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Drug therapies for obstructive sleep apnoea: a systematic review and meta-analysis protocol

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ABSTRACT

Introduction Obstructive sleep apnoea (OSA) is a common disorder that can affect the quality of life and increase the risk for psychiatric, neurological and cardiometabolic diseases. Despite the significant burden, it poses on health and well-being, there is a lack of evidence regarding the use of drug therapies in these patients. This work aims to evaluate the efficacy and safety of pharmacological treatment alternatives for patients with OSA.

Methods and analysis Databases, including PubMed, Embase, Web of Science, SciELO, LILACS, Scopus, Cochrane Register of Controlled Trials and ClinicalTrials.gov, will be used for the search. A search strategy was developed to retrieve clinical trials that have evaluated polysomnographic primary outcome (Apnoea-Hypopnoea index) and secondary outcomes (eg, daytime sleepiness, adverse events) of any drug therapy used for OSA. No date or language restrictions will be applied. Two authors will independently select the studies meeting the inclusion criteria by screening the title, abstract and full text. Data will be extracted, and the risk of bias will be evaluated using the Cochrane Risk of Bias Tool. Review Manager V.5.4.1 will be used for data synthesis. The Grading of Recommendation Assessment, Development and Evaluation will be used to assess the strength of the evidence.

Ethics and dissemination As a review of published data, it is not necessary to obtain ethical approval. The findings of this systematic review will be published in a peer-reviewed journal.

PROSPERO registration number CRD42022362639.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ There have been important developments and publications regarding the use of pharmaceutical preparations in the last few years, worth to be reviewed.
⇒ A well-designed protocol contributes both to the robustness of the evidence that will be provided and to the transparency of science.
⇒ The heterogeneity of the interventions in the eligible studies may impose a limitation on data synthesis.
⇒ The small number of patients included in well-conducted clinical trials may limit the strength of the evidence obtained by the review.

INTRODUCTION

Description of the condition

Sleep is a foundational aspect of human biology. Grandner and Fernandez compared our need for sleep with that for air, food and water.[1] Impairment in sleep can cause a decrease in the quality of life and contribute to cardiovascular, metabolic, neurological and psychiatric disorders.[2–8] Conversely, the American Heart Association recently added sleep as one of the essential factors in cardiovascular health (Life's Essential 8).[8 9]

Obstructive sleep apnoea (OSA) is a condition in which repetitive upper airway closure occurs during sleep, leading to decreased oxygen saturation and impaired sleep architecture.[10–13] It is estimated to affect approximately one billion people worldwide.[14]

According to the American Academy of Sleep Medicine (AASM), the criteria for diagnosing OSA is the occurrence of five or more predominantly obstructive respiratory events per hour in polysomnography associated with signs and symptoms (sleepiness, fatigue, insomnia, snoring and observed apnoea), medical conditions (hypertension, coronary artery disease, atrial fibrillation, diabetes, cognitive dysfunction or mood disorder), or the occurrence of more than 15 events per hour even in the absence of symptoms and medical conditions.[11]

The sum of sleep apnoea and hypopnoea events per hour is used to calculate the Apnoea–Hypopnoea Index (AHI). The AASM manual recommends scoring of an apnoea event when there is a reduction of at least 90% of the baseline airflow with a minimum duration of 10 s and hypopnoea scoring when there is a 30% reduction of airflow associated with either arousal or a drop of oxygen saturation of 3% (AHI3) (recommended) or a 4% desaturation (AHI4) (optional). AHI

is used to classify OSA into mild (5<AHI<15), moderate (15<AHI<30) and severe (AHI>30).[15]

Moreover, other metrics have been studied in the search for a correlation between the hypoxic burden with symptoms and cardiovascular risks, such as the Oxygen Desaturation Index (ODI), time below 90% saturation, and minimum saturation.[16 17]

Description of the intervention

There are many possible treatments for OSA that must be individually assessed for each patient. These go from behavioural measures, myofascial exercises, oral appliances, surgeries and positive airway pressure (PAP) to hypoglossal nerve stimulators.[18–21] Although continuous PAP treatment remains the leading treatment choice for moderate and severe OSA, its adherence rate is low.[22]

Many pharmaceutical preparations have been studied to treat OSA throughout the years, most with limited results and none have specific approval for this use so far.[23] However, the recent understanding of pathophysiology brought light to new possible targets in pharmacotherapy.[24]

How the intervention might work

The OSA pathophysiological traits, or endotypes, are the anatomy of the upper airway susceptible to collapse, the poor pharynx dilator muscle responsiveness, the low arousal respiratory threshold and the oversensitive ventilatory control system (high loop gain).[25]

Each of these endotypes can present itself as a possible target for pharmacotherapy. The upper airway collapsibility could be treated with weight loss medication, diuretics and nasal decongestions. Muscle responsiveness could be addressed by noradrenergic, serotoninergic and antimuscarinic agents. The arousal threshold could be modified by sedatives and antidepressants. High loop gain could be targeted by carbonic anhydrase inhibitors, acetylcholinesterase inhibitors, opioid antagonists and xanthines.[24]

Why it is important to conduct this review

Drug therapy intended for the management of sleep apnoea has been investigated, but no robust evidence that supports the benefits of its recommended use has been found to date.

Objectives

The aim of this systematic review and meta-analysis is to summarise the evidence on pharmacotherapy intended for the treatment of OSA in adults.

MATERIALS AND METHODS

This systematic review and meta-analysis protocol conforms to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA).[26 27] This protocol is registered in PROSPERO (CRD42022362639).

Inclusion criteria

Randomised and quasi-randomised clinical trials that investigated both the efficacy and safety of any pharmacological therapy to treat sleep apnoea in adults (>18 years of age) will be included.

Exclusion criteria

This review will not analyse observational studies, case reports and studies involving children or those that do not assess the predefined outcomes. Moreover, studies investigating central sleep apnoea, OSA at high altitude and medical gas therapy (eg, supplemental oxygen or carbon dioxide) will also be excluded.

Patient, intervention, comparison, outcome and type of study

The patient, intervention, comparison, outcome and type of study strategy for this study is as follows. The population used will include patients aged 18 years or older diagnosed with OSA according to the AASM criteria, including studies that consider both AHI3 or AHI4, higher than 5 with reported symptoms or higher than 15 even in the absence of symptoms. The intervention is defined as any pharmacological treatment with a theoretical pathophysiological mechanism for OSA treatment. The comparator is defined as PAP and/or lifestyle modifications and/or surgery and/or myofascial exercises and/or placebo. The assessed outcomes will be AHI, ODI, minimal oxygen saturation, time with saturation below 90%, Epworth Sleepiness Scale (ESS),[28] health-related quality of life, cardiovascular events, sleep efficiency, arousal index, per cent of time on sleep stage N1 and REM, insomnia severity index score, patient-reported adverse events and death. The types of included studies will be randomised clinical trials and quasi-randomised clinical trials.

Primary outcome

The primary evaluated outcome will be the reduction in AHI.

Secondary outcomes

The secondary outcomes will be ODI, minimal oxygen saturation, time with saturation below 90%, health-related quality of life measures, ESS, cardiovascular events, sleep efficiency, arousal index, per cent of the time on sleep stage N1 and REM, insomnia severity index score, patient-reported adverse events and death.

Patient and public involvement

This study is a systematic review protocol, which means that individual patient data will not be included. A thorough search of existing literature will be conducted using specified databases. As a result, there will be no engagement of patients in the planning or application process of the study, nor during the analysis or dissemination of the findings.

Search strategy

A thorough search of the following databases will be conducted: PubMed, Embase, Web of Science, SciELO,

Table 1 Search strategy for PubMed

	MeSh terms and keywords
1	Sleep apnea syndromes
2	Obstructive sleep apnea
3	Sleep apnea
4	OR / 1–3
5	Drug therapy
6	Pharmaceutical preparations
7	OR / 5–6
8	Polysomnography
9	Death
10	Myocardial Infarction
11	Stroke
12	Adverse effects
13	Health-related quality of life
14	Sleep quality
15	Disorders of Excessive Somnolence
16	Snoring
17	Sleep Initiation and Maintenance Disorders
18	Weight loss
19	Oximetry
20	OR / 8–19
21	4 AND 7 AND 20

LILACS, Scopus, Cochrane Register of Controlled Trials and Clinical Trials.gov. An initial search strategy was developed for PubMed and adapted for each individual database (table 1). The search will be conducted on 7 January 2024.

The following Medical Subject Headings terms will be used for the search: ((sleep apnea syndromes) OR (obstructive sleep apnea) OR (sleep apnea)) AND ((drug therapy) OR (pharmaceutical preparations)) AND ((polysomnography) OR (death) OR (Myocardial Infarction) OR (stroke) OR (adverse effects) OR (health-related quality of life) OR (sleep quality) OR (Disorders of Excessive Somnolence) OR (Snoring) OR (Sleep Initiation and Maintenance Disorders) OR (weight loss) OR (oximetry)).

Data collection and analysis

Study selection

After the search is conducted in each database, the retrieved studies will be exported to the reference manager software Rayyan (Mourad Ouzzani, University of Oxford, UK). Duplicates will be removed. Two independent authors (MLN and NS) will select the studies that meet the inclusion criteria, screen the titles, and select the abstract and full text. Any discrepancy between the selections of the two reviewers will be resolved by a third reviewer (AKG). The selection process is shown in the PRISMA flow diagram (figure 1).

Data extraction

Two authors (MLN and KSM) will extract the data from the selected studies following a designed form (online supplemental appendix S1). Any occasional discrepancies will be resolved by conducting a discussion with a third reviewer (AKG).

Missing data

In the event of missing data from the selected studies, the authors of the article in question will be contacted by email. If it is not possible to retrieve the missing information, the data will be imputed or deleted, which will be covered in the 'Discussion' section.

Data synthesis

The data extracted from the selected studies will be imported into Review Manager V.5.4.1 software (RevMan, The Cochrane Collaboration, 2020) for quantitative synthesis. The heterogeneity of the studies will be assessed using I^2 statistics, considering <25% as low heterogeneity, 25%–50% as moderate heterogeneity and >50% as high heterogeneity. The decision to use a random effect or a fixed effect model on data synthesis will be based on the heterogeneity results; if I^2 is ≤50%, a fixed effect model will be applied, whereas, in the case of I^2>50%, a random effect model will be used.

For outcomes measured in continuous data measured by the same instruments, the mean difference with a 95% CI will be presented, if an outcome is measured in different ways or scales the standardised mean difference will be used.[29] The risk ratio will be calculated for dichotomous data.

Subgroup analysis will be performed depending on the differences in the population (such as age groups, sex or severity of OSA) or the interventions (medication dosages or follow-up period) of the assessed studies.

If applicable, a sensitivity analysis will be conducted to assess the robustness of the findings and identify particular decisions or missing data that may influence the results of the qualitative synthesis.

For outcomes that cannot be analysed by meta-analysis, a qualitative summary of the findings will be presented in the form of a table.

Quality assessment

Two reviewers (MLN and ACAS) will independently assess the risk of bias using the Cochrane Risk of Bias Tool.[30] Each study will be evaluated for the randomisation process, deviations from intended interventions, missing outcome data, measurement of the outcome and selection of the reported results.

Publication bias will be assessed using Egger's funnel plot if at least 10 studies are included in the meta-analysis.

Assessing certainty in the findings

The Grading of Recommendations Assessment, Development and Evaluation will be used to classify the strength of the evidence obtained by the meta-analysis for each outcome.[31]

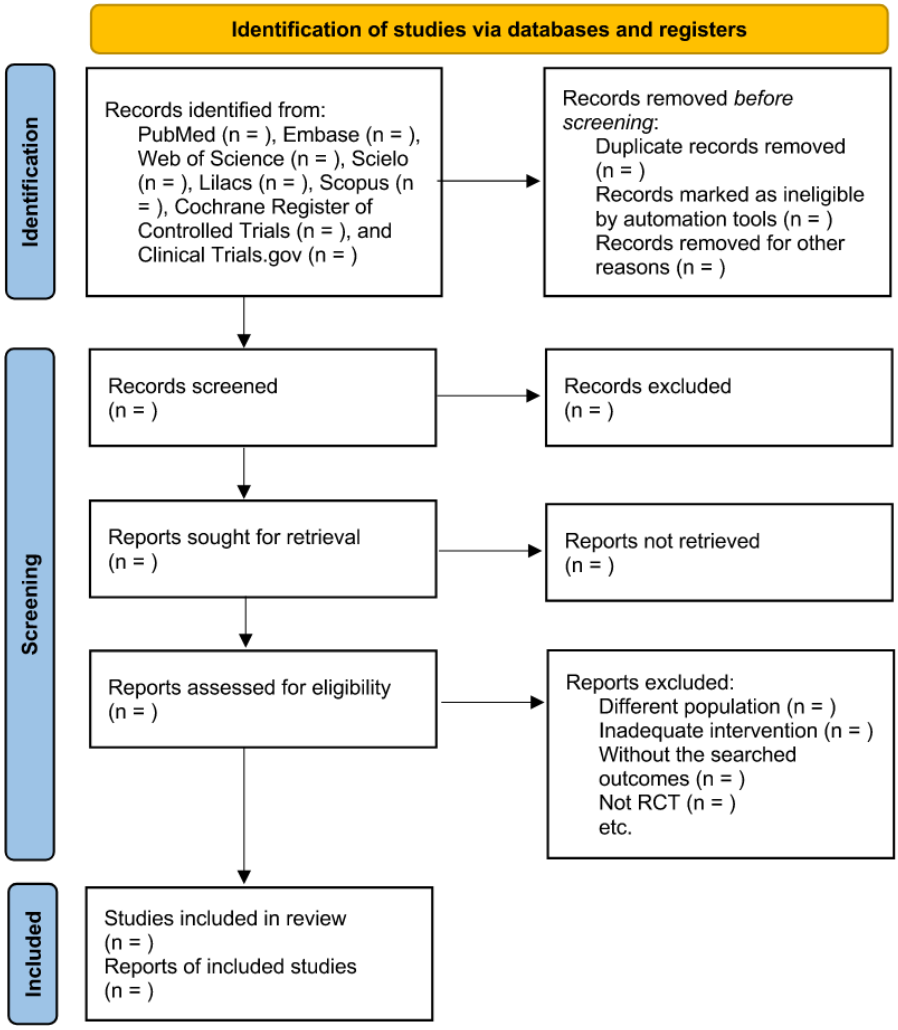

Figure 1 PRISMA flow diagram for systematic review and meta-analysis. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses. RCT: randomised control trial.

DISCUSSION

The increasing prevalence of OSA can be attributed to several factors, such as the ageing of the population and obesity.[32 33] Despite the undoubted burden of untreated OSA, many patients with this condition are not adequately treated.[34 35] The role of endotypes and phenotypes in personalised treatment has been discussed.[36 37] However, PAP treatment remains the leading choice for individuals with symptomatic OSA of any severity, even though it has a low compliance rate.[35 38]

To face these growing challenges, searching for alternative therapeutic approaches is imperative. Drug therapy has been proposed for patients with mild-to-moderate OSA or those who are intolerant to continuous PAP. The possible mechanisms for these pharmacological approaches include an increase in the tone of the upper airway dilator muscles, ventilatory drive and arousal threshold.[38]

Mason *et al*[23] conducted a systematic review addressing this topic. They revealed that there is insufficient evidence to recommend the use of drug therapy for treating OSA. In the last 10 years, since then, studies that present new possibilities for managing OSA have been conducted and published.[39 40]

A potential limitation of the proposed study is the possibility of high heterogeneity among the included articles, which can impair quantitative synthesis. Differences in the medications, administration periods, outcome measures and included populations can pose a drawback.

Ethics and dissemination

This study will only use previously published data; therefore, it does not require an ethics committee's approval. The result of this research will be submitted for publication in a peer-reviewed journal.

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Contributors MLN, ACAS and AKG were responsible for the review's design. MLN, KSM and NS wrote the draft of the protocol's manuscript, and and JDJ and AKG revised it and complemented the work. MLN and KSM developed search strategies. MLN and NS completed formatting. All authors approved the final version for submission.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

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Data extraction (Drug therapy for OSA)

IDENTIFICATION								
Study ID								
First Author								
Publication Year								
Setting								
METHODS								
Design								
Population								
Intervention								
Comparator								
Follow up								
No of patients per arm	Control:				Intervention:			
RESULTS								
AHI	Control				Intervention			
	Before:	After:	Mean	SD	Before:	After:	Mean	SD
ODI	Control				Intervention			
	Before:	After:	Mean	SD	Before:	After:	Mean	SD
Minimal oxygen saturation	Control				Intervention			
	Before:	After:	Mean	SD	Before:	After:	Mean	SD
Time with saturation below 90%	Control				Intervention			
	Before:	After:	Mean	SD	Before:	After:	Mean	SD
HRQoL	Control				Intervention			
	Before:	After:	Mean	SD	Before:	After:	Mean	SD
ESS	Control				Intervention			
	Before:	After:	Mean	SD	Before	After:	Mean	SD
Sleep efficiency	Control				Intervention			
	Before:	After:	Mean	SD	Before:	After:	Mean	SD
Arousal index	Control				Intervention			
	Before:	After:	Mean	SD	Before:	After:	Mean	SD
% N1 sleep	Control				Intervention			
	Before:	After:	Mean	SD	Before:	After:	Mean	SD
% REM sleep	Control				Intervention			
	Before:	After:	Mean	SD	Before:	After:	Mean	SD
CV event (any)	Control:				Intervention:			
MI	Control:				Intervention:			
Stroke	Control:				Intervention:			
Adverse events	Control:				Intervention:			
Death	Control:				Intervention:			

AHI: apnea-hypopnea index, ODI: oxygen desaturation index, ESS: Epworth sleepiness scale, SD: standard deviation, CV: cardiovascular, MI: myocardial infarction