

## SLEEP APNEA PHENOTYPES AND ENDOTYPES: A LITERATURE REVIEW



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### ABSTRACT

**Objectives:** This study explores the relevance of identifying phenotypes and endotypes in the diagnosis and management of OSAS, offering an evidence-based systematic review. It seeks to consolidate scientific advances, address clinical challenges, and discuss controversies, aiming at a more effective and patient-centered clinical practice. It is expected to promote individualized strategies that improve the health and quality of life of patients. **Method:** The research is a literature review, with a survey in PubMed using the keywords "endotypes and phenotypes in obstructive sleep apnea". We used 17 articles published between 2019 and 2024, in English and with free full text, excluding studies on comorbidities, treatments, and specific ethnicities. **Results:** Obstructive sleep apnea syndrome (OSAS) is a chronic disorder characterized by recurrent collapse of the upper airways during sleep, resulting in hypoxemia and sleep fragmentation. Symptoms include snoring, daytime sleepiness, fatigue and cognitive impairments, affecting quality of life. OSAS is a prevalent and underdiagnosed comorbidity, often associated with cardiovascular, metabolic, and neuropsychiatric diseases. Anatomical factors, such as obesity and craniofacial alterations, and non-anatomical factors, such as instability in ventilatory control, influence its development. Personalized treatment, considering endotypes and phenotypes, is crucial to improve therapeutic efficacy, such as CPAP, medications, mandibular advancement devices, and nerve stimulation. **Conclusion:** Knowing that OSAS is a chronic and heterogeneous respiratory disorder, whose diagnosis and management are challenging, it is of paramount importance to integrate new approaches, such as the classification of subgroups based on phenotypes and endotypes, enhancing clinical practice, providing a more accurate and robust diagnosis with personalized treatments and better clinical outcomes, promoting patient-centered care.

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## INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) is a chronic and progressive respiratory disorder that represents a relevant public health problem. It is characterized by recurrent episodes of partial or complete obstruction of the upper airways during sleep, resulting in hemodynamic, neurological and behavioral repercussions, which affect the general health of individuals. Estimates indicate that the prevalence of OSAS varies between 3.7% and 26%, depending on the diagnostic criteria used and the population studied (Piltche et al., 2014; Abu; Khraiche; Amatory, 2024). This breadth highlights the complexity of the disease and its multifaceted etiology.

Among the most common symptoms of OSAS, there are frequent snoring, excessive daytime sleepiness, persistent fatigue, and cognitive disorders that significantly impact the quality of life of patients. In addition, the condition increases the risk of cardiovascular diseases, car accidents, and decreased productivity (Piltche et al., 2014; Boulos; Dharmakulaseelan, 2024). These impacts reinforce the need for early diagnosis and effective management to minimize complications and improve clinical outcomes.

The etiology of OSAS is complex, involving both anatomical factors, such as soft tissue enlargement and retrognathia, and functional alterations, such as reduced pharyngeal muscle activity during sleep (Piltche et al., 2014). Risk factors, such as obesity, male gender, and advanced age, play central roles, although the disease also affects postmenopausal women and children with adenotonsillar hypertrophy (McNicholas; Korkalainen, 2023). This etiological diversity underscores the need for personalized approaches that consider the different underlying causes of upper airway obstruction.

Despite the available options, the management of OSAS in clinical practice faces considerable challenges, being underdiagnosed and undertreated. Polysomnography, although the gold standard for diagnosis, has access limitations and can cause discomfort to the patient, making it difficult to apply it widely (Piltche et al., 2014). From a therapeutic point of view, adherence to the use of continuous positive airway pressure (CPAP) devices, especially in moderate and severe cases, is often low, compromising treatment results. This reality reinforces the need to explore alternatives, such as surgical interventions, intraoral devices, and behavioral therapies (Arredondo et al., 2022; Pépin et al., 2022).

In this scenario, the characterization of clinical phenotypes and physiological endotypes emerges as a promising approach to overcome these challenges. Phenotypes make it possible to identify subgroups of patients based on observable characteristics, such

as symptoms and risk factors (Pépin et al., 2022), while endotypes analyze specific pathophysiological mechanisms, such as airway collapsibility, loop gain, and arousal threshold (Cheng et al., 2023; Dutta et al., 2021; Malhotra et al., 2021). This strategy allows you to personalize treatments, optimize adherence, and improve clinical outcomes by filling critical gaps in the care currently offered.

The present study aims to explore the relevance of identifying phenotypes and endotypes in the diagnosis and management of OSAS, providing an evidence-based systematic review. It seeks to consolidate the available scientific advances, address the clinical challenges and discuss the controversies that still exist, contributing to a more effective and patient-centered clinical practice. Thus, it is expected to promote individualized strategies that positively impact the health and quality of life of patients affected by this condition.

## METHODOLOGY

This study is a literature review, in which a bibliographic survey was carried out in the PubMed database, through the keywords *endotypes and phenotypes in obstructive sleep apnea*, and 51 articles were found, which were submitted to a careful selection.

Publications in the period from 2019 to 2024, English language and full text available for free were used as inclusion criteria, resulting in 25 articles that were read in full. After that, exclusion criteria such as correlation with other comorbidities, specific treatment testing, and studies on characteristic ethnicities were used, resulting in 17 articles used as a basis for the production of the present study.

## RESULTS

The analysis of studies on Obstructive Sleep Apnea revealed fundamental information related to the pathophysiology, endotypes, phenotypes, and clinical implications of the disease. Intermittent hypoxemia and sleep fragmentation, characteristic of OSAS, can trigger cellular and molecular responses that promote sympathetic activation, systemic inflammation, and other pathological changes, contributing to the appearance of neurocognitive disorders, such as excessive daytime sleepiness and reduced quality of life (McNicholas; Korkalainen, 2023). In addition, untreated OSAS is associated with cardiovascular and metabolic comorbidities, as well as high socioeconomic costs. It is estimated that this syndrome affects approximately 936 million adults worldwide,

constituting a significant public health problem, marked by high prevalence and underdiagnosis (McNicholas; Korkalainen, 2023).

Studies have indicated the influence of anatomical factors on the pathophysiology of OSAS, such as narrowing of the airways due to craniofacial changes, obesity (accumulation of fat in the neck), and adenotonsillar hypertrophy (McNicholas; Korkalainen, 2023). Other elements include pharyngeal collapsibility, ventilatory loop gain, arousal threshold, and compensatory function of the airway dilator muscle (Cohen et al., 2024). Non-anatomical factors, such as unstable ventilatory control, low muscle responsiveness, and increased sensitivity to arousals, also aggravate the intermittent upper airway (VAS) collapse, which characterizes OSAS (Malhotra et al., 2021). This collapse results from an imbalance between the negative pressure generated by inspiration and the strength of the dilator muscles of the VAS. In addition, genetic polymorphisms related to serotonin metabolism, inflammation, and obesity have been associated with susceptibility to OSAS (McNicholas; Korkalainen, 2023).

The heterogeneity of OSAS allows it to be classified into subtypes that directly influence the response to treatment. Endotypes reflect the underlying mechanisms, while clinical phenotypes encompass different presentations of the disease (McNicholas; Korkalainen, 2023). With regard to sex differences, one study showed that men had greater airway collapsibility, greater gain in ventilatory loop, and higher arousal threshold when compared to women. Such differences explain up to 30% of the variations in the apnea-hypopnea index (AHI) during NREM sleep. In addition, men and women may respond differently to certain treatments, underscoring the importance of personalized approaches (Eckert et al., 2020).

On the other hand, studies have highlighted the growing interest in personalized treatments for OSAS, especially for patients who are intolerant or non-compliant with CPAP. Therapeutic strategies include drugs that modulate upper airway muscle tone, neurotransmitters, and the autonomic nervous system. Among the drugs investigated are sodium oxybate, which has been shown to increase airway muscle tone, serotonin/norepinephrine reuptake inhibitors, evaluated for their ability to improve muscle response during sleep, and drugs that act to reduce ventilatory instability (Arredondo et. al, 2022).

In addition to these options, mandibular advancement devices (MAD), positional therapies, and hypoglossal nerve stimulation were considered as promising alternatives

(McNicholas; Korkalainen, 2023). In addition, the use of sedatives to increase the arousal threshold and the supply of supplemental oxygen to reduce loop gain have also been shown to be effective in reducing the apnea-hypopnea index (AHI). MAD, for example, works by reducing the passive collapsibility of the upper airways, being an important anatomical therapy (Bosi et al., 2021).

Thus, the development of personalized therapies, based on endotypic and phenotypic characteristics, represents a significant advance. Such strategies not only aim to improve the response to treatment, but also contribute to a higher quality of life of patients with OSAS. Considering the variability of endotypes and phenotypes, the personalization of clinical management emerges as a necessity to adequately meet the particularities of each individual (McNicholas; Korkalainen, 2023).

## **DISCUSSION**

### **OBSTRUCTIVE SLEEP APNEA**

Obstructive sleep apnea is a recurrent collapse of the upper airways during sleep (Eckert et al., 2021), being a disorder characterized by apneas and hypopneas defined as a  $\geq 30\%$  reduction in nasal pressure with paradoxical movements of the chest and abdomen, resulting in a  $\geq 4\%$  desaturation of oxygen saturation (Cheng et al., 2023).

The pathogenesis of OSAS occurs due to anatomical factors of a collapsible or narrow upper airway as assessed by the Mallampati score, by the accumulation of soft tissue in the neck due to obesity or within the upper airways due to adenotonsillar hypertrophy (McNicholas; Korkalainen, 2023), as well as non-anatomical factors defined as physiological endotypes (Eckert et al., 2021). This pathology arises from a periodic blockage of the upper airways during sleep, when the negative pressure generated during inspiration exceeds the force that is exerted by the dilator muscles of the pathway. This imbalance can occur due to factors that increase this negative pressure or decrease the effectiveness of upper airway dilating muscle contractions. As a result of this obstruction, the airflow becomes reduced or absent, generating hypopnea or apnea (McNicholas; Korkalainen, 2023).

The diagnosis of OSAS is made through polysomnography, which uses measures such as electroencephalogram, peripheral saturation, and ventilation. The apnea-hypopnea index (AHI) is calculated by counting the number of obstructed breathing events divided by

the total sleep time and is interpreted as the average number of apneas and hypopneas per hour of sleep, being used as an indicator of apnea severity (Finnsson et al., 2021).

In addition, there can be several consequences caused by this disease, but the main ones are: daytime sleepiness, poor sleep quality, reduced work productivity, premature cardiovascular and cerebrovascular diseases, chronic kidney disease, neurodegeneration, traffic accidents, among others (Eckert et al., 2021).

It is a very prevalent problem in society, affecting, in 2019, approximately one billion people worldwide. Furthermore, it is a public health pathology because it contributes to harmful effects on quality of life (Eckert et al., 2021) and also leads to an economic cost for medical expenses and lost productivity. Despite its high prevalence and important health consequences, this disease remains underdiagnosed, emphasizing the urgency of effective treatment strategies (McNicholas; Korkalainen, 2023).

## PHENOTYPES

A phenotype is defined as the physical and behavioral characteristics of an individual. Obstructive sleep apnea is a heterogeneous disorder and due to differences in clinical presentations, individuals are currently classified into three groups: disturbed sleep, minimally symptomatic and excessive daytime sleepiness (Eckert et al., 2020). In addition, daytime sleepiness, insomnia, hypertension, and cardiovascular events are factors that also reflect individual disease variability (Hoshino et al., 2022). In addition, the subtypes of symptoms that patients present are predictors of cardiovascular and cerebrovascular diseases prevalent in moderate or severe OSAS.

Most patients in the daytime sleepiness group have classic symptoms of OSAS such as snoring and pauses in breathing. Individuals from the other groups may also present it, but less frequently (Eckert et al., 2021). Furthermore, a prevalent clinical phenotype in the population is rapid eye movement OSAS, which affects an average of 18% of patients and is characterized by moments of apnea and hypopnea, especially during REM sleep.

## 4.3 ENDOTYPES

Obstructive sleep apnea is a heterogeneous syndrome with several endotypical traits and symptoms (Cheng et al., 2023). Endotypes are underlying mechanisms that include anatomical dysfunctions, impaired pharyngeal dilator muscle function, unstable ventilatory control, and low arousal threshold (predisposition to waking up with respiratory



disturbances). These endotypes may be related to risk factors for diseases such as post-traumatic stress disorder due to low arousal threshold and neuromuscular diseases due to upper airway dilator muscle dysfunction (Malhotra et al., 2021).

In addition, endotypes correspond to the pathophysiological mechanisms of the disease, being used for the severity categories that are defined by polysomnography and to determine treatment, by identifying which characteristics need to be achieved (Pevernagie, 2021). Currently, there are two methods for determining apnea endotypes, one involves dropping CPAP pressure and finally measuring the ventilation response when the pressure returns to normal and the other performing a measurement of the respiratory impulse response to obstruction using esophageal manometry or diaphragm electromyogram. However, these methods have several drawbacks and a new method for endotyping is being proposed by Sands et al, called "Phenotyping using polysomnography" or PUP, where endotypes can be estimated from a standard PSG (Finnsson et al., 2021).

There are sex differences in endotypes, which indicates that men and women may respond differently to treatments, emphasizing the need for a personalized approach. As an example, one can cite the fact that men have greater airway collapsibility, greater loop gain, and higher arousal threshold compared to women (Eckert et al., 2020). In addition, the endotypes during REM sleep and NREM sleep are different, this can be proven by the fact that patients with OSAS that predominates during REM sleep and isolated OSAS have low respiratory arousal thresholds compared to patients with the predominant disease in non-REM sleep (Hoshino et al., 2022). In addition, there are differences in AHI levels observed in NREM sleep, but not in REM (Eckert et al., 2020).

It is concluded that respiratory endotyping is a promising method for precision medicine, considering the specific differences to treat this heterogeneous condition (Eckert et al., 2020). Personalized medicine is based on genetic, biomarker, phenotypic, or psychosocial characteristics that distinguish one patient from another. Its main goal is to improve clinical outcomes for individual patients by decreasing side effects. Therefore, an endotype-based therapy allows the customization of various devices such as mandibular advancement, hypoglossal nerve stimulation, and emerging pharmacological interventions (Pevernagie, 2021).



## CONCLUSION

OSAS is a chronic respiratory disorder characterized by its heterogeneity, which makes diagnosis and management challenging. This study highlighted the relevance of the approach based on phenotypes and endotypes, which allows a better understanding of the clinical and pathophysiological diversity of the disease. Phenotypes, defined by observable characteristics and endotypes, based on underlying mechanisms, are fundamental tools to personalize therapeutic strategies and improve clinical outcomes (Malhotra et al., 2021; Dutta et al., 2021).

Advances in the characterization of patient subgroups based on phenotypes and endotypes have the potential to transform clinical practice by providing a more accurate and robust diagnosis. The integration of additional metrics into polysomnography, such as biomarkers and new analysis tools, allows for the identification of individual features with greater accuracy, while scalable methods such as the PUP model expand the accessibility and practical application of these tools (Finnsson et al., 2021; Hoshino et al., 2022). In the therapeutic field, personalized strategies, including mandibular advancement devices, hypoglossal nerve stimulation, and pharmacological interventions targeting specific endotypes, offer effective solutions, especially for patients who cannot tolerate CPAP (Arredondo et. al, 2022; Bosi et al., 2021). These approaches highlight the impact of precision medicine on the management of OSAS, promoting greater adherence and better clinical outcomes.

It is noteworthy that, despite the advances, there are still important gaps, such as the absence of large population studies to validate clinical definitions of endotypes and understand how they interact with phenotypes in determining therapeutic responses. In addition, the variability in the presentation of OSAS, particularly in subgroups such as women and patients with isolated REM OSAS, reinforces the need for additional research to explore personalization of treatment (Finnsson et al., 2021; Abu; Khraiche; Amatoury, 2024).

It is concluded that the adoption of approaches based on phenotypes and endotypes represents a fundamental step towards personalized medicine in the management of OSAS. Such strategies not only optimize clinical outcomes, but also promote patient-centered care, which is more effective and adapted to the particularities of each individual. Thus, this review contributes to consolidating the evidence base and directing future

scientific efforts towards a more accurate and efficient management of OSAS (Eckert et al., 2021; Pevernagie, 2021).

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