



Canadian Agency for
Drugs and Technologies
In Health

RAPID RESPONSE REPORT: SUMMARY WITH CRITICAL APPRAISAL

TITLE: Pseudoephedrine for Adults with Sinus Congestion: A Review of the Clinical Effectiveness, Safety and Guidelines

DATE: 25 Mar 2015

CONTEXT AND POLICY ISSUES

Pseudoephedrine is a sympathomimetic amine with a long history of use.¹ Marketed over several decades as a nasal decongestant, pseudoephedrine has been suggested to offer temporary symptomatic relief from sinus congestion.^{1,2} As a common symptom of colds, influenzae and allergies, sinus congestion occurs when nasal and adjacent tissues become swollen due to blood vessels inflammation.

Pseudoephedrine is an α -adrenergic and β 2-adrenergic agonist. Through direct action on the α -adrenergic receptors located in the mucosa of the respiratory tract, pseudoephedrine leads to vasoconstriction that tightens nasal capacitance vessels to reduce blood flow to the nasal vasculature.²⁻⁴ Inflammation of the nasal membranes is therefore reduced alongside a decrease in mucus production to decrease airflow resistance and alleviate symptoms of sinus congestion.^{2,4} The activation of β 2-adrenergic receptors by pseudoephedrine further relaxes bronchial smooth muscles and dilates the bronchial vessels to improve breathing.² To achieve optimal symptomatic relief, pseudoephedrine can be use alone as a single-ingredient or in combination with other products.⁵ Other medications that are commonly combined with pseudoephedrine include paracetamol (e.g., acetaminophen), antihistamines, guaifenesin, dextromethorphan and NSAIDs.⁵

As an older drug, it is unclear the level and the quality of the clinical evidence supporting the use of pseudoephedrine as a nasal decongestant. The purpose of this review is therefore to assess the effectiveness and safety of pseudoephedrine, with or without acetaminophen, for patients with sinus congestion. Evidence-based guidelines on the use of pseudoephedrine (with or without acetaminophen) are also identified and assessed.

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RESEARCH QUESTIONS

1. What is the clinical effectiveness and safety of pseudoephedrine compared to placebo for adults with sinus congestion?
2. What is the clinical effectiveness and safety of pseudoephedrine plus acetaminophen compared to placebo for adults with sinus congestion?
3. What is the comparative clinical effectiveness of pseudoephedrine and pseudoephedrine plus acetaminophen for adults with sinus congestion?
4. What are the evidence-based guidelines for the use of pseudoephedrine (with or without acetaminophen) for adults with sinus congestion?

KEY FINDINGS

Current evidence suggests that pseudoephedrine, in combination with acetaminophen, is effective compared to placebo in providing temporary symptom relief from nasal congestion due to upper respiratory tract infections or cold-like symptoms. No comparative evidence exists that has evaluated single-ingredient pseudoephedrine against combination therapy of pseudoephedrine and acetaminophen. The safety profile remains uncertain: adverse events appear to be minor when administered acutely with greater risk of serious adverse events over long-term use. Evidence-based guidelines generally recommend the use of decongestant, limited as adjuncts to provide temporary symptom relief, in patients with non-infectious rhinitis/rhinosinusitis or allergic rhinitis. Several of the identified guidelines caution its use in patients with hypertension, ischemic heart disease, glaucoma, prostatic hypertrophy and/or diabetes mellitus.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2015, Issue 2), University of York Centre for Reviews and Dissemination (CRD) databases, 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, 2010 and February 25, 2015.

Selection Criteria and Methods

One reviewer screened the literature search results to identify relevant publications, including: health technology assessments (HTAs); systematic reviews (SRs) and meta-analyses (MA); randomized controlled trials (RCTs); non-randomized studies; and clinical practice guidelines (CPGs). The initial screen was based on title and abstract, which was followed by a full-text screen. Studies considered for inclusion were based on the selection criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adults 18 to 60 years experiencing sinus congestion (e.g., nasal congestion, sinus pressure caused by colds, influenza, sinusitis, allergies) with no history of cardiovascular disease or hypertension
Intervention	Pseudoephedrine Pseudoephedrine + acetaminophen
Comparator	Placebo
Outcomes	Clinical effectiveness (improve nasal airflow, relieve congestion, relieve pain, quality of life); Safety; Guidelines and recommendations
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, nonrandomized studies, evidence-based guidelines

Exclusion Criteria

Articles were excluded if there were a duplicate report of the same study; if they were already included in a selected SR or HTA; if they were published prior to 2010; or if they did not meet the specified inclusion criteria. Guidelines were excluded if they had unclear methodology.

Critical Appraisal of Individual Studies

SRs were appraised using the AMSTAR (A Measurement Tool to Assess Systematic Reviews) checklist.⁶ Items considered in the AMSTAR checklist include: a priori design of the review; duplicate independent reviewers; a priori defined eligibility criteria; comprehensive search of information sources; transparent reporting of study selection; clear presentation of study characteristics; assessment of studies' quality; scientifically-sound interpretation of the results; appropriate methods to combine data from studies; assessment of publication bias; and reporting of funding sources.⁶

Randomized controlled trials were appraised using the Downs and Black checklist.⁷ Concepts evaluated within this 27-item checklist included: reporting; external validity; internal validity (separated into bias and confounding); and power.⁷

Guidelines were appraised using the Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument.⁸ The items included in the AGREE instrument include: scope and purpose of the guideline; stakeholder involvement; rigor of development; clarity and presentation; applicability; and editorial independence.⁸

In conducting the critical appraisal, an overall numeric score was not calculated for each study. Instead, the selected instrument helped identify strengths and limitations that were subsequently reviewed narratively for the included publications.

SUMMARY OF EVIDENCE

Quantity of Research Available

A total of 390 citations were identified from the literature search. Following screening of titles and abstracts, 19 potentially relevant reports were selected for full-text review. With the inclusion of four reports from grey literature sources, seven publications were found to have met

the inclusion criteria and were included in this report. Of the studies included, one was a SRs,⁹ two were RCTs,^{10,11} and four were CPGs.¹²⁻¹⁵ No HTA reports were identified from the literature search. Appendix 1 presents the PRISMA flowchart¹⁶ detailing the study selection.

Additional references of potential interest that do not meet the selection criteria are provided in Appendix 2.

Summary of Study Characteristics

The table summarizing study characteristics is provided in Appendix 3.

Systematic review

One Cochrane SR,⁹ conducted by a group of international authors, addressed the comparative clinical efficacy and safety of oral antihistamine-decongestant-analgesic combinations for the common cold. The literature search spanned from the inception of the databases to December 2011 and included RCTs that studied combination therapy in adults and children whom were otherwise healthy outside of their common cold symptoms.⁹

Specifically, amongst the identified studies involving oral decongestants and analgesic combinations, one compared pseudoephedrine + acetaminophen to placebo while another was a three-arm study comparing pseudoephedrine + ibuprofen against pseudoephedrine or placebo.⁹ As this SR was mainly focused on combination therapy, the comparison between pseudoephedrine and placebo was not reported in any further detail. The study that evaluated pseudoephedrine (60 mg every 6 hours) + acetaminophen (1000 mg every 6 hours) against placebo randomized 430 adult participants with common cold symptoms. Patients were assessed following two doses of the study medication over a single day. The outcomes extracted by the SR authors, if available, included: general recovery; nasal congestion; rhinorrhea; sneezing; cough and adverse events.

Randomized controlled trials

Two placebo-controlled RCTs,^{10,11} both conducted in the United States, were identified. These studies reported the clinical efficacy and safety of pseudoephedrine, alone or in combination with acetaminophen.

In the RCT conducted by Sherkat et al,¹¹ pseudoephedrine (240 mg once a day) was assessed in a cross-over trial design. Fourteen patients who suffered from perennial allergic rhinitis were given either pseudoephedrine or placebo over a two week period, followed by a one week wash-out before being exposed to the other treatment. Clinical efficacy was assessed in this study, measured in terms of patients' sleep-related symptoms, symptoms of allergic rhinitis and quality of life.¹¹

The other RCT was a four-arm trial involving 644 adult patients with upper respiratory tract infection (i.e., confirmed acute pharyngitis and nasal congestion from rhinosinusitis).¹⁰ Patients were randomized to receive a single dose of: pseudoephedrine (30 mg) + acetylsalicylic acid (500 mg); pseudoephedrine (60 mg) + acetylsalicylic acid (1000 mg); pseudoephedrine (60 mg) + acetaminophen (1000 mg), or placebo. Both efficacy, defined as pain relief and pain intensity, and safety were assessed in this study for up to six hours following drug administration.¹⁰

Evidence-based guidelines and recommendations

Four CPGs were found that addressed pseudoephedrine, one published in 2011¹⁵ and three from 2013.¹²⁻¹⁴ The majority were from groups in the United States: two from the University of Michigan Health System^{13,14} and one from the Institute for Clinical Systems Improvement.¹² The last was unendorsed but produced by researchers from the UK.¹⁵

Two of the CPGs were specific to an adult population^{14,15} while the remainder provided guidelines applicable to both adult and pediatric populations.^{12,13} In both adult-specific guidelines, recommendations were for patients suffering from acute rhinosinusitis¹⁴ or acute sinusitis.¹⁵ In the remaining two guidelines, one specifically addressed patients with allergic rhinitis¹³ while the other broadly covered respiratory illness in both children and adults.¹²

All of these guidelines covered a broad range of medical therapies such as avoidance, conservative therapies, antibiotics, anticholinergics, antihistamines, corticosteroids, decongestants, leukotriene receptor blockers, and mast cell stabilizers.¹²⁻¹⁵

Two of the guidelines^{12,15} appraised the quality of their recommendations according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. The remaining two guidelines from the University of Michigan employed a two-part grading system that was based on the level of evidence (i.e., randomized controlled trials, controlled trials, observational trials, expert panel opinion) and the strength of the particular recommendation.^{13,14} The level of evidence was evaluated on an alphabetic grading scale of A to D (i.e., A: randomized controlled trials; B: nonrandomized controlled trials; C: observation trials; D: expert panel opinion) while the strength of a recommendation was graded on a 3 point scale (i.e., I to III) in which I corresponded to recommendations that generally should be performed while III corresponded to recommendations that generally should not be performed.^{13,14}

Summary of Critical Appraisal

A summary of the critical appraisal is presented in Appendix 4.

Systematic review

The Cochrane SR⁹ was overall well conducted and followed rigorous methodology. The inclusion criteria were set *a priori* and were clearly described; a comprehensive set of databases were searched; and data selection and extraction was done in duplicate and independently. A list of included and excluded studies was provided as part of the report. The risk of bias assessment, conducted as part of the SR, found that the majority of the selected studies including the two studies of interest to this review, had unclear risk of bias from poor reporting on randomization, allocation concealment and blinding although they had a low risk of attrition and reporting bias.⁹ The risk of publication bias was not addressed.

Randomized controlled trials

Both RCTs clearly described the interventions and the outcomes of interest and ensured sufficient number of subjects were recruited, as specified from their *a priori* sample size calculation. Randomization was appropriately conducted in both trials and, in the two-arm RCT by Schachtel et al.,¹⁰ no observable differences were found in the baseline characteristics

between study arms. As patients served as their own control in the cross-over study by Sherkat et al.,¹¹ confounding covariates are less of a concern as long as the order of treatment was properly randomized. Both studies however were found to be unclear in reporting allocation concealment.

In the study by Sherkat et al.,¹¹ other strengths include the fact that no dropout or loss-to-follow-up occurred thereby preserving randomization. Appropriate statistical tests were further conducted to address issues specific to cross-over study designs, such as: repeated measures, period effects, order effects, and carry-over effects. However, reporting issues exist in this study. Despite being described as a double-blinded study, it remained unclear how blinding was conducted. It also remained unclear why certain outcomes, not specified in the methods section, were reported in the results. There were furthermore no details provided on the patients' baseline characteristics. Although they are expected to be balanced given the cross-over design, this limited the external validity of this study.

The study by Schachtel et al.¹⁰ was more transparent in reporting. Not only did they describe the study as double blinded, they further described how blinding was conducted. Multiple comparisons were specified *a priori*. Patient disposition was clearly explained and overall, a low and balanced rate of dropouts was observed amongst the study arms. The authors state the use of intention-to-treat principles to handle missing data, although four patients who discontinued from the study were in fact excluded from the statistical analysis. Despite this discrepancy, given the small numbers excluded, this is likely to have a small effect and the potential for bias from missing data or treatment group imbalance was therefore low. Despite rescue medication being permitted, only one patient required remedial treatment, and as such this practice was unlikely to be a confounder to the observed study effects. In this instance, the patient was instructed to provide efficacy assessment prior to the use of rescue medication with any missing scores extrapolated according to the last observation carried forward approach.

Evidence-based guidelines and recommendations

All CPGs clearly described their scope, purpose and intended target user(s). Potential conflicts of interest were clearly stated in all cases. Excluding the CPG by Ah-See,¹⁵ all the remaining guidelines¹²⁻¹⁴ involved extensive stakeholder involvement, including patient views and preferences in one instance.¹² Most further described the external review process.¹²⁻¹⁴

However, it remained unclear in all cases how the SR, to inform the development of the guideline recommendations, was conducted (e.g., selection criteria, screening methodology). Despite this, the recommendations were overall clearly described and involved a balanced consideration of both efficacy and safety outcomes. Both guidelines that were developed for the University of Michigan Health System^{13,14} further considered the cost of drug therapy. Only the guideline by the Institute for Clinical Systems Improvement provided explicit timelines for the next scheduled guideline update.¹²

Summary of Findings

Main study findings and author conclusions are provided in Appendix 5.

Comparative clinical effectiveness and safety of pseudoephedrine for adults with sinus congestion

Clinical outcomes: Pseudoephedrine versus Placebo

Sherkat et al¹¹ conducted a cross-over RCT comparing pseudoephedrine against placebo in patients who suffered from perennial allergic rhinitis. Congestion, measured on a five point Likert scale, improved while on active treatment than during the placebo control (difference: -0.59, 95% confidence interval [CI]: -1.22 to 0.04) but the difference was not statistically significant ($P = 0.06$).¹¹ Outcomes relating to sleep were found not to be statistically significant. Despite this, the authors suggested that some of the improvements observed may be clinically significant, including: nocturnal rhinoconjunctivis quality of life (26.22 [pseudoephedrine] vs. 26.91 [placebo], $P = 0.88$), sleep time problems (5.38 [pseudoephedrine] vs. 6.34 [placebo], $P = 0.48$) and daytime somnolence (6.5 [pseudoephedrine] vs. 8 [placebo], $P = 0.1$); whereby, a lower score represents better outcomes. However, this must be interpreted cautiously as no minimally clinical important difference was defined for the above outcomes. The only outcome that demonstrated statistical difference between the two treatment groups was 'intimate relationships and sexual activity'. While on pseudoephedrine, the score was lower than while on placebo (3.42 [pseudoephedrine] vs. 3.70 [placebo]) and, for this outcome, a smaller score is indicative of greater difficulty.¹¹

Clinical outcomes: Pseudoephedrine with acetaminophen versus Placebo

The SR, which identified a single study evaluating pseudoephedrine + acetaminophen vs. placebo, found that nasal obstruction improved significantly in the treatment group at both two hours following the first dose ($P = 0.002$) and two hours after the second dose ($P = 0.03$).⁹ However, following administration of the first dose, improvement in other symptoms such as rhinorrhea, sneezing and cough were not found to be different between the treatment groups.⁹

The RCT conducted by Schachtel et al.¹⁰ found that pain outcomes improved for patients receiving pseudoephedrine + acetaminophen compared to placebo ($P < 0.01$) with differences appearing after 60 minutes of dosing and persisting over the remaining course of the study duration (i.e., six hours). Over the study duration, one patient in the combination therapy group required remedial therapy while no patient in the placebo group required remedial therapy.

Clinical outcomes: Pseudoephedrine with acetaminophen versus Pseudoephedrine

No studies were identified that have addressed the comparative efficacy between pseudoephedrine monotherapy and pseudoephedrine with acetaminophen amongst adults experiencing sinus congestion.

Safety: Pseudoephedrine versus Placebo

No studies were found that have evaluated the safety of pseudoephedrine compared to placebo in adults with sinus congestion.

Safety: Pseudoephedrine with acetaminophen versus Placebo

One RCT¹⁰ reported lower rates of adverse events for pseudoephedrine + acetaminophen therapy (6.8%) than for placebo (8.2%). No serious adverse events were observed six hours after dosing.

However, within the SR, adverse events were more frequently observed in the treatment arm of pseudoephedrine + acetaminophen according to the single study that was included. Incidence of adverse events that were higher in patients on combination therapy than in patients on placebo related to nervousness, nausea, dizziness, dry mouth and somnolence.⁹

Safety: Pseudoephedrine with acetaminophen versus Pseudoephedrine

No studies were identified that have addressed the comparative safety of pseudoephedrine with acetaminophen compared to pseudoephedrine alone in adults experiencing sinus congestion.

Evidence-based guidelines and recommendations for pseudoephedrine (with or without acetaminophen) in adults with sinus congestion

In the health care guideline published by the Institute for Clinical Systems Improvement,¹² the role of decongestants is dependent on the respiratory illness. Decongestant is not recommended for acute bacterial sinusitis. No controlled trials were identified addressing the efficacy of decongestants for the treatment of acute sinusitis. Some low quality evidence exist and the guideline acknowledged that , although clinical experience may support the use of decongestants as adjunctive therapy for sinusitis, further studies are needed. Similarly, with viral upper-respiratory infections, the guidelines found that high-quality studies do not clearly show a benefit of decongestants in shortening or ameliorating symptoms. The use of decongestants is only recommended in patients with moderate or severe non-infectious rhinitis or allergic rhinitis whom require sporadic symptom resolution [supporting evidence: other guidelines]. Caution is noted against long-term and routine daily use of pseudoephedrine due to a higher risk of rhinitis medicamentosa [supporting evidence: other guidelines] and hypertension [supporting evidence: meta-analysis].

The University of Michigan Health Systems guideline for allergic rhinitis¹³ suggests that the goal of therapy should be to relieve symptoms. The following treatment hierarchy is proposed based on the quality and strength of the available evidence: avoidance of allergens [IA] > over-the-counter non-sedating antihistamines [IA] > other medications, with the recommendation for other medications dependent on the presenting symptoms.¹³ The guidelines state that oral decongestants (i.e., pseudoephedrine) may be used until symptoms resolve [IA] and may be combined with oral antihistamines or with other agents. Caution, though, was recommended for geriatric patients and patients with hypertension, ischemic heart disease, glaucoma, prostatic hypertrophy or diabetes mellitus. Topical decongestants were recommended for short-term (3-5 days) use alongside intranasal corticosteroids given the risk of rhinitis medicamentosa or atrophic rhinitis associated with chronic use.¹³

The University of Michigan Health Systems guideline for acute rhinosinusitis¹⁴ recommends that antibiotics should only be prescribed following a risk-benefit assessment. Amoxicillin and trimethoprim/sulfamethoxazole are considered the first-line antibiotics for acute bacterial rhinosinusitis as they are superior to placebo and are as effective as other more expensive antibiotics. The guideline authors found little evidence supporting ancillary therapies (i.e., decongestant, topical anticholinergics, high-dose nasal steroids [IIA]). Although decongestants may improve symptoms, no evidence was identified suggesting that they can alter the disease course. Based on the existing RCTs, the guideline suggested that it may be reasonable to prescribe decongestants (especially topical decongestants such as oxymetazoline) as they may decrease nasal congestion and improve drainage. The guideline stated that topic decongestant treatment should be limited to 3 days due to risk of rebound vasodilation or atrophic rhinitis.¹⁴

In patients with clinically-diagnosed or radiologically/ bacteriologically-confirmed acute sinusitis, the guideline by Ah-See¹⁵ recommends corticosteroids based on studies that have shown that intranasal corticosteroids may increase the proportion of patients reporting an improvement or resolution of symptoms compared to patients on placebo. Antibiotics were found unlikely to be beneficial in patients with clinically-diagnosed sinusitis. In patients with radiologically or bacteriologically confirmed acute sinusitis, amoxicillin or amoxicillin-clavulanic acid combinations were unlikely to be beneficial and a lack of consistent evidence exists to support administration of cephalosporin, macrolide, doxycycline and long-course antibiotic regimens. According to this guideline, the efficacy of decongestants is unknown as no SRs and RCTs evidence were identified.¹⁵

Limitations

The clinical evidence identified in this review consists of two primary RCTs and one SR, as well as four guidelines based on literature reviews. A limitation found in this review is the significant variation observed in terms of outcome reporting (i.e., the types and method for outcome assessment) and non-identical trial methodology (i.e., patient population, study duration, dosing frequency). This may hinder the conduct of meta-analysis. Furthermore, the majority of existing studies are based on young adults (i.e., mean age ranging from 19.5 to 28.6), and this may limit external validity. Lastly, most of the included trials have discussed statistical significance although it is unclear what the minimally clinically important difference would be for the outcome measures employed. Only the crossover study¹¹ mentioned clinical significance although no rationale was provided on how this was defined.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

This review assessed the efficacy and safety of pseudoephedrine, alone or in combination with acetaminophen, compared to placebo for the treatment of sinus congestion. Although few studies met the inclusion/exclusion criteria, the ones identified were overall well-conducted. The trials had adequate enrolment, as determined through *a priori* sample size calculation, and proper randomization (leading to a balance in the baseline prognostic factors; or, in the case of the cross-over RCT, a control on potential order effects).

In this review, the evidence on pseudoephedrine monotherapy is specific to patients with sinus congestion due to allergic rhinitis; while the evidence on pseudoephedrine with acetaminophen is specific to patients with upper respiratory tract infections or patient presenting cold-like symptoms. Pseudoephedrine, alone, was shown to reduce congestion in patients following two weeks of therapy although this was not statistically significant ($P > 0.06$). Compared to placebo, pseudoephedrine + acetaminophen has been shown in separate studies to statistically reduce congestion and congestion-related pain symptoms in the short-term. Beyond congestion relief, no between-group differences were observed for the remaining outcomes that have been studied (e.g., sneezing, coughing, rhinorrhea, sleep quality, daytime somnolence). The safety of pseudoephedrine and pseudoephedrine + acetaminophen remains unclear though. In the case of pseudoephedrine + acetaminophen, there is a lack of consistency between existing studies; while, for the case of pseudoephedrine monotherapy, the single included study in this review did not report on safety outcomes. It is important to note that existing studies have all been on acute administration and that this review did not identify any comparative evidence between pseudoephedrine monotherapy vs. pseudoephedrine + acetaminophen.

Several guidelines have discussed the use of pseudoephedrine, or decongestants in general, for a range of respiratory illnesses. Most guidelines caution against long-term use given the increased risks of hypertension, rebound vasodilation, rhinitis medicamentosa, and atrophic rhinitis. In patients with non-infectious rhinitis/ rhinosinusitis or allergic rhinitis, decongestant use was recommended to be limited as adjuncts to offer sporadic symptom relief. Decongestants were generally not recommended in patients presenting with acute bacterial sinusitis or viral upper-respiratory symptoms.

In conclusion, the current evidence points toward the use of pseudoephedrine, alone or in combination with acetaminophen, to offer temporary relief from congestion in patients with allergic or non-infectious rhinitis/rhinosinusitis when compared to placebo. The safety profile remains uncertain although, in most patients, adverse events appear minor when administered acutely. Guidelines recommend against the long-term use of pseudoephedrine given the increased risks of more serious adverse events. Caution is further noted for patients with hypertension, ischemic heart disease, glaucoma, prostatic hypertrophy or diabetes mellitus.

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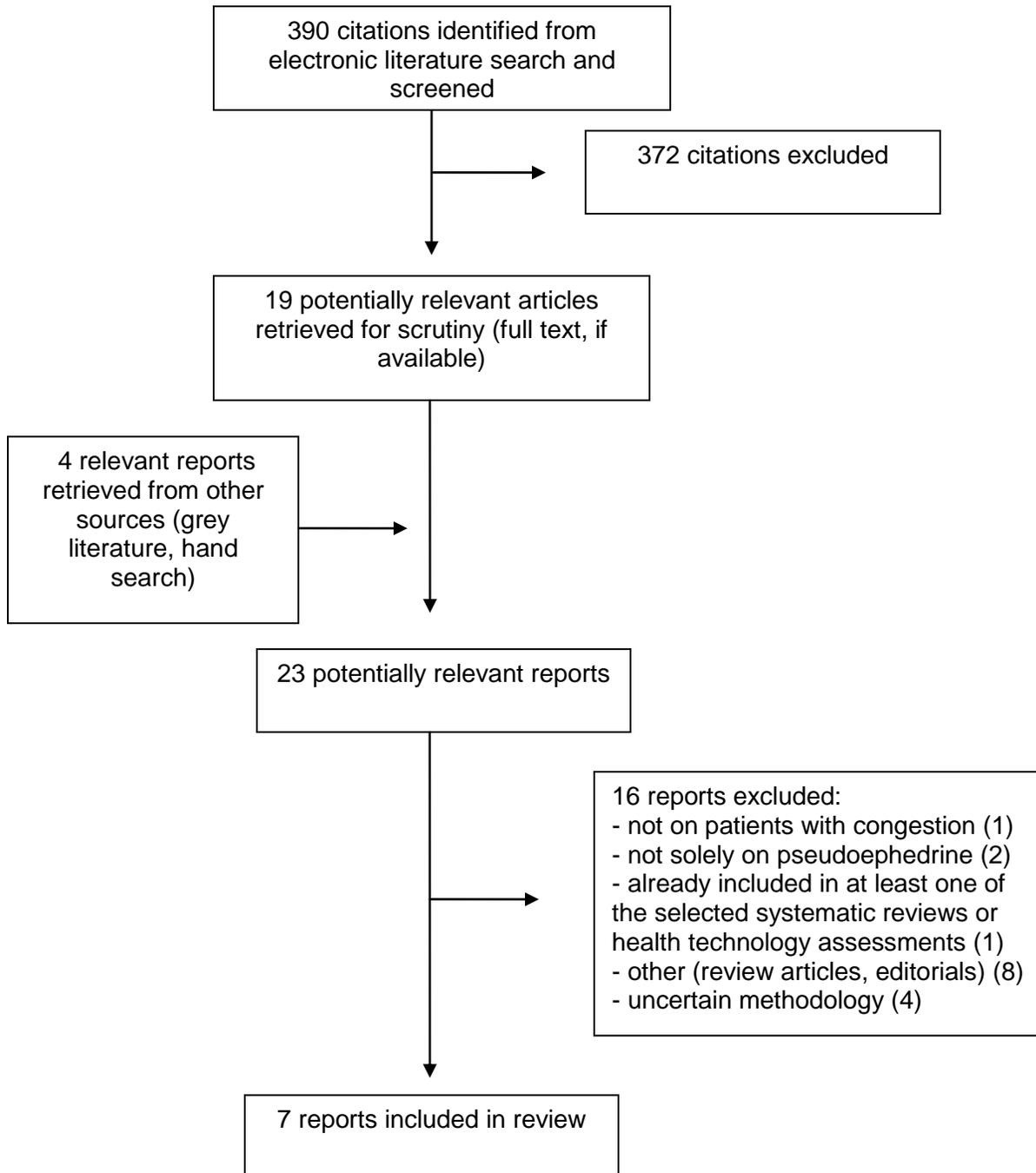
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APPENDIX 1: Selection of Included Studies



APPENDIX 2: Additional References of Potential Interest

Observational Study – Any Decongestant (in which pseudoephedrine was the most common)

Hernandez RK, Mitchell AA, Werler MM. Decongestant use during pregnancy and its association with preterm delivery. *Birth Defects Res A Clin Mol Teratol*. 2010 Sep;88(9):715-21. [PubMed: PM20672347](#)

Clinical Practice Guidelines – Methodology Uncertain/ Not Provided

de Mello JF, Jr., de Godoy Mion O, de Andrade NA, Anselmo-Lima WT, Stamm AE, de Cerqueira Almeida WL, et al. Brazilian Academy of Rhinology position paper on topical intranasal therapy. *Braz J Otorhinolaryngol* [Internet]. 2013 May [cited 2015 Feb 27];79(3):391-400. Available from: http://www.scielo.br/pdf/bjorl/v79n3/en_v79n3a20.pdf
[PubMed: PM23743757](#)

See: Nasal decongestants

APPENDIX 3: Characteristics of Included Publications

First Author, Publication Year, Country	Study design, Length of Follow-up	Patients Characteristics, Sample Size (n)	Intervention (dosage strength)	Comparator(s)	Outcomes
Systematic Reviews					
De Sutter, 2012, ⁹ Belgium	SR of RCTs on the combination therapy for the common cold Cochrane review, included literature up to December 2011. No language restriction.	27 studies, 5117 patients: one compared PSE + APAP vs placebo; one compared PSE vs. placebo [results not reported]. PSE + APAP (n=216), 66.2% female, mean age: 27.6 Placebo (n=214), 66.4% female, mean age: 28.6	Decongestant + analgesic	Placebo; Combination therapy involving antihistamine, decongestant and/or analgesic	<ul style="list-style-type: none"> - General recovery - Nasal obstruction - Rhinorrhea - Sneezing - Cough - Adverse events
Randomized Controlled Trials					
Sherkat, 2011, ¹¹ US	Double-blind, single-center crossover RCT Duration of each treatment period: 2 weeks (with one week wash-out)	14 participants, demographic details not reported Inclusion criteria: 18-65 years of age; history of allergic rhinitis (perennial allergen to indoor mold, dog, cat or mite); in general good health; history of daytime sleepiness, poor sleep or fatigue	PSE (240 mg q.d.)	Placebo	<ul style="list-style-type: none"> - Sleep (e.g., quality, functional outcome) - Allergic rhinitis (e.g., symptoms and severity) - Quality of Life
Schachtel, 2010, ¹⁰ US	Double-blind, dual-center RCT Length of follow-up: 6 hours	PSE + APAP (n=158), 58.9% female, mean age: 19.5 PSE + ASA (n=164), 56.7% female, mean age: 19.9 PSE + ASA (n=159), 59.7% female, mean age: 20.0 Placebo (n=159), 59.7% female, mean age: 20.0	PSE (60 mg) + APAP (1000 mg) PSE (30 mg) + ASA (500 mg) PSE (60 mg) + ASA (1000 mg)	Placebo	<ul style="list-style-type: none"> - Pain relief - Pain intensity - Adverse events

First Author, Publication Year, Country	Study design, Length of Follow-up	Patients Characteristics, Sample Size (n)	Intervention (dosage strength)	Comparator(s)	Outcomes
		Inclusion criteria: ≥18 years; painful tonsillo-pharyngitis and nasal congestion from rhinosinusitis; onset of sore throat within past 5 days			
Clinical Practice Guidelines					
ICSI. Diagnosis and treatment of respiratory illness in children and adults. 2013, ¹² US	CPG	Guideline developed from a literature search. Transitioning towards GRADE criteria to assess quality of guideline recommendations.	Medical therapies covered include: avoidance, antihistamines, decongestants, mast cell stabilizer, corticosteroids, anticholinergics, leukotriene receptor blocker, conservative therapy and antibiotics.		- Patient management (e.g., diagnosis efficacy and safety of treatments)
UMHS Allergic Rhinitis guidelines. 2013, ¹³ US	CPG	Guideline developed from a literature search. Recommendations graded according to its strength and level of evidence.	Medical therapies covered include: avoidance, antihistamines, decongestants, mast cell stabilizer, corticosteroids, anticholinergics, leukotriene receptor blocker and immunotherapy.		- Patient management (e.g., diagnosis, differential diagnosis, efficacy and safety of treatments, follow-up and referrals, special subpopulations)
UMHS Acute Rhinosinusitis in Adults guidelines. 2013, ¹⁴ US	CPG	Guideline developed from a literature search. Recommendations graded according to its strength and level of evidence.	Medical therapies covered include: antibiotics, ancillary therapies (e.g., symptom control).		- Patient management (e.g., diagnosis, differential diagnosis, efficacy and safety of treatments, follow-up and referrals)
Clinical Evidence Sinusitis (acute). 2011, ¹⁵ UK	CPG	Guideline developed from a systematic literature review. GRADE criteria applied to guideline development.	Medical therapies covered include: antihistamines, decongestants, corticosteroids, adjunctive therapy and antibiotics.		- Patient management (e.g., efficacy and safety of treatments)

APAP = acetaminophen; ASA = acetylsalicylic acid; CPG = clinical practice guidelines; GRADE = Grading of Recommendations, Assessment, Development, and Evaluation; ICSI = institute for clinical systems improvement; q.d. = quaque die (once per day); PSE = pseudoephedrine; RCT = randomized controlled trial; SR = systematic review; UK = United Kingdom; UMHS = University of Michigan Health System; US = United States of America.

APPENDIX 4: Critical Appraisal of Included Publications

First Author, Publication Year, Country	Strengths	Limitations
SRs		
De Sutter, 2012, ⁹ Belgium	<p>A priori-designed SR with meta-analysis, if appropriate.</p> <p>Clear description of literature search, including grey literature, with duplicate independent study selection performed.</p> <p>Provides list of included & excluded studies alongside the characteristics of the included studies.</p> <p>Critical appraisal (incl. risk of bias assessment) conducted.</p> <p>Addressed homogeneity in the conduct of the meta-analysis.</p> <p>Includes a section disclosing potential conflict of interest.</p> <p>Publication bias considered.</p>	Publication bias not considered.
RCTs		
Sherkat, 2011, ¹¹ US	<p>Randomization conducted on the order in which treatment administered.</p> <p>As a cross-over study, confounding covariates are reduced as each patient serves as their own control.</p> <p>Outcome assessment appears to be standardized.</p> <p>A priori sample size calculation. The enrolment numbers matched the study requirements.</p> <p>Statistical tests appear appropriate to address issues specific to cross-over study designs.</p> <p>It appears that no dropouts/loss-to-follow-up occurred; in which case, study would be based on ITT principles.</p>	<p>Allocation concealment unclear.</p> <p>Double-blinded. However, it is not clear how blinding was ensured in the patients.</p> <p>Lack transparent reporting of patients' baseline characteristics, thereby limiting the potential external validity of study.</p> <p>Potential for selective outcome reporting bias. Some of the results reported were not specified a priori in their methods section.</p>
Schachtel, 2010, ¹⁰ US	<p>Randomization, stratified by baseline pain levels, was clearly reported and appeared to have been correctly conducted. No observable differences were found in baseline characteristics.</p> <p>Clear description of subject characteristics, the interventions studied and standardization of outcome assessment.</p>	<p>Allocation concealment unclear.</p> <p>Statistical analysis reported as ITT. However, four patients who discontinued the study were not assessed.</p>

First Author, Publication Year, Country	Strengths	Limitations
	<p>Double-blinded. Clear description on how blinding was ensured in study subjects.</p> <p>A priori sample size calculation. Final number of patients recruited in each study arm was within margin of these pre-specified values.</p> <p>According to authors, multiple comparisons were specified a priori.</p> <p>Clear explanation of patient disposition with relatively low and balanced rates of dropouts.</p> <p>Rescue medication was permitted. As only one patient required remedial medication, this is unlikely to be a study confounder.</p>	
CPGs		
<p>ICSI. Diagnosis and treatment of respiratory illness in children and adults. 2013,¹² US</p>	<p>Clear description of scope and purpose. Intended target user for guideline clearly defined.</p> <p>Guideline development group includes individuals from relevant professional groups and patient representation.</p> <p>Balanced consideration of efficacy and safety. Recommendations are clearly presented with flowchart guiding clinical decision-making.</p> <p>Methods to formulate recommendations based on GRADE methodology.</p> <p>Conflicts of interests have been addressed.</p> <p>Clear list of external reviewers.</p> <p>Scheduled plan for updating guideline.</p>	<p>Although literature review was conducted, details are not reported.</p> <p>Cost implications not considered.</p>
<p>UMHS Allergic Rhinitis guidelines. 2013,¹³ US</p>	<p>Clear description of scope and purpose. Intended target user for guideline clearly defined.</p> <p>Guideline development group includes individuals from relevant professional groups.</p> <p>Balanced consideration of efficacy and safety. Recommendations are justified with flowchart guiding clinical decision-making and order of medication based on patient's presenting symptoms.</p> <p>Methods to formulate recommendations based on their own methodology that considers strength of recommendation and the level of</p>	<p>Patient views and preferences were not sought.</p> <p>Although systematic review was conducted, details are not reported.</p> <p>No procedure mentioned for updating guideline.</p>

First Author, Publication Year, Country	Strengths	Limitations
	<p>evidence.</p> <p>Conflicts of interests have been addressed.</p> <p>Clear list of external reviewers.</p> <p>Brief consideration of cost implications.</p>	
<p>UMHS Acute Rhinosinusitis in Adults guidelines. 2013,¹⁴ US</p>	<p>Clear description of scope and purpose. Intended target user for guideline clearly defined.</p> <p>Guideline development group includes individuals from relevant professional groups.</p> <p>Balanced consideration of efficacy and safety. Recommendations are justified with flowchart guiding clinical decision-making and order of medication based on patient's presenting symptoms.</p> <p>Methods to formulate recommendations based on their own methodology that considers strength of recommendation and the level of evidence.</p> <p>Conflicts of interests have been addressed.</p> <p>Clear list of external reviewers.</p> <p>Brief consideration of cost implications.</p>	<p>Patient views and preferences were not sought.</p> <p>Although systematic review was conducted, details are not reported.</p> <p>No procedure mentioned for updating guideline.</p>
<p>ClinicalEvidence Sinusitis (acute). 2011,¹⁵ UK</p>	<p>Clear description of scope and purpose. Intended target user for guideline clear.</p> <p>Balanced consideration on both efficacy and safety.</p> <p>Methods to formulate recommendations based on GRADE.</p> <p>Recommendations are clearly presented.</p> <p>Conflicts of interests have been addressed.</p>	<p>Guideline developed by single individual without involvement of relevant professional groups or an external review.</p> <p>Patient views and preferences were not sought.</p> <p>Although systematic review was conducted, details are not reported.</p> <p>No procedure mentioned for updating guideline. Cost implications not mentioned.</p>

CPG = clinical practice guidelines; GRADE = Grading of Recommendations, Assessment, Development, and Evaluation; ICSI = institute for clinical systems improvement; ITT = intention-to-treat; MA = meta-analysis; q.d. = quaque die (once per day); P = probability value; RCT = randomized controlled trial; SR = systematic review; UK = United Kingdom; UMHS = University of Michigan Health System; US = United States of America.

APPENDIX 5: Summary of Main Study Findings and Author’s Conclusions

First Author, Publication Year, Country	Main Study Findings	Authors’ Conclusions
Systematic reviews		
De Sutter, 2012, ⁹ Belgium	<ul style="list-style-type: none"> • 27 RCTs comprising 5,117 patients. 2 trials identified: i. PSE + ibuprofen vs. PSE vs. placebo, and ii. PSE + APAP vs. placebo. Only results of relevant combination therapy presented: • <i>Clinical effectiveness</i>: <ul style="list-style-type: none"> ○ <i>Nasal obstruction (subjective assessment)</i>: mean difference in nasal obstruction score in favor of PSE+APAP than placebo two hours after first dose (effect size = 1.06, $P = 0.002$); two hours after second dose, administration still favored PSE + APAP ($P = 0.03$). ○ <i>Other symptoms</i>: Following first dose, no significant effects between treatment groups with respect to rhinorrhea, sneezing, cough. • <i>Safety</i>: Higher incidence of adverse events in PSE + APAP arm than placebo group, including: nervousness, nausea, dizziness, dry mouth and somnolence. 	<p>“Current evidence suggests that antihistamine-analgesic-decongestant combinations have some general benefit in adults and older children. These benefits must be weighed against the risk of adverse effects.” (p. 2)</p>
RCTs		
Sherkat, 2011, ¹¹ US	<ul style="list-style-type: none"> • 14 patients (PSE: 14; placebo: 14) • After 2 weeks of treatment: <ul style="list-style-type: none"> ○ <i>Congestion (subjective assessment)</i>: rated less severe when receiving PSE (effect size: -0.59; 95% CI: -1.22 to 0.04; $P = 0.06$). ○ <i>Other symptoms</i>: no between-group differences in rhinorrhea, sneezing, itchy nose, irritated eyes. ○ <i>Sleep-related outcomes</i>: no between-group statistically significant differences on the sleep outcome measures (i.e., functional outcomes of sleep questionnaire, Epworth sleepiness scale, sleep QoL questionnaire, Stanford sleepiness scale, nocturnal rhinoconjunctivitis QoL) except worsening in intimate relationship and sexual activities when on PSE (effect size: -0.28; 95% CI: -0.54 to -0.03; $P = 0.03$). 	<p>“Our research suggests that sleep quality is not significantly affected by pseudoephedrine. As expected, congestion is reduced, but side effects such as a decline of intimate relationships and sexual activity may interfere with quality of life.” (p. 97)</p>
Schachtel, 2010, ¹⁰ US	<ul style="list-style-type: none"> • 644 patients (ASA 500 + PSE 30: 164; ASA 1000 + PSE 60: 159; APAP + PSE:158; placebo: 159) <ul style="list-style-type: none"> ○ Well matched in terms of baseline demographic and clinical features. APAP (1000 mg) permitted as rescue medication. • 6 hours after administration: <ul style="list-style-type: none"> ○ <i>Total pain-relief</i>: significant improvement in APAP+PSE compared to placebo ($P < 0.01$) ○ <i>Summed pain intensity difference</i>: significant improvement in APAP+PSE compared to placebo ($P < 0.01$) ○ Overall, APAP+PSE differed significantly from placebo on pain relief and pain intensity differences beginning at 60 minutes after administration ($P < 0.05$) throughout six hours 	<p>Conclusions specific to PSE and ASA combination</p> <p>“From these findings, we conclude that ASA 500mg and ASA 1000 mg combined with PSE 30 mg and 60 mg, respectively, are safe, effective analgesic agents for patients with pain and nasal congestion associated with URTI.” (p. 1436)</p>

First Author, Publication Year, Country	Main Study Findings	Authors' Conclusions
	<ul style="list-style-type: none"> ○ <i>Safety</i>: APAP+PSE 6.8%, placebo 8.2%. No serious adverse events and only one patient in APAP+PSE required remedial therapy after the 6-hour trial 	
Clinical practice guidelines		
<p>ICSI. Diagnosis and treatment of respiratory illness in children and adults. 2013,¹² US</p>	<ul style="list-style-type: none"> • Treatments for the following respiratory illnesses: <ul style="list-style-type: none"> ○ For viral upper-respiratory infection: primary treatment should be education base. Decongestants have not clearly shown benefit in shortening or ameliorating symptoms [high quality evidence]. ○ For moderate or severe non-infectious rhinitis: recommended treatment is intranasal steroids. Oral decongestant recommended to manage sporadic symptoms ○ For allergic seasonal rhinitis: primary treatment should be patient education on avoidance and medication therapy. Decongestant likely to have pronounced effects on congestion symptoms [other guidelines] although caution against routine daily use due to risk of rhinitis medicamentosa and hypertension [meta-analysis]. ○ For acute bacterial sinusitis: Antibiotic treatment is recommended. Decongestant not recommended for use as adjunctive therapy [other guidelines] <p>Oral and topical decongestant should be used with caution in: older adults, children under the age of six, patients, of any age, with history of: arrhythmia, angina, cerebrovascular disease, hypertension, bladder neck obstruction, glaucoma, hyperthyroidism.</p>	
<p>UMHS Allergic Rhinitis guidelines. 2013,¹³ US</p>	<ul style="list-style-type: none"> • Goal of therapy should be to relieve symptoms. General hierarchy of therapy: avoidance [IA] > over-the-counter non-sedating antihistamines [IA] > other medication (i.e., corticosteroids [IA], oral decongestants [IA], leukotriene inhibitors [IIA], intranasal cromolyn [IIA], intranasal antihistamines [IIA], ocular preparations [IIA]) <ul style="list-style-type: none"> ○ Order of 'other medication' addition depends on presenting symptom (i.e., nasal obstructive symptom, rhinorrhea without obstruction, comorbid persistent asthma) ○ Oral decongestant may be used until symptoms resolve although caution needed in patients with hypertension, ischemic heart disease, glaucoma, prostatic hypertrophy or diabetes mellitus. Geriatric patients may be more sensitive to side effects of oral decongestant. ○ Topical decongestant should only be used short-term (3-5 days) with intranasal corticosteroids. <p>In general, special therapeutic consideration required for pediatric, geriatrics, pregnant females, severe asthmatics and severe atopic dermatitis patients</p>	
<p>UMHS Acute Rhinosinusitis in Adults guidelines. 2013,¹⁴ US</p>	<ul style="list-style-type: none"> • Antibiotics should be prescribed based on assessment of benefits and risks. • Little evidence supporting ancillary therapies. They may improve symptoms although not shown to change course of disease. Reasonable efficacy expected with decongestants (especially topical decongestants), topical anticholinergics and nasal steroids [IIA]. <p>Topical decongestant may decrease nasal congestion and improve drainage. Treatment should be limited to 3 days due to risk of rebound vasodilation or atropic rhinitis</p>	
<p>ClinicalEvidence Sinusitis (acute). 2011,¹⁵ UK</p>	<p>For clinically diagnosed or radiologically/bacteriologically-confirmed acute sinusitis: intranasal corticosteroids likely to be beneficial. Unknown effectiveness with decongestants as no systematic reviews or RCTs have been identified.</p>	

APAP = acetaminophen; ASA = acetylsalicylic acid; CI = confidence interval; HR = hazard ratio; ICSI = institute for clinical systems improvement; P = probability value; PSE = pseudoephedrine; QoL = quality of life; RCT = randomized controlled trial; SR = systematic review; UK = United Kingdom; UMHS = University of Michigan Health System; US = United States of America.