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OBSTRUCTIVE SLEEP APNOEA – DIAGNOSIS, TREATMENT AND SELECTED COMORBIDITIES. A NARRATIVE REVIEW

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ABSTRACT

Obstructive sleep apnoea (OSA) is a highly prevalent, chronic sleep-related breathing disorder associated with intermittent hypoxaemia, sleep fragmentation, and multisystem morbidity. Despite established diagnostic and therapeutic frameworks, substantial clinical heterogeneity and underdiagnosis persist. This narrative review synthesises current evidence regarding selected diagnostic modalities, established and emerging therapeutic strategies, and selected psychiatric, cardiovascular, respiratory, neurocognitive, and oncological comorbidities in OSA. Attended polysomnography remains the diagnostic gold standard, whereas validated questionnaires (notably STOP-Bang), home sleep apnoea testing, wearable dual-sensor systems (ANNE Sleep), and exhaled breath metabolomics facilitate scalable screening and multi-night monitoring. Continuous positive airway pressure (CPAP) remains first-line therapy; however, personalised alternatives including tirzepatide for obesity-related OSA, aroxybutynin–atomoxetine (AD109) targeting pharyngeal neuromuscular hypotonia, bilateral hypoglossal nerve stimulation, non-permanent orthodontic maxillary expansion, mandibular advancement devices, myofunctional therapy, pulmonary rehabilitation, and paediatric adenotonsillectomy—demonstrate clinically meaningful efficacy. Furthermore, untreated OSA exhibits complex, often bidirectional associations with major depressive disorder, ventricular arrhythmogenesis and sudden cardiac death, asthma–OSA overlap syndrome, blood–brain barrier dysfunction and cognitive impairment, and carcinogenesis.

KEYWORDS

Obstructive Sleep Apnoea, Continuous Positive Airway Pressure, Polysomnography, Tirzepatide, Pulmonary Rehabilitation, Adenotonsillectomy

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1. Introduction

Obstructive sleep apnoea (OSA) is a chronic sleep-related breathing disorder characterised by recurrent episodes of partial or complete upper airway collapse, resulting in reduced airflow (hypopnoea) or cessation of airflow (apnoea), respectively, despite continued respiratory effort. These episodes can lead to intermittent hypoxaemia, brief arousals, and sleep fragmentation, thereby disrupting normal sleep architecture. OSA constitutes a significant public health concern due to its high prevalence, detrimental effects on quality of life, and association with multiple comorbidities (Abbasi et al., 2021; Chang et al., 2023; McNicholas and Pevernagie, 2022).

The estimated prevalence of OSA in the adult population ranges from 9% to 38%, varying by age, sex, body weight, and diagnostic criteria applied (Hynes and Mansfield, 2024). According to epidemiological estimates cited by McNicholas and Pevernagie (2022), approximately 936 million individuals aged 30–69 years globally may meet criteria for at least mild OSA, while approximately 425 million have moderate-to-severe disease. The principal risk factors include obesity, male sex, advancing age, and anatomical abnormalities that contribute to upper airway narrowing (Abbasi et al., 2021; Hynes and Mansfield, 2024; McNicholas and Pevernagie, 2022).

The pathophysiology of OSA is multifactorial, involving anatomical abnormalities as well as disturbances in neuromuscular and central respiratory control. The fundamental mechanism underlying the disorder is increased pharyngeal collapsibility during sleep, arising from an imbalance between the negative pressure generated during inspiration and the activity of the pharyngeal dilator muscles, particularly the genioglossus. Ventilatory control instability and individual differences in the arousal threshold also play important roles. Recurrent episodes of upper airway obstruction lead to intermittent hypoxaemia, sympathetic activation, oxidative stress and inflammation, which may contribute to the development of systemic complications (Abbasi et al., 2021; Chang et al., 2023; McNicholas and Pevernagie, 2022).

The clinical presentation of OSA is heterogeneous. Characteristic nocturnal symptoms include loud snoring, witnessed apnoeas, awakenings with a sensation of breathlessness and restless sleep. During the day, patients may report excessive sleepiness, persistent fatigue, morning headaches, impaired concentration and memory, and reduced psychomotor performance. These symptoms may substantially impair quality of life and increase the risk of road traffic accidents. However, symptom burden does not always correlate with disease severity, and some patients with OSA do not experience overt daytime sleepiness (Abbasi et al., 2021; McNicholas and Pevernagie, 2022; Hynes and Mansfield, 2024).

The diagnosis of OSA is based on clinical assessment and objective sleep testing, with polysomnography remaining the reference standard. The principal measure used to classify disease severity is the apnoea–hypopnoea index (AHI), which represents the number of apnoeas and hypopnoeas per hour of sleep. OSA is classified as mild (AHI 5–14.9 events/h), moderate (AHI 15–29.9 events/h) or severe (AHI ≥30 events/h). Given the limited correlation of AHI with symptom burden and the risk of complications, assessment of nocturnal hypoxaemia, clinical presentation and comorbidities is also important. The European expert consensus emphasises the importance of standardised definitions and a comprehensive approach to the diagnosis of OSA (Chang et al., 2023; McNicholas and Pevernagie, 2022; Olszewska et al., 2024).

OSA is associated with a range of cardiovascular, metabolic and neurological conditions, including hypertension, heart failure, atrial fibrillation, stroke, type 2 diabetes mellitus and cognitive impairment. These relationships may be bidirectional: OSA may contribute to the development or exacerbation of certain conditions, while comorbidities may increase susceptibility to sleep-disordered breathing. Nevertheless, the extent to which these associations reflect direct causal relationships remains under investigation (Abbasi et al., 2021; Chang et al., 2023; McNicholas and Pevernagie, 2022).

The management of OSA primarily involves positive airway pressure therapy, particularly continuous positive airway pressure (CPAP), alongside weight reduction, positional therapy, oral appliances and selected surgical interventions. Treatment selection should take into account disease severity, symptom burden and individual patient characteristics (Abbasi et al., 2021; McNicholas and Pevernagie, 2022; Hynes and Mansfield, 2024).

This review aims to present current knowledge of the diagnosis and treatment of obstructive sleep apnoea and to discuss its associations with selected comorbidities.

2. Methods

This paper is a narrative review. PubMed/MEDLINE, Scopus, and Web of Science were searched for publications available up to November 2026, using combinations of search terms related for the obstructive sleep apnea (OSA, polysomnography, positive airway pressure, tirzepatide, pulmonary rehabilitation, adenotonsillectomy), diagnostics, treatment and comorbidities. It is based on a defined set of 93 full-text publications selected for their relevance to treatments, diagnostics and comorbidities of OSA. No separate systematic database search was conducted specifically for this review, and no protocol was registered. Publications were eligible if they addressed OSA with preference given to meta-analyses, randomized controlled trials, systematic reviews and cohort studies. The resulting evidence base comprised 93 publications dating from 2013 to 2026. Estimates are presented as reported by the original authors, and where discrepancies between sources were identified, the reported range is provided instead of a pooled estimate.

3. Results

3.1. Diagnostics

3.1.1. Polysomnography

Polysomnography (PSG) remains the diagnostic gold standard for OSA, allowing comprehensive assessment of sleep-disordered breathing and sleep architecture. The examination involves the simultaneous recording of neurophysiological and cardiorespiratory parameters, including electroencephalography (EEG), electrooculography (EOG), electromyography (EMG), electrocardiography (ECG), airflow, thoracic and abdominal respiratory movements, and peripheral oxygen saturation (SpO_2). Recording cerebral electrical activity, eye movements and muscle tone enables the identification of individual sleep stages, measurement of total sleep time (TST) and detection of arousals associated with respiratory events (Hussein et al., 2024; Kapur et al., 2017).

The principal measure used to assess OSA severity is the AHI, defined as the mean number of apnoeas and hypopnoeas per hour of sleep. Apnoea is defined as a reduction in airflow of at least 90% from baseline, lasting at least 10 seconds. Hypopnoea is characterised by a reduction in airflow of at least 30% lasting at least 10 seconds, accompanied by an oxygen desaturation of at least 3% or a cortical arousal; alternative criteria require an oxygen desaturation of at least 4%. Differences in hypopnoea scoring criteria may affect the calculated AHI and the classification of disease severity (Hussein et al., 2024; Kapur et al., 2017).

According to the American Academy of Sleep Medicine (AASM) guidelines, PSG is particularly recommended in patients with significant cardiorespiratory disease, suspected sleep-related hypoventilation, respiratory muscle weakness due to neuromuscular disease, chronic opioid use, a history of stroke or severe insomnia. PSG should also be performed when home sleep apnoea testing (HSAT) yields a negative, inconclusive or technically inadequate result and clinical suspicion of OSA persists (Kapur et al., 2017). Unlike conventional polysomnography, most simplified home sleep studies do not allow direct assessment of sleep stages. Consequently, the respiratory event index (REI) is calculated using monitoring time rather than actual sleep time. This may lead to underestimation of disease severity, particularly in patients who spend prolonged periods awake during the recording (Hussein et al., 2024).

Despite its high diagnostic value, laboratory-based PSG has important limitations, including high costs, limited access to specialist centres and discomfort associated with the use of multiple sensors. Another factor that may influence the findings is the first-night effect, which involves changes in sleep quality and architecture in an unfamiliar environment (Braun et al., 2024; Pinilla et al., 2025). Home polysomnography (hPSG) offers an alternative, allowing neurophysiological and respiratory signals to be recorded outside the sleep laboratory. In a systematic review by Braun et al. (2024), comprising 30 studies and 14,465 participants, the pooled technical failure rate for hPSG was 7.8% (95% CI: 5.5–10.1%), supporting the technical feasibility of this approach, although substantial heterogeneity was observed (Braun et al., 2024). A 2025 Cochrane review (van Doorn et al., 2025), including three randomised controlled trials involving 1,143 participants, found that the use of level III sleep studies instead of full PSG did not result in significant differences in daytime sleepiness or quality of life over a follow-up period of 4–6 months. These findings support the use of simplified diagnostic methods in appropriately selected patients, but do not establish their full diagnostic equivalence to PSG (van Doorn et al., 2025).

One emerging diagnostic approach is ANNE Sleep, a wireless system comprising two flexible sensors placed over the suprasternal notch and on the index finger. The device records cardiac activity, thoracic respiratory movements, body position, oxygen saturation and changes in peripheral arterial tone using peripheral arterial tonometry (PAT), among other parameters. Unlike conventional PSG, the system does not incorporate EEG, EOG or EMG; instead, sleep and respiratory events are assessed using indirect physiological signals and analytical algorithms (Pinilla et al., 2025; Davies et al., 2022). In a multicentre study by Davies et al. (2022), involving 225 patients, ANNE Sleep demonstrated a sensitivity of 89.7%, a specificity of 97.5% and an overall diagnostic accuracy of 95.1% for detecting moderate-to-severe OSA (AHI ≥15 events/h), compared with simultaneously performed polysomnography. A strong correlation was also observed between AHI values obtained using the two methods ($r = 0.93$), although the system was less accurate in distinguishing moderate from severe disease (Davies et al., 2022). In a subsequent study, Walter et al. (2023) evaluated ANNE Sleep in the home setting, reporting positive percentage agreement of 85% with Alice NightOne and 58% with WatchPAT for the identification of moderate-to-severe OSA. In addition, monitoring over multiple nights resulted in reclassification of disease severity in 17% of participants, suggesting potential benefits from

repeated measurements (Walter et al., 2023). Despite these promising findings, ANNE Sleep does not replace full polysomnography when detailed assessment of sleep architecture or evaluation of complex sleep-related breathing disorders is required (Kapur et al., 2017; Pinilla et al., 2025).

In summary, polysomnography remains the principal reference standard for diagnosing OSA, particularly in patients with comorbidities or an inconclusive clinical presentation. Advances in home polysomnography and novel physiological monitoring systems may improve access to diagnostic testing and reduce the associated logistical burden. However, the choice of diagnostic method should take into account the pre-test probability of OSA, the patient's clinical status and the diagnostic limitations of individual devices (Kapur et al., 2017; Pinilla et al., 2025; van Doorn et al., 2025).

3.1.2. Screening questionnaires

Screening questionnaires provide a simple, inexpensive means of assessing the likelihood of OSA and prioritising patients for objective sleep testing. Commonly used instruments include the STOP-Bang, STOP and Berlin questionnaires, whilst the Epworth Sleepiness Scale (ESS) assesses subjective daytime sleepiness and has limited value as independent screening tool for OSA (Amra et al., 2018). STOP-Bang combines snoring, tiredness, witnessed apnoeas and hypertension with body mass index, age, neck circumference and sex. A threshold of ≥3 favours sensitivity, although its low specificity results in frequent false-positive findings. In a meta-analysis of patients attending sleep clinics, pooled sensitivity and specificity for moderate-to-severe OSA, defined as an apnoea-hypopnoea index ≥15 events/hour, were 95% and 27% for STOP-Bang, compared with 90% and 29% for STOP and 84% and 30% for Berlin questionnaire (Bernhardt et al., 2022). A separate meta-analysis comprising 47 studies and 26,547 participants supported the use of STOP-Bang for triaging patients referred to sleep clinics, whilst demonstrating geographical variation in its performance (Pivetta et al., 2021). Evidence also supports its application in community and occupational settings, although the findings in commercial drivers were based on only two studies involving 185 participants (Chen at al., 2021). Among surgical patients, STOP-Bang demonstrated pooled sensitivity of 88% and specificity of 29% for moderate-to-severe OSA; corresponding estimates in patients with cardiovascular risk factors were 90.7% and 22.5%, respectively (Hwang et al., 2021; Hwang et al., 2022). These findings indicate that questionnaires therefore support clinical assessment and referral decisions but do not replace PSG or appropriate home sleep apnoea testing (Bernhardt et al., 2022; Hwang et al., 2022).

3.1.3. Biomarkers

In the non-invasive diagnosis of OSA, the analysis of exhaled breath composition is gaining increasing importance. This approach utilizes biomarkers metabolites that reflect biochemical and physiological changes within the body and is applied both in initial diagnosis and in the objective monitoring of treatment adherence and the efficacy of CPAP therapy (Nowak et al., 2021; Bernhardt et al., 2021; Kee et al., 2018).

Advanced analytical techniques, such as secondary electrospray ionization high-resolution mass spectrometry (SESI-HRMS) and gas chromatography-mass spectrometry (GC-MS), are employed to identify molecular markers in exhaled breath. These methods enable the detection of volatile organic compounds (VOCs) including unsaturated aldehydes, furans, thiazoles, and benzenoid compounds which form a unique metabolomic signature characteristic of OSA. Clinical studies involving a randomized CPAP-withdrawal trial have demonstrated that the recurrence of apnea symptoms is associated with alterations in the exhaled breath profile, involving dozens of molecular features (Nowak et al., 2021; Bernhardt et al., 2021).

Independent studies conducted on cohorts of patients with untreated OSA, those undergoing CPAP therapy, and control groups have confirmed the presence of consistent markers. Statistical analysis revealed a significant increase in the concentrations of specific metabolites in patients with Untreated OSA compared to those whose condition is effectively managed. The presence of furans in exhaled air may be linked to changes in the composition of the gut microbiome caused by recurrent intermittent hypoxia, while the presence of aldehydes (such as 4-hydroxy-2-octenal) reflects increased lipid peroxidation induced by oxidative stress in the context of OSA (Nowak et al., 2021; Kee et al., 2018).

Pilot studies have reported promising AUROC values (0.84–0.87); however, these parameters were lower in broader validation studies (AUROC 0.66, sensitivity 76%, specificity 42%). Machine learning models show varying degrees of effectiveness—ranging from an AUC of 0.80 (sensitivity 73%, specificity 80%) when distinguishing between untreated and treated patients, to an AUC of 0.60 in screening tasks. Given the complexity of the data and the lack of extensive population-based validation, this method requires further clinical investigation (Nowak et al., 2021; Kee et al., 2018).

3.2. Treatment

3.2.1. Positive airway pressure

Positive airway pressure (PAP) therapy involves delivering pressurised air to the upper airway via a mask, thereby maintaining airway patency. The aim of this treatment is to eliminate apnoeas and hypopnoeas. In patients with OSA, PAP therapy is recommended throughout the entire sleep period, with a minimum acceptable level of adherence generally defined as ≥4 hours per night. PAP is the first-line treatment for OSA (Patil et al., 2019; Martelli et al., 2022).

Several PAP modalities are available, including CPAP, which maintains a constant pressure throughout the respiratory cycle; bilevel positive airway pressure (BPAP), in which inspiratory pressure is higher than expiratory pressure; and auto-adjusting positive airway pressure (APAP), which uses flow-sensor-based algorithms to increase pressure in response to detected obstructive events and periodically reduce it when such events are absent (Patil et al., 2019).

Several considerations are important when selecting the appropriate treatment modality. Initiating therapy with home APAP and pressure titration have been shown to produce equivalent outcomes. APAP and CPAP are similarly effective, whereas BPAP should not be used routinely but may be considered in patients who are unable to tolerate CPAP or require pressures exceeding the capabilities of standard CPAP devices. For patients who are unable to tolerate PAP therapy, alternative treatment options include mandibular advancement devices and positional therapy, particularly in patients with positional OSA. Other available interventions include weight reduction and surgical treatment (Patil et al., 2019; Song et al., 2026).

PAP therapy in patients with OSA reduces disease severity, with the apnoea–hypopnoea index (AHI) decreasing from 32.7 to 4.1 events per hour following treatment. It also reduces daytime sleepiness and improves quality of life, as reflected by increased sleep latency on the Maintenance of Wakefulness Test (MWT) or the Oxford Sleep Resistance (OSLER) test (standardised mean difference [SMD] 0.5; 95% CI: 0.2–0.8). Furthermore, PAP therapy reduces blood pressure and the risk of road traffic accidents, while improving oxygen saturation by 2.1 percentage points (Patil et al., 2019; Martelli et al., 2022; Song et al., 2026; Tanayapong et al., 2025; Benjafield et al., 2025).

The adverse effects of PAP therapy are primarily associated with discomfort related to the mask and airflow. These include nasal and oral dryness and mucosal irritation, nasal obstruction, mask leakage, facial skin irritation, aerophagia and sleep disturbances. The nature of these adverse effects depends on the type of interface and PAP modality used. Appropriate mask selection and air humidification may help alleviate some of these symptoms (Patil et al., 2019; Song et al., 2026; Tanayapong et al., 2025).

3.2.2. Non-permament orthodontic intraoral device

OSA associated with craniofacial anatomical abnormalities, such as transverse maxillary constriction, maxillary hypoplasia or mandibular retrognathia, may be managed using intraoral orthodontic appliances, such as the Daytime-Nighttime Appliance (DNA), as part of the Complete Airway Repositioning and Expansion (CARE) approach. This represents a potentially advantageous treatment option, associated with reduced patient discomfort compared with conventional fixed orthodontic appliances and surgical treatment (Kushida et al., 2025; Dao et al., 2023; Katz et al., 2022; Aksilp et al., 2025).

Daily use of these appliances for an average of 10–16 hours is recommended. This provides intermittent orthodontic forces that facilitate gradual and effective maxillary expansion. Clinical and retrospective studies have demonstrated a reduction in the AHI in both paediatric patients (by a mean of 29.3%) and adults (by a mean of 46–49%) (Kushida et al., 2025; Dao et al., 2023; Katz et al., 2022; Aksilp et al., 2025). Studies conducted by Dao et al. (2023) and Katz et al. (2022) reported complete resolution of OSA, based on the AHI criteria adopted in the respective studies, in 25.9–28% of patients. As polysomnographic assessments were performed with the appliance removed from the oral cavity, the observed improvements may suggest sustained anatomical remodelling of the bony and soft-tissue structures of the upper airway. This makes the approach a promising alternative to other treatment modalities for OSA associated with craniofacial anatomical abnormalities (Kushida et al., 2025; Dao et al., 2023; Katz et al., 2022; Aksilp et al., 2025).

3.2.3. Tirzepatide

Overweight and obesity are among the risk factors for OSA, as excessive adipose tissue accumulation around the upper airways leads to their physical narrowing and increases their propensity to collapse during sleep. In addition, the development of insulin resistance may adversely affect muscle function (Falcon et al., 2026).

To date, therapeutic management has focused primarily on mechanical interventions, such as PAP therapy, and behavioural interventions. The introduction of incretin-based medications, particularly tirzepatide — a dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist — has represented a major advance in the treatment of patients with OSA and concomitant obesity (Malhotra et al., 2024; Kanu et al., 2025).

The SURMOUNT-OSA trials demonstrated that treatment with tirzepatide at the maximum tolerated dose (10 mg or 15 mg once weekly) resulted in a substantial reduction in the AHI, with mean reductions of 25.3–29.3 events per hour. The primary mechanism underlying the improvement in respiratory function during sleep is substantial weight loss (exceeding 18–20%), which leads to a reduction in adipose tissue deposits within the pharyngeal soft tissues and upper airways, as well as a decrease in systemic inflammation (Falcon et al., 2026; Malhotra et al., 2024).

Tirzepatide has an acceptable safety profile, with the most commonly reported adverse events being gastrointestinal in nature (diarrhoea, nausea, vomiting, constipation, eructation, gastro-oesophageal reflux disease, dyspepsia and abdominal pain), together with injection-site reactions. In addition, two cases of acute pancreatitis were reported. Adverse events were observed predominantly during dose escalation. Importantly, the efficacy of treatment in reducing the AHI and hypoxic burden appears to be maintained irrespective of concomitant PAP therapy or patients' baseline demographic characteristics. The resulting improvements in polysomnographic parameters and patients' quality of life offer new perspectives for the comprehensive and holistic management of patients with OSA and obesity (Falcon et al., 2026; Malhotra et al., 2024; Kanu et al., 2025; McGowan et al., 2025).

3.2.4. Aroxybutynin with atomoxetine (AD109)

The mechanism of action is based on the synergistic combination of atomoxetine and aroxybutynin, which target the neuromuscular mechanisms underlying OSA. Atomoxetine, a noradrenaline reuptake inhibitor, stimulates the hypoglossal motor nucleus, thereby restoring the tone of the upper airway dilator muscles during sleep. Aroxybutynin acts synergistically by supporting muscle activation and counteracting the potentially adverse effects of atomoxetine on sleep architecture. This combination may therefore help maintain pharyngeal airway patency without the need for CPAP therapy (Strollo et al., 2026; Rosenberg et al., 2022).

AD109 is a fixed-dose oral combination of a novel-generation antimuscarinic agent, aroxybutynin (2.5 mg), and a selective noradrenaline reuptake inhibitor, atomoxetine (75 mg). Its mechanism of action is based on the synergistic stimulation of the hypoglossal motor nucleus and enhancement of genioglossus muscle tone, thereby preventing upper airway collapse during both non-rapid eye movement (NREM) and rapid eye movement (REM) sleep. Phase II and III clinical trials have demonstrated the significant efficacy of this therapeutic approach compared with placebo. The results showed a statistically significant and clinically meaningful reduction in the apnoea–hypopnoea index (AHI), with a model-estimated reduction of 44.1% in the phase III trial compared with 17.6% in the placebo group ($P < 0.0001$), together with substantial improvements in oxygenation parameters. Compared with placebo, AD109 treatment in the 26-week SynAIRgy trial resulted in an additional reduction in the oxygen desaturation index (ODI) of 4.5 events per hour ($P = 0.001$), while hypoxic burden decreased by 39.6% relative to the control group ($P < 0.0001$). The most common adverse events affecting treatment tolerability include dry mouth, insomnia, nausea and urinary hesitancy, which occur predominantly during the initial phase of treatment. Owing to its once-daily oral administration at bedtime and its targeted action on the underlying neuromuscular dysfunction, AD109 represents a promising alternative for patients who are unable or unwilling to undergo conventional mechanical treatment, particularly CPAP therapy (Strollo et al., 2026; Rosenberg et al., 2022; Schweitzer et al., 2023).

3.2.5. Myofunctional therapy

Myofunctional therapy is a non-invasive adjunctive treatment for OSA, based on isometric and isotonic exercises targeting the muscles of the tongue, soft palate, pharynx and orofacial structures. The exercises also involve retraining of breathing, swallowing and chewing functions. The proposed mechanism of action involves improving the tone, strength and coordination of the muscles responsible for maintaining upper airway patency, thereby potentially reducing airway collapse during sleep. However, the precise mechanism

of action remains incompletely understood, and the contribution of individual exercises to the observed improvements has yet to be established (Camacho et al., 2015; Rueda et al., 2020).

Research findings suggest that myofunctional therapy may be effective in reducing OSA severity, although the magnitude of the observed effects varies across studies. In a meta-analysis by Camacho et al. (2015), the AHI in adults decreased by approximately 50%, from 24.5 ± 14.3 to 12.3 ± 11.8 events/h ($p < 0.0001$). A beneficial effect on AHI was also reported in a Cochrane systematic review, which demonstrated a mean reduction of 13.20 events/h compared with sham therapy (95% confidence interval [CI]: −18.48 to −7.93), although the certainty of the evidence was rated as low (Rueda et al., 2020). Similarly, a meta-analysis by Ferreira et al. (2025) demonstrated a significant reduction in AHI of 8.85 events/h following myofunctional therapy alone (95% CI: −13.42 to −4.28). In contrast, Xu et al. (2025) reported a reduction in AHI of 8.73 events/h that did not reach statistical significance (95% CI: −21.19 to 3.74; $p = 0.17$). These discrepancies indicate that, although myofunctional therapy may reduce the frequency of sleep-disordered breathing events, its efficacy in this regard has not been conclusively established.

More consistent findings have been reported regarding the effects of myofunctional therapy on OSA-related symptoms. In the meta-analysis by Camacho et al. (2015), daytime sleepiness, assessed using the Epworth Sleepiness Scale (ESS), decreased from 14.8 ± 3.5 to 8.2 ± 4.1 points. Similar findings were reported by Rueda et al. (2020), who demonstrated a 4.52-point reduction in ESS scores compared with sham therapy (95% CI: −6.67 to −2.36). In a more recent meta-analysis, Xu et al. (2025) found significant improvements in both daytime sleepiness (mean difference [MD] = −3.54; $p = 0.004$) and subjective sleep quality, assessed using the Pittsburgh Sleep Quality Index (PSQI; MD = −2.24; $p = 0.0003$). A reduction in snoring intensity was also observed, although the decrease in snoring frequency was not statistically significant. These findings suggest that myofunctional therapy may improve patients' subjective well-being and daily functioning (Xu et al., 2025).

Beneficial outcomes have also been observed in paediatric populations. A meta-analysis by Bandyopadhyay et al. (2020) demonstrated a 43% reduction in AHI, from 4.32 to 2.48 events/h ($p < 0.0001$). A small increase in mean oxygen saturation was also observed, without a significant improvement in minimum oxygen saturation. Furthermore, Camacho et al. (2015) reported a 62% reduction in AHI among children with residual OSA following adenotonsillectomy. Despite these promising findings, the efficacy of myofunctional therapy in this age group requires further confirmation owing to the limited number of randomised controlled trials and the heterogeneity of the treatment protocols employed (Rueda et al., 2020; Xu et al., 2025).

An important consideration is the potential role of myofunctional therapy as an adjunct to CPAP treatment. In the review by Rueda et al. (2020), myofunctional therapy alone was less effective than CPAP in reducing AHI, with a difference of 9.60 events/h in favour of CPAP. Similarly, Xu et al. (2025) confirmed the superiority of CPAP in reducing AHI, while finding no significant additional benefit from combining CPAP with myofunctional exercises. The available evidence therefore supports considering myofunctional therapy primarily as an adjunctive intervention rather than an alternative with efficacy equivalent to that of CPAP. (Rueda et al., 2020; Xu et al., 2025).

Myofunctional therapy is considered a non-invasive intervention with a potentially low risk of complications; however, the lack of systematic reporting of adverse events in the available studies precludes a definitive assessment of its safety (Rueda et al., 2020).

The main limitations of myofunctional therapy include the need for regular exercise, the dependence of treatment outcomes on patient adherence, and the lack of standardised treatment protocols. Adherence is particularly challenging in paediatric patients, with higher adherence rates reported for passive (89%) than active (43.4%) myofunctional therapy (Bandyopadhyay et al., 2020). A further challenge is the lack of objective monitoring of exercise adherence, which limits the assessment of the relationship between treatment intensity and therapeutic efficacy (Xu et al., 2025). The reliability of the available evidence is also limited by small sample sizes, heterogeneity of interventions, and short follow-up periods. Further research is therefore needed to establish optimal treatment protocols and determine the long-term durability of therapeutic effects (Rueda et al., 2020; Ferreira et al., 2025; Xu et al., 2025).

3.2.6. Bilateral hypoglossal nerve stimulation

Bilateral hypoglossal nerve stimulation (biHNS) represents an alternative treatment for OSA, primarily intended for patients who are unable to tolerate PAP therapy or who derive insufficient benefit from it. Its mechanism of action involves electrical stimulation of both hypoglossal nerves, inducing contraction of the genioglossus muscles and anterior displacement of the tongue, thereby increasing upper airway patency and

reducing pharyngeal collapsibility during sleep. The studies employed the Genio system, comprising a small implant positioned in the submental region and an external controller that powers the device and delivers electrical impulses according to an individually programmed stimulation cycle, without requiring synchronisation with respiration (Eastwood et al., 2020; Woodson et al., 2025).

The efficacy of biHNS has primarily been demonstrated through significant reductions in the AHI. In a prospective study, Eastwood et al. reported a reduction in mean AHI from 23.7 ± 12.2 to 12.9 ± 10.1 events/h after six months of treatment ($p < 0.0001$), corresponding to a mean individual reduction of 47.3%. A therapeutic response according to the Sher criteria, defined as an AHI reduction of at least 50% and a final AHI below 20 events/h, was achieved in 50% of patients in the modified intention-to-treat analysis and 57.9% in the per-protocol analysis. Similarly, Heiser et al. demonstrated a reduction in mean AHI from 39.9 ± 14.8 to 19.2 ± 14.0 events/h after three months ($p = 0.008$), with a therapeutic response rate of 66% (Eastwood et al., 2020; Heiser et al., 2022).

The most robust evidence regarding treatment efficacy comes from the multicentre study by Woodson et al., in which mean AHI decreased from 27.8 ± 11.5 to 9.5 ± 9.4 events/h after 12 months ($p < 0.001$). A therapeutic response according to the Sher criteria was achieved in 63.5% of all participants, compared with 81.8% in the per-protocol analysis. This difference highlights the importance of the analytical approach when assessing treatment effectiveness, as the higher response rate was observed only among patients who completed the study in accordance with the protocol (Woodson et al., 2025).

Reductions in AHI were accompanied by significant improvements in the oxygen desaturation index (ODI). Eastwood et al. reported a decrease in mean ODI from 19.1 ± 11.2 to 9.8 ± 6.9 events/h ($p < 0.0001$), whilst Heiser et al. observed a reduction from 37.6 ± 13.1 to 19.5 ± 11.2 events/h ($p = 0.008$). In the study by Woodson et al., ODI decreased from 26.9 ± 14.4 to 9.2 ± 9.6 events/h ($p < 0.001$), with 71.3% of all participants achieving a reduction of at least 25%. Furthermore, a significant reduction in supine AHI, from 49.4 ± 20.7 to 22.7 ± 19.9 events/h ($p < 0.001$), suggests that treatment efficacy is maintained during sleep in the supine position (Eastwood et al., 2020; Heiser et al., 2022; Woodson et al., 2025).

Improvements in respiratory parameters were accompanied by enhanced quality of life, reduced daytime sleepiness and decreased snoring severity. Eastwood et al. reported a reduction in the Epworth Sleepiness Scale (ESS) score from 11.0 to 8.0 points, alongside an increase in the Functional Outcomes of Sleep Questionnaire (FOSQ-10) score from 15.3 to 17.2 points. Similar findings were reported by Woodson et al., who observed a decrease in ESS score from 9.7 to 6.2 points and an increase in FOSQ-10 score from 16.0 to 18.2 points ($p < 0.001$). The proportion of patients with severe snoring decreased from 96% to 35% and from 83.5% to 30.4%, respectively.Findings regarding sleep architecture were also inconsistent: Eastwood et al. demonstrated improved sleep efficiency, whereas Woodson et al. found no significant changes in total sleep time or sleep-stage distribution (Eastwood et al., 2020; Woodson et al., 2025).

A direct comparison between bilateral and unilateral hypoglossal nerve stimulation revealed no statistically significant differences in treatment efficacy. Therapeutic response rates according to the Sher criteria were 66% and 70%, respectively. Although these findings suggest broadly comparable clinical effectiveness, the small sample sizes and non-randomised study design preclude definitive conclusions regarding the equivalence of the two techniques (Heiser et al., 2022).

The safety profile of biHNS was considered acceptable, although the procedure is not without complications. Eastwood et al. reported no serious device-related adverse events, although three patients experienced serious postoperative complications. Woodson et al. documented 11 serious adverse events affecting 8.7% of participants, eight of which were associated with the device or implantation procedure. Common adverse effects included swallowing difficulties, dysarthria, discomfort during stimulation and skin irritation caused by the adhesive patch securing the external controller. Most non-serious adverse events resolved within the first postoperative month; however, implant migration or loss of effective stimulation occasionally necessitated further surgical intervention (Eastwood et al., 2020; Woodson et al., 2025).

The principal challenges associated with biHNS include accurate electrode implantation, gradual optimisation of stimulation parameters and the need for daily use of an external controller. In the study by Eastwood et al., stimulation optimisation required up to four months, whilst 48.7% of participants in the study by Woodson et al. had not achieved optimal settings after six months of treatment. Despite these challenges, most evaluated patients reported regular device use, although the absence of objective monitoring of usage duration limits the reliability of these findings (Eastwood et al., 2020; Woodson et al., 2025).

In conclusion, bilateral hypoglossal nerve stimulation demonstrates significant efficacy in reducing sleep-disordered breathing, improving nocturnal oxygenation and enhancing selected quality-of-life outcomes.

Nevertheless, the predominantly non-randomised study designs, selective patient populations, participant attrition and limited comparative evidence highlight the need for further research to establish long-term efficacy, safety and any potential advantages over unilateral hypoglossal nerve stimulation (Eastwood et al., 2020; Heiser et al., 2022; Woodson et al., 2025).

3.2.7. Mandibular advancement device design

Mandibular advancement devices (MADs) are one of the treatment options for OSA. Their mechanism of action involves maintaining the mandible and tongue in an anterior position, thereby increasing upper airway patency and reducing its collapsibility during sleep. MADs can be classified into monoblock appliances, which restrict mandibular movement, and biblock appliances, which allow adjustment of mandibular protrusion, including midline traction and bilateral thrust designs (Uniken Venema et al., 2021; Ishiyama et al., 2019).

Studies have demonstrated the efficacy of MADs in reducing the AHI, although no particular design has been consistently shown to be superior. In a meta-analysis by Ishiyama et al. (2019), monoblock appliances achieved a significantly greater reduction in AHI than biblock appliances, with a mean difference of 2.92 events/hour (95% CI: 1.26–4.58; $p = 0.0006$). However, a larger meta-analysis by Uniken Venema et al. (2021) found no statistically significant advantage of monoblock appliances over bilateral thrust designs. More favourable outcomes were reported for midline traction appliances, with 57% of patients achieving an AHI below 5 events/hour, compared with 47% using monoblock appliances. In another study, short-term treatment success rates were 79% and 51% for midline traction and bilateral thrust appliances, respectively. Treatment success rates ranged from 26% to 72% for custom-made appliances and from 17% to 52% for thermoplastic devices, although pooled analysis did not demonstrate a significant difference in AHI reduction. No significant differences between appliance designs were observed in improvements in daytime sleepiness, as assessed using the Epworth Sleepiness Scale (ESS). Beneficial treatment effects were also reported after 24 months, although long-term evidence remains limited (Ishiyama et al., 2019; Uniken Venema et al., 2021).

An important limitation of MAD therapy is the occurrence of adverse effects, particularly dento-occlusal changes and temporomandibular or masticatory muscle symptoms. Long-term use may lead to reductions in overjet and overbite, with greater changes observed in adjustable appliances. However, adjustable designs were associated with fewer temporomandibular joint and masticatory muscle complaints. Musculoskeletal symptoms were generally transient, whereas occlusal changes could be permanent. No significant skeletal changes or conclusive evidence of periodontal damage were identified (Wang et al., 2025).

Challenges associated with MAD therapy include determining the optimal degree of mandibular protrusion, ensuring adequate appliance retention and maintaining treatment adherence. Excessive protrusion may increase adverse effects, whereas insufficient advancement may compromise treatment efficacy. Custom-made appliances demonstrated greater patient acceptance and adherence but were more expensive than thermoplastic devices, which may also be affected by material deterioration over time (Uniken Venema et al., 2021; Wang et al., 2025).

An emerging development is the use of smart MADs, which enable treatment monitoring and automatic adjustment of mandibular protrusion in response to physiological parameters. These devices may potentially improve treatment efficacy and safety; however, their clinical superiority over conventional appliances has not yet been established. Additional limitations include technological costs and concerns regarding patient data protection (Yang et al., 2024).

In conclusion, MADs are effective in reducing sleep-related respiratory disturbances in patients with OSA. Nevertheless, appliance selection should be guided by individual treatment response, tolerability and the risk of adverse effects. Definitive comparisons between different designs remain challenging because of study heterogeneity, small sample sizes and limited evidence regarding long-term efficacy and the effects of treatment on cardiovascular events and mortality (Ishiyama et al., 2019; Uniken Venema et al., 2021; Wang et al., 2025; Yang et al., 2024).

3.2.8. Pulmonary rehabilitation

In the complex treatment of OSA, pulmonary rehabilitation (PR) is a crucial, non-pharmacological complementary management option. PR does not replace CPAP therapy in terms of reduction of AHI. However, structured programs that combine improved general condition, targeted respiratory muscle training, education, psychological support, and dietary guidance significantly reduce functional impairment and improve health-related quality of life (HRQoL) (Agarwal et al., 2022; Sykes et al., 2022; Shen et al., 2024; Mittal et al., 2024; Guerro-Vega et al., 2026; Pierobon et al., 2023; Iftikhar et al., 2024).

The basis of the effectiveness of PR is primarily the improvement of the tonicity and efficiency of the muscles of the upper airways, which reduces the risk of collapse during sleep (Beatty et al., 2025). In this context, the aimed inspiratory muscle training (IMT) relieves the respiratory system, which is prone to constant resistance and recurrent dyspnea episodes (Dar et al., 2022). Meta-analyses have shown that IMT significantly increases maximal inspiratory pressure (Pimax, SMD = 1,73; p=0,004) and volume FEV1 (SMD = 0,74; p = 0,007) (Dar et al., 2022). In the patients' daily functioning, this translates into a significant improvement in subjective sleep quality, as measured by the PSQI scale (SMD = -1.29; $p < 0.0001$), and a noticeable reduction in daytime sleepiness, as measured by the ESS scale (SMD = -1.08; $p = 0.003$) (Dar et al., 2022).

Except for IMT, a multidisciplinary program of exercises (aerobic and resistance training) aids weight reduction, improves effort tolerance, and improves night oxygenation (Agarwal et al., 2022; Sykes et al., 2022; Guerro-Vega et al., 2026; Pierobon et al., 2023; Iftikhar et al., 2024; Dar et al., 2022). Combining exercise with CPAP produces a synergistic effect, improving efficiency (VO2peak), endothelial function, and blood pressure control. It is worth noting certain differences in the literature: some authors show that the positive cardiovascular results ensue from increased metabolic reserve and general efficiency, but not from direct changes in resting hemodynamic parameters (Sykes et al., 2022; Mittal et al., 2024; Iftikhar et al., 2024).

A particular challenge is combining clinical phenotypes like COPD-OSA overlap syndrome. In this group of patients, 20-week rehabilitation protocols significantly improve exertional tolerance (6MWD) and dyspnea scores (mMRC). Diaphragm ultrasound examinations show improved diaphragm excursion and thickness fraction (DTF), with over half of patients (57%) demonstrating a positive functional response characterized by improved ventilation (FEV1%), higher arterial oxygenation (PaO2), and diaphragmatic mobility (Shen et al., 2024).

Digital platforms and telerehabilitation are the least burdensome form of support, as they bypass barriers associated with traditional, in-person rehabilitation—such as travel costs or geographical limitations. Online monitoring, mobile applications, and teleconsultation help maintain regular home-based exercises and improve adherence to recommendations for concurrent CPAP use (Hnatiak et al., 2023; Peng et al., 2026).

3.2.9. Adenotonsillectomy

Adenotonsillectomy is the primary treatment for OSA in children with adenotonsillar hypertrophy. The procedure reduces anatomical obstruction of the upper airway. Treatment decisions should take into account disease severity, symptoms and quality of life; a particularly individualised approach is required in mild OSA, for which watchful waiting with supportive care and reassessment may be an alternative (Tsikopoulos et al., 2024; Chinnadurai et al., 2017).

Studies demonstrate that adenotonsillectomy is superior to watchful waiting in terms of changes in AHI (SMD = −0.60; 95% CI: −0.79 to −0.41), with an AHI difference of approximately −4.81 events/h favouring surgery, and quality of life assessed using the OSA-18 questionnaire (SMD = −0.79; 95% CI: −0.97 to −0.61). A greater improvement in AHI was also demonstrated in mild and mild-to-moderate OSA (Tsikopoulos et al., 2024; Chinnadurai et al., 2017).

However, surgery is not necessary for every child with mild OSA. In the CHAT trial, polysomnographic findings normalised in 46% of children managed with watchful waiting. This supports considering conservative management in selected patients with non-severe OSA and no complications. Follow-up is essential, as spontaneous improvement is not guaranteed and the disease may worsen (Tsikopoulos et al., 2024).

Partial removal of the palatine tonsils as part of adenotonsillotomy (ATT) is an alternative to their complete removal in adenotonsillectomy (ATE); both procedures include removal of the adenoids. Conventional ATE was compared with coblation ATT (Borgström et al., 2019). Children reported resolution of pain earlier after ATT, with a median of 5 days compared with 8 days after ATE ($p = 0.021$). However, significant differences were found in only two of the six pain-related outcomes. No differences were observed in the duration of analgesic use or the time to resumption of a normal diet. Intraoperative blood loss was lower with ATT: 28.6 versus 55.1 ml ($p < 0.001$). Postoperative bleeding occurred in 5% of children following ATE and in none following ATT, although this difference was not statistically significant ($p = 0.494$) (Borgström et al., 2019; Fehrm et al., 2020).

Approximately 12 years after tonsillotomy or tonsillectomy, quality of life was similarly good, but reoperation rates were 6.9% and 1.0%, respectively; tissue regrowth was a common reason for reoperation following partial removal. However, this retrospective study, with a response rate of 27% and no follow-up polysomnography, does not establish sustained resolution of OSA. OSA may also persist after ATE,

particularly in patients with obesity, craniofacial abnormalities or more severe disease at baseline, highlighting the need for follow-up assessment (Tsikopoulos et al., 2024; Virkkunen et al., 2025).

Adenotonsillectomy improves sleep-related respiratory parameters and quality of life in children with OSA, whereas the cognitive benefits are less clear. The choice of surgical technique requires consideration of pain, bleeding and the potential need for reoperation, and postoperative improvement does not always indicate complete resolution of OSA (Tsikopoulos et al., 2024; Chinnadurai et al., 2017; Borgström et al., 2019; Fehrm et al., 2020; Virkkunen et al., 2025; Waters et al., 2020; Taylor et al., 2016).

3.3. Comorbidities

3.3.1. Depression

Depression is an important comorbidity of OSA, associated with poorer quality of life and difficulties with treatment adherence. Studies have estimated the prevalence of major depressive disorder among individuals with OSA at 17% (95% CI: 9–30%). Substantial heterogeneity among the studies included in the meta-analysis by Yeşiloğlu et al. (2026) limits the precision of this estimate. Furthermore, the co-occurrence of these conditions does not establish causality, and further research is therefore needed to clarify their relationship (Yeşiloğlu et al., 2026).

Proposed mechanisms underlying the development of a depressive episode in patients with OSA include sleep fragmentation, intermittent hypoxia and reoxygenation, oxidative stress, inflammation, disturbances in serotonergic neurotransmission and dysregulation of the hypothalamic–pituitary–adrenal axis. Structural and metabolic changes in brain regions involved in emotional regulation, including the hippocampus, amygdala and frontal cortex, may also play a role. Obesity, cardiovascular disease and metabolic disorders may further contribute to a shared susceptibility to both conditions; however, the contribution of each mechanism remains incompletely understood (Yeşiloğlu et al., 2026; Jackson et al., 2021; Zheng et al., 2019).

The diagnosis of depression is complicated by overlapping symptoms of fatigue, sleep disturbance and impaired concentration; therefore, an elevated score on questionnaires used to assess depression should not be equated with a clinical diagnosis. Particular importance should be placed on a clinical history addressing core affective symptoms, especially anhedonia and low mood, and their relationship to OSA-related symptoms (Jackson et al., 2021). Estimates of comorbidity are also influenced by the diagnostic method: studies using structured psychiatric interviews and polysomnography generally report a higher prevalence of co-occurrence than analyses based on administrative codes (Yeşiloğlu et al., 2026).

Treatment with CPAP reduces depressive symptom severity on average, although the pooled effect is small and its clinical significance remains uncertain (Zheng et al., 2019; Balk et al., 2024; Yang et al., 2020). In the SAVE analysis, which included patients with moderate or severe OSA and cardiovascular disease, CPAP reduced the odds of exceeding the threshold for depressive symptoms on the HADS-D scale (adjusted OR = 0.80; 95% CI: 0.65–0.98). The benefit was greater among patients with depressive symptoms at baseline and persisted after adjustment for changes in daytime sleepiness (Zheng et al., 2019).

In a smaller randomised trial, depression diagnosed by clinical interview was present after four months in 7% of assessed patients receiving CPAP and 35% of those in the waiting-list group; however, the small sample, missing data and absence of sham CPAP limit confidence in this finding (Jackson et al., 2021). Improvements in depression scale scores have also been observed following surgery for OSA, but limitations of the available studies preclude firm conclusions regarding its equivalence to CPAP in this respect (Marrero-Gonzalez et al., 2025).

These findings support assessing mood in patients with OSA and considering the possibility of coexisting OSA in people with depression, particularly when symptoms persist and risk factors are present. However, improvements in mood following treatment of sleep-disordered breathing should not be equated with confirmed remission of a depressive disorder (Yeşiloğlu et al., 2026; Jackson et al., 2021).

3.3.2. Sudden cardiac death

Sudden cardiac death (SCD) may be a serious consequence of OSA; however, the available evidence does not conclusively establish an independent causal relationship. In the meta-analysis by Zou et al. (2025), the overall estimate of the association between OSA and SCD did not reach statistical significance (OR = 1.41; 95% CI: 0.91–2.16), whereas increased odds of this outcome were observed in the subgroup with untreated OSA (OR = 3.87; 95% CI: 1.09–13.81).

Potential arrhythmogenic mechanisms include intermittent hypoxaemia and hypercapnia, arousals and sympathetic activation, oxidative stress, and fluctuations in intrathoracic pressure and myocardial loading,

which may be accompanied by abnormalities in ventricular repolarisation. Recurrent haemodynamic changes may promote arrhythmias through myocardial stretch and mechano-electric coupling, while autonomic imbalance may contribute to both tachyarrhythmias and nocturnal bradyarrhythmias and sinus pauses (Kwon et al., 2017; Domaradzki et al., 2022). The importance of nocturnal hypoxaemia is supported by observations cited in the analysed publications suggesting that the depth of desaturation may predict SCD independently of other factors. Gami et al. (2013) reported an HR of 1.81 (95% CI: 1.28–2.56) for a minimum nocturnal SpO_2 threshold of 78%, highlighting the importance of assessing the severity of hypoxaemia alongside the AHI.

Indirect evidence of increased arrhythmic susceptibility is provided by the higher incidence of appropriate implantable cardioverter-defibrillator (ICD) therapies in patients with OSA and heart failure with reduced ejection fraction (RR = 1.43; 95% CI: 1.01–2.03). These therapies include shocks and antitachycardia pacing and indicate ventricular arrhythmias requiring device intervention; however, they are not equivalent to SCD, and findings from this specific population should not be directly extrapolated to all patients with OSA (Kwon et al., 2017). The reported shift towards nocturnal occurrence of SCD and arrhythmias suggests a role for apnoea-related disturbances, although the circadian pattern of electrical abnormalities is not uniform. In the analysis by Schlatzer et al. (2018), the longest QTc intervals were observed between 18:00 and 24:00, whereas findings regarding a nocturnal peak in ICD therapies were inconsistent: some studies found a higher incidence of interventions between midnight and 06:00, while others did not confirm this association (Kwon et al., 2017; Schlatzer et al., 2018).

CPAP may reduce the frequency of premature ventricular contractions and episodes of non-sustained ventricular tachycardia, particularly in patients with marked oxygen desaturation and a nocturnal predominance of arrhythmias. In the study by Domaradzki et al. (2022), reductions in both types of arrhythmia were observed after three months of treatment, with greater reductions in premature ventricular contractions among patients with a minimum SpO_2 ≤80%. Treatment may also improve indices of repolarisation: in an analysis of a randomised trial, the mean 24-hour QTc interval decreased by 11.3 ms compared with subtherapeutic CPAP, with the effect largely driven by patients with a baseline QTc >430 ms (Schlatzer et al., 2018). However, it has not been conclusively demonstrated that improvements in these parameters translate into a reduction in SCD. In a study of patients with heart failure and an ICD, the difference in the incidence of appropriate shocks between the CPAP and control groups was not statistically significant (12.5% versus 22.5%; $p = 0.24$), despite a reduction in premature ventricular contraction burden and improvements in electrocardiographic parameters (Seyis et al., 2018).

When evaluating these associations, SCD should be consistently distinguished from cardiovascular and all-cause mortality, as increases in these broader mortality measures do not establish the mechanism of death and do not provide specific evidence of an increased risk of sudden cardiac death (Heilbrunn et al., 2021; Zou et al., 2025).

3.3.3. Asthma

OSA and asthma often occur together, a combination described in the literature either as asthma–OSA overlap syndrome (aOVS) or as a distinct clinical endophenotype. Patients with asthma are two to three times more likely to develop OSA than the general population, and this risk climbs steeply with disease severity. In severe asthma, concomitant OSA affects nearly 90% of patients. Long-term data from the Wisconsin Sleep Cohort also point to a duration effect: every additional five years of living with asthma incrementally raises the risk of developing sleep apnea. This interaction is bidirectional. Each condition aggravates the symptom burden and clinical course of the other (Prasad et al., 2019; Español et al., 2025).

Unrecognized OSA directly alters airway physiology in asthmatic patients. Repeated apneic episodes expose the respiratory tract to cyclical oxidative stress and mechanical microtrauma, while chronic airway inflammation remodels soft tissues and makes the upper airway more collapsible during sleep. At the same time, intermittent hypoxia and fragmented sleep trigger a pro-inflammatory cascade that speeds up bronchial remodeling and heightens airway hyperresponsiveness (Prasad et al., 2019; Saxena et al., 2023).

Treating asthma without addressing coexisting sleep apnea rarely yields full symptom control. Standard anti-inflammatory inhalers cannot compensate for the mechanical stress of upper airway collapse at night. Introducing CPAP in patients with aOVS eliminates apneic and hypopneic events, which in turn reduces the frequency of asthma exacerbations. When paired with weight management and targeted treatment of comorbidities, CPAP stabilizes both upper and lower airway function. Patients with difficult-to-treat or refractory asthma should therefore be routinely screened for OSA (Prasad et al., 2019; Español et al., 2025; Pardo-Manrique et al., 2021; Sundbom et al., 2018).

3.3.4. Cognitive impairment

Untreated OSA carries a high risk of neurobiological injury, driven largely by intermittent hypoxia and fragmented sleep. Repeated drops in blood oxygen during apneic cycles generate reactive oxygen species (ROS) that alter the redox state of occludin, a key tight-junction protein in the cerebral vascular endothelium. Once the blood–brain barrier weakens, systemic inflammatory mediators cross into the brain parenchyma and provoke local neuroinflammation. This process impairs synaptic plasticity within dendritic spines and triggers neuronal apoptosis, particularly in hypoxia-sensitive regions like the hippocampus and prefrontal cortex. Sleep fragmentation and the loss of slow-wave sleep further compound this damage by slowing down the glymphatic system, which clears neurotoxic waste at night. When glymphatic clearance fails, pathological proteins (such as amyloid-beta and tau) accumulate faster, raising the long-term risk of neurodegenerative dementia (Caporale et al., 2020; Lim and Pack, 2013; Legault et al., 2021).

Clinically, cognitive deficits in OSA vary from patient to patient, though executive functions suffer most often. Patients typically struggle with planning, cognitive flexibility, response inhibition, and decision-making, alongside a noticeable drop in daytime vigilance. On standardized tests such as the Montreal Cognitive Assessment (MoCA), a large share of untreated OSA patients score below the 26-point cutoff for mild cognitive impairment (Caporale et al., 2020; Legault et al., 2021; Davidescu et al., 2024).

These deficits look quite different in adults than they do in children. In adults, impairments in working memory, attention, and decision-making develop gradually; over years, chronic oxidative stress and inflammation cause structural brain damage that may not fully reverse even after starting CPAP. Children present differently. Instead of classic daytime sluggishness, pediatric OSA patients often react to fragmented sleep with hyperactivity, impulsivity, and irritability that closely mimic attention-deficit/hyperactivity disorder (ADHD). Although sleep-disordered breathing during key developmental windows can hurt school performance, the high neuroplasticity of the pediatric brain means that early treatment usually restores normal cognitive function (Caporale et al., 2020; Krysta et al., 2016).

In adult patients, how much cognitive function returns on CPAP depends on how long the apnea went untreated and whether permanent structural damage has already occurred. By stopping nocturnal hypoxia and consolidating sleep architecture, CPAP quickly improves alertness, attention, and working memory. Reversing structural loss, such as reduced gray matter density, takes much longer and often remains incomplete if diagnosis is delayed (Caporale et al., 2020; Legault et al., 2021).

3.3.5. Malignant neoplasm/ tumors

Growing epidemiological and experimental data link obstructive sleep apnea to cancer development. Untreated OSA appears to support tumor initiation, speed up local tumor growth, and promote metastasis. In clinical cohorts, patients with severe OSA face a several-fold higher risk of cancer mortality than individuals with normal breathing during sleep, with higher incidence rates reported for lung, kidney, breast, and gastrointestinal cancers, as well as cutaneous melanoma (Kendzerska et al., 2020; Marrone et al., 2020).

Three main pathways connect OSA to carcinogenesis: intermittent hypoxia, oxidative stress, and sleep fragmentation. Rapid reoxygenation after apneic pauses generates excess ROS, causing DNA microdamage and chronic inflammation that favor somatic mutations. Frequent night-time arousals also keep the sympathetic nervous system chronically active, elevating circulating catecholamines and cortisol. This neuroendocrine shift weakens cell-mediated immunity by blunting the cytotoxic activity of CD8+ T lymphocytes and natural killer (NK) cells, making it harder for the immune system to clear mutated cells. Meanwhile, cyclical drops in oxygen stabilize hypoxia-inducible transcription factors (HIF-1α and HIF-2α), which upregulate vascular endothelial growth factor (VEGF) and stimulate angiogenesis in both pulmonary and tumor tissues (Kendzerska et al., 2020; Marrone et al., 2020; Yuan et al., 2024).

Identifying sleep apnea in oncology patients and starting CPAP early may help dampen systemic inflammation and correct tissue hypoxia. Because tumor hypoxia often drives treatment resistance, controlling nocturnal desaturations could serve as a useful supportive measure alongside standard anticancer therapies (Marrone et al., 2020; Yuan et al., 2024).

4. Discussion

4.1. Interpretation of the findings

The evidence synthesised in this narrative review underscores that OSA should be conceptualised not merely as a localised mechanical disorder of the upper airway, but as a complex, heterogeneous, multisystem condition driven by interacting anatomical and non-anatomical endotypes (Abbasi et al., 2021; Chang et al., 2023; McNicholas and Pevernagie, 2022; Guerrero-Vega et al., 2026; Beatty et al., 2025). While overnight attended PSG remains the unequivocal diagnostic reference standard—particularly in patients with cardiorespiratory or neurological comorbidities or suspected hypoventilation (Hussein et al., 2024; Kapur et al., 2017) - its high cost, limited accessibility, and susceptibility to the first-night effect have accelerated the adoption of ambulatory alternatives (Braun et al., 2024; Pinilla et al., 2025). Home polysomnography, level III portable monitors, and emerging wireless dual-sensor platforms such as ANNE Sleep demonstrate high diagnostic concordance with laboratory PSG for moderate-to-severe OSA, facilitating multi-night evaluation to mitigate night-to-night variability in the AHI (Braun et al., 2024; van Doorn et al., 2025; Davies et al., 2022; Walter et al., 2023). Conversely, although screening questionnaires such as STOP-Bang exhibit high sensitivity for triaging high-risk cohorts, their persistently low specificity precludes their use as standalone diagnostic tools (Bernhardt et al., 2022; Pivetta et al., 2021; Chen et al., 2021; Hwang et al., 2022; Hwang et al., 2021). Similarly, while secondary electrospray ionisation high-resolution mass spectrometry (SESI-HRMS) of exhaled breath reveals reproducible metabolomic signatures linked to oxidative stress and intermittent hypoxia, diminished discriminatory accuracy in broader validation cohorts indicates that breathomics currently remains an investigational adjunct rather than a routine clinical assay (Nowak et al., 2021).

A major paradigm shift is evident in the therapeutic landscape of OSA. CPAP remains the primary gold-standard intervention, effectively abolishing obstructive respiratory events, improving daytime alertness and health-related quality of life, and reducing systemic blood pressure (Patil et al., 2019; Martelli et al., 2022; Tanayapong et al., 2025; Benjafield et al., 2025). However, suboptimal long-term patient adherence significantly curtails its real-world effectiveness, necessitating targeted, mechanism-based alternatives (Martelli et al., 2022; Strollo et al., 2026; Eastwood et al., 2020; Woodson et al., 2025). For patients with obesity-related OSA, the dual GIP/GLP-1 receptor agonist tirzepatide represents a transformative pharmacological milestone, achieving substantial reductions in AHI and hypoxic burden predominantly through marked weight loss and attenuation of pharyngeal adiposity and systemic inflammation (Falcon et al., 2026; Malhotra et al., 2024; Kanu et al., 2025; McGowan et al., 2025). Simultaneously, the fixed-dose oral combination of aroxybutynin and atomoxetine (AD109) directly targets sleep-related neuromuscular hypotonia by enhancing hypoglossal motor output, offering a viable once-daily pharmacotherapy across mild-to-severe OSA in patients intolerant of or refusing positive airway pressure (Strollo et al., 2026; Rosenberg et al., 2022; Schweitzer et al., 2023).

In patients with specific anatomical or neuromuscular phenotypes, device-based and surgical interventions provide valuable non-CPAP pathways. biHNS achieves clinically meaningful reductions in AHI, ODI, and supine respiratory events without requiring implanted batteries or thoracic sensing leads, demonstrating efficacy comparable to unilateral systems (Eastwood et al., 2020; Woodson et al., 2025; Heiser et al., 2022). Orthodontic slow maxillary expansion via non-permanent intraoral appliances (DNA/CARE) promotes sustained skeletal and soft-tissue upper airway remodelling in both adults and children with transverse maxillary constriction (Kushida et al., 2025; Dao et al., 2023; Katz et al., 2022; Aksilp et al., 2025), whereas custom-made mandibular advancement devices (MADs)—across monoblock and titratable biblock designs—remain effective alternatives for mild-to-moderate OSA, provided clinicians balance protrusive efficacy against long-term dento-occlusal changes (Uniken Venema et al., 2021; Ishiyama et al., 2019; Wang et al., 2025). In paediatric OSA driven by adenotonsillar hypertrophy, adenotonsillectomy remains superior to watchful waiting for improving respiratory indices and disease-specific quality of life, though partial tonsillotomy reduces early postoperative morbidity at the expense of higher long-term regrowth and reoperation rates (Tsikopoulos et al., 2024; Chinnadurai et al., 2017; Borgstrom et al., 2019; Fehrm et al., 2020; Virkkunen et al., 2025). Furthermore, non-pharmacological rehabilitative strategies—encompassing myofunctional therapy, inspiratory muscle training, structured aerobic and resistance exercise, and remotely supervised telerehabilitation—consistently improve functional exercise capacity, daytime sleepiness, and quality of life, even when AHI reductions are modest, reinforcing the need to evaluate therapeutic success beyond polysomnographic indices alone (Camacho et al., 2015; Rueda et al., 2020; Ferreira et al., 2025; Xu et al., 2025; Bandyopadhyay et al., 2020; Agarwal et al., 2022; Sykes et al., 2022; Shen et al., 2024; Mittal et al.,

2024; Guerrero-Vega et al., 2026; Pierobon et al., 2023; Iftikhar et al., 2024; Beatty et al., 2025; Dar et al., 2022; Hnatiak et al., 2023; Peng et al., 2026).

Finally, the reviewed evidence highlights profound bidirectional and pathophysiological links between OSA and major systemic comorbidities. Intermittent hypoxaemia, oxidative stress, sympathetic hyperactivation, and sleep fragmentation serve as unifying mechanisms linking untreated OSA to major depressive disorder (Yeşiloğlu et al., 2026; Jackson et al., 2020; Zheng et al., 2019; Balk et al., 2024; Yang et al., 2020; Marrero-Gonzalez et al., 2024), ventricular arrhythmogenesis and sudden cardiac death (particularly in untreated patients with severe nocturnal desaturation) (Zou et al., 2025; Kwon et al., 2017; Domaradzki et al., 2022; Gami et al., 2013; Schlatzer et al., 2018; Seyis et al., 2018; Heilbrunn et al., 2021), asthma–OSA overlap syndrome (Prasad et al., 2019; Espanol et al., 2025; Saxena et al., 2023; Pardo-Manrique et al., 2024), blood–brain barrier disruption and neurocognitive decline (Caporale et al., 2020; Lim et al., 2013; Legault et al., 2021; Davidescu et al., 2024; Krysta et al., 2016), and carcinogenesis via hypoxia-inducible factor (HIF-1α/HIF-2α) stabilisation, angiogenesis, and impaired antitumour immunity (Kendzerska et al., 2020; Marrone et al., 2020; Yuan et al., 2024). Crucially, while CPAP therapy alleviates depressive symptoms, suppresses nocturnal arrhythmias, improves asthma control, and partially restores cognitive vigilance, delayed diagnosis may permit irreversible structural neural and airway remodelling (Zheng et al., 2019; Domaradzki et al., 2022; Prasad et al., 2019; Caporale et al., 2020; Legault et al., 2021).

4.2. Limitations

Several methodological limitations of both this narrative review and the underlying primary literature must be acknowledged when interpreting these findings. First, as a narrative synthesis rather than a formal systematic review, this work was not prospectively registered, did not follow a strict PRISMA quantitative meta-analytic protocol, and did not employ formal risk-of-bias grading tools (such as Cochrane RoB 2 or GRADE) across all 93 included publications, which introduces a potential risk of selection bias. Second, substantial clinical and methodological heterogeneity exists across the cited studies, including variations in hypopnoea scoring criteria (3% oxygen desaturation or cortical arousal versus 4% desaturation thresholds), differences between laboratory PSG and level III/IV portable devices that rely on monitoring time rather than electroencephalographically confirmed sleep time, and inconsistent definitions of therapeutic success (Hussein et al., 2024; Kapur et al., 2017; van Doorn et al., 2025; Bernhardt et al., 2022).

Third, the certainty of evidence for several emerging modalities remains constrained by study design limitations. Evaluations of bilateral hypoglossal nerve stimulation (Eastwood et al., 2020; Woodson et al., 2025), orthodontic maxillary expansion (Dao et al., 2023; Katz et al., 2022), and smart MADs (Yang et al., 2024) rely heavily on single-arm, non-randomised, or retrospective cohorts lacking active comparator groups, while trials of myofunctional therapy (Camacho et al., 2015; Rueda et al., 2020; Ferreira et al., 2025; Xu et al., 2025; Bandyopadhyay et al., 2020) and inspiratory muscle training (Dar et al., 2022) are frequently limited by small sample sizes, heterogeneous exercise protocols, short follow-up durations, and reliance on self-reported rather than objective adherence data. Similarly, in pharmacological trials such as MARIPOSA and SynAIRgy, notable early discontinuation rates due to antimuscarinic or noradrenergic adverse events attenuate intention-to-treat effect sizes (Strollo et al., 2026; Schweitzer et al., 2023). Finally, with respect to comorbidities such as depression, sudden cardiac death, and malignancy, much of the epidemiological evidence derives from observational cohorts in which residual confounding by shared risk factors—most notably obesity, age, smoking, and cardiometabolic disease—precludes definitive causal inference (Yeşiloğlu et al., 2026; Zou et al., 2025; Heilbrunn et al., 2021; Kendzerska et al., 2020; Marrone et al., 2020).

4.3. Directions for Future Research

Future investigations should prioritise large-scale, multicentre randomised controlled trials with extended follow-up durations to establish long-term efficacy, durability, safety, and hard cardiovascular and mortality endpoints across emerging pharmacological, surgical, and rehabilitative therapies (Benjafield et al., 2025; Strollo et al., 2026; Woodson et al., 2025; Uniken Venema et al., 2021; Guerrero-Vego et al., 2026). Head-to-head comparative effectiveness trials are particularly warranted to evaluate oral pharmacotherapies (such as AD109 and incretin-based agents) against CPAP and mandibular advancement devices (Malhotra et al., 2024; Strollo et al., 2026), as well as direct randomised comparisons between bilateral and unilateral hypoglossal nerve stimulation (Woodson et al., 2025; Heiser et al., 2022). In parallel, research into non-invasive diagnostics—including multi-night wearable sensors (Walter et al., 2023) and exhaled breath metabolomics (Nowak et al., 2021)—should focus on analytical standardisation, external validation in diverse

primary care and community populations, and integration with clinical prediction scores to enhance diagnostic specificity.

Furthermore, future studies should move beyond reliance on the AHI as the sole primary endpoint by systematically incorporating metrics of hypoxic burden, arousal threshold, loop gain, and validated patient-reported outcome measures (McNicholas et al., 2022; Strollo et al. 2026; Guerrero-Vega et al., 2026; Beatty et al., 2025). Identifying phenotypic and endotypic predictors of treatment response—such as baseline upper airway muscle compensation, craniofacial morphology, and comorbidity profiles—will be essential to advance precision medicine in OSA (Song et al., 2025; Beatty et al., 2025). Finally, well-powered longitudinal interventional trials are required to determine whether early, sustained treatment of OSA directly modifies the trajectory of neurocognitive decline, prevents incident malignancy, and reduces sudden cardiac death in high-risk patient subgroups (Zou et al., 2025; Heilburnn et al., 2021; Legault et al., 2021; Marrone et al., 2020).

5. Summary

OSA is a multifactorial, multisystem disorder whose clinical consequences extend far beyond nocturnal upper airway obstruction (Abbasi et al., 2021; Chang et al., 2023; McNicholas et al., 2022). While attended PSG remains the diagnostic gold standard (Hussein et al. 2024; Kapur et al., 2017), advancements in home sleep testing (Braun et al., 2024; van Doorn et al., 2025), wearable sensor technologies (Davies et al., 2022; Walter et al. 2023), validated screening questionnaires (Bernhardt et al., 2022; Pivetta et al., 2021; Chen et al., 2021; Hwang et al., 2022; Hwang et al., 2021), and breath metabolomics (Nowak et al., 2021) are expanding opportunities for accessible risk stratification and multi-night monitoring. Although CPAP remains the cornerstone of treatment (Patil et al., 2019; Martelli et al., 2022), the therapeutic armamentarium has diversified considerably to encompass targeted pharmacotherapies—such as tirzepatide for obesity-related OSA (Falcon et al., 2026; Malhotra et al., 2024; Kanu et al., 2025; McGowan et al., 2025) and aroxybutynin–atomoxetine (AD109) for neuromuscular dysfunction (Strollo et al., 2026; Rosenberg et al., 2022; Schweitzer et al., 2023)—alongside bilateral hypoglossal nerve stimulation (Eastwood et al., 2020; Woodson et al. 2025; Heiser et al., 2022), orthodontic maxillary expansion (Kushida et al., 2025; Dao et al., 2023; Katz et al., 2022; Aksilp et al., 2025), custom mandibular advancement devices (Uniken Venema et al., 2021; Ishiyama et al., 2019; Wang et al., 2025; Yang et al., 2024), paediatric adenotonsillectomy (Tsikopoulos et al., 2024; Chinnadurai et al., 2017; Borgström et al., 2019; Fehrm et al., 2020; Virkkunen et al., 2025; Waters et al., 2020; Taylor et al., 2016), and structured pulmonary and myofunctional rehabilitation (Camacho et al., 2015; Rueda et al. 2020; Ferreira et al., 2025; Xu et al., 2025; Bandyopadhyay et al., 2020; Agarwal et al., 2022; Sykes et al., 2022; Schen et al., 2024; Mittal et al., 2024; Guerrero-Vega et al., 2026; Pierobon et al., 2023; Iftikhar et al., 2024; Beatty et al., 2025; Dar et al., 2022; Hnatiak et al., 2022; Peng et al., 2026). Recognising and managing the bidirectional interplay between OSA and psychiatric, cardiovascular, respiratory, neurocognitive, and oncological comorbidities is critical to improving long-term clinical outcomes (Yeşiloğlu et al., 2026; Jackson et al., 2020; Zheng et al., 2019; Balk et al., 2024; Yang et al., 2020; Marrero-Gonzalez et al., 2024; Zou et al., 2025; Kwon et al., 2017, Domaradzki et al., 2022; Gami et al., 2013; Schlatzer et al., 2018; Seyis et al., 2018; Heilbrunn et al., 2021; Prasad et al., 2019; Espanol et al., 2025; Saxena et al., 2023; Pardo-Manrique et al., 2024; Sundbom et al., 2018; Caporale et al., 2020; Lim et al., 2013; Legault et al., 2021; Davidescu et al., 2024; Krysta et al., 2016; Kendzerska et al., 2020; Marrone et al., 2020; Yuan et al., 2024). Ultimately, transitioning towards an individualised, phenotype-guided, multidisciplinary model of care offers the greatest potential to mitigate disease burden and enhance patient quality of life (Chang et al., 2023; McNicholas et al., 2022; Song et al., 2026; Guerrero-Vega et al., 2026).

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