Chapter 1

Sleep Apnea – Recent Updates

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Abstract

Sleep apnea is highly prevalent and underdiagnosed. It is associated with multiple medical conditions including cardiac dysrhythmia, stroke, hypertension, diabetes and congestive heart failure. In the last few decades, advances in diagnosis and treatment of sleep apnea have been robust. In this review, we will emphasize primarily developments in the area of sleep apnea that occurred in the past 5 years. These include changes in the nomenclature of sleep apnea in the International Classification in Sleep Disorders (ICSD)-3, physiologic approach of treating sleep apnea, eligibility for CPAP (continuous positive airway pressure) treatment, home sleep testing (HST), sleep apnea in pregnancy, updates in oral device treatment and other emerging concepts on sleep apnea.

Keywords: sleep apnea, sleep apnea updates, obstructive sleep apnea, apnea, recent updates of sleep apnea

1. Introduction

Obstructive sleep apnea (OSA) is a prevalent condition associated with increased risk of developing hypertension, heart failure, type 2 diabetes, cardiac rhythm disturbances, stroke and increased all-cause mortality [1–7]. It is also associated with reduced quality of life and sleepiness. In the field of sleep disorders particularly diagnosis and treatment of sleep apnea continues to evolve. In this review article, we consider advances in our understanding of pathophysiology, diagnosis and treatment sleep apnea with emphasis on recent advances over the past 5 years.

Sleep disordered breathing (SDB) events are classified as *obstructive*, *central* or *mixed*. Furthermore, events are usually subdivided into *apneas* (complete or almost complete cessation of airflow), *hypopneas* (reduction of airflow by 30-90% associated with EEG

arousals and/or 3-4 % oxygen desaturation) and *respiratory event-related arousals* (RERA—reduction of airflow by <30% associated with flow limitation and arousals on EEG) [8]. Obstructive events occur as a result of partial or complete obstruction of the upper airway at the level of the oro and/or nasopharynx with continuing respiratory efforts. Central events occur as a result of partial or complete cessation of efferent respiratory signals from the brainstem. Mixed events start out as central and evolve into obstructive events. Disordered breathing events (DBE) may be associated with reductions in oxygen saturation, sympathetic and parasympathetic surges and, in the case of obstructive events, large swings in intrathoracic pressure. Treatments for obstructive sleep apnea have classically included CPAP, certain types of upper airway surgery, dental orthotic or mandibular advancement devices, weight loss and positional therapy [9].

In the ensuing review, we discuss recent advances in the field including means of diagnosis and treatment in light of currently available literature.

2. Sleep-related breathing disorders nomenclature in ICSD-3

In the year of 2014, the American Academy of Sleep Medicine (AASM) released the 3rd edition of International Classification in Sleep Disorders (ICSD) [10]; this was an upgrade to the ICSD-2, 2011 edition. This shows progressive evolution of the nosology as knowledge and literature related to sleep disorders become more robust. There is a significant content change in the new edition, and one of them is within the sleep-related breathing disorders section. Treatment-central sleep apnea now appears as an isolated term to be used to describe central sleep apnea in the context of positive airway pressure treatment for obstructive sleep apnea. Other central sleep apneas like Cheyne-Stokes and substance induced are not classified in the same category. The other change in the SDB section is a separate diagnosis called sleep-related hypoxemia. This was under the same category of hypoventilation in the previous edition. In the ICSD-2, different categories based on the causes of the hypoxemia/hypoventilation that include medical and neurologic were listed separately. In ICSD-3, the cause of the hypoxemia/hypoventilation has to be diagnosed separately. Sleep-related hypoxemia diagnosis is assigned if a sleep study showed a sustained drop in SaO_2 but normal or not measured $PaCO_2$. In ICSD-3, obesity hypoventilation is also listed as a separate disorder due to its distinct clinical behavior. This requires a documentation of awake $PaCO_2$ >45 mm Hg. Refer to ICSD-3 for detailed review of the changes in all other sections [10].

3. Home sleep testing (HST)

OSA is prevalent and carries numerous physiologic and clinical consequences. The most recent prevalence estimates are that OSA is found in 33.9% of men and 17.4% of women [11]. These estimates are greater than previous ones, possibly due to increased sensitivity of detection, changes in definitions of types of "events," and/or increasing rates of obesity [11, 12]. Furthermore, as untreated sleep apnea is associated with a range of adverse consequences

[13], it has become clear that diagnostic testing needs to be convenient and available. Traditionally, in-laboratory attended polysomnography (PSG), in which sleep staging and cardiorespiratory variables are continuously recorded, has been the preferred method for diagnosing OSA. However, relatively high cost and growing wait times have provided the impetus for simplified portable unattended systems suitable for diagnosis of OSA outside the laboratory environment. In 1994 [14], AASM published a classification scheme grading the complexity of diagnostic sleep testing (see **Table 1**). Under this system, level 1 refers to commonly used in-laboratory attended PSG, level 2 refers to equally complex attended studies at home (rarely done) and levels 3 and 4 refer to unattended studies most commonly done at home, or out of the sleep laboratory. Since the original AASM classification system was published, technological advances have led to the availability of portable monitoring devices that may not neatly fit into the classification scheme. A revised system was presented in 2011 [15] similar to the 1994 system, but categorized portable devices according to the type of recording channel and the technology utilized. One of the primary issues is whether or not the device can adequately differentiate sleep from wakefulness and even stages of sleep. Many portable monitoring systems do not directly measure sleep using an EEG, but rather use derivative signals such as movement (actigraphy), pulse wave coupling or other derivative signals. For many systems, disease severity is more appropriately expressed as "respiratory disturbance index (RDI)" or "respiratory event index (REI)" (number of apneas/hypopneas per hour in bed) rather than the traditional apnea hypopnea index (apneas/hypopneas per hour of sleep) (AHI).

Level	Characteristics
1	Attended full PSG—the "gold standard" (EEG, sleep staging with four or more additional parameters, attended) CPT code: 95810 (Dx); 95811 (PAP, RAD); 95805 (MSLT/MWT)
2	Full PSG unattended/out of laboratory: as above—minimum 7 channels. HCPCS: G0398
3	Unattended, recording HR, O_2 saturation, respiratory airflow, respiratory effort; minimum of four channels, CPT: 95806; HCPCS: G0399
4	Unattended, HR, O_2 saturation, respiratory analysis; one or two channels, usually O_2 saturation or nasal airflow; CPT 95800 (includes estimated sleep time); 95801 (no sleep time); HCPCS G0400

Table 1. Levels of sleep testing (4).

A complete review of all home testing systems available is beyond the scope of this review. However, **Table 2** presents examples of several of the available simpler systems that have been validated. Both the AASM and the Canadian Sleep Society have published guidelines for use of portable monitors, most recently in 2010 [10]. These guidelines generally follow the highly selective study criteria outlined in validation studies. Portable monitoring devices are appropriate for patients with a high pretest probability of moderate-to-severe OSA (AHI of 15 or greater), but are not appropriate for routine screening in asymptomatic patients, or patients with concomitant medical or sleep disorders, such as central sleep apnea or periodic limb movement disorder. The Centers for Medicare and Medicaid Services (CMS) has approved coverage for PAP devices for patients diagnosed with OSA using portable monitoring [11].

System	Level	Principles/comments	References
Apnea risk evaluation system (ARES)[R]: SleepMed, Inc	3	Directly measures airflow, estimates respiratory effort from forehead vein, measures O_2 saturation and pulse rate. Approximates sleep time using lack of head movement	[6]
WatchPat[R] device: Itamar Medical Ltd	3*	Uses proprietary algorithm combined peripheral arterial tonometry, oximetry, heart rate, actigraphy to estimate sleep time and calculate respiratory disturbance index	[7]
Photoplethysmograph[R]: MorpheusOx; Widemed ltd.	3*	Measures O_2 saturation, pulse, peripheral arterial tone from optical volumetric signals. Proprietary algorithm detects sleep, respiration and disordered breathing events	[8]
ApneaStrip[R]: S.L.P. Ltd	3*	Simple device records airflow overnight and estimates sleep time	[9]

*Level claimed by manufacturer.

Table 2. Examples of portable home testing equipment (validation studies).

Many third party payers have followed CMS' lead; and in fact, many have instituted policies whereby portable sleep testing is required for all covered patients, with certain exceptions. Indeed in the highly selected patient populations studied for validation of portable testing, the correlation and even clinical outcomes are comparable between using portable diagnostic and in-laboratory testing [12–14]. However, as pointed out in an editorial by Collop [15], the issue is not the test *per se*, but how the test is utilized when it is "generalized." Most home sleep testing studies are done with highly selected patients (for the study quoted in Ref. [16], 272 patients were highly screened, 102 were randomized, approximately half to home testing). Furthermore, patients were evaluated by sleep experts, and scoring was done by well-trained and motivated technologists. Exclusions for significant medical, psychiatric and sleep disorders were rigidly carried out. However, in the "real world," as insurance carriers try to minimize costs, the experience is often that these conditions are not met. The decision to accept and indeed to "push for" home testing is often made on the basis of business and finance rather than patient benefit. While home or out of center sleep testing offers a number of advantages compared with in-laboratory PSG, there is no evidence that using this approach for all or the majority of patients is advantageous, even financially. The initial costs are generally less than those of in-laboratory testing. Furthermore, home testing offers a more rapid method of assessing the many patients with undiagnosed OSA who have limited access to, or who are reluctant to undergo, in-laboratory PSG. However, Chervin et al. [17] performed a careful cost utility analysis, comparing in-laboratory PSG, out of center testing and no testing (with treatment based on clinical characteristics). Their outcomes were based on costs per quality-adjusted life years over 5 years. These authors concluded that standard in-lab PSG provides greater quality-adjusted life years over 5 years than either out of center testing or no testing. Reuveni et al. [18] modeled costs of in-laboratory PSG versus out of center testing, accounting for the published technical failure rate of out of center testing, and the published European costs for PSG. They demonstrated that there was no long-term cost saving using out of center testing versus in-laboratory PSG.

Given that sleep apnea is under-diagnosed, another advantage of HST is diagnosing patients in a hospital setting and arranging follow-ups for complete evaluation in out-patient settings. Kauta et al. [19] evaluated 104 cardiac patients with SDB symptoms who are hospitalized for heart failure, arrhythmia and myocardial infarction. They performed type III portable sleep study, and 78% had SDB (AHI >5 events/h). Patients diagnosed with SDB were started with PAP treatment. At 30 days, adherence to PAP and 30-day readmission rate were assessed. None (0%) of patients (0/19) with adequate adherence, 30% of patients with partial adherence (6/20) and 29% of non-users (5/17) were readmitted or visited emergency room for cardiac issues ($p = 0.025$).

4. Effects of different definitions of DBEs on CPAP eligibility

Treatment with CPAP is known to significantly reduce the risk of important cardiovascular events and overall health care utilization [20, 21]. Thus, diagnosis and treatment of OSA would be expected to have a considerable beneficial impact on public health. Eligibility for CPAP treatment is usually based on disease severity, and this is usually expressed as the AHI. Of course, the number of events must perforce be based on the specific definitions of apneas, hypopneas and specified comorbid conditions. In 2012, the AASM adopted modified definitions of DBEs [8]. However, some insurance carriers including CMS continued to use the 2007 AASM definitions of DBEs [22]. The definitions of apneas between 2007 and 2012 have not changed [23], that is, a >90% reduction in airflow with continuing respiratory effort (for obstructive events). However, the 2012 AASM definition of hypopneas [8] calls for a 30–90% reduction in airflow associated with either a 3% reduction in O_2 saturation or a terminal arousal. The current CMS definition of hypopneas calls for the same reduction in airflow, but associated with a 4% reduction in O_2 saturation [23]. Further CMS defines the eligibility for CPAP treatment based on the AHI as follows: Patients are eligible for CPAP treatment for AHI ≥ 15, or if AHI is 5–14, only if the patient has a specified comorbidity, including hypertension, excessive sleepiness, impaired cognition, mood disorder, insomnia, ischemic heart disease, and history of stroke. Since CMS is often used by other insurance carriers as a model for designing their own treatment criteria, the differences in hypopnea definitions or in designation of treatment eligibility could have real significance.

Ho et al. [24] recently reviewed data on 6441 patients from the sleep heart health study and found, not surprisingly, that there was a discrepancy in the AHI depending on the definitions used for hypopneas, the discrepancy being greater at low AHIs than at high ones. Korotinsky et al. [25] recently compared AHI's calculated using both AASM (2012) and CMS definitions of hypopneas, as well as eligibility for CPAP treatment in a convenience sample of 112 consecutive patients studied in their sleep laboratory. Eighty-five patients were <65 years old and 27 were >65 years old (eligible for Medicare). They found the largest discrepancies in the younger patients, but a nonstatistically significant difference in the older patients. Furthermore, because of the presence of comorbidities in the older patients, there were no differences in eligibility for CPAP no matter which set of criteria were used. Thus, in younger patients, application of the stricter CMS criteria would have resulted in fewer patients being eligible for CPAP treatment, but not in the older patients. Thus, in the

younger patients, application of the stricter CMS criteria for eligibility for CPAP treatment would have resulted in fewer patients with relatively mild (AHI, 5–14) OSA being treated with CPAP. The question as to whether there is a healthcare advantage for treatment of younger patients with mild disease is still unsettled with opinions on both sides of the question [25].

5. Toward a physiologic approach to treating OSA

Breathing involves a complex neurologic interaction of various types of inspiratory muscles. During inspiration, pressures down the airway are slightly negative, since air must move from atmospheric pressure (= 0) to alveoli (pressure slightly negative). Prior to activation of the diaphragm, there is the activation of upper airway/pharyngeal dilator muscles that prevent collapse of the upper airway during inspiration. Thus, the upper airway performs an important function during respiration, and if function is compromised, obstruction could result as in OSA [26, 27]. CPAP is one of the preferred treatments for moderate-to-severe OSA. However, since upper airway dilator stimulation is thought to be inadequate to maintain upper airway patency during sleep, especially during REM sleep when skeletal muscle tone is suppressed, the concept developed that electrical stimulation of upper airway dilator muscles during inspiration could help maintain airway patency. Thus, a number of systems have been developed whereby stimulation of a hypoglossal nerve through an implantable device, timed to the patient's normal inspiration could help to maintain airways patency and alleviate sleep apnea. This approach would be particularly useful in patients who cannot tolerate or refuse to tolerate CPAP or other treatments. Several clinical trials have been carried out on devices implanted subcutaneously that are, once activated, triggered by the patient's own inspiratory effort [27–33]. The largest of these [33], a multisite clinical trial of patients with moderate-to-severe OSA, surgically implanted a hypoglossal nerve stimulator in OSA patients who were CPAP intolerant or refused CPAP treatment. The primary outcome measures were AHI and the ODI4 (oxygen desaturation index—number of times per hour, O_2 saturation fell by at least 4%). Secondary outcomes included the Epworth Sleepiness Scale (ESS), the Functional Outcomes of Sleep Questionnaire and the percent of sleep time with oxygen saturation <90%. This single cohort included 126 patients. At the end of 1 year, the median AHI decreased from 29.3 per hour to 9.0 per hour with similar improvements in the ODI4. Quality of life (QOL) measures also improved at the end of 1 year. At the end of 1 year, 46 patients participated in a 1:1 randomized therapy withdrawal trial. In this phase, participants who had therapy withdrawn demonstrated return of disease severity compared with those in whom therapy was not withdrawn. **Table 3** lists appropriate criteria for therapy with a hypoglossal stimulator. Finally, it should be pointed out that implantation of a hypoglossal nerve stimulator is part of a comprehensive program that extends well beyond the surgical procedure. The complete details are beyond the scope of this review, but involve selection based on criteria presented in **Table 3**, endoscopic evaluation of pharyngeal collapse, training of patients and staff, and various stages of activation and titration of stimulation parameters.

Eligibility criteria
Age> 22 years
AHI (AASM) 20–65 events per hour sleep
Less than 25% of DBEs are central or mixed events
Body Mass Index (BMI)<32 Kg/m^2
Unable or unwilling to use CPAP (including non-compliers)
Based on criteria presented in Ref. [33].

Table 3. Criteria for consideration for hypoglossal nerve implantation.

6. Sleep apnea and telemedicine

As compared to the past few decades, there is a better sleep disorders recognition and understanding of the impacts. As a result, a number of patients who need integrated expertise of sleep medicine care have increased. However, there is a substantial shortage of sleep medicine specialists across the United States. AASM recognized telemedicine could be used as a tool to improve the specialist gap and deliver a cost-effective care while still maintaining high-quality care. The The American Telemedicine Association defines telemedicine as the use of medical information exchanged from one site to another via electronic communications to improve a patient's clinical health status. This includes e-mail, smart phones, wireless tools, two-way video and other forms of telecommunications technology [34].

Telemedicine has been implemented in the majority of the medical disciplines. In the early days, telemedicine was used in the field of sleep medicine mainly to promote and reinforce CPAP therapy adherence and showed mixed results. In other instances, transmission of sleep studies by non-specialist to a sleep specialist for review has been used [35]. Taylor et al. [36] randomly grouped patients to usual care and telemedicine-based adherence for CPAP. Usual care patients visited practitioners in clinics and patients on telemedicine group had computer-based monitoring device that did not include video conferencing. Participants are contacted either by phone or by computer-based system. The study found no significant difference between the two groups. Other limited telemedicine application was doing sleep studies and diagnosing sleep disorders. Mendelson et al. [37] in 2014 randomized a total of 107 hypertensive patients to CPAP care (n = 53) and CPAP care with a telemedicine intervention (n = 54). Patients assigned to telemedicine uploaded blood pressure (BP) measurement, CPAP adherence, sleepiness and quality of life data and in return on regular bases they received recommendations. The main outcome was home self-measurement of BP improvement. Telemedicine-supported CPAP users did not improve BP and cardiovascular risk in high-risk OSA patients.

In 2008, the Milwaukee Veterans Administration Medical Center evaluated the application of telemedicine in sleep medicine [38]. Based on electronic consult eligibility for portable study, patients were assessed and sleep study orders were placed by sleep specialists. The need for in-

person assessment was also evaluated, and appointments were scheduled. CPAP was ordered for confirmed sleep apnea. Baig et al. [38] retrospectively assessed the 5-year trend in accessibility to and receipt of care after the program was implemented. They found that, in spite of increased volume of services, the interval between sleep consult and PAP prescription decreased from >60 days to <7 days. However, there was no change in clinic wait time of >60 days.

In the past decade, the use of tele-sleep medicine has been expanded to include patient's sleep evaluation. Before AASM came up with recommendation on telemedicine for sleep medicine, there were studies that supported telemedicine could be used for complete evaluation of sleep medicine patients. A pilot study by Spaulding et al. [39] showed the application of telemedicine that included video conferencing. The group established tele-heath service in a rural area of Kansas after training nurses and Registered Polysomnography Technologists (RPSGT) on how to use the videoconferencing webcam and intraoral camera for examining severity of airway narrowing. There were 18 new patients visits and four follow-ups. They reported that telemedicine was effective for physician-patient interaction and visualizing the upper airway. The only problem was nurses had to be trained to present patients and use the video cam and oral camera.

The AASM published a position paper in 2015 [40] that telemedicine can be used to improve access to sleep medicine services provided by board-certified sleep medicine specialist and improve communications with other specialties. Telemedicine applications can be broadly categorized into two: synchronous and asynchronous interactions. Synchronous is a live, real-time, bidirectional, audio-video conferencing provider-patient interaction who are distant apart. Tele-stethoscope and mobile cameras can be used for physical exam that is done in the presence of a presenter who usually is a trained nurse practitioner, physician assistant, respiratory therapist, RPSGT or medical office assistant. The patient presenter gives a clinical support and assistance with physical exam. Asynchronous evaluation uses multiple models and involves the encounters occur at different times and are communicated one directionally between patients and providers electronically. AASM recommended providers to adopt technical requirements from the American Telemedicine Guidelines [40]. AASM believes if the technical, organizational and healthcare professional requirements are met, synchronous encounters could function as live office visits.

In January 2016, the AASM officially launched AASM SleepTM. This is a telemedicine platform designed for the sleep medicine field. Some centers have implemented telemedicine. Issues that need further clarification while implementing telemedicine include cost uncertainties, reimbursement structure and licensing rules. Currently, expansion of telemedicine to all sleep disorders has its own restrictions and providers should refer to their local standard for the technical and organizational requirements.

7. Sleep apnea and pregnancy

7.1. Screening OSA during pregnancy

In general, sleep disturbances are highly prevalent during pregnancy including SDB. Self-reported snoring is common with a prevalence of 14–41% as compared with 4–17% in non-

pregnant women [41–46]. Recognition of sleep apnea in pregnant women in particular is difficult because pregnancy is dynamic process and multiple studies at different time points during pregnancy may not be feasible. In 2015, there were two articles that tried to assess the screening tools for sleep apnea in pregnancy. Lockhart et al. [47] assessed 218 third trimester pregnancies of which 12% had sleep apnea diagnosed using portable home sleep testing. In this study STOP, STOP BANG, Berlin, American Society of Anesthesiologist Checklist and ESS were not successful in detecting sleep apnea. However, some of the elements such as BMI, neck circumference, diagnosis of hypertension (HTN) and falling asleep while talking to others where more predictive based on univariate and multivariate analysis. Tantrakul et al. [48] evaluated Berlin and STOP BANG questionnaires to detect OSA across trimesters of high-risk pregnancy. They consisted of n = 72 (first trimester n = 23, second trimester n = 24 and third trimester n = 25), and with prevalence of OSA by trimester from first to third was 30.4%, 33.3% and 32.0%, respectively. Overall, predictive values of Berlin and STOP BANG were fair (AUC 0.72 for Berlin, P = 0.003, 0.75 for STOP BANG, P = 0.0001). The predictive values performed poorer during the first trimester. Multivariant analyses showed pre-pregnancy BMI, snore frequently and weight gain/BMI were significantly associated with OSA in first, second and third trimesters, respectively. Izci et al. [46] demonstrated third trimester pregnant females have smaller mean pharyngeal areas when compared with postpartum in supine, lateral and seated positions with a mean difference of 0.20 (95% CI 0.06–0.35), 0.26 (95% CI 0.12–0.39) and 0.18 (95% CI 0.02–0.32), respectively.

7.2. OSA and perinatal outcomes

Repeated upper airway resistance and/or obstruction during sleep due to DBEs that causes chronic intermittent hypoxia, hypercarbia and sleep disruptions is believed to be a culprit for higher incidence of negative perinatal outcomes. However, studies have shown conflicting results. Tauman et al. [49] recruited 122 pregnant women with habitual snoring and 39% had SDB. In those pregnant women who snored had increased markers of fetal distress, which are circulating nucleated RBC, EPO and IL-6. However, there was no difference in neonatal outcome. Trudell et al. [50] conducted a study with the aim to develop a tool for airway assessment to predict adverse pregnancy outcomes. They hypothesized that higher Mallampati score (MS) is associated with adverse perinatal outcomes. Outcomes were compared between low MS and high MS in a total of 1823 term births. No significant difference was found in the risk of small for gestational age (SGA) [adjusted odds ratio 0.9 (95% CI 0.6–1.2), preeclampsia adjusted odds ratio 1.2 (95% CI 0.8–1.9) or neonatal acedemia 0.8 (95% CI 0.3–2)]. In recent population-based retrospective study (n = 636,227), Bin et al. [51] found that OSA was significantly associated with HTN, planned delivery, preterm birth, 5-min Apgar <7, admission to neonatal ICU/special care nursery and large for gestational age infant but was not associated with gestational diabetes, Cesarean section, perinatal death or SGA.

Trauman et al. [52] prospectively studied 74 pregnant women (24% with OSA) and full-term infants for general movements and neurodevelopment at 48 h, 8–11 weeks, 14–16 weeks and at 12 months. Infant developmental inventory and infant brief questioner were administered. At 12 months, 64% of infants born to SDB mothers showed low social developmental score as compared to 25% of infants born to controls (P = 0.36, odds ratio 16.7). In neonatal and infant

neuromotor development, there was no difference between infants born to SBD mother or controls. Another study that failed to show negative outcome was by Bassan et al. [53]. The group studied 44 women (25% had SDB) with full-term infants showed that there was no difference in birthweight, gestational age, 5-min APGAR score and neurological exam score between infants born to SDB and non-SDB mothers.

Ravishankar et al. [54] studied the effect of SDB on histopathology and immune-histochemical markers of placental perfusion and hypoxia. The placentas of women with OSA (n = 23), habitual snoring (n = 78) and non-snorers (n = 47) were accessed. Fetal normoblastemia was prevalent in OSA as compared to snorers and controls (56.5%, 34.6%, and 6.4% respectively). Increased tissue hypoxia marker, carbonic anhydrase IX immunoreactivity, was demonstrated in OSA pregnant women as compare to non-snorers and controls (81.5%, 91.3% and 57.5%, respectively). Uteroplacental and reperfusion score were similar in all groups.

Further studies in the future are warranted to assess the effect of SDB on perinatal and neonatal outcome.

8. Update on oral appliance therapy

In 2015, the AASM published an update of clinical practice guidelines of treatment for OSA and snoring with oral appliance therapy [55]. The new guidelines continued to recommend oral appliance therapy and gave increased focus on patient preference. An oral appliance can now be considered for all levels of OSA severity (mild, moderate and severe), if the patient fails or refuses CPAP, or even if they simply prefer an oral appliance to CPAP.

Subjective adherence with oral appliance therapy is better overall than objective adherence with CPAP in adult patients with OSA. CPAP is superior to oral appliance therapy in improving the AHI and lowering the arousal index and the ODI, but the new guidelines suggest that the overall therapeutic effectiveness of oral appliances may be comparable with CPAP because of the significant difference in adherence rates.

These new guidelines recommend that sleep physicians prescribe oral appliances for patients who request treatment of primary snoring. When prescribed for OSA patient, it suggests that a qualified dentist use a custom, titratable appliance. It also recommends that sleep physicians consider prescription of oral appliances for adult patients with OSA who are intolerant of CPAP therapy or prefer alternate therapy. Qualified dentists should provide oversight of oral appliance therapy in OSA patients, and sleep physicians should conduct follow-up sleep testing to improve or confirm treatment efficacy.

Studies have demonstrated efficacy of oral appliance therapy comparable to CPAP in selected patients [56, 57]. While oral appliances help to decrease AHI/RDI/REI across all severity levels, there are few reported factors that consistently predict improvement in OSA using oral appliances. A number of possible predictors have been examined. Among these are changes in pharyngeal geometry under drug-induced sleep endoscopy (DISE) [58] and nasoendoscopy to assess velopharynx/oro/hypopharyngeal geometry [59]. In the study of Gjerde [57], low oxygen levels carried a high predictive value for failure with oral appliance therapy.

9. Update on PAP devices

Many types of PAP devices are used to treat the whole spectrum of SDB including CPAP, autotitrating CPAP (APAP), bilevel PAP, autotitrating bilevel PAP, volume-assured pressure support and adaptive servoventilation. CPAP and APAP are most commonly used, whereas the other modes are reserved for patients needing respiratory assist. For CPAP and APAP, data collection systems can track compliance, pressure, leak and efficacy. Refer to Johnson et al. [60] for a comprehensive review of the technological aspects of PAP devices in general with its algorithms, including event detection, sampling rates, cycling, targets, rate and pressure adjustments as well as suggested settings.

APAP has been shown to be an effective means to determine therapeutic CPAP levels. The question remains as to whether APAP is suitable for long-term treatment of patients with OSA. In the past 5 years, at least three different meta-analyses [61–63] have been performed comparing the efficacy of CPAP to APAP and demonstrating similar effectiveness. These three studies have found that APAP and CPAP produce comparable reductions in AHI, decreased sleepiness, comparable long-term compliance and improvements in sleep architecture. Because the treatment effects are similar between APAP and CPAP, the therapy of choice may depend on other factors such as patient preference, specific reasons for non-compliance and cost [62].

Although CPAP and APAP appear comparable, other investigators have looked at the use of alternative PAP modalities presumed to be more comfortable for therapy in OSA patients with the hopes of leading to improved compliance. These have included auto-bi-level pressure relief-positive airway pressure (ABPR-PAP). Four studies [64–67] showed similar improvements in symptoms using an auto-bi-level mode and CPAP. Compliance was generally better with the auto-bi-level modes than CPAP, even in CPAP patients selected for poor compliance [65, 67].

10. Emerging concepts

Over the past 5 years, there continues to be advancement in understanding of all aspects of OSA. Major categories have been covered in other areas of this review. Below is a selected group of topics with new emerging points of view that deserve increased focus in the future.

10.1. Interventions to improve CPAP compliance

CPAP is not accepted by many users. Educational, supportive and behavioral interventions may help people with OSA recognize the need for regular and continued use of CPAP. An updated review on the effect of these intervention modalities was performed in 2014. Thirty randomized controlled studies (2047 participants) were included [68]. Low-to-moderate quality evidence showed that all three types of interventions led to increased machine usage in CPAP-naive patients with moderate-to-severe OSA. Compared with usual care, supportive ongoing interventions increased CPAP use by 50 min per night and increased the number of patients who used CPAP for longer than 4 hours per night from 59% to 75%. Educational interventions increased CPAP use by 35 min per night and increased the number of patients

who used CPAP for longer than 4 h per night from 57% to 70%. Behavioral therapy led to an improvement in CPAP use of 1.44 h per night and increased the number of patients who used CPAP for longer than four hours per night from 28% to 47%.

10.2. More focus on the relationship between smoking and OSA

It has been suspected for some time that smoking and OSA adversely affect each other, leading to increased comorbidity; however, this is still a matter of debate. There seems to be a synergistic effect between smoking and OSA, which may lead to increase in cardiovascular morbidity [69]. However, the evidence is less than conclusive. Cigarette smoking may increase the severity of OSA through alterations in sleep architecture, upper airway neuromuscular function, arousal mechanisms and upper airway inflammation. And untreated OSA may be associated with smoking addiction. The effect of smoking cessation on OSA remains to be determined. Future studies are needed in order to establish the strength of the association of both conditions [70].

11. Patient-specific therapy and customization of therapy

11.1. Focus on pathophysiology

There has been an increased focus on the importance of pathophysiological factor identification for customized therapy in OSA patients and more investigation of different group phenotypes or individual characteristics to personalize OSA therapy. Differentiated OSA phenotypes have been proposed: a small pharyngeal airway with a low resistance to collapse (increased critical closing pressure), an inadequate response of pharyngeal dilator muscles (wakefulness drive to breathe), an unstable ventilator responsiveness to hypercapnia (high loop gain) and an increased propensity to wake related to upper airway obstruction (low arousal threshold) [71]. If an accurate pathophysiological pattern for each OSA patient can be identified, customized—and presumably more effective—therapy would potentially be feasible [71].

A large cohort of 1249 patients (age 47 years; AHI 18.9/h; BMI 27.2 ± 3.7 kg/m^2) underwent PSG and DISE to determine upper airway (UA) collapse patterns [72]. Palatal collapse was the most frequent (81%). Multilevel collapse was noted in 68.2% of patients; the most frequent multilevel pattern was a combination of palatal and tongue base collapse (25.5%). The prevalence of complete collapse, multilevel collapse and hypopharyngeal collapse increased with increasing severity of obstructive sleep apnea (OSA). Multilevel and complete collapses were more prevalent in obese patients and in those with more severe OSA. Both higher BMI and AHI values were associated with a higher probability of complete concentric palatal collapse. However, UA collapse patterns during DISE cannot be fully explained by selected baseline polysomnographic and anthropometric characteristics.

Age may play a significant role. A study in which 10 young (20–40 year) and old (60 year and older) patients with OSA matched by BMI and sex suggested that airway anatomy/collapsibility plays a relatively greater pathogenic role in older adults whereas sensitive ventilatory control system is more prominent trait in younger adults [73].

11.2. Focus on mild OSA

There remains to be a debate about how significant is the effect of mild OSA on adverse health outcomes, to the point that unless not accompanied by specific medical conditions or symptoms, insurers will not cover therapy. The American Thoracic Society in 2016 published a research statement hoping to find answers to this lingering question [74]. The specific goals of this statement were to appraise the evidence regarding whether long-term adverse neurocognitive and cardiovascular outcomes are attributable to mild OSA and evaluate whether or not treatment of mild OSA is effective at preventing or reducing these adverse outcomes.

Unfortunately, studies were incongruent in their definitions of mild OSA, and data were inconsistent regarding the relationship between mild OSA and daytime sleepiness. It was concluded that treatment of mild OSA may improve sleepiness in patients who are sleepy at baseline and improve quality of life. There was limited or inconsistent evidence pertaining to the impact of therapy of mild OSA on other adverse outcomes.

11.3. More focus on perioperative care of OSA patients

The Society of Anesthesia and Sleep Medicine published in 2016 guidelines on preoperative screening and assessment of OSA patients [75]. This guideline emphasizes again the increased risks of perioperative complications in patients with OSA and recommended that practice groups consider making OSA screening a standard part pre-anesthetic evaluation. It did not go as far as recommending cancelling or delaying surgery to diagnose OSA unless there is evidence of an associated significant or uncontrolled systemic disease or additional problems with ventilation or gas exchange. The use of PAP therapy in previously undiagnosed, but suspected OSA patients should be considered case by case. Continued use of PAP therapy at previously prescribed settings in OSA is recommended during periods of sleep while hospitalized, both preoperatively and postoperatively. These guidelines strongly recommended for protocols for known or suspected OSA to be developed by individual institutions taking into account the patients' conditions, extent of interventions and available resources.

11.4. More focus on commercial motor vehicle OSA screening and treatment

A recommendation overview of commercial motor vehicle OSA screening and treatment was published in 2016. This document goes over prior recommendations and details the small differences present in other statements regarding this topic. There is a need for federal regulations to clarify the issue. Among the recommendations by the authors are the following [76]:

Out of service evaluation is recommended when admitted sleepiness while driving, motor vehicle collision attributable to falling asleep, ESS score >10, and OSA without objective documentation of sufficient therapy efficacy and/or adherence for OSA testing. PSG is preferred diagnostic test; however, HST may be a reasonable alternative in selected patients based on the sleep specialist assessment.

AHI, RDI or REI >20/h are recommended to have treatment. PAP therapy is generally the most expeditious treatment available. Surgical evaluation may be considered based on com-

prehensive assessment findings. Weight loss is recommended as adjunct. AHI, RDI or REI ≥5/h with sleepiness or sleepiness-related accident should be counseled to initiate treatment for OSA.

Documentation of efficacy of therapy is recommended. PAP therapy usage below published minimum recommendations (≥4 h for ≥70% of nights) could result in removal from service by the certified medical examiner. PAP therapy adherence should be objectively monitored by a sleep specialist assessing therapy adherence and efficacy. Printed reports of therapy adherence data should be made available to the certified medical examiner.

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