National Institute for Health and Care Excellence

Draft

Obstructive sleep apnoea/ hypopnoea syndrome and obesity hypoventilation syndrome in over 16s

Evidence review K: Rhinitis

NICE guideline

Intervention evidence review

March 2021

Draft for Consultation

Developed by the National Guideline Centre

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Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and, where appropriate, their carer or guardian.

Local commissioners and providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

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1 Treatment of rhinitis to improve OSAHS

1.1 Review question: What is the clinical and cost effectiveness of treatment of rhinitis to improve symptoms of obstructive sleep apnoea/hypopnoea syndrome (OSAHS), obesity hypoventilation syndrome (OHS) or COPD-OSAHS overlap syndrome?

1.2 Introduction

Patients treated for OSAHS may suffer with nasal congestion otherwise known as rhinitis which may impact on their compliance with CPAP. Rhinitis, the inflammation of the inside of the nose can be sub divided into two broad groups. The first group where rhinitis symptoms are caused by an allergy for example pollen are known as allergic rhinitis. The symptoms of allergic rhinitis can include, a runny nose, blocked nose, sneezing, reduced sense of smell as well as mild irritation or discomfort around the nose. The second group causing rhinitis symptoms is the non-allergic type. Symptoms of non-allergic rhinitis are somewhat similar to allergic rhinitis except patients may have less itching and irritation. The clinical appearance of the mucosa may also differ with allergic rhinitis demonstrating more paler lining. The trigger factors are different for the two groups: the defining difference is that allergic rhinitis usually starts soon after exposure to an allergen whereas non-allergic rhinitis is often the result of swollen blood vessels and a build-up of fluid in the tissues of the nose. Rhinitis effects the sleep of patients and subsequently can impact on the quality of sleep and can contribute to upper airway narrowing and increase snoring. Treatment and management of rhinitis is similar in both types with a primary objective to avoid the allergen or possible trigger, in conjunction with using nasal irrigation, intranasal steroids, antihistamines, decongestant, leukotriene receptor agonist (if concomitant asthma) or any combination of these.

The aim of this review was to examine the clinical and cost effectiveness of treatment of rhinitis to improve symptoms of obstructive sleep apnoea/hypopnea syndrome, obesity hypoventilation syndrome or COPD-OSAHS overlap syndrome.

1.3 PICO table

For full details see the review protocol in appendix A.

Table 1: PICO characteristics of review question

Population	People (16 and older) with OSAHS, OHS or COPD-OSAHS overlap syndrome with chronic rhinitis.
Interventions	Treatment of rhinitis (for example with intranasal (IN) saline douches, IN steroids, in anticholinergics or antihistamines, radiofrequency ablation of turbinates). Treatments (for example CPAP, oral devices) for OSAHS/OHS/ COPD-OSAHS overlap syndrome with treatment of rhinitis.
Comparisons	No treatment of rhinitis/placebo. Treatments for OSAHS without treatment of rhinitis.
Outcomes	**Critical** • generic or disease specific quality of life measures (continuous)

	• mortality (dichotomous)
	
	Important
	• sleepiness scores (continuous, e.g. Epworth)
	• apnoea-hypopnoea index or respiratory disturbance index (continuous)
	• oxygen desaturation index (continuous)
	• CO_2 control (continuous)
	• minor adverse effects of treatment (rates or dichotomous)
	• adherence (continuous)
	• driving outcomes (continuous)
	• neurocognitive outcomes (continuous)
	• impact on co-existing conditions:
	  ○ HbA1c for diabetes (continuous)
	  ○ cardiovascular events for cardiovascular disease (dichotomous)
	  ○ systolic blood pressure for hypertension (continuous)

Study design	• RCTs only • minimum duration of follow-up 1 months • parallel or crossover to be included

1.4 Clinical evidence

1.4.1 Included studies

OSAHS

One randomised cross over trial[3] was included in the review. The study assessed the effects of topical decongestion (xylometazoline) in patients with OSAHS and chronic nasal congestion. The participants had severe OSAHS (based on mean AHI). No evidence was available for mild and moderate OSAHS. There was no evidence available for any other treatment for rhinitis/nasal congestion.

OHS

There was no evidence for people with OHS.

COPD-OSAHS overlap syndrome

There was no evidence for people with COPD-OSAHS overlap syndrome.

See also the study selection flow chart in appendix C, study evidence tables in appendix D, forest plots in appendix E and GRADE tables in appendix H.

1.4.2 Excluded studies

See the excluded studies list in appendix I.

1.4.3 Summary of clinical studies included in the evidence review

Table 2: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Clarenbach 2008[3] Cross over trial Switzerland	N=12 Intervention 1: Cross-over block-design with two 1-week treatment periods separated by a 1-week washout period was used. Patients applied every evening xylometazoline (0.1% solution, three drops, 0.15 mg) in each nostril. (n=12) Intervention 2: placebo Patients applied every evening an identically looking placebo (sodium chloride, 0.9% solution) in each nostril. 1-week treatment periods Assessments were performed at the end of each treatment period. N=12	Successive patients diagnosed with OSA (defined by a complaint of excessive daytime sleepiness, an Epworth sleepiness score >8, and an apnoea/hypopnea index >10/h) were included if they also suffered from chronic nasal congestion defined by a complaint of impaired nasal breathing that interfered with subjective sleep quality on at least three nights per week during at least the last 3 months. Age - Mean (SD): 49.1 ± 11.1; Gender (M:F): 10:2 BMI: 30.7 ± 5.1 kg/m^2, AHI: 32.6 ±24.5 events/h Sleepiness ESS: 11.8 ± 4.5	• AHI • ESS • Mean oxygen saturation (%)	Severe OSAHS based on mean AHI 1-week treatment periods. Assessments were performed at the end of each treatment period.

1.4.4 Quality assessment of clinical studies included in the evidence review

Table 3: Clinical evidence summary xylometazoline versus placebo

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Xylometazoline versus placebo (95% CI)
AHI entire night (lower values better)	12 (1 study) 1 week	⨁⊖⊖⊖ VERY LOW1,2 due to indirectness, imprecision		The mean AHI entire night in the control groups was 32.2	The mean AHI entire night in the intervention groups was 2.9 lower (29.03 lower to 23.23 higher)
ESS (Epworth Sleepiness Scale) Lower values better	12 (1 study) 1 week	⨁⨁⊖⊖ LOW1,2 due to indirectness, imprecision		The mean ESS in the control groups was 11.8	The mean ESS in the intervention groups was 1.3 lower (4.59 lower to 1.99 higher)
Mean oxygen saturation (%) Higher values better	12 (1 study) 1 week	⨁⊖⊖⊖ VERY LOW1,2 due to indirectness, imprecision		The mean oxygen saturation (%) in the control groups was 93	The mean oxygen saturation (%) in the intervention groups was 1 higher (1.4 lower to 3.4 higher)
Mortality					No evidence available
Quality of life					No evidence available

1 Includes AHI>10/h (both moderate-severe OSAHS)
2 Downgraded by one increment if the confidence interval crossed one MID and downgraded by two increments if the confidence interval crossed both MIDs. Established MIDs for ESS -2.5, mean oxygen saturation- 5%. GRADE default MID (0.5XSD)) used for AHI.

1.5 Economic evidence

1.5.1 Included studies

No relevant health economic studies were identified.

1.5.2 Excluded studies

No health economic studies that were relevant to this question were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in appendix G.

1.5.3 Health economic modelling

This area was not prioritised for new cost-effectiveness analysis.

1.5.4 Health economic evidence statements

No relevant economic evaluations were identified.

1.6 The committee's discussion of the evidence

1.6.1 Interpreting the evidence

1.6.1.1 The outcomes that matter most

The committee considered the outcomes of health-related quality of life as critical outcome for decision making. Other important outcomes included sleepiness scores (e.g. Epworth), Apnoea-Hypopnoea index (AHI), Oxygen desaturation index (ODI), hours of use, minor adverse effects of treatment, adherence, CO2 control, driving outcomes and neurocognitive outcomes. The committee were also interested in the impact on co-existing conditions such as HbA1c for diabetes, cardiovascular events for cardiovascular disease and systolic blood pressure for hypertension.

No evidence was available for the outcomes of health-related quality of life, hours of use, minor adverse effects of treatment, adherence, CO2 control, driving outcomes, neurocognitive outcomes and the impact on co-existing conditions.

1.6.1.2 The quality of the evidence

OSAHS

One randomised cross over trial was included in the review. The study assessed the effects of topical decongestion (xylometazoline) in patients with severe OSAHS and chronic nasal congestion. No evidence was available for mild and moderate OSAHS. There was no evidence available for any other treatment for rhinitis/nasal congestion.

The committee considered the clinical importance for AHI on a case by case basis, taking into consideration the baseline AHI and the improvement in severity of sleep apnoea.

The quality of the evidence varied from low to very low; evidence was downgraded due to imprecision and indirectness. There was some uncertainty across the effect sizes, with some confidence intervals crossing the MID thresholds or line of no effect. Study was downgraded for indirectness as it included a mixed severity population (participants with moderate and severe OSAHS).

OHS

There was no evidence available for OHS.

COPD-OSAHS overlap syndrome

There was no evidence available for COPD-OSAHS overlap syndrome.

1.6.1.3 Benefits and harms

Severe OSAHS and chronic nasal congestion

Xylometazoline versus placebo

The evidence suggested that there was no clinically important difference between xylometazoline and placebo for the outcomes of AHI, ESS and mean oxygen saturation (%) in people with severe OSAHS and chronic nasal congestion. No evidence was available for people with mild and moderate OSAHS. There was no evidence for OHS and COPD-OSAHS overlap syndrome.

Due to lack of sufficient evidence the committee made the recommendations based on their collective experience and knowledge of current practice.

The committee discussed that nasal obstruction/congestion has a definite impact on sleep disordered breathing (both snoring and OSAHS) and leads to mouth breathing which worsens mandibular and base of tongue retraction thus exacerbating upper airway obstruction. The committee hence agreed that treating rhinitis and other causes of nasal obstruction may help people use CPAP more comfortably and has a positive impact on sleep disorders. They noted that nasal obstruction can be due to anatomical/physiological/pathological aetiology. Anatomical considerations could be deviated nasal septum, nasal polyps, enlarged turbinates. Pathophysiological conditions include allergic or non-allergic/vasomotor rhinitis. Hence the committee agreed that people with nasal congestion and OSAHS should be assessed for the presence of underlying allergic or vasomotor rhinitis. If rhinitis is diagnosed, then the committee agreed that treatment should be considered.

The committee agreed that initial treatment should be offered with topical nasal corticosteroids or antihistamines for allergic rhinitis and topical nasal corticosteroids for vasomotor rhinitis.

The committee were aware that some patients using CPAP report non-allergic rhinitis, dryness and irritation as a result of persistent high air pressure, which can affect tolerance of CPAP. Therefore, managing rhinitis symptoms and treating other nasal conditions may help people use CPAP more comfortably and has a positive impact on sleep disorders. Changing the interface from a nasal to an orofacial mask and addition of humidification can also help.

The committee advised that current practice should be followed for initial treatment, and that referral to an ear, nose and throat specialist may be needed for further assessment of persistent symptoms. The committee however did not want to make a specific recommendation for treatments after ENT referral as this would be decided on a case by case basis, taking patient factors into account.The committee agreed that the recommendations reflect current practice in most NHS centres, so the committee agreed there is likely to be little change in practice.

Even though there was limited evidence on managing rhinitis in people with OSAHS, based on their experience the committee made strong recommendations hence they did not make any research recommendation for this topic.

OHS

No evidence was available for people with OHS. The committee agreed that recommendations for OSAHS are applicable to people with OHS as well. The committee agreed, based on their knowledge and experience, that treating rhinitis and other causes of nasal obstruction has a positive impact on sleep disorders. The committee were aware that some patients using CPAP or non-invasive ventilation report non-allergic rhinitis, dryness and irritation, which can affect tolerance of CPAP or non-invasive ventilation. Therefore, managing rhinitis symptoms and treating other nasal conditions may help people use CPAP or non-invasive ventilation more comfortably. Changing the interface from a nasal to an orofacial mask and addition of humidification can also help. The committee agreed that when patients do not respond to medical treatment or if there is any anatomical nasal obstruction, they would need ENT referral for further management. The committee agreed that the recommendations reflect current practice in most NHS centres, so there is likely to be little change in practice.

Even though there was a lack of evidence on managing rhinitis in people with OHS, based on their experience the committee made strong recommendations hence they did not make any research recommendation for this topic.

COPD-OSAHS overlap syndrome

No evidence was available for people with COPD-OSAHS overlap syndrome. The committee agreed that recommendations for OSAHS are applicable to people with COPD-OSAHS overlap syndrome as well. The committee agreed, based on their knowledge and experience, that treating rhinitis and other causes of nasal obstruction has a positive impact on sleep disorders. The committee were aware that some patients using CPAP report non-allergic rhinitis, dryness and irritation, which can affect tolerance of CPAP. Therefore, managing rhinitis symptoms and treating other nasal conditions may help people use CPAP more comfortably. The committee agreed that when patients do not respond to medical treatment or if there is any anatomical nasal obstruction, they would need ENT referral for further management. The committee agreed that the recommendations reflect current practice in most NHS centres, so there is likely to be little change in practice.

Even though there was a lack of evidence on managing rhinitis in people with COPD-OSAHS overlap syndrome, based on their experience the committee made strong recommendations hence they did not make any research recommendation for this topic.

1.6.2 Cost effectiveness and resource use

There were no relevant health economic evaluations and little clinical evidence available for this review question. The committee therefore made a consensus recommendation based on their expertise.

In the first instance, when it is deemed appropriate to provide an intervention for people with OSAHS, OHS or COPD-OSAHS overlap syndrome who also have allergic rhinitis, the committee agreed that nasal steroid or antihistamines were an appropriate course of treatment. Where patients do not respond to this treatment or they have anatomical obstruction then they should be referred onwards to ENT. This method of treatment for the specific population under consideration is current practice and therefore the committee highlighted that there would not be a significant resource impact.

After referral to ENT, the committee were of the view that treatment would be based on clinical symptoms which would vary from patient to patient; therefore, providing standard guidance at this stage of the management pathway would not be helpful. Finally, the committee highlighted that CPAP can worsen or cause rhinitis which could then subsequently impact on people’s adherence to the device. This lack of adherence could result in increased downstream risk of cardiovascular disease and other clinical complications linked with untreated OSAHS, which would result in greater expenditure for the NHS and worse health outcomes for patients. Therefore, the committee have raised caution by guiding clinicians to be aware of the connection between rhinitis and CPAP.

1.6.3 Other factors the committee took into account

Current practice in the management of patients receiving treatment with CPAP who also experience symptoms of rhinitis is to manage symptoms through individualised treatment. Some patients may find that humidification added to their CPAP device is sufficient to reduce rhinitis symptoms generated by CPAP air flow and pressure, whereas others benefit from a targeted nasal steroid spray to reduce inflammation.

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Appendices

Appendix A: Review protocols

Table 4: Review protocol: Rhinitis

ID	Field	Content
0.	PROSPERO registration number	Not registered
1.	Review title	Rhinitis
2.	Review question	What is the clinical and cost effectiveness of treatment of rhinitis to improve symptoms of obstructive sleep apnoea/hypopnoea syndrome, obesity hypoventilation syndrome or COPD-OSAHS overlap syndrome?
3.	Objective	To determine the clinical and cost effectiveness of treatment of rhinitis to improve symptoms of obstructive sleep apnoea/hypopnoea syndrome, obesity hypoventilation syndrome or COPD-OSAHS overlap syndrome.
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE • Epistemonikos Searches will be restricted by: • English language • Human studies • Letters and comments are excluded. Other searches: • Inclusion lists of relevant systematic reviews will be checked by the reviewer.

		The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review.
5.	Condition or domain being studied	Obstructive sleep apnoea/hypopnoea syndrome is the most common form of sleep disordered breathing. The guideline will also cover obesity hypoventilation syndrome and COPD-OSAHS overlap syndrome (the coexistence of obstructive sleep apnoea/hypopnoea syndrome and chronic obstructive pulmonary disease).
6.	Population	• People (16 and older) with OSAHS, OHS or COPD-OSAHS overlap syndrome (only if formal diagnosis methods) with chronic rhinitis Population will be stratified by: • OSAHS vs OHS vs COPD-OSAHS overlap syndrome • Mild vs moderate vs severe (based on AHI/ODI) • De novo rhinitis vs rhinitis secondary to CPAP When a mixed severity population is included the severity of the majority of the population will be used by taking the mean AHI of the patients included and the study will be downgraded for indirectness. Severity: Mild OSAHS: AHI >5 but <15 Moderate OSAHS: AHI >/= 15 but <30 Severe OSAHS: AHI >/= 30

7.	Intervention/Exposure/Test	• Treatment of rhinitis (for example with intranasal (IN) saline douches, IN steroids, IN anticholinergics or antihistamines, radiofrequency ablation of turbinates) • Treatments (for example CPAP, oral devices) for OSAHS/OHS/COPD-OSAHS overlap syndrome with treatment of rhinitis • Classes of drugs will be pooled
8.	Comparator/Reference standard/Confounding factors	• No treatment of rhinitis/placebo • Treatments for OSAHS without treatment of rhinitis
9.	Types of study to be included	• RCTs only • Minimum duration of follow-up 1 months • Parallel or crossover to be included
10.	Other exclusion criteria	None
11.	Context	N/A
12.	Primary outcomes (critical outcomes)	• Generic or disease specific quality of life measures (continuous) • Mortality (dichotomous)
13.	Secondary outcomes (important outcomes)	• Sleepiness scores (continuous, e.g. Epworth) • Apnoea-Hypopnoea index or respiratory disturbance index (continuous) • Oxygen desaturation index (continuous) • CO2 control (continuous) • Minor adverse effects of treatment (rates or dichotomous) • Adherence (continuous)

		• Driving outcomes (continuous) • Neurocognitive outcomes (continuous) • Impact on co-existing conditions: o HbA1c for diabetes (continuous) o Cardiovascular events for cardiovascular disease (dichotomous) o Systolic blood pressure for hypertension (continuous) Outcomes will be separated into short term (latest follow-up to 6 months) and long term (latest follow-up beyond 6 months)
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. EviBASE will be used for data extraction.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. • Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) • Randomised Controlled Trial: Cochrane RoB (2.0) 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary. .

16.	Strategy for data synthesis	• Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). • GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/ • Where meta-analysis is not possible, data will be presented, and quality assessed individually per outcome. • WinBUGS will be used for network meta-analysis, if possible, given the data identified. Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. An I^2 value greater than 50% will be considered indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented pooled using random-effects.
17.	Analysis of sub-groups	• High risk occupational groups (for example heavy goods vehicle drivers) vs general population • Sleepiness – Epworth >9 vs Epworth 9 or less • Coexisting conditions – type 2 diabetes vs atrial fibrillation vs hypertension vs none • BMI – obese vs non-obese • Treatment of rhinitis – intranasal saline douches vs medical treatment (steroids, anticholinergics, antihistamines) vs invasive treatment (radiofrequency ablation)
18.	Type and method of review	☒ Intervention ☐ Diagnostic ☐ Prognostic ☐ Qualitative ☐ Epidemiologic ☐ Service Delivery ☐ Other (please specify)
19.	Language	English

20.	Country	England
21.	Anticipated or actual start date	NA – not registered on PROSPERO
22.	Anticipated completion date	NA – not registered on PROSPERO
24.	Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail SleepApnoHypo@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and the National Guideline Centre
25.	Review team members	From the National Guideline Centre: Carlos Sharpin, Guideline lead Sharangini Rajesh, Senior systematic reviewer Audrius Stonkus, Systematic reviewer Emtiyaz Chowdhury (until January 2020), Health economist David Wonderling, Head of health economics Agnes Cuyas, Information specialist (till December 2019) Jill Cobb, Information specialist
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website:

		https://www.nice.org.uk/guidance/indevelopment/gid-ng10098
29.	Other registration details	NA – not registered
30.	Reference/URL for published protocol	NA – not registered
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
32.	Keywords	
33.	Details of existing review of same topic by same authors	N/A
35..	Additional information	N/A
36.	Details of final publication	www.nice.org.uk

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2 **Table 5: Health economic review protocol**

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below.

Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2003, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[8] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed, and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded, then a health economic evidence table will not be completed, and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies. *Setting:* • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2003 or later but that depend on unit costs and resource data entirely or predominantly from before 2003 will be rated as 'Not applicable'. • Studies published before 2003 will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:*

	• The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

1
2

Appendix B: Literature search strategies

Sleep Apnoea search strategy 11 rhinitis

This literature search strategy was used for the following review;

- What is the clinical and cost effectiveness of treatment of rhinitis to improve symptoms of obstructive sleep apnoea/hypopnoea syndrome, obesity hypoventilation syndrome or COPD-OSAHS overlap syndrome?

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[8]

For more information, please see the Methods Report published as part of the accompanying documents for this guideline.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 6: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 6 July 2020	Exclusions Randomised controlled trials Systematic review studies Observational studies
Embase (OVID)	1974 – 6 July 2020	Exclusions Randomised controlled trials Systematic review studies Observational studies
The Cochrane Library (Wiley)	Cochrane Reviews to 2020 Issue 7 of 12 CENTRAL to 2020 Issue 7 of 12	None
Epistemonikos (Epistemonikos Foundation)	Inception – 29 November 2018	None

Medline (Ovid) search terms

1.	exp Sleep Apnea Syndromes/
2.	(sleep* adj4 (apn?ea* or hypopn?ea*)).ti,ab.
3.	(sleep* adj4 disorder* adj4 breath*).ti,ab.
4.	(OSAHS or OSA or OSAS).ti,ab.
5.	(obes* adj3 hypoventil*).ti,ab.
6.	pickwick*.ti,ab.
7.	or/1-6
8.	limit 7 to English language
9.	letter/
10.	editorial/
11.	news/

12.	exp historical article/
13.	Anecdotes as Topic/
14.	comment/
15.	case report/
16.	(letter or comment*).ti.
17.	or/9-16
18.	randomized controlled trial/ or random*.ti,ab.
19.	17 not 18
20.	animals/ not humans/
21.	exp Animals, Laboratory/
22.	exp Animal Experimentation/
23.	exp Models, Animal/
24.	exp Rodentia/
25.	(rat or rats or mouse or mice).ti.
26.	or/19-25
27.	8 not 26
28.	exp Rhinitis/
29.	(rhinit* or rhinopath* or rhinosinusit* or rhinoconjunctivitis or ozena* or hayfever or hay fever or pollinosis or pollenosis or pollonosis or allerg*).ti,ab.
30.	((nasal or nose) adj3 (congest* or stuffy or clog*)).ti,ab.
31.	(NARES or NAR or LAR or NANIPER or AR or SAR).ti,ab.
32.	exp Histamine Antagonists/
33.	(antihistamin* or anti-histamin* or (histamin* adj3 antagonist*)).ti,ab.
34.	(Desloratadine or Fexofenadine or Ketotifen).ti,ab.
35.	Ketotifen/
36.	Nasal Lavage/ or Administration, Intranasal/ or Nasal Sprays/
37.	((intranasal or intra-nasal or nasal or nose) adj3 (wash* or spray* or mist* or irrigat* or rins* or douch* or lavage* or administrat*)).ti,ab.
38.	(anticholinergic* or anti-cholinergic* or cholinergic antagonist*).ti,ab.
39.	(antimuscarinic* or anti-muscarinic* or muscarnic antagonist*).ti,ab.
40.	Ipratropium.ti,ab.
41.	Ipratropium/
42.	exp Cholinergic Antagonists/
43.	((intranasal or intra-nasal or nasal or inhal*) adj3 (steroid* or corticosteroid*)).ti,ab.
44.	(Beclometasone or Budesonide or Fluticasone or Mometasone).ti,ab.
45.	Beclometasone/
46.	Budesonide/
47.	Fluticasone/
48.	Mometasone Furoate/
49.	(RFA or RFAIT or RFTR or RFVTR).ti,ab.
50.	((radiofrequency or ablat* or reduct*) adj4 (turbinate* or turbinoplast*)).ti,ab.
51.	or/28-50
52.	27 and 51
53.	randomized controlled trial.pt.
54.	controlled clinical trial.pt.
55.	randomi#ed.ti,ab.

56.	placebo.ab.
57.	randomly.ti,ab.
58.	Clinical Trials as topic.sh.
59.	trial.ti.
60.	or/53-59
61.	Meta-Analysis/
62.	exp Meta-Analysis as Topic/
63.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
64.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
65.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
66.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
67.	(search* adj4 literature).ab.
68.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
69.	cochrane.jw.
70.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
71.	or/61-70
72.	Epidemiologic studies/
73.	Observational study/
74.	exp Cohort studies/
75.	(cohort adj (study or studies or analys* or data)).ti,ab.
76.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
77.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
78.	Controlled Before-After Studies/
79.	Historically Controlled Study/
80.	Interrupted Time Series Analysis/
81.	(before adj2 after adj2 (study or studies or data)).ti,ab.
82.	or/72-81
83.	exp case control studies/
84.	case control*.ti,ab.
85.	or/83-84
86.	82 or 85
87.	Cross-sectional studies/
88.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
89.	or/87-88
90.	82 or 89
91.	82 or 85 or 89
92.	52 and (60 or 71 or 91)

1 **Embase (Ovid) search terms**

1.	exp Sleep Disordered Breathing/
2.	(sleep* adj4 (apn?ea* or hypopn?ea*)).ti,ab.
3.	(sleep* adj4 disorder* adj4 breath*).ti,ab.

4.	(OSAHS or OSA or OSAS).ti,ab.
5.	(obes* adj3 hypoventil*).ti,ab.
6.	pickwick*.ti,ab.
7.	or/1-6
8.	limit 7 to English language
9.	letter.pt. or letter/
10.	note.pt.
11.	editorial.pt.
12.	case report/ or case study/
13.	(letter or comment*).ti.
14.	or/9-13
15.	randomized controlled trial/ or random*.ti,ab.
16.	14 not 15
17.	animal/ not human/
18.	nonhuman/
19.	exp Animal Experiment/
20.	exp Experimental Animal/
21.	animal model/
22.	exp Rodent/
23.	(rat or rats or mouse or mice).ti.
24.	or/16-23
25.	8 not 24
26.	exp Rhinitis/
27.	(rhinit* or rhinopath* or rhinosinusit* or rhinoconjunctivitis or ozena* or hayfever or hay fever or pollinosis or pollenosis or pollonosis or allerg*).ti,ab.
28.	((nasal or nose) adj3 (congest* or stuffy or clog*)).ti,ab.
29.	(NARES or NAR or LAR or NANIPER or AR or SAR).ti,ab.
30.	exp antihistaminic agent/
31.	(antihistamin* or anti-histamin* or (histamin* adj3 antagonist*)).ti,ab.
32.	(Desloratadine or Fexofenadine or Ketotifen).ti,ab.
33.	nasal lavage/
34.	intranasal drug administration/
35.	nose spray/
36.	((intranasal or intra-nasal or nasal or nose) adj3 (wash* or spray* or mist* or irrigat* or rins* or douch* or lavage* or administrat*)).ti,ab.
37.	(anticholinergic* or anti-cholinergic* or cholinergic antagonist*).ti,ab.
38.	(antimuscarinic* or anti-muscarinic* or muscarnic antagonist*).ti,ab.
39.	Ipratropium.ti,ab.
40.	cholinergic receptor blocking agent/
41.	exp cholinergic receptor blocking agent/
42.	((intranasal or intra-nasal or nasal or inhal*) adj3 (steroid* or corticosteroid*)).ti,ab.
43.	(Beclometasone or Budesonide or Fluticasone or Mometasone).ti,ab.
44.	beclometasone/
45.	budesonide/
46.	fluticasone/
47.	mometasone furoate/

48.	(RFA or RFAIT or RFTR or RFVTR).ti,ab.
49.	((radiofrequency or ablat* or reduct*) adj4 (turbinate* or turbinoplast*)).ti,ab.
50.	or/26-49
51.	25 and 50
52.	random*.ti,ab.
53.	factorial*.ti,ab.
54.	(crossover* or cross over*).ti,ab.
55.	((doubl* or singl*) adj blind*).ti,ab.
56.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
57.	crossover procedure/
58.	single blind procedure/
59.	randomized controlled trial/
60.	double blind procedure/
61.	or/52-60
62.	systematic review/
63.	meta-analysis/
64.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
65.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
66.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
67.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
68.	(search* adj4 literature).ab.
69.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
70.	cochrane.jw.
71.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
72.	or/62-71
73.	Clinical study/
74.	Observational study/
75.	family study/
76.	longitudinal study/
77.	retrospective study/
78.	prospective study/
79.	cohort analysis/
80.	follow-up/
81.	cohort*.ti,ab.
82.	80 and 81
83.	(cohort adj (study or studies or analys* or data)).ti,ab.
84.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
85.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
86.	(before adj2 after adj2 (study or studies or data)).ti,ab.
87.	or/73-79,82-86
88.	exp case control study/
89.	case control*.ti,ab.

90.	or/88-89
91.	87 or 90
92.	cross-sectional study/
93.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
94.	or/92-93
95.	87 or 94
96.	87 or 90 or 94
97.	51 and (61 or 72 or 96)

1 **Cochrane Library (Wiley) search terms**

#1.	MeSH descriptor: [Sleep Apnea Syndromes] explode all trees
#2.	(sleep* near/4 (apnea* or apnoea* or hypopnea* or hypopnoea*)):ti,ab
#3.	(sleep* near/4 disorder* near/4 breath*):ti,ab
#4.	(OSAHS or OSA or OSAS):ti,ab
#5.	(obes* near/3 hypoventil*):ti,ab
#6.	pickwick*:ti,ab
#7.	(OR #1-#6)
#8.	MeSH descriptor: [Rhinitis] explode all trees
#9.	(rhinit* or rhinopath* or rhinosinusit* or rhinoconjunctivitis or ozena* or hayfever or hay fever or pollinosis or pollenosis or pollonosis or allerg*):ti,ab
#10.	((nasal or nose) near/3 (congest* or stuffy)):ti,ab
#11.	(NARES or NAR or LAR or NANIPER or AR or SAR):ti,ab
#12.	MeSH descriptor: [Histamine Antagonists] explode all trees
#13.	(antihistamin* or anti-histamin* or (histamin* near/3 antagonist*)):ti,ab
#14.	(Desloratadine or Fexofenadine or Ketotifen):ti,ab
#15.	MeSH descriptor: [Ketotifen] this term only
#16.	MeSH descriptor: [Nasal Lavage] this term only
#17.	MeSH descriptor: [Administration, Intranasal] this term only
#18.	MeSH descriptor: [Nasal Sprays] this term only
#19.	((intranasal or intra-nasal or nasal or nose) near/3 (wash* or spray* or mist* or irrigat* or rins* or douch* or lavage* or administrat*)):ti,ab
#20.	(anticholinergic* or anti-cholinergic* or cholinergic antagonist*):ti,ab
#21.	(antimuscarinic* or anti-muscarinic* or muscarnic antagonist*):ti,ab
#22.	Ipratropium:ti,ab
#23.	MeSH descriptor: [Ipratropium] explode all trees
#24.	MeSH descriptor: [Cholinergic Agonists] explode all trees
#25.	((intranasal or intra-nasal or nasal or inhal*) near/3 (steroid* or corticosteroid*)):ti,ab
#26.	(Beclometasone or Budesonide or Fluticasone or Mometasone):ti,ab
#27.	MeSH descriptor: [Beclomethasone] this term only
#28.	MeSH descriptor: [Budesonide] this term only
#29.	MeSH descriptor: [Fluticasone] this term only
#30.	MeSH descriptor: [Mometasone Furoate] this term only
#31.	(RFA or RFAIT or RFTR or RFVTR):ti,ab
#32.	((radiofrequency or ablat* or reduct*) near/4 (turbinate* or turbinoplast*)):ti,ab
#33.	(or #8-#32)
#34.	#7 AND #33

Epistemonikos search terms

1.	((title:((sleep apnea syndromes) OR (sleep* AND (apn?ea* OR hypopn?ea*)) OR (sleep* AND (apn?ea* OR hypopn?ea*)) OR (sleep* AND (disorder* OR breath*)) OR (OSAHS OR OSA OR OSAS) OR (obes* AND hypoventil*) OR pickwick*) OR abstract:((sleep apnea syndromes) OR (sleep* AND (apn?ea* OR hypopn?ea*)) OR (sleep* AND (apn?ea* OR hypopn?ea*)) OR (sleep* AND (disorder* OR breath*)) OR (OSAHS OR OSA OR OSAS) OR (obes* AND hypoventil*) OR pickwick*)))

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to sleep apnoea population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA – this ceased to be updated after March 2018) with no date restrictions. NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional searches were run on Medline and Embase for health economics and quality of life studies.

B.2.1 Health economic studies strategy

Table 7: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	2014 – 6 July 2020	Exclusions Health economics studies
Embase	2014 – 6 July 2020	Exclusions Health economics studies
Centre for Research and Dissemination (CRD)	HTA - Inception – 31 March 2018 NHSEED - Inception to March 2015	None

Medline (Ovid) search terms

	exp Sleep Apnea Syndromes/
1.	(sleep* adj4 (apn?ea* or hypopn?ea*)).ti,ab.
2.	(sleep* adj4 disorder* adj4 breath*).ti,ab.
3.	(OSAHS or OSA or OSAS).ti,ab.
4.	(obes* adj3 hypoventil*).ti,ab.
5.	pickwick*.ti,ab.
6.	or/1-6
7.	limit 7 to English language
8.	letter/
9.	editorial/
10.	news/
11.	exp historical article/
12.	Anecdotes as Topic/
13.	comment/
14.	case report/
15.	(letter or comment*).ti.
16.	or/9-16
17.	randomized controlled trial/ or random*.ti,ab.
18.	17 not 18

19.	animals/ not humans/
20.	exp Animals, Laboratory/
21.	exp Animal Experimentation/
22.	exp Models, Animal/
23.	exp Rodentia/
24.	(rat or rats or mouse or mice).ti.
25.	or/19-25
26.	8 not 26
27.	Economics/
28.	Value of life/
29.	exp "Costs and Cost Analysis"/
30.	exp Economics, Hospital/
31.	exp Economics, Medical/
32.	Economics, Nursing/
33.	Economics, Pharmaceutical/
34.	exp "Fees and Charges"/
35.	exp Budgets/
36.	budget*.ti,ab.
37.	cost*.ti.
38.	(economic* or pharmaco?economic*).ti.
39.	(price* or pricing*).ti,ab.
40.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
41.	(financ* or fee or fees).ti,ab.
42.	(value adj2 (money or monetary)).ti,ab.
43.	or/28-43
44.	27 and 44

1 **Embase (Ovid) search terms**

1.	exp Sleep Disordered Breathing/
2.	(sleep* adj4 (apn?ea* or hypopn?ea*)).ti,ab.
3.	(sleep* adj4 disorder* adj4 breath*).ti,ab.
4.	(OSAHS or OSA or OSAS).ti,ab.
5.	(obes* adj3 hypoventil*).ti,ab.
6.	pickwick*.ti,ab.
7.	or/1-6
8.	limit 7 to English language
9.	letter.pt. or letter/
10.	note.pt.
11.	editorial.pt.
12.	case report/ or case study/
13.	(letter or comment*).ti.
14.	or/9-13
15.	randomized controlled trial/ or random*.ti,ab.

16.	14 not 15
17.	animal/ not human/
18.	nonhuman/
19.	exp Animal Experiment/
20.	exp Experimental Animal/
21.	animal model/
22.	exp Rodent/
23.	(rat or rats or mouse or mice).ti.
24.	or/16-23
25.	8 not 24
26.	health economics/
27.	exp economic evaluation/
28.	exp health care cost/
29.	exp fee/
30.	budget/
31.	funding/
32.	budget*.ti,ab.
33.	cost*.ti.
34.	(economic* or pharmaco?economic*).ti.
35.	(price* or pricing*).ti,ab.
36.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
37.	(financ* or fee or fees).ti,ab.
38.	(value adj2 (money or monetary)).ti,ab.
39.	or/26-38
40.	25 and 39

NHS EED and HTA (CRD) search terms

#1.	MeSH DESCRIPTOR Sleep Apnea Syndromes EXPLODE ALL TREES
#2.	(sleep* adj4 (apn?ea* or hypopn?ea*))
#3.	(sleep* adj4 disorder* adj4 breath*)
#4.	(OSAHS or OSA or OSAS)
#5.	(obes* adj3 hypoventil*)
#6.	(pickwick*)
#7.	#1 OR #2 OR #3 OR #4 OR #5 OR #6

B.2.2 Quality of life studies strategy

Table 8: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	1946 – 26 November 2019	Exclusions Quality of life studies
Embase	1974 – 26 November 2019	Exclusions Quality of life studies

Medline (Ovid) search terms

1.	exp Sleep Apnea Syndromes/

2.	(sleep* adj4 (apn?ea* or hypopn?ea*)).ti,ab.
3.	(sleep* adj4 disorder* adj4 breath*).ti,ab.
4.	(OSAHS or OSA or OSAS).ti,ab.
5.	(obes* adj3 hypoventil*).ti,ab.
6.	pickwick*.ti,ab.
7.	or/1-6
8.	limit 7 to English language
9.	letter/
10.	editorial/
11.	news/
12.	exp historical article/
13.	Anecdotes as Topic/
14.	comment/
15.	case report/
16.	(letter or comment*).ti.
17.	or/9-16
18.	randomized controlled trial/ or random*.ti,ab.
19.	17 not 18
20.	animals/ not humans/
21.	exp Animals, Laboratory/
22.	exp Animal Experimentation/
23.	exp Models, Animal/
24.	exp Rodentia/
25.	(rat or rats or mouse or mice).ti.
26.	or/19-25
27.	8 not 26
28.	quality-adjusted life years/
29.	sickness impact profile/
30.	(quality adj2 (wellbeing or well being)).ti,ab.
31.	sickness impact profile.ti,ab.
32.	disability adjusted life.ti,ab.
33.	(qal* or qtime* or qwb* or daly*).ti,ab.
34.	(euroqol* or eq5d* or eq 5*).ti,ab.
35.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
36.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
37.	(hui or hui1 or hui2 or hui3).ti,ab.
38.	(health* year* equivalent* or hye or hyes).ti,ab.
39.	discrete choice*.ti,ab.
40.	rosser.ti,ab.
41.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
42.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.

43.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
44.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
45.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
46.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
47.	or/28-46
48.	27 and 47

1 **Embase (Ovid) search terms**

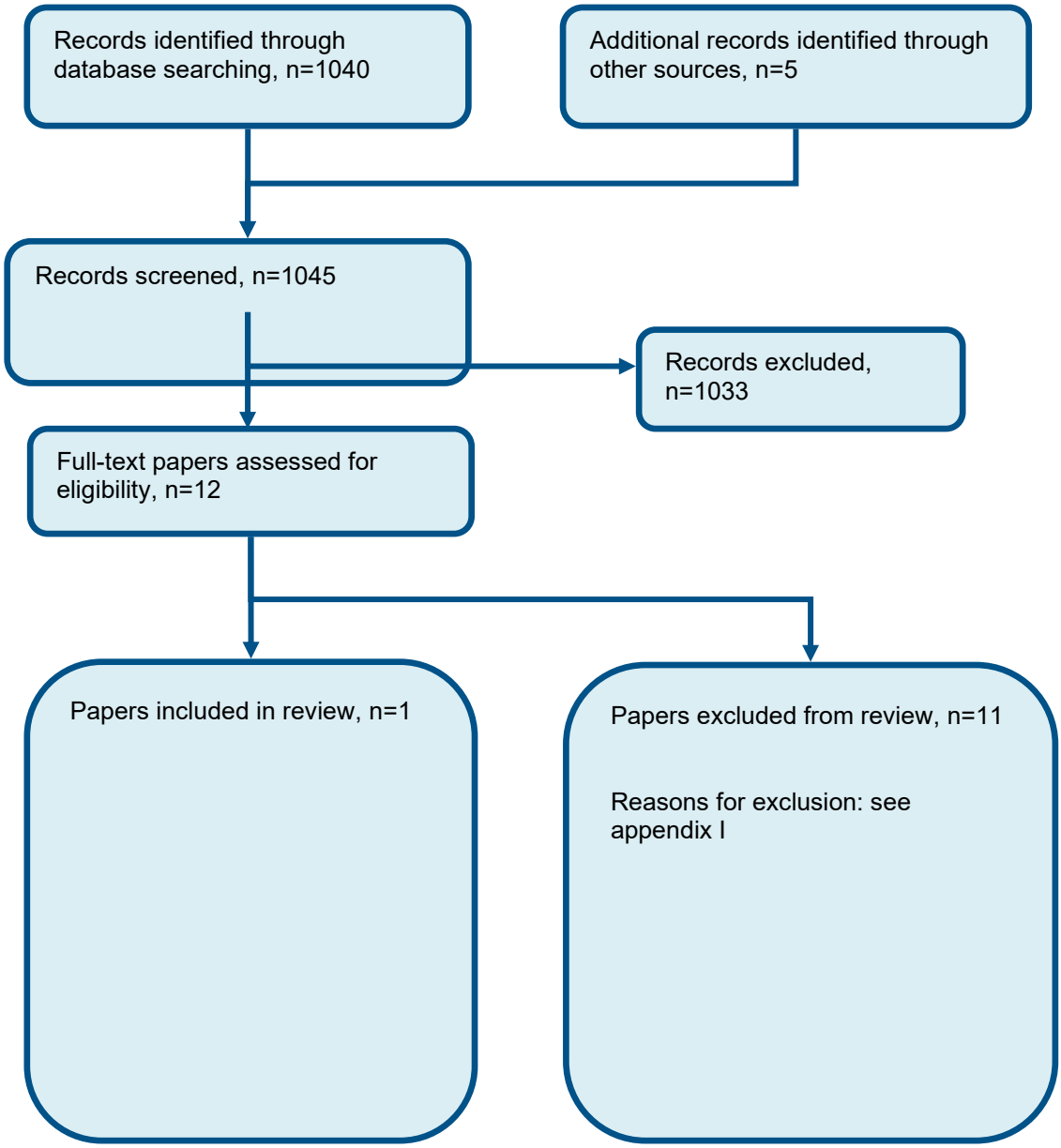
1.	exp Sleep Disordered Breathing/
2.	(sleep* adj4 (apn?ea* or hypopn?ea*)).ti,ab.
3.	(sleep* adj4 disorder* adj4 breath*).ti,ab.
4.	(OSAHS or OSA or OSAS).ti,ab.
5.	(obes* adj3 hypoventil*).ti,ab.
6.	pickwick*.ti,ab.
7.	or/1-6
8.	limit 7 to English language
9.	letter.pt. or letter/
10.	note.pt.
11.	editorial.pt.
12.	case report/ or case study/
13.	(letter or comment*).ti.
14.	or/9-13
15.	randomized controlled trial/ or random*.ti,ab.
16.	14 not 15
17.	animal/ not human/
18.	nonhuman/
19.	exp Animal Experiment/
20.	exp Experimental Animal/
21.	animal model/
22.	exp Rodent/
23.	(rat or rats or mouse or mice).ti.
24.	or/16-23
25.	8 not 24
26.	quality adjusted life year/
27.	"quality of life index"/
28.	short form 12/ or short form 20/ or short form 36/ or short form 8/
29.	sickness impact profile/
30.	(quality adj2 (wellbeing or well being)).ti,ab.
31.	sickness impact profile.ti,ab.
32.	disability adjusted life.ti,ab.
33.	(qal* or qtime* or qwb* or daly*).ti,ab.
34.	(euroqol* or eq5d* or eq 5*).ti,ab.
35.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
36.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.

37.	(hui or hui1 or hui2 or hui3).ti,ab.
38.	(health* year* equivalent* or hye or hyes).ti,ab.
39.	discrete choice*.ti,ab.
40.	rosser.ti,ab.
41.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
42.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
43.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
44.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
45.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
46.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
47.	or/26-46
48.	25 and 47

1
2

Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the review of treatment of rhinitis



Appendix D: Clinical evidence tables

Study (subsidiary papers)	Clarenbach 2008[3]
Study type	RCT (Patient randomised; cross over)
Number of studies (number of participants)	1 (n=12)
Countries and setting	Conducted in Switzerland; Setting: hospital
Line of therapy	Not applicable
Duration of study	Intervention + follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Severe OSAHS
Subgroup analysis within study	Not applicable
Inclusion criteria	Successive patients diagnosed with OSA (defined by a complaint of excessive daytime sleepiness, an Epworth sleepiness score >8 , and an apnoea/hypopnea index >10/h) were included if they also suffered from chronic nasal congestion defined by a complaint of impaired nasal breathing that interfered with subjective sleep quality on at least three nights per week during at least the last 3 months.
Exclusion criteria	Nasal surgery within the last 6 months, current treatment with nasal decongestants or topical steroids, sleep disorders other than obstructive sleep apnoea, internal medical or psychiatric disorders that interfered with sleep.
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): 49.1 ± 11.1; Gender (M: F): 10:2. Ethnicity: Not stated

Study (subsidiary papers)	Clarenbach 2008[3]
Further population details	1. BMI: 30.7 ± 5.1 kg/m^2, 2. AHI: 32.6 ±24.5 events/h 3. Sleepiness ESS: 11.8 ± 4.5
Indirectness of population	No indirectness
Interventions	(n=12) Intervention 1: Cross-over block-design with two 1-week treatment periods separated by a 1-week washout period was used. Patients applied every evening xylometazoline (0.1% solution, three drops, 0.15 mg) in each nostril. (n=12) Intervention 2: placebo Patients applied every evening an identically looking placebo (sodium chloride, 0.9% solution) in each nostril. 1-week treatment periods Assessments were performed at the end of each treatment period.
Funding	Academic or government funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: Xylometazoline versus Placebo

Protocol outcome 1: ESS
- Actual outcome for ESS ; Group 1: n=,12, mean (SD) 10.5 ± 3.8;Group 2: mean (SD)11.8 ± 4.4); n=12
Risk of bias: All domain - low, Selection - Low, Blinding - Low, Incomplete outcome data - low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness

Protocol outcome 2: AHI
- Actual outcome for Apnoea/hypopnea index entire night (/h) ; Group 1: mean (SD) 29.3 ± 32.5; n=12, Group 2: mean (SD) 32.2 ± 32.8; n=12
Risk of bias: All domain - low, Selection - Low, Blinding - Low, Incomplete outcome data - low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness

Protocol outcome 3: Mean oxygen saturation

Study (subsidiary papers)	Clarenbach 2008[3]
- Actual outcome for Mean oxygen saturation (%) ; Group 1: mean (SD) 94 ± 3; n=12, Group 2: mean (SD); 93 ± 3 ; n=12 Risk of bias: All domain - low, Selection - Low, Blinding - Low, Incomplete outcome data - low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	quality of life; Mortality; CO2 control; minor adverse effects of treatment; adherence; driving outcomes; neurocognitive outcomes; impact on co-existing conditions: HbA1c for diabetes, cardiovascular events for cardiovascular disease, systolic blood pressure for hypertension.

Appendix E: Forest plots

E.1 Xylometazoline versus placebo- severe OSAHS

Figure 2: AHI entire night (l/h) (lower values better)

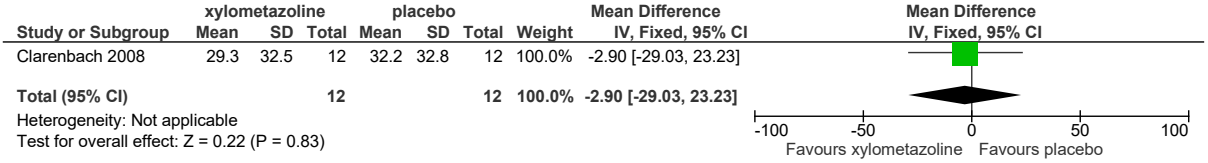


Figure 3: ESS (0 to 24) (lower scores better)

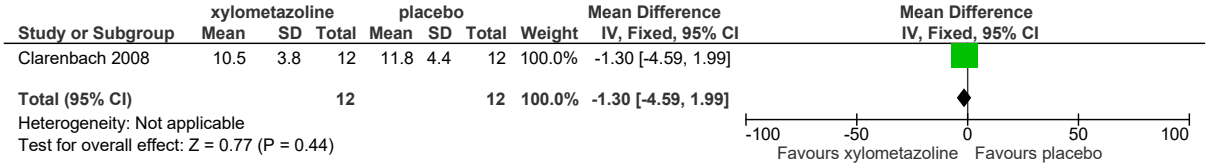
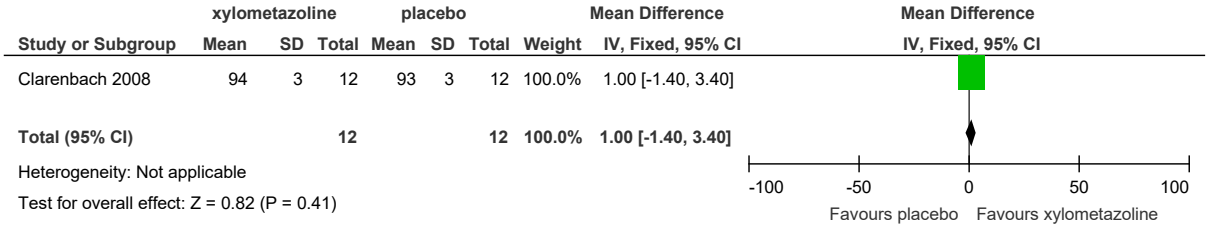


Figure 4: Mean oxygen saturation (%) (higher scores better)



Appendix F: GRADE table

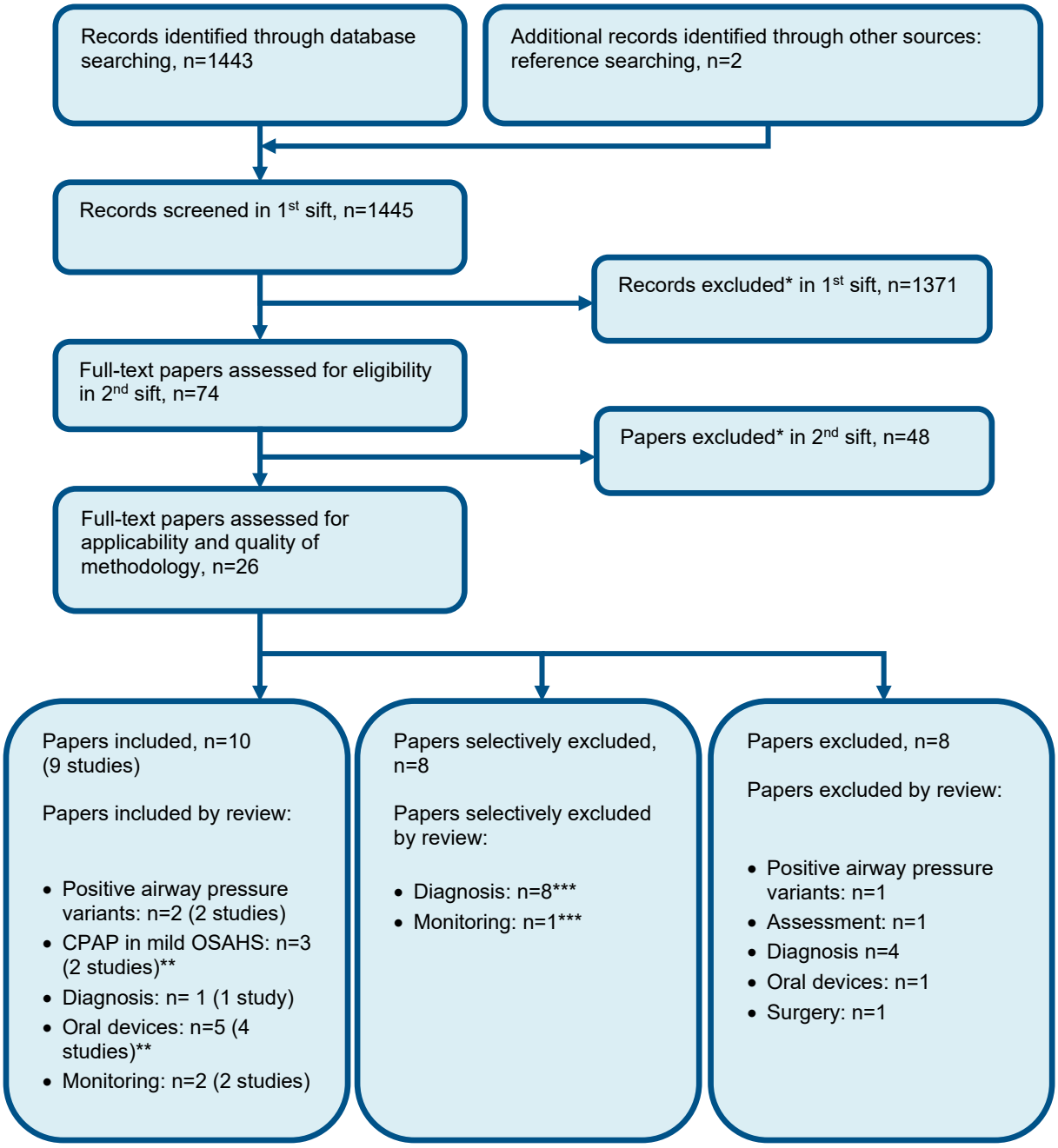
Table 9: xylometazoline vs placebo for rhinitis – severe OSAHS

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Xylometazoline	Placebo	Relative (95% CI)	Absolute		
AHI entire night (l/h) (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2]	none	12	12	-	MD 2.9 lower (29.03 lower to 23.23 higher)	⊕OOO VERY LOW	IMPORTANT
ESS (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[2]	none	12	12	-	MD 1.3 lower (4.59 lower to 1.99 higher)	⊕⊕OO LOW	IMPORTANT
mean oxygen saturation (%) (Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2]	none	12	12	-	MD 1 higher (1.4 lower to 3.4 higher)	⊕OOO VERY LOW	IMPORTANT
Mortality												
No evidence available												CRITICAL
Quality of life												
No evidence available												CRITICAL

1 Includes AHI>10/h (both moderate-severe OSAHS)
2 Downgraded by one increment if the confidence interval crossed one MID and downgraded by two increments if the confidence interval crossed both MIDs. Established MIDs for ESS -2.5, mean oxygen saturation-5% .GRADE default MID (0.5XSD) used for AHI. .

Appendix G: Health economic evidence selection

Figure 5: Flow chart of health economic study selection for the guideline



* Non-relevant population, intervention, comparison, design or setting; non-English language
** Two studies (in three papers) were included for two different questions
*** One study was considered for two different questions

Appendix H: Excluded studies

H.1 Excluded clinical studies

Reference	Reason for exclusion
Acar 2013[1]	Number of participants in each group not reported
Charakorn 2017[2]	Systematic review checked references
Gaisl 2019[4]	Systematic review- on efficacy of pharmacotherapy for OSA in adults. Screened for relevant references.
Kiely 2004[5]	Cross over study- no washout
Koutsourelakis 2013[6]	Inappropriate population.
McLean 2005[7]	No useable outcomes
NCT 2016[9]	This is an ongoing trial which was due to finish in Aug 2020, at the moment no results have been published.
Phoophiboon 2019[10]	Conference abstract- citation only.
Smith 2019[11]	Full text paper not available
Strobel 2011[12]	Inappropriate population
Wijesuriya 2019[13]	Less than minimum duration

H.2 Excluded health economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2003 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below:

None.