	**0.001**	0.059	**0.02**	**0.0007**
At 3 months follow up	**0.0003**	0.40	0.60	**0.01**

AAR = active anterior rhinomanometry, C = control (saline) treatment, T = thermal w ater treatment

There was a statistically significantly greater improvement in nasal endoscopic findingsin the T group compared to the C group (P= 0.03)

Adverse effects
It was reported that no local side effects attributable to the use of thermal water were recorded

Table A6: Summary of Findings of Included Clinical Studies

Authors' Conclusions

"Our results indicate that nasal irrigations with thermal water had a good effect on endoscopic objective signs, nasal resistances, and epithelial trophism." Page 657

Ottaviano,[5] 2011, Italy

Main Findings

Findings from the RCT comparing treatments with sulfurous, salty, bromic, iodic thermal water (SSBI) and control saline i.e. isotonic sodium chloride solution (ISCS) in patients with chronic rhinosinusitis

Efficacy

Endoscopic findings: Compared to baseline, there was a statistically significant improvement in endoscopic clinical features with both the SSBI and ISCS treatments (P = 0.005 for SSBI and 0.01 with ISCS)

Microbiological findings:

Before treatment bacteria were identified in 5 patients in the SSBI treatment group and 4 patients in the ICSC treatment group. After treatment, no bacteria were detected in either of the treatment groups.

Cytological findings:

Treatment	HSS+ rate (%)		*P* value
	Baseline	After 1 month of treatment	
SSBI	27 ± 13	25 ± 17	0.84
ISCS	22 ± 16	26 ± 13	0.21

HSS = hyperchromatic supranuclear stria, ISCS = isotonic sodium chloride solution, SSBI = sulfurous, salty, bromic, iodic thermal water

HSS+ rate is the ratio of HSS-positive ciliated cells to the total cells

Nasal resistance:

Treatment	Nasal resistance (Pa) as assessed by active anterior rhinomanometry		*P* value
	Baseline	After 1 month of treatment	
SSBI	0.22 ± 0.20	0.15 ± 0.08	**0.01**
ISCS	0.17 ± 0.24	0.14 ± 0.06	0.25

ISCS = isotonic sodium chloride solution, Pa = Pascal, SSBI = sulfurous, salty, bromic, iodic thermal water

Adverse effects

Adverse events that may be related to the nasal irrigation treatment were recorded only in the SSBI treatment group. In the SSBI group, 6 patients reported mild nasal irritation and local burning sensation and 5 patients reported extremely limited epistaxis.

Authors' Conclusions

"Both types of nasal irrigation improved the endoscopic and microbiological features of patients with nonallergic chronic rhinosinusitis, whereas only SSBI irrigations significantly reduced total nasal resistance. Further investigations are needed based on longer treatments and follow-up periods to establish whether the HSS+ rate is useful for monitoring clinical improvements in chronic rhinosinusitis treated with nasal irrigations." Page 235

Valerieva,[7] 2015, Bulgaria

Main Findings

Findings from the RCT comparing treatments with hydroxypropylmethylcellulose (HPMC) puff with lactose (as placebo) puff for allergic rhinitis

Efficacy

Peak nasal inspiratory flow (PNIF); There was no statistically significant difference in PNIF between the two groups on days 1 and 8 but the PNIF was 26% greater with HPMC compared with placebo on day 15 and it

Table A6: Summary of Findings of Included Clinical Studies

was statistically significant ($P = 0.014$)

Assessment of symptoms using the Visual Analog Scale (VAS)

Symptom	Time point	Treatment	VAS[a] (mean ± SE)	P value with respect to baseline	P value for HPMC vs placebo
Congestion	Baseline	HPMC	65.0 ± 4.1	NA	NS
		Placebo	56.6 ± 4.9	NA	
	Day 8	HPMC	42.6 ± 6.4	0.004	NS
		Placebo	43.6 ± 5.7	0.04	
	Day 15	HPMC	36.2 ± 6.7	< 0.001	NS
		Placebo	47.2 ± 5.8	NS	
Total symptoms	Baseline	HPMC	70.2 ± 5.2	NA	NS
		Placebo	68.4 ± 5.1	NA	
	Day 8	HPMC	43.7 ± 6.0	= 0.002	NS
		Placebo	39.6 ± 5.8	< 0.001	
	Day 15	HPMC	34.2 ± 6.5	< 0.001	NS
		Placebo	41.7 ± 5.7	< 0.001	

[a]VAS: smaller values indicate less symptoms

HPMC = hydroxypropylmethylcellulose , NA = not applicable, NS = not significant, SE = standard error, VAS = visual analog scale

Rescue medication use: The median (25^{th} to 75^{th} percentile) numbers of times the patients resorted to rescue medication with oxymetazoline during day 8 to day 15 of the study were 8.5 (1 to 15.5) for HMPC group and 16 (11.5 to 16) for placebo group ($P = 0.076$). The authors stated that this difference in use of rescue medication between groups did not achieve statistical significance as there was wide variability.

Adverse effects

Adverse events were mild and infrequent and were not persistent or considered to be related to the product.

Treatment	Adverse effects
HPMC	2 patients had headache, 2 patients had intermittent coughing, 1 patients had common cold symptoms, and 1 patients dysmenorrhea
Placebo	3 patients had headache, and 1 had flu-like symptoms

HPMC = hydroxypropylmethylcellulose

Authors' Conclusions

"In conclusion, our proof-of-concept study demonstrated that micronized HPMC powder enhances the decongestant effect of nasal oxymetazoline in patients with allergic rhinitis. It also showed that 1 week of such regular combined treatment reduced nasal congestion in these patients, and this effect carries over for another week after its discontinuation. Thus, HPMC appears to be a safe and inexpensive adjunct to the therapy of allergic rhinitis." Page e138-e139

Table A6: Summary of Findings of Included Clinical Studies

Observational study

Nguyen,[3] 2014, USA

Main Findings

Findings from the prospective observational study on patients with allergic rhinitis treated with saline irrigation

Efficacy

Outcome	Baseline value (mean ± SD)	Post treatment value (mean ± SD)		*P* value
		At 4 weeks	At 8 weeks	
mRQLQ overall score	36.7 ± 20.48	14.9 ± 11.03	10.1 ± 10.6	<0.001 using one-way ANOVA; <0.05 using post hoc Duncan's multiple comparison tests
NPIF	237.1 ± 123.4	224.9 ± 95.2	232.9 ± 97.6	Not significant

mRQLQ = mini rhinoconjunctivitis quality of life questionnaire (each question is scored on a scale of 0 [not troubled] to 6 [extremely troubled] , NPIF = nasal peak inspiratory flow

Adverse effects

It was reported that the patients did not experience any adverse effects.

Authors' Conclusions

"Large-volume, low–positive pressure nasal irrigation with isotonic saline is an effective adjunctive therapy to improve quality of life in patients with allergic rhinitis already on intranasal corticosteroid therapy." Page: 308