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STATE OF THE ART REVIEW

Evaluation and Management of Adults with Obstructive Sleep Apnea Syndrome

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Abstract

Obstructive sleep apnea syndrome (OSAS) is a common and underdiagnosed medical condition characterized by recurrent sleep-dependent pauses and reductions in airflow. While a narrow, collapsible oropharynx plays a central role in the pathophysiology of OSAS, there are other equally important nonanatomic factors including sleep-stage dependent muscle tone, arousal threshold, and loop gain that drive obstructive apneas and hypopneas. Through mechanisms of intermittent hypoxemia, arousal-related sleep fragmentation, and intrathoracic pressure changes, OSAS impacts multiple organ systems. Risk factors for OSAS include obesity, male sex, age, specific craniofacial features, and ethnicity. The prevalence of OSAS is rising due to increasing obesity rates and improved sensitivity in the tools used for diagnosis. Validated questionnaires have an important but limited role in the identification of patients that would benefit from formal testing for OSA. While an in-laboratory polysomnography remains the gold standard for diagnosis, the widespread availability and accuracy of home sleep apnea testing modalities increase access and ease of OSAS diagnosis for many patients. In adults, the most common treatment involves the application of positive airway pressure (PAP), but compliance continues to be a challenge. Alternative treatments including mandibular advancement device, hypoglossal nerve stimulator, positional therapies, and surgical options coupled with weight loss and exercise offer possibilities of an individualized personal approach to OSAS. Treatment of symptomatic patients with OSAS has been found to be beneficial with regard to sleep-related quality of life, sleepiness, and motor vehicle accidents. The benefit of treating asymptomatic OSA patients, particularly with regard to cardiovascular outcomes, is controversial and more data are needed.

Keywords Sleep apnea · Obstructive · Sleep apnea syndromes · State of the art review · Pathophysiology

Abbreviations

OSAS	Obstructive sleep apnea syndrome
AASM	American Academy of Sleep Medicine
AHI	Apnea–hypopnea index
BMI	Body mass index
REM	Rapid eye movement
NREM	Non-REM
PAP	Positive airway pressure
PSG	Polysomnography
HST	Home sleep test
OCST	Out-of-center sleep testing
MMA	Maxillomandibular advancement
UPPP	Uvulopharyngopalatoplasty

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Introduction

Obstructive sleep apnea syndrome (OSAS) is a sleep-related breathing disorder characterized by partial reductions (hypopnea) and complete pauses (apnea) in ventilation. These respiratory disturbances cause intermittent hypoxemia, intrathoracic pressure changes, and fragmented sleep, which not only impair quality of life, but also lead to significant impacts on physical and mental health.

The American Association of Sleep Medicine (AASM) has outlined the clinical and sleep testing criteria for OSAS in the third edition of the International Classification of Sleep Disorders (ICSD-3) (Table 1) [1]. The severity of OSAS can be classified according to the number of respiratory events observed per hour, termed the apnea hypopnea index (AHI): mild OSA (AHI 5–14.9/hour), moderate OSA (AHI 15–29.9/hour), and severe OSA (> 30/hour) [2]. It is worth noting that by grading severity of disease based upon the number of observed events, it is implied that a higher

Table 1 Diagnostic Criteria for Adult OSA from the AASM International Classification of Sleep Disorders, 3rd edition [1]

A. The presence of one or more of the following symptoms:
a. Patient complains of:
(i) Sleepiness, nonrestorative sleep, fatigue or insomnia
(ii) Awakens with breath holding, gasping, or choking
b. Bed-partner or other observer reports habitual snoring, breathing interruptions, or both during the patient's sleep
c. The patient has been diagnosed with hypertension, a mood disorder, cognitive dysfunction, coronary artery disease, stroke, congestive heart failure, atrial fibrillation, or type 2 diabetes mellitus
B. Polysomnography (PSG) or OCST (out-of-center sleep test) demonstrates:
a. 5 or more predominantly obstructive respiratory events per hour of sleep (PSG) or monitoring (OCST)
C. PSG or OCS demonstrates:
a. 15 or more predominantly obstructive respiratory events per hour of sleep (PSG) or monitoring (OCST)

Diagnosis requires (A and B) or C to satisfy criteria

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frequency of events portends worse symptoms and clinical outcomes of OSAS; however, this is an oversimplification of the pathophysiology of OSAS [3, 4]. In fact, this designation of severity of disease was initially proposed by the AASM task force in 1999 as a guideline for research purposes only and not for clinical use [2, 5] and as such, recent reports have called for reevaluating the value of AHI in predicting disease severity [4].

OSAS is both a common and underdiagnosed condition [5, 6]. Furthermore, its prevalence has increased with time, mirroring trends in obesity. Independent of obesity, the increased prevalence is also a reflection of the improved sensitivity in the tools used to identify hypopneas and apneas as well as changes in scoring criteria [7, 8]. For these reasons, the exact prevalence of OSAS is a moving target. A recent systematic review reported a 9% to 38% prevalence of OSAS in the general population when using an AHI cut-off of ≥ 5 events/hour and a 6% to 17% prevalence when using an AHI cut-off of ≥ 15 events/hour [9].

Pathophysiology

While the underlying basis of OSAS is understood easily from the standpoint of a narrow and collapsible pharynx, its pathophysiology is far more complex [10]. A wide variety of factors can influence the caliber of the upper airway during sleep and thereby affect the propensity to sleep-disordered breathing. The end result of these anatomic and nonanatomic factors is recurrent upper airway collapse that leads to cyclic hypoxemia, intrathoracic pressure

Table 2 Proposed evaluation of patients with suspected obstructive sleep apnea syndrome

Detailed medical and sleep history:
Symptoms of sleep apnea (see text and Table 1)
Evaluate for concomitant sleep disorders (i.e., insomnia, delayed sleep phase)
Assess for coexisting and possibly confounding medical conditions (i.e., thyroid disease, depression or anxiety)
Physical examination, high-risk features of OSAS:
Obese BMI
Crowded oropharynx (High Mallampati Score) [148]
Micrognathia or retrognathia
Enlarged neck circumference [149]
Tongue size [150]
Sleep testing:
Home sleep testing (HST) indications:
Patients with high pretest probability of moderate to severe OSAS
Absence of cardiopulmonary disease that may degrade the accuracy HST
Absence of comorbid sleep disorders, including central sleep apnea, insomnia, periodic limb movements of sleep
In-lab polysomnography (PSG) indications:
Patients not meeting above criteria for HST

swings, sleep fragmentation, and a resulting inflammatory cascade, felt to be the basis for the adverse health outcomes seen with OSAS [10] (Fig. 1). The following factors contribute to the pathophysiology of OSAS:

1. Structural factors: The human airway has undergone multiple evolutionary anatomic changes to allow for complex speech and language while maintaining its swallowing and air conducting functions. These changes have led to a species-specific predisposition for obstructive events during sleep [11]. Such anatomic changes are compounded by factors such as obesity, aging, and craniofacial abnormalities.
2. Neuromuscular factors and pharyngeal collapsibility: A number of factors determine the critical closing pressure of the pharynx (P_{crit}) during sleep, particularly upper airway muscle tone or muscle responsiveness. Upper airway muscle tone is primarily determined by two reflexive feedback mechanisms: 1) airway mechanoreceptors that sense negative pharyngeal pressure and 2) peripheral and central chemoreceptors that activate the Pre-Bötzinger complex, a cluster of medullary neurons which serve as the respiratory rhythm generator [12]. Compared to wake, sleep results in reduced upper airway muscle tone, especially during rapid eye movement (REM) sleep as compared to non-REM (NREM) sleep; as a result, obstructive events tend to be more severe and prolonged during REM sleep vs NREM sleep [12–15].
3. Instability of central motor output and arousal thresholds: The output of the respiratory generator and maintenance of sleep state have important stabilizing influences on upper airway tone. The effect of "unstable ventilatory patterns" is evident in those with low arousal threshold [13]. Arousal-induced hyperventilation causes a fall in the arterial carbon dioxide levels to below the apneic threshold which in turn leads to central apneas with a simultaneous reduction in respiratory generator output. The loss of respiratory generator output is accompanied by a loss of vagal and hypoglossal output to the upper airway dilators ultimately resulting in a narrowed airway [15–17]. This tendency for central apneas and hypopneas is therefore determined by the complex interplay of apneic thresholds (highest carbon dioxide tension at which a subject remains apneic), loop gain (defined as the ratio of ventilatory response/ventilatory disturbance), and arousal threshold [10, 13–17]. Ventilatory response during sleep is mainly determined by the net effect of central and peripheral chemoreceptor output to changing CO_2 values, the main controller of breathing in NREM sleep [10].

Risk Factors

Risk factors contributing to the development of OSA include obesity, male sex, increasing age, craniofacial differences, and ethnicity. Perhaps the most important risk factor for sleep apnea is obesity, which causes fat deposition in the tongue, reducing the caliber of the upper airway and increasing the likelihood of its collapse [18, 19]. In addition, patients with central obesity develop abdominal compression, with lessening of end-expiratory lung volume reducing caudal traction and increasing upper airway collapsibility [20]. Three large epidemiologic studies have demonstrated a direct relationship between weight gain and sleep apnea [21–23]. The Wisconsin Sleep Cohort study found that a 10% increase in weight predicted a six-fold increase in the odds of developing moderate to severe sleep-disordered breathing [22]. Interestingly, while the severity of obstructive sleep apnea is often attenuated by weight loss, it never completely resolves, often converting it into a supine-predominant disease [19, 24]. Male sex is an independent risk factor for OSAS, with an estimated male to female prevalence of 1.5:1 [25]. This higher prevalence is due to anatomic differences such as increased airway collapsibility [26, 27] and higher fat deposition in the abdomen and neck in male patients [28, 29] as well as the protective effect of female hormones such as progesterone and estrogen [30]. The prevalence of sleep apnea increases with age [31, 32]. One study suggested that while the prevalence seems to increase with age, the severity seems to decrease [32]. While the exact mechanisms leading to increased OSA and higher severity of OSA in sleep studies in elderly are yet to be understood, a number of possible factors have been identified which include age-related upper airway narrowing, upper airway dilator muscle activity, changes in lung volume, arousal thresholds, and ventilatory control stability [32]. Certain facial phenotypes are also associated with increased risk of OSAS [33–35]. One study used MRI to assess the dimensions of specific facial structures and found a high correlation between tongue volume, midface width, and lower face width with sleep apnea [34]. Another study used three-dimensional photography to identify anatomic risk factors predicting sleep apnea [35]. Ethnicity is also an important risk factor. A recent global, multicenter study demonstrated that South Americans and Asians are more susceptible to the effects of obesity on OSA severity, whereas African Americans were least impacted [36].

Screening Questionnaires

Screening questionnaires for OSAS were developed in order to identify high-risk patients who may benefit from a comprehensive sleep evaluation. This may be of particular value in low resource settings with limited capabilities to refer

or perform sleep testing. While the US Preventative Services Task Force argues that there is insufficient evidence for screening all asymptomatic adult patients for OSA [37], the AASM recommends screening certain high-risk asymptomatic populations who may be at high-risk of sleep apnea, using validated OSA-specific questionnaires [38, 39]. These high-risk patients include those with atrial fibrillation, resistant hypertension, congestive heart failure, obesity, diabetes mellitus, nocturnal dysrhythmias, pulmonary hypertension, high-risk driving populations (i.e.,truck drivers), and preoperative patients for bariatric surgery [39].

Commonly utilized questionnaires include the STOP-BANG [40], Berlin questionnaire [41], and Epworth Sleepiness Scale [42]. A meta-analysis comparing the Berlin questionnaire, STOP, STOP-BANG, and Epworth Sleepiness Scale found significant heterogeneity with regard to their respective diagnostic accuracy [43]. Although the STOP-BANG performed the best, with a sensitivity of 90% and 93% in moderate and severe sleep apnea, respectively, its specificity was only 35% in severe sleep apnea [43]. Furthermore, a 2018 AASM task force to evaluate currently available clinical screening and assessment tools did not identify a single tool that met its criteria for clinical validity and feasibility [44].

Clinical Symptoms and Signs of OSAS

The evaluation for sleep apnea is typically triggered by a patient's report of sleep or sleep-related symptoms to a primary care provider who then refers them to a sleep specialist. Symptoms of OSAS can be both nocturnal and diurnal and are wide ranging. While sleepiness, defined as an increased propensity to sleep during situations where a person would be expected to be alert, is widely considered the defining symptom of OSAS, it is not reported as a primary complaint by most OSAS patients [45]. In fact, some patients with OSAS may be more likely to describe daytime impairment using terms such as fatigue, tiredness, or lack of energy [46]. One study found that the presence of nocturnal choking and gasping was highly specific for the diagnosis of OSAS, while snoring was highly prevalent but much less specific [47]. It is important to consider that the presentation of sleep apnea can also vary by sex [48]. One study found that among patients referred for sleep testing, women were more likely to underreport the presence and intensity of their snoring, compared to their male counterparts [49]. Men are more likely to complain of snoring and apneas than women who are diagnosed with sleep apnea [50]. A comparative study found that compared to men, women with sleep apnea were more likely to complain of atypical symptoms as insomnia, restless legs, depression, nightmares nocturnal palpitations, and hallucinations [51].

Evaluation for OSAS: Sleep Testing

A proposed sleep evaluation for a patient with suspected OSAS is described in Table 2. In patients who have a compatible history and/or physical examination features that are concerning for OSAS, sleep testing is recommended. Screening tools or questionnaires alone, in the absence of sleep testing, should not be used to diagnose or exclude sleep apnea because of a low level of accuracy [52, 53].

In-lab polysomnography (PSG) or level 1 attended polysomnography is considered the gold standard for diagnosis of suspected sleep-related breathing disorders in addition to other sleep disorders such as narcolepsy, parasomnias, and sleep-related movement disorders. During an in-lab PSG, a patient spends the night in a sleep laboratory where they are monitored by a sleep technician. The following sleep monitoring equipment is applied and their corresponding parameters or signals allow comprehensive monitoring of sleep: (1) To determine stages of sleep and wake, a combination of electroencephalogram (EEG), electrooculography (EOG), and chin electromyogram (EMG) is utilized, (2) Respiration during sleep is assessed by continuous pulse oximetry, airflow signals (via nasal pressure and/or oronasal thermal flow) as well as chest and abdomen belts (via respiratory inductance plethysmography), (3) Limb movement is detected by EMG of the anterior tibialis, and 4) Cardiac rate and rhythm is assessed by a single ECG lead. The AASM scoring manual outlines the recommended parameters of PSG in further detail [54]. The primary metric of sleep-disordered breathing counts the total number of respiratory events and divides this by the total sleep time, giving the apnea hypopnea index or the AHI. Obstructive respiratory events can be identified by diminished respiratory flow with continued thoracoabdominal effort or paradox, often followed by an oxygen desaturation. If a PSG does not demonstrate significant sleep-disordered breathing, a repeat PSG may be considered [52]; alternatively, rather than a repeat PSG, a home sleep apnea test (HSAT) can be performed as a second test in selected patients [55].

In-lab PSG is an expensive procedure and can be inconvenient for patients, particularly those who do not live in close proximity to a sleep laboratory or who may have medical comorbidities making mobility difficult. In contrast, home sleep apnea testing (HSAT) or out-of-center sleep testing (OCST) offers the convenience of sleep monitoring in the home setting, but with some limitations [56]. In 2007, the AASM published guidelines recommending HSAT for diagnosis of patients with a high pretest probability of moderate to severe sleep apnea (defined as having excessive daytime sleepiness occurring on most days AND at least two of the three symptoms: snoring, witnessed apneas/gasping/choking, or hypertension [52]); these guidelines did not recommend HSAT for diagnosing patients with significant

Table 3 Treatments for obstructive sleep apnea syndrome

Treatment	Indications	Downsides to treatment
Positive airway pressure (PAP)	First line therapy for OSAS	- Compliance to therapy can be poor due to: nasal congestion, oral dryness, skin irritation, oropharagia, claustrophobia, etc.
Mandibular advancement device (MAD)	Alternate therapy for patients who are intolerant or seek an alternate to PAP therapy Primary therapy for snoring without OSA [90]	- Less effective than PAP therapy in reduction and normalization of AHI [88] - Difficult to predict individual treatment success - Dental complaints: Temporomandibular joint pain, sore teeth, gum pain, excessive salivation, etc. - Absence of feedback on compliance and efficacy of therapy
Positional therapy	Alternate therapy for patients with positional sleep apnea who are intolerant or seek an alternate to PAP therapy Adjunct therapy with PAP or MAD	- Traditional methods ("tennis ball technique") have poor long-term compliance - Next generation positional devices report good short-term compliance but there is a lack of long term data - While the next generation devices offer feedback on compliance to therapy, it does not provide data on night to night efficacy
Weight loss	Recommended for all overweight and obese patients diagnosed with OSAS	- Severity of sleep apnea often improves with weight loss but does not always completely resolve, sometimes converting into positional sleep apnea
Hypoglossal nerve stimulator	Alternate therapy for patients with moderate to severe OSA who have failed PAP therapy	- Available for only a subset of patients. Requirements for treatment include absence of complete concentric collapse at the soft palate, age 22+, central and mixed apneas < 25% of AHI - Surgical risks: bleeding, nerve damage, infection, tongue soreness or weakness, problems with speaking or swallowing
Upper airway surgery	Primary treatment for patients with mild OSA and severe obstructing anatomy deemed surgically correctable Alternate therapy for patients who have failed PAP therapy or MAD Adjunct therapy with PAP or MAD	- Surgical risks of procedure - Wide variety and scope of surgical options that are patient and surgeon dependent - Limited data with regards to cardiovascular and other important clinical outcomes with surgical treatment of OSAS

cardiopulmonary disease or concomitant sleep disorders such as insomnia [57]. Despite this, HSAT has been studied and validated in patients with mild to moderate probability of disease [58], heart failure [59, 60], COPD [61, 62], and morbid obesity [63]. Furthermore, the COVID pandemic and resulting closures of many in-lab testing facilities has consequently stretched the limits of using HSAT to diagnose patients with sleep-disordered breathing and we are likely to see its use expand in the future.

HSAT is typically accomplished using a Level III modified portable sleep apnea test which measures air flow, respiratory effort, oxygen saturation, and heart rate; it does not include EEG or EMG monitoring and as such cannot stage sleep or detect limb movements. Although often used interchangeably with the AHI, the primary metric used to designate the frequency of respiratory events is the respiratory event index (REI) since total recording time, rather than total sleep time, is used. The use of total recording time often leads to an underestimation of the severity or presence of sleep-disordered breathing [64]. The overall sensitivity and specificity of HSAT are considered acceptable. A meta-analysis of 8 studies utilizing level III HSAT, when using an REI cut-off of ≥ 15/hour, found a sensitivity of 79% and specificity of 79% [65]. It is important to note that there may be significant night-to-night variability in severity of OSA, resulting in misclassification of sleep apnea severity with one night of home sleep testing [66]. As a result of these limitations, the false negative rate of HST is reported to be as high as 17% [57]. As such, it is recommended that if initial sleep testing by HST does not demonstrate significant sleep-disordered breathing (or is technically inadequate or inconclusive), repeat evaluation with a PSG be performed, because the latter is a more sensitive test [52].

Peripheral arterial tonometry (only capable currently through WatchPAT, Itamar Medical Ltd) is a unique mode of home unattended sleep monitoring that rather than

measuring airflow, uses a combination of peripheral arterial tone, oxyhemoglobin saturation, pulse rate, and actigraphy to detect respiratory events and stage sleep. The WatchPAT is increasingly being utilized to detect sleep-disordered breathing. The device is an option for patients who are referred for OCST, including those with atrial fibrillation [67, 68]. An advantage of the WatchPAT over a standard level III modified portable sleep apnea test is the simplicity of its application and wearability since its most recent iteration consists of only a wristband and a finger probe without chest/abdomen bands and nasal pressure transducers. A recent study systematically tested 500 patients with suspected sleep apnea using simultaneous PSG and WatchPAT devices. For WatchPAT AHI of ≥ 15/hr, a sensitivity of 91%, specificity of 61%, positive predictive value of 76%, and negative predictive value of 83% was found [67]. While the results of the WatchPAT are generated by an automated proprietary algorithm, employing a manual editing algorithm has been shown to improve correlation with PSG [69]. Similar to a Type III device, a negative result on a WatchPAT should prompt consideration of further testing with an attended PSG [52].

Management

Treatment approaches for OSAS are summarized in Table 3. Management strategies to date have focused on the use of continuous positive airway pressure (CPAP) for nearly all patients with OSAS. However, as more is understood about the pathophysiology of sleep apnea, it is becoming increasingly clear that a personalized approach accounting for important mechanistic sub-types of OSA is necessary and worthwhile. These so-called endotypes of OSA, which can be identified from both invasive and noninvasive techniques, have been proposed and include the following: high loop gain, low arousal threshold, poor upper airway dilator responsiveness to collapse during sleep, and anatomical narrowing leading to lowering of the critical closing pressure during sleep [3]. By accounting for endotypes as well as patients' phenotypic traits (such as excessive sleepiness), we can tailor specific treatment strategies for patients (precision medicine) with the goal of more effectively addressing an individuals' symptoms and disease risk [3, 16, 70, 71]. While such a strategy is exciting and shows promise, at this time, its applicability and utility for routine care of OSAS are limited.

Positive Airway Pressure

Positive airway pressure (PAP) has long been considered first-line treatment for most patients with OSAS because it is efficacious, cost-effective, and noninvasive. PAP directly counters the collapse of the oropharynx by delivering pressure through a nasal or oronasal mask during sleep. PAP can be delivered in three modes: (1) continuous (CPAP), where a fixed pressure is applied; bilevel (BPAP), where two different pressures are applied at inhalation and exhalation; and autotitrating (APAP), where delivered pressure varies depending upon machine feedback. In order to determine the ideal pressure needed to prevent oropharyngeal collapse, patients can undergo further attended in-lab PSG. If sleep apnea is already diagnosed, then the study can be performed as a titration where the patient spends the entire night on PAP with varied pressure settings; if sleep apnea needs to be diagnosed, then the study can be performed as a split night where the first half of the night is spent solely on monitoring for the purpose of diagnosis and the second half of the night is spent on titration. For patients with moderate to severe OSA without significant comorbidities such as congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), central sleep apnea, or hypoventilation, an alternative home-based approach is considered appropriate. This can be accomplished with an autotitrating CPAP, which varies delivered pressure based upon feedback from measures of airflow, pressure changes, and airway resistance [72]. This latter home-based approach, when compared to an attended in-lab titration approach, has been found to be equally efficacious, possibly with improved compliance [73]. Clinical practice guidelines issues by the AASM on PAP therapy have been recently published [74]. Long-term monitoring of PAP compliance and efficacy can be obtained remotely even though validation of this approach to assess OSAS in longitudinal studies is lacking [75]. While PAP is an effective form of therapy for many patients, it is not always well tolerated and as such, nonadherence is its major limitation. A literature review that examined twenty years of reported data found that over a third of patients used their CPAP less than 7 h per night [76]. Another study examining long-term compliance found that only 54% of OSA patients were using CPAP at a mean of 64 months postdiagnosis. Improving compliance is important because the impact of CPAP usage on specific outcomes such as sleepiness and cardiovascular mortality appear to be dose-dependent [77]. Strategies to improve PAP compliance include education, mask fitting, increased humidification, and the use of alternate pressure delivery systems including BPAP [78–81].

Mandibular Advancement Device

For OSA, an alternative treatment to PAP therapy is a mandibular advancement device (MAD) [82, 83]. A MAD forces the mandible into a protruded position during sleep, simultaneously increasing the caliber of the airway and also activating stretch receptors to reduce upper airway collapsibility [84–86]. Although MAD can be ready-made for patients, a

customized device fit by a dentist for an individual patient improves efficacy, comfort, and compliance [87]. The rate of reported success with MAD treatment is extremely variable, largely due to variable definitions of "efficacy," with some studies defining success as an AHI < 5, others as an AHI < 10 and still others calling success a 50% AHI reduction[86]. A large multicenter study on over 400 patients treated with a MAD found that 37% had complete resolution of their OSA (AHI < 5), 52% had a reduction of their AHI to < 10, and 64% had their AHI more than halved [88]. A meta-analysis showed that MAD reduces blood pressure comparably to PAP therapy [89]. A significant downside of MAD therapy is difficulty in predicting treatment success. Indeed, several studies have attempted to phenotype "responders" and "nonresponders" using individual patient characteristics (i.e., weight, age, or sex), as well as structural characteristics (craniofacial measurements, site of oropharyngeal collapse), or sleep study characteristics (supine-predominant sleep apnea) but most of these findings have been inconsistent or impractical to apply in practice [86]. The most recent combined AASM/AADSM (American Association of Dental Sleep Medicine) practice guidelines recommend post-MAD sleep testing to ensure adequacy of therapy [90].

Hypoglossal Nerve Stimulator

In patients who fail noninvasive management, surgical approaches, including the hypoglossal nerve stimulator, can be considered. The hypoglossal nerve stimulator works by unilaterally stimulating the hypoglossal nerve, thereby activating the genioglossus muscle allowing for opening of the upper airway during sleep. An international multicenter prospective single group trial enrolled adult patients who had failed or not tolerated noninvasive management of their moderate to severe OSA. Exclusion criteria included an AHI less than 20 or greater than 50, a more than 25% of respiratory events being central or mixed apneas/hypopneas, supine-predominant disease (AHI nonsupine < 10), and concentric collapse of the retropalatal airway during drug-induced sleep endoscopy [91]. At 12 months, the median AHI decreased from 29.3 to 9 events per hour; 66% of patients had surgical success as defined by postoperative reduction in AHI of ≥ 50% and an AHI < 20/h. The rate of serious adverse events related to the device was < 2%. Significant improvements in the ESS and sleep -related quality of life as measured by the Functional Outcomes of Sleep Questionnaire was also observed [91]. A pooled cohort analysis of four large hypoglossal nerve studies found that the following factors were associated with greater postoperative reduction in AHI: higher preoperative AHI, older patient age, and lower body mass index [92].

Surgical Approaches

Appropriate candidates for surgical treatment of OSAS include patients with obstructing anatomy (i.e., large tonsils that obstruct the airway) and those who fail or cannot tolerate PAP therapy [39]. There are numerous upper airway surgical procedures that aim to relieve areas of obstruction during sleep; these can be categorized by their intended anatomic target: nasal (septoplasty, nasal valve surgery), oral/palatal (uvulopalatoplasty, tonsillectomy), hypopharyngeal (radiofrequency ablation of tongue), and other (maxillomandibular advancement or MMA, tracheostomy) [93]. Multilevel surgery incorporates more than one surgical procedure and is helpful for addressing multiple sites of airway collapse [93]. Surgical success has traditionally been defined as a ≥ 50% reduction in AHI and critics have argued that such a definition artificially inflates its efficacy, particularly when this intervention is compared to PAP therapy which typically defines cure or success as an AHI ≤ 5 or AHI ≤ 10 [94]. The disparate outcomes are evident in a recent meta-analysis of MMA for OSA which found that while this procedure resulted in a significant overall AHI reduction of 47.8/h, it yielded a 85.5% surgical success rate if a ≥ 50% reduction in AHI was achieved but only a 38.5% surgical cure rate when applying an AHI ≤ 5/hr [95]. A recent trial randomized adults who had failed conventional treatment for their OSA to medical management (positional therapy, weight loss) vs. a multilevel surgical approach (modified UPPP with radiofrequency ablation of the tongue). While a significant reduction in both AHI and ESS was observed in the surgical group, only 26% of the surgical group achieved an AHI < 10 [96]. Furthermore, there is currently a dearth of well-done clinical trials examining cardiovascular outcomes after upper airway surgery for OSA [97]. A recent systematic review concluded that the best evidence for reduced cardiovascular outcomes was for tracheostomy, which is largely considered an antiquated and overly morbid procedure for OSA. This same review also found that pharyngeal surgery, including uvulopalatopharyngoplasty (UPPP) resulted in mixed improvements in cardiovascular endpoints and MMA showed some evidence for improved hypertension [97]. Since this aforementioned review was published, a randomized clinical trial has been performed showing that a multilevel surgical approach (which includes UPPP and radiofrequency tongue ablation) improves both AHI and ESS in adults who have failed PAP therapy for their moderate to severe OSAS [96].

Positional Therapy

Positional OSA was first defined by the so-called Cartwright criteria, where a supine AHI is more than 2 × greater than the nonsupine AHI [98]; since then, there have been multiple

reiterations in its definition [99]. A recent study utilizing the Cartwright definition of positional OSA found a 35.3% prevalence of positional sleep apnea among a large population of patients with severe OSA [100]. When moving from the nonsupine to the supine position, there are multiple anatomic and physiologic changes that can increase propensity to sleep-disordered breathing. This includes a decrease in the magnitude of airway geometry [101], a decrease in functional residual capacity [102], and an increase in loop gain [103]. Positional therapy can be used both as an adjunct with other therapies such as PAP or MAD and by itself, particularly in patients whose sleep-disordered breathing resolves in the nonsupine position. Traditional methods of positional therapy were variations of the "tennis ball technique" (TBT) whereby the patient sleeps with a fixed object on their back to discourage supine sleep. While this approach is simple and affordable, it is usually not possible to monitor how effective therapy is on a night-to-night basis and furthermore, long-term compliance is poor with one study finding that at 2.5 years, only 6% of patients adhered to TBT, largely stopping due to discomfort [104]. In response to the downsides of the tennis ball technique, devices have been developed which utilize vibratory stimulation to train patients to stay off of their backs; these devices allow sleep providers to track compliance and monitor the effectiveness of therapy [99]. A meta-analysis that included four randomized controlled trials found that these devices resulted in a 54% reduction in AHI and an 84% reduction in time spent supine [99]. When compared to the TBT, the next-generation devices are superior with respect to compliance, sleep quality, and quality of life [105]. More studies evaluating long-term compliance past 6 months for these devices are needed [99].

Weight Loss and Exercise

Overweight and obese patients with OSA should be prescribed weight loss as an adjunct to other therapies for sleep apnea [106, 107]. Bariatric surgery can be an effective means of weight loss but should not be the sole means of OSA treatment [107]. Exercise is often recommended in combination with weight loss. When employed as a sole intervention, general exercise can improve OSA severity, but likely only to a modest degree [108]. In a heart failure population, exercise alone was associated with a significant decrease in AHI and exercise with CPAP was associated with an even greater decrease in AHI [109]. Oral myofunctional therapy is a specific form of exercise therapy which focuses on isotonic and isometric strengthening of the muscles of the tongue, throat, and face. A meta-analysis of oral myofunctional therapy for OSAS noted an approximately 50% reduction in AHI in addition to improved oxygen nadir, decreased snoring, and improved ESS [110]; however, a lack of a defined and consistent myofunctional therapy protocol makes these findings difficult to apply in general practice [111].

Pharmacotherapy

A recent systematic review and meta-analysis on pharmacotherapy for OSA did not find sufficient evidence supporting its use [112]. While two recent studies, one using a combination of atomoxetine and oxybutynin [113] and another using a cannabinoid [114], both showed impressive results with regard to AHI reduction, their patient population was small- and larger-scale trials evaluating side effects as well as both short-term and long-term treatment outcomes are needed.

Outcomes

While severe OSA has been associated with a wide range of disease including cardiovascular, neurocognitive, and metabolic disorders (Fig. 2), similar associations in those with mild to moderate OSA have been less consistent and more difficult to establish [115, 116]. The reason for this discrepancy is likely two-fold. First, sleep-specific indices such as AHI may not accurately reflect disease severity. Indeed, better sleep-specific indices of disease beyond the AHI [4] along with "big data" analytics have the potential to further our understanding of disease outcomes from untreated OSA [117]. Second, the expression of OSAS is complex and related to a multitude of patient-specific factors such as age, sex, race, obesity, comorbidities, genetic factors, specific OSA "phenotypes," environmental exposures, socioeconomic factors, lifestyle, and behaviors such as physical inactivity, smoking, and addictions [115].

Whether treatment of OSA with PAP therapy leads to improved health outcomes is an ongoing debate, largely dependent on both the patient population and the health outcome that is being assessed. A prime example of an active area that requires ongoing investigation is the impact of PAP therapy on cardiovascular outcomes in asymptomatic (i.e.,nonsleepy) patients with moderate to severe obstructive sleep apnea. Although several large studies have demonstrated a credible relationship between untreated OSA and increased risk of stroke, hypertension, and cardiovascular morbidity and mortality [118], it is unclear whether PAP therapy, which is widely considered our most effective therapy for sleep-disordered breathing, ameliorates these cardiovascular outcomes for all patients. Indeed while observational studies have shown a positive impact of PAP therapy [119, 120], four randomized controlled trials [121–124] have failed to demonstrate a reduction in cardiovascular morbidity and mortality with PAP treatment of nonsleepy moderate to severe OSA. Sleepy

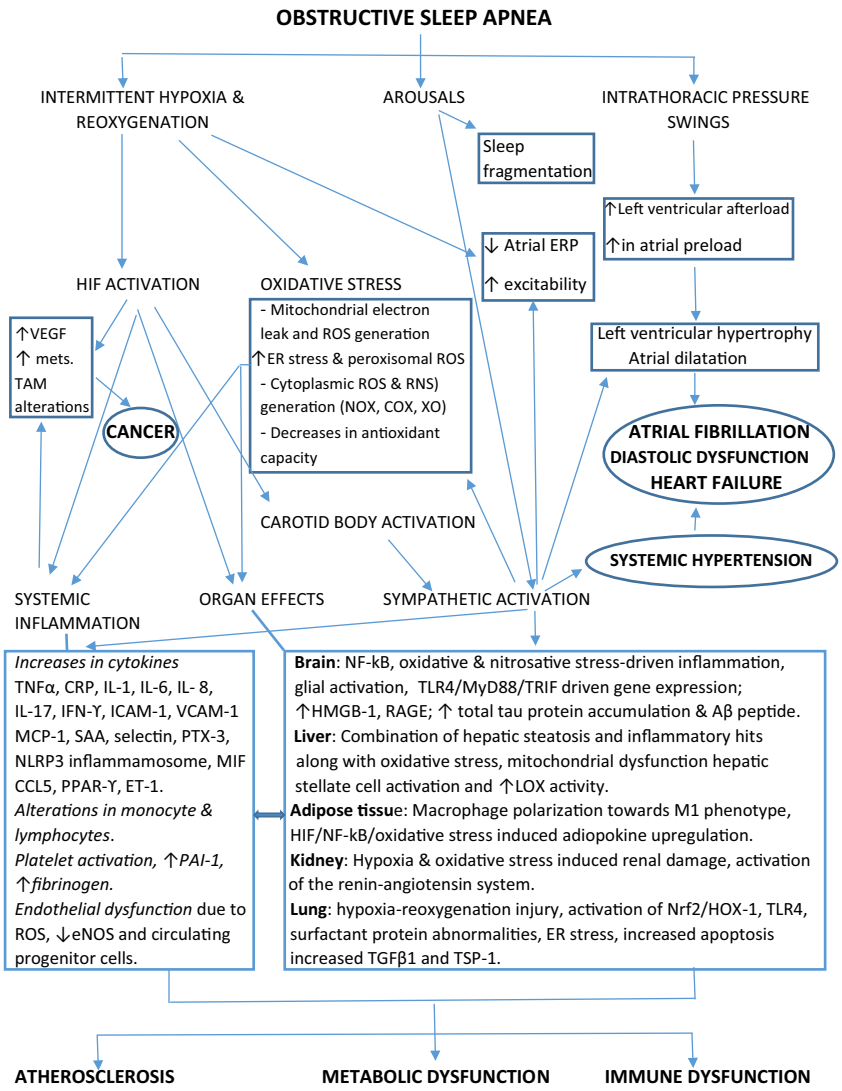

Fig. 1 Complex interplay of multitudinal effects of obstructive sleep apnea. By mechanisms of induced intermittent hypoxia, intrathoracic pressure swings, and sleep fragmentation, OSA can lead to chronic disease in multiple organs. Systemic changes can occur such as increased atherosclerosis and arterial stiffness, metabolic dysfunction (pancreatic β-cell dysfunction, insulin resistance, increased circulating free-fatty acids), and immune dysfunction (risk of viral infections, cancer and autoimmune disease) – details not shown. A number of transcriptional pathways are activated in different cells that include hypoxia inducible factor (HIF), nuclear factor kappa-light-chain-enhancer (NFkB), activator protein-1 (AP-1), nuclear factor-like 2 (Nrf2), and nuclear factor of activated T cells (NFAT). *ERP* effective refractory period, *VEGF* vascular endothelial growth factor, *mets* metastases, *TAM* tumor-associated macrophages, *ROS* reactive oxygen species, *ER* endoplasmic reticulum, *RNS* reactive nitrogen species, *NOX* NADPH oxidase, *COX* cyclooxygenase, *XO* xanthine oxidase, *TNFα* tumor necrosis factor-alpha, *CRP* C-reactive protein, *IL* interleukin, *IFN-Ɣ* interferon-gamma, *ICAM-1* intercellular adhesion molecule, *VCAM-1* vascular adhesion molecule-1, *MCP-1* monocyte chemoattractant protein-1, *SAA* serum amyloid A, *PTX-3* pentraxin-3, *NLRP3* NLR family pyrin domain containing 3, *MIF* macrophage migration inhibition factor, *CCL5* chemokine (C–C motif) ligand 5, *PPAR-Ɣ* peroxisome proliferator-activated receptor gamma, *ET-1* endothelin-1, *PAI* plasminogen activator inhibitor-1, *eNOS* endothelial nitric oxide synthase, *TLR4/MyD88/TRIF* toll-like receptor 4/myeloid differentiation primary response 88/TIR-domain containing adapter protein-inducing interferon, *HMGB1* high mobility group box 1 protein, *RAGE* receptor for advanced glycation end-products, *Aβ* amyloid beta, *HOX-1* heme oxygenase 1, *TGFβ1* transforming growth factor beta 1 and *TSP-1*, thrombospondin-1 [141, 151–168]

patients were excluded in these trials because of ethical considerations. While these randomized trials were well done, there were several limitations worth discussion. First, the authors identified "nonsleepy" patients by the ESS score using the following cut-offs: < 10 [123], ≤ 10 [122, 124], or ≤ 15[121]. This is problematic because the ESS has known problems with respect to both reproducibility and accuracy [125–127]; therefore, using the ESS

to define a patient population that may benefit or not benefit from treatment of sleep apnea is problematic. Second, like many PAP trials, the treatment arm had low CPAP adherence. The best known of these trials, the SAVE trial, despite having a CPAP "run-in" period with exclusion of initially noncompliant patients, only had a compliance of 3.3 h per night[121]. Lastly, two of these trials [121, 124] excluded patients with severe cardiac disease, who may benefit more from treatment with PAP therapy.

Current data support the use of PAP therapy in the treatment of OSA with regard to improvement in sleepiness, sleep-related quality of life, and motor vehicle accidents [128]. While the impact of PAP therapy on hypertension is well established, the effect appears to be relatively mild [128] with a greater impact seen in those with resistant hypertension [129]. Nondipping nocturnal blood pressure, which is often missed by routine ambulatory blood pressure assessments, has been found to be a predictor of OSA [130]. In patients with obesity hypoventilation syndrome, PAP therapy has been found to be associated with improvements in both comorbid OSA and hypoventilation. As such, the most recent consensus guidelines recommend PAP as first-line therapy in this population [131].

While data exist for the positive impacts of PAP therapy in other disease states, more information and randomized clinical trials are needed to establish its true efficacy. These diseases include COPD [132], chronic cough [133], asthma [134], neurocognitive disorders [135], depression [136], stroke [137], diabetes mellitus [138], glaucoma [139, 140], atrial fibrillation [137], and chronic renal disease [141].

Despite these discrepancies and the gaps in our understanding of the relationship between OSAS and clinical outcomes, there have been recent strides made in the implications of oxygenation abnormalities, intrathoracic pressure changes, and sleep fragmentation on the systemic manifestations of OSAS (Fig. 1). Carotid body excitation and subsequent sympathetic activation with OSA-associated desaturations in rodent models have conclusively established the connection between intermittent hypoxia and systemic hypertension, the most common disease associated with OSA [142]. Recent work focused on re-oxygenation driven oxidant injury have led to a better understanding of the effects of sustained vs. intermittent hypoxia and highlighted the need to delineate tissue-specific pathways of cellular adaptation and recovery from hypoxia and re-oxygenation [143, 144]. The frequent finding of oxidative stress, systemic inflammation, and heart-rate variability alterations in patients with OSA is representative of the wide scope of disease expression from OSA-related intermittent hypoxia and sleep fragmentation [145].

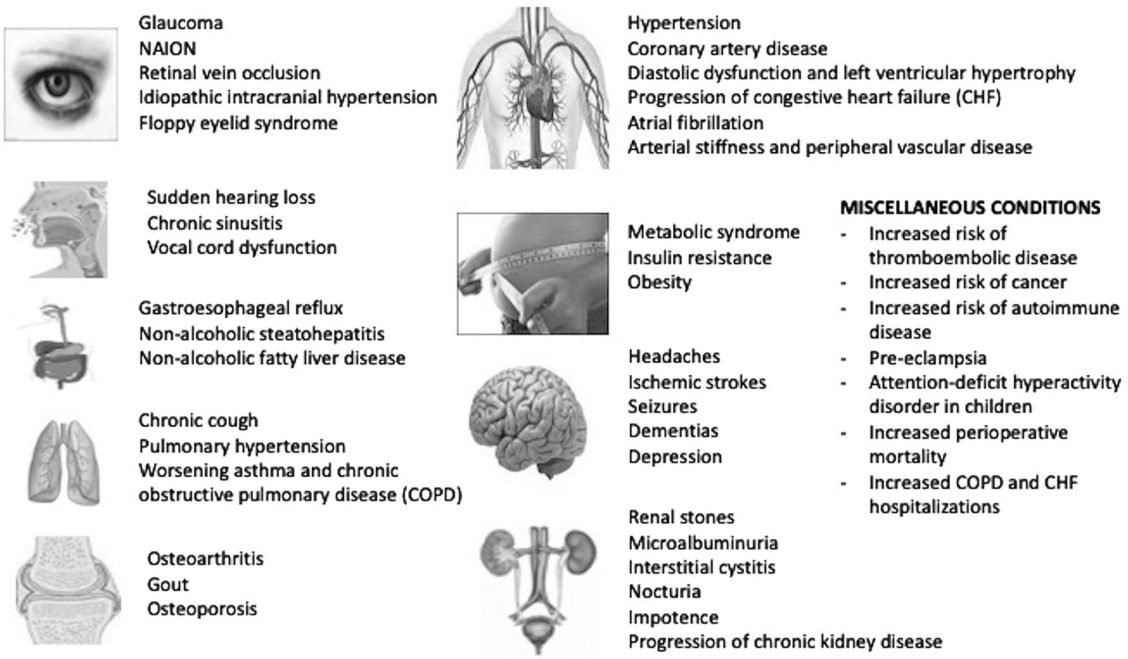

Fig. 2 Diseases associated with or worsened by obstructive sleep apnea syndrome. *NAION* Nonarteritic anterior ischemia optic neuropathy, *IIH* Idiopathic intracranial hypertension, *GERD* Gastro-esophageal reflux disease, *NASH* Nonalcoholic steatohepatitis, *NAFLD* Non-alcoholic fatty liver disease, *LVH* Left ventricular hypertrophy, *CHF* Congestive heart failure, *PAD* Peripheral arterial disease, *ADHD* Attention deficit/hyperactivity disorder

Conclusions

The importance of identifying and treating OSAS tracks alongside the importance of sleep to human health, economy, and society [146]. Despite its high prevalence in the community, OSAS remains under diagnosed; as such, education of both patients and healthcare providers regarding the symptoms and consequences of this disease is necessary. Significant strides have been made in our understanding of OSA pathophysiology in the last few decades. Future research should focus on the application of this knowledge towards better understanding the various disease phenotypes/endotypes of OSAS with the goal of successfully tailoring therapy and implementing novel treatments in the future [71, 147].

Compliance with Ethical Standards

Conflict of interest JJ Lee have no conflict of interest. KM Sundar Site PI for study of iVAPS EPAP algorithm funded by Resmed Inc.; Co-founder, Hypnoscure LLC.

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