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REVIEW

Recent advances in the diagnosis and management of obstructive sleep apnea

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ABSTRACT

Affecting a large number of middle-aged, frequently overweight subjects, obstructive sleep apnea (OSA) is the most common sleep related breathing disorder. Partial or complete upper airway (UA) collapse during sleep causing repeated apneic episodes, which is the leading pathophysiological mechanism underlying the disorder, results in arterial oxygen desaturation and recurrent arousals from sleep to re-establish airway patency. Untreated OSA is commonly associated with a range of adverse consequences, including cardiovascular complications, such as arterial and/or pulmonary hypertension, arrhythmias, stroke, as well as diabetes mellitus and metabolic syndrome, and motor vehicle accidents. Evidence-based guidelines are presently available for the diagnosis and management of OSA, and a variety of updated testing and treatment procedures and devices including some that are able to identify the site and degree of airway obstruction are becoming increasingly available. As the "one size fits all" approach falls to the wayside, a tailored personal therapeutic strategy is becoming increasingly popular in the field of sleep medicine. The aim of this review is to provide an overview for practicing clinicians on recent advances in the evaluation and management of obstructive sleep apnea in adults.

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Affecting a large proportion of middle-aged overweight subjects, with an approximate prevalence of 14.3% in men and 5% in women, obstructive sleep apnea (OSA) is the most common sleep related breathing disorder. A recent literature review reported that 1/5 Caucasian adults have sleep-related obstructive apneas of mild severity and 1/15 have obstructive apneas of moderate severity.[2] Signs, symptoms and consequences linked to OSA are due to repeated episodes of total (apnea) and/or partial (hypopnea) pharyngeal collapse during sleep, associated with an intermittent reduction in arterial Oxygen Saturation (SaO_2), CO_2 retention, marked alterations in intrathoracic pressure, sympathetic nervous system hyperactivity, and recurrent arousals from sleep to re-establish airway patency.[3, 4] Several evidence-based guidelines are available for the diagnosis and treatment of OSA. Diagnosis/treatment options have, in fact, been advancing rapidly and now include a variety of

simplified sleep monitors, appliances and procedures. The aim of this review was to provide practicing clinicians with a general overview of relevant literature on this topic and of recent advances in the evaluation and management of obstructive sleep apnea in adults.

Overview of obstructive sleep apnea

Susceptibility to pharyngeal collapse during sleep resulting in ongoing inspiratory effort is regarded the most relevant mechanism underlying obstructive apneas. The pharyngeal airway is a structure with complex anatomical relationships including three different compartments: 1) the nasopharynx whose function is mainly respiratory; 2) the oropharynx which has respiratory, swallowing and reflex functions; and 3) the laryngopharynx that plays an important role in speech production, swallowing and in respiration. From a pathophysiological viewpoint, a 'balance of forces' model describes the mechanisms by which closure and patency of the upper airway (UA) during sleep is achieved (Figure 1).[5] Indeed, increased activity of the pharyngeal dilator muscles due to protective reflex mechanisms during wakefulness can effectively counterbalance the propensity for UA collapse, but patency can be compromised during sleep due to inadequate ventilatory drive from the respiratory centers. Starling properties of the UA and adherence of mucosal surfaces can favor occlusion and persistence of airway collapse during increasing ventilatory efforts. It is the anatomy of the patient that determines whether obstruction or near-obstruction (hypopnea) occurs when airway tone and activation falls below the threshold that maintains patency, causing snoring and, in the event of complete obstruction, sleep apnea.[6, 7] A number of investigations on anatomical variants predisposing to UA occlusion have identified susceptibilities due to a variety of craniofacial and oropharyngeal features, including large neck circumference, retro- or micrognazia, nasal obstruction, enlarged tonsils/ adenoids, macroglossia and low-lying soft palate.[8]

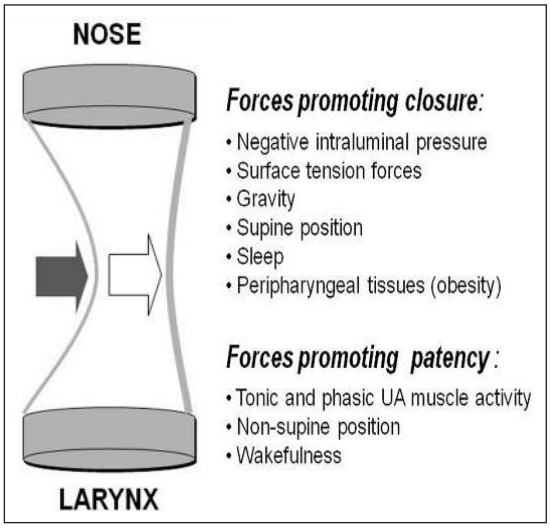

Figure 1.—Model of the 'balance of forces', including factors that promote closure or patency of the upper airway.

Clinically, patients themselves or their partner/cohabitant often describe nocturnal snoring, choking, gasping sounds and breathing interruptions. Excessive daytime sleepiness is also a common complaint, and the patient may describe fatigue, lack of energy, tiredness or daytime sleeping spells. Other frequent complaints include a sense of unrefreshing sleep, insomnia with or without abrupt awakenings, nocturnal sweating, nicturia, morning headaches, dry mouth or sore throat.[9] Untreated, OSA is commonly associated with a range of serious consequences, including cardiovascular (CV) complications, such as arterial hypertension (HT), pulmonary HT, arrhythmias, stroke, as well as diabetes mellitus and metabolic syndrome, and motor vehicle accidents.[10-13] Patients with OSA are, in fact, at a three- to four-fold higher mortality risk compared to the general population.[14]

Diagnosis of OSA is based upon a comprehensive sleep history, clinical signs and symptom, and testing of breathing patterns and oxygen levels during sleep. Diagnostic criteria for OSA, which were first published in 1999 by the American Academy of Sleep Medicine (AASM), included the following:

— excessive daytime sleepiness that is not better explained by other factors;

— two or more of the following that are not better explained by other factors:

— choking or gasping during sleep;
— recurrent awakening from sleep;
— unrefreshing sleep;
— daytime fatigue;
— impaired concentration;
— overnight monitoring demonstrating five or more obstructed breathing events (apneas/hypopneas) per hour during sleep (Apnea Hypopnea Index [AHI]>5).

Patients with suspected OSA must fulfil criterion A or B, plus criterion C.[3]

The severity of OSA syndrome (OSAS) was defined by the AASM, depending on the number of apneas and hypopneas per hour of sleep, according to the following cut-offs:
— mild: 5-15 events/hour;
— moderate: 15-30 events/hour;
— severe: more than 30 events/hour.

Two years later, the AASM published a new set of criteria in *The International Classification of Sleep Disorders diagnostic and coding manual* (ICSD).[15] The main difference with respect to the precedent one was the absence of clearly defined criteria for the number of apneas and hypopneas needed for a diagnosis of OSAS.

Four years later, in 2005, a new edition of the ICSD was published by the AASM with a new version of diagnostic criteria for OSA.[16] The most important difference with respect to the precedent one was that the disorder's official name was changed from "Obstructive Sleep Apnea Syndrome" to "Obstructive Sleep Apnea" (OSA). In addition, the disorder was defined as either 5 obstructive events/hour of sleep with symptoms or 15 obstructive events without symptoms.

Diagnosing OSA remains nevertheless challenging, and it continues to be a disorder that is considerably underdiagnosed, despite increasing awareness on the part of both clinicians and the public.[17]

The ''gold standard'' for overnight monitoring continues to be laboratory polysomnography (PSG), which is an expensive, time consuming procedure that is dependent on the availability of a sleep laboratory, all leading to unreasonably long waiting lists. As a result, attempts have been made to develop screening tools based on sleep apnea symptoms, self-report questionnaires, anthropometric measurements (*e.g*., body mass index, neck circumference) and the presence of major comorbidities (*e.g*. blood pressure, stroke) in order to stratify patients and identify those at highest risk of the disorder. The most used screening questionnaires include the Epworth Sleepiness Scale,[18] the Berlin Questionnaire,[19] the STOP,[20] the STOP-Bang [21] and the American Society of Anesthesiologist (ASA) checklist.[22] A systematic review by Abrishami *et al*. concluded that STOP and STOP-Bang questionnaires for screening of OSA in the surgical population are more suitable due to their higher methodological quality and easy-to-use features.[23] When the Clinical Practice Guideline of the American College of Physicians compared the sensitivities and specificities of different questionnaires in diagnosing sleep apnea in adults with symptoms suggestive of disordered sleep, they reached the conclusion that although the Berlin Questionnaire may be helpful in predicting risk for OSA, evidence is insufficient to determine the diagnostic accuracy of screening questionnaires with respect to PSG.[24]

Since the early 90's technological advances have led to the availability of a variety of portable monitoring (PM) devices that can record sleep, noctural breathing and oxygenation at home.[25] There is nevertheless a paucity of evidence demonstrating that PM is equivalent to formal PSG and most comparative studies have been inconclusive.[26-28]

Treatment of OSA includes a wide range of options. According to a number of Consensus Statements and Recommended Clinical Procedures, the first choice of treatment for patients with moderate or severe OSA is continuous positive airway pressure (CPAP).[3, 29, 30] Positive pressure devices work by forcing air into the upper airway via a nasal mask and splinting the airway open to facilitate proper airflow. The pressure that is required varies with the severity of OSA; higher pressures are needed to treat those apneas occurring during rapid eye movement sleep, when the patient is in the supine position, or in the presence of severe obesity. OSA

patients who comply with CPAP treatment have been found to have lower blood pressure levels and arterial stiffness and they show a lower risk of having a cardiovascular event compared with those with untreated moderate-severe OSA.[31] Schwarz *et al*. who recently reviewed data on OSA patients randomized to continue or suspend CPAP found that both systolic and diastolic blood pressure increased in the CPAP-withdrawal compared to the CPAP-compliance group by +5.4 mmHg (95% CI 1.8-8.9 mmHg, P=0.003) and +5.0 mmHg (95%CI 2.7-7.3 mmHg, P<0.001), respectively.[32]

Since its first description in 1981,[33] many technological advancements in the delivery of positive airway pressure have been made in the effort to increase patient comfort/compliance.[34] Positive Airway Pressure (PAP) technologies alternative to CPAP, such as autotitrating PAP (APAP) and bilevel PAP (BiPAP), have been devised for patients with special needs.[34] But despite technological improvements, approximately two thirds of OSA patients complain about side-effects linked to CPAP such as skin irritation, dry nose/throat, nasal stuffiness, eye puffiness, or gastric fullness and even nightmares. Compliance to PAP therapy remains thus relatively poor, leading sleep specialists to search for alternative treatment options.[35] Different types of mouth devices including mandibular advancement devices (MADs), also known as mandibular advancement splints or dental devices, and tongue-retaining devices have also been proposed as an alternative to CPAP in some situations.[29, 36] Lifestyle interventions such as exercise programs, weight loss via dietary regimen and positional therapies have also been found to be effective treatments for overweight/obese patients with mild or asymptomatic OSA leading to a reduction in the AHI and beneficial effects on other cardio-metabolic-related risk factors.[37, 38] To achieve major weight loss, bariatric surgery is specifically indicated for individuals with Body Mass Index (BMI)≥40 kg/m^2 or those with BMI≥35 kg/m^2 and the presence of important comorbidities who have failed weight loss programs.[3] In a recent study, 80.6% of obese patients with severe OSA who underwent laparoscopic sleeve gastrectomy showed a significant improvement in AHI at a 5-year follow-up.[39] Finally, a wide variety of upper airway surgical reconstructive or bypass procedures aiming to directly reduce sleep apnea severity have been recommended to patients with specific anatomical obstructions, including Maxillo-Mandibular Advancement (MMA), and Uvulo-Palato-Pharyngoplasty (UPPP), one of the oldest, most widely studied and used procedures.[40]

Advances in diagnosis

In theory, OSA is relatively simple to diagnose, but in practice PSG, the standard diagnostic test, is intrusive, cumbersome and costly. As a result, attention on the diagnosis of OSA has recently focused on the validity/reliability of home testing as an alternative to in-laboratory PSG, and in fact a growing number of guidelines include portable sleep monitoring as a diagnostic option. Recent advances have produced novel sleep testing procedures to reduce the burden of diagnosing OSA and to identify the level and degree of airway obstruction in the attempt to "personalize" therapeutic intervention. Finally, new diagnostic criteria for OSA patients have also been recently introduced.

New classification system: ICSD-3

In 2014, the third edition of the *International Classification of Sleep Disorders* (ICSD-3) was published and the AASM once again revised the classification of sleep disorders.[41] Important modifications were made in the definition and classification of Sleep-Related Breathing Disorder (SRBD) and other sleep disorders. The most significant change with respect to the ICSD-2 was that a respiratory event index (based on hours of monitoring time) can now be produced in out-of-center sleep testing (OCST). Since the diagnosis of OSA can now be made not only in a sleep laboratory but also on the basis of OCST testing, it is presumable that there will be a progressive transitioning from the gold standard PSG to home sleep testing.

The core criteria for the diagnosis of OSA are for the most part unvaried with respect to the ICSD-2, and OSA is now defined as 5-15 respiratory events per hour in the presence of selected risk factors and comorbidities (*i.e*., cardiovascular diseases, type II diabetes and mood disorders), regardless of the clinical symptoms that are reported. Finally, primary snoring, originally listed in a separate chapter ("Isolated symptoms, normal variations and unsolved problems"), is now considered a SRBD.[42]

New ambulatory screening methods: peripheral arterial tonometry and pulse wave analysis

As noted above, there is increasing evidence that diagnosis and treatment of OSA can be managed outside of sleep centers. The American College of Physicians (ACP) recently recommended portable sleep monitors for patients without serious comorbidities as an alternative to PSG when it is not available for diagnostic testing.[30] Along with technical advancements in the portable devices currently available, including improved automatic scoring algorithms, some diagnostic tools which measure other biological signals have also been proposed. Devices using peripheral arterial tonometry (PAT), such as the WatchPAT device (Itamar Medical, Ltd),[43] are acquiring popularity. A relatively novel technique, the user-friendly sensor measures autonomous nervous function by gauging peripheral arterial tone making it possible to track hemodynamic changes and to identify subcortical arousals which accompany apneas. By correlating PAT with other parameters (SaO_2, body position, and microphone), the sensor indirectly assesses autonomous and respiratory arousals, and sleep status. The data can be analyzed by a previously developed algorithm to calculate the AHI and Respiratory Disturbance Index (RDI).[44] When Yalamanchali *et al*. recently reviewed fourteen studies to assess the correlation between PAT and PSG as measured by AHI, RDI, and Oxygen Desaturation Index (ODI), they found a high correlation between RDI and AHI (r=0.889[95% CI, 0.862-0.911], P<0.001). Studies comparing the RDI between PAT and PSG found a combined correlation of 0.879 (95% CI, 0.849-0.904, P<0.001), while in those comparing the AHI, the correlation was 0.893 (0.857-0.920, P<0.001). In addition, those studies that compared ODI found a correlation of 0.942 (0.894-0.969, P<0.001).[45]

Pulse transit time (PTT), which is the time it takes for pulse pressure to travel from the aortic valve to the periphery, is measured as the time delay between the R-wave on an electrocardiogram (ECG) and the arrival of the pulse wave at the finger (detected by an infrared oximeter probe). PTT has been shown to be inversely correlated with blood pressure and is capable of revealing acute changes during pulsus paradoxus, generated by high pleural pressure swings encountered during UA resistance during sleep.[46] As PTT is a direct index of arterial stiffness possibly reflecting its vegetative tonus, it may be used to detect sleep apnea/hypopnea events. Based on the measurement of PTT and/or other physiologic measures, pulse wave analysis (PWA) technology is increasingly being used for OCST, and a photoplethysmography-derived PWA is another newly proposed diagnostic tool (Somnocheck Micro, Weinmann Medical Technology, Hamburg, Germany). The latter is a sleep screening device equipped with a sensor that measures SaO_2 and has a nasal cannula to detect mild obstructive events; it also determines a new severity parameter called "Cardiac Risk Index" (CRI) which is gauged during a nighttime measurement and supplies, as its name implies, information about the patient's cardiovascular risk.[47, 48]

Biomarkers of OSA: breath analysis

Biomarkers are widely used to detect and monitor disease states and to evaluate risk of disease progression or response to a given treatment. Since the prevalence of OSA is far greater than what can be diagnosed by sleep laboratory testing and poor compliance can affect treatment outcome, simple biomarkers could facilitate diagnosis and management of OSA patients.

Breath analysis, a non-invasive technique, is a promising biomarker for OSA. Nitric oxide (NO), found in exhaled breath, is already an established biomarker for lung disease, and fractional exhaled NO (FENO) is used in routine clinical practice to measure airway inflammation predicting response to inhaled corticosteriod therapy. The test is simple, non-invasive and provides an objective measure within minutes. Just as other biomarkers that are found in blood, urine or other tissues or fluids, exhaled breath condensate (EBC) is a matrix in which countless biomarkers can be identified. EBC is obtained as breath is exhaled from the lungs into a cooled collecting device, thereby condensing the vapor and aerosolized droplets emerging with the breath. All nonvolatile compounds found in EBC are liberated from the airway lining fluid (ALF) in the form of droplets or are reaction products of volatiles that enter EBC from the gas phase.[49] Amann *et al*. have developed a sampling system enabling analysis of a patient's exhaled volatile organic compounds (VOCs) during sleep.[50]

Although the specific underlying mechanism remains unknown, it has been hypothesized that airway inflammation plays a key role in the pathogenesis of OSA and its complications.[51] At the same time, emerging evidence suggests that episodes of hypoxemia secondary to repetitive airway obstruction, intermittent apnea and subsequent reoxygenation trigger the formation of free radical species, igniting a cascade of oxidative stress markers.[52] Based on these assumptions, researchers continue to search for new markers of airway inflammation and oxidative stress in the EBC of OSA patients.

Carpagnano *et al*. measured morning 8-isoprostane and IL-6 levels in 43 individuals using a specific enzyme immunoassay of EBC in OSA patients, in subjects who were obese and in healthy controls. IL-6 and 8-isoprostane levels were elevated in the obese participants but were highest in the group with OSA.[53] A follow-up study by the same researchers assessed the effect of overnight CPAP on serum and EBC 8-isoprostane levels in subjects with OSA. Eight-isoprostane levels were elevated in both the blood serum and EBC at 8:00 am in the study group consisting of 18 OSA subjects (compared with 12 weight-matched control subjects without OSA), but the levels were significantly reduced after overnight CPAP.[54]

Recently investigating acetone, butanol, and carbon dioxide levels as potential biomarkers of OSA, Bayarakli *et al*. reported that the butanol concentration in the expired air of awakening OSA patients was higher with respect to that in healthy subjects.[55] In a systematic review, Bikov *et al*. (2016) evaluated a number of studies reporting abnormal airway inflammatory profiles and oxidative stress uncovered by exhaled breath methodologies both in adults and children with OSA. The authors concluded that abnormalities in mediator levels were significantly correlated to the severity of OSA and could be normalized by CPAP therapy.[56]

Although several potential biomarkers have recently been investigated, utilization of exhaled breath analysis has not yet been validated sufficiently for clinical use with regard to OSA due to methodological problems linked to sampling procedures. In addition, as OSA is frequently a comorbid disorder it is difficult to ascertain to what degree elevations are attributable to it alone. New research findings outlining standards and methodological procedures and verifying its utility in identifying or staging OSA are hopefully forthcoming.

Upper airway evaluation: drug-induced sleep endoscopy and snoring endoscopy

Evaluation of the UA is crucial when OSA has been suspected or diagnosed. The aim of UA evaluation is to identify obstruction site(s) and to improve treatment outcomes by guiding treatment decisions.[57] Clinical examination of the UA is nevertheless only partially relevant because it is performed during wakefulness and in static conditions which do not represent its dynamic behavior during snoring. Its prognostic value is, moreover, debatable as some authors have not found any correlations between anatomic variations of the UA (high Mallampati/Friedmann index, and tonsil size, for instance) and OSA.[58, 59]

Sleep nasendoscopy, which was introduced by Croft and Pringle in 1991 and is commonly referred to as drug-induced sleep endoscopy (DISE),[60] is a diagnostic tool that allows direct visualization of the site(s) of obstruction and assessment of the UA collapse pattern during sedation, a condition that more closely resembles sleep rather than wakefulness.[61] DISE is considered the gold standard for selecting OSA patients for surgical UA interventions and for oral appliance therapy.[62] The surgical procedures available for OSA patients are outlined in Table I.[3]

Based on DISE assessment, Pringle *et al.* (1993) developed a grading scale to classify snoring and obstruction. The scale, which considers both the site and severity of airway collapse, was delineated as follows: grade 1 = simple palatal level snoring; grade 2 = single palatal level obstruction; grade 3 = palatal level obstruction with intermittent orohypopharyngeal involvement; grade 4 = sustained multi-segment involvement; grade 5 = tongue-base level obstruction.[63] The Velum Oropharynx Tongue-Base Epiglottis (VOTE) system, a new classification system, has become increasingly popular because of its easy-to-use features and because it is possible to evaluate multilevel obstruction that is typical of patients with moderate to severe OSA.[64, 65]

Although DISE has become a widely used diagnostic tool and is carried out in multiple hospitals to diagnose and to stage the severity of OSA, it is dubious if the procedure will become commonplace clinical practice in view of economic and logistic considerations. In addition, the technique still presents multiple methodological limitations, including time constraints, the single body position limitation, the potential risk of anesthetic side effects especially in patients with cardio-respiratory diseases, and lack of consensus by a comprehensive classification and documentation system.[48] Herzog *et al*. (2006) devised the snoring endoscopy (SE), an endoscopic examination of UA during simulated snoring (SS) through the mouth in awake patients, in the attempt to at least partially overcome these problems. Those investigators found that the patients with a high degree of pharyngeal collapse at the tongue base, in combination with dorsalization of the tongue base had a 75% probability of having an AHI higher than 10 and a 92% probability of having an AHI higher than 5.[66] Lovato *et al*. recently examined 20 consecutive patients (simple snorers and OSA subjects) with the intent of evaluating if any of three awake procedures (fiberoptic nasopharyngoscopy with modified Muller Maneuver [FNMM], nasal snoring endoscopy [NSE], or oral snoring endoscopy [OSE]) could efficiently predict the grade or pattern of UA collapse uncovered with DISE. Those Authors reported that the pattern agreement between OSE and DISE was very high at the oropharyngeal level (k=0.82, P<0.00001), moderate at a hypopharyngeal level (k=0.55, P=0.0002), and nearly significant at the velopharyngeal level (k=0.20, P=0.07). In addition, there was also a significant association between AHI and grade of collapse with NSE at the velopharyngeal and oropharyngeal levels. Based on these results, they concluded that NSE and OSE can effectively predict the pattern of UA collapse found during DISE.[57]

TABLE I.—*Surgical procedures for patients with obstructive sleep apnea (from Epstein* et al.*)*[3].

Nasal procedures	Septoplasty
	Functional rhinoplasty
	Nasal valve surgery
	Turbinate reduction
	Nasal polypectomy
	Endoscopic procedures
Oral, oropharyngeal, and nasopharyngeal procedures	Uvulopalatopharyngoplasty (UPPP) and variations
	Palatal advancement pharyngoplasty
	Tonsillectomy and/or adenoidectomy
	Excision of tori mandibularis
	Palatal implants
Hypopharyngeal procedures	Tongue reduction
	– Partial glossectomy
	– Tongue ablation
	– Lingual tonsillectomy
	Tongue advancement/stabilization
	– Genioglossus advancement
	– Hyoid suspension
	– Mandibular advancement
	Tongue suspension
Laryngeal procedures	Epiglottoplasty
	Hyoid suspension
Global airway procedures	Maxillomandibular advancement
	Bariatric surgery

Advances in treatment and management

Although clinical experience proves otherwise, many think that people diagnosed with the same disease have the same underlying pathology and will respond in the same way to the same treatment. The 'one size fits all' theory has for the most part been superseded by personalized medicine also in the field of sleep medicine.[67] Supporting this approach, studies over the last decade on OSA patients and healthy individuals have provided new insights on the pathophysiological mechanisms underlying obstructive apneas and have shown that, although pharyngeal narrowing is a major contributor to airway closure, non-anatomical traits, including pharyngeal dilator muscle dysfunction, unstable ventilatory control, and/or an impaired arousal threshold from sleep all play an important role in the development of apnea in many patients.[68] Determining the underlying cause of the obstruction is critical then for a personalized therapeutic approach. While it is thought that procedures involving anatomical manipulation, such as UPPP can aid patients with compromised anatomy, particularly at the velopharynx level, patients whose apnea is primarily caused by other factors will probably not benefit from them.

As far as a mechanistic approach is concerned, numerous treatment options including therapies that can enlarge pharyngeal anatomical dimension and those that can alter UA reflex and/or ventilatory control are under examination (Figure 2). These treatments can for the most part be classified as "Airway Pressure Therapies" and "Non-Airway Pressure Therapies".

Airway pressure therapies

Nasal expiratory positive airway pressure

Nasal expiratory PAP (nEPAP), consisting of disposable one-way resister valves which are placed over the nostrils with an adhesive tape and using a patient's own breathing to create positive end-expiratory pressure that pre-

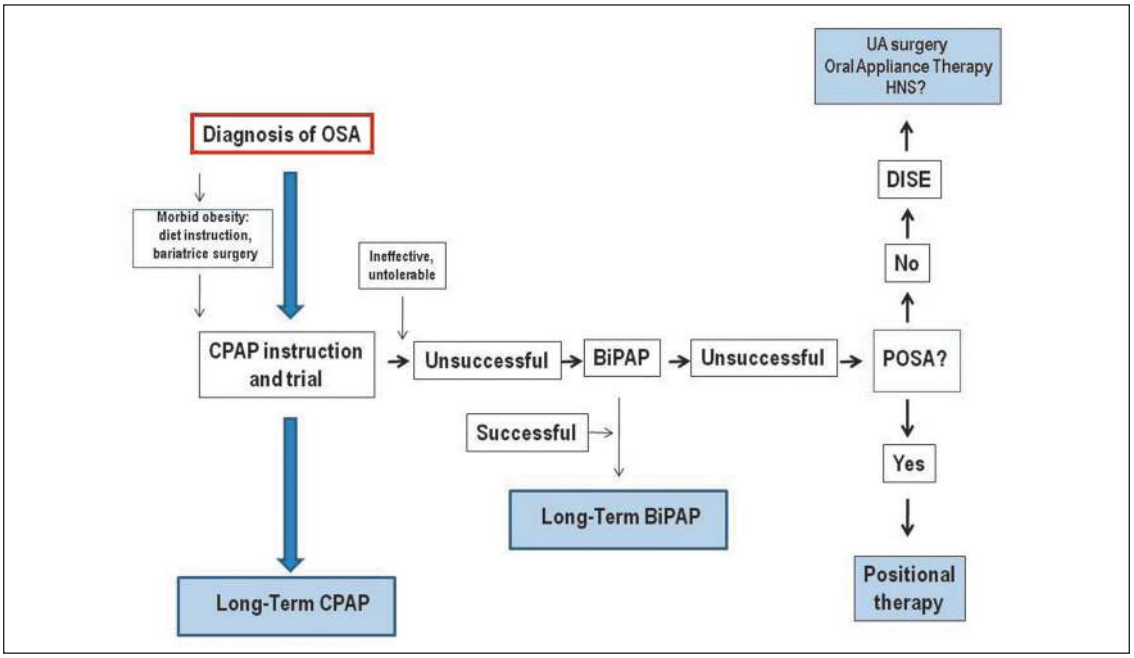

Figure 2.—Treatment options for obstructive sleep apnea.
BiPAP: bilevel positive airway pressure; CPAP: continuous positive airway pressure; DISE: drug-induced sleep endoscopy; HNS: hypoglossal nerve stimulation; OSA: obstructive sleep apnea; POSA: positional obstructive sleep apnea; UA: upper airway.).

vents obstructive breathing, is an alternative to CPAP (Figure 3). The valves have a minimal inspiratory resistance and an expiratory resistance of 80 cm H_2O/L/sec at a flow rate of 100 mL/sec.[69] An EPAP nasal device (Provent Sleep Apnea Therapy, Ventus Medical Inc., Belmont, CA, USA) which was developed for patients with mild to moderate OSA, has been found to significantly reduce snoring and the AHI score, and it also improves subjective daytime sleepiness. The side effects of EPAP treatment were mild. Adherence, as reported by patient diaries, was excellent, with the nasal EPAP device worn all night for approximately 89% of nights at the 12 month follow-up examination.[73] Although well tolerated, the efficacy of this device in patients with moderate to severe OSA is nevertheless controversial, and data are currently insufficient to include nEPAP in the list of recommended treatment options.[70]

Oral negative pressure

In light of the intolerability of PAP to many OSA sufferers, oral pressure therapy (OPT) has recently been developed. The OPT system is composed of a bedside console containing a pump, a soft polymer mouthpiece, and a flexible tube connecting the mouthpiece to the console. The console contains a pump that creates vacuum in the oral cavity intended to pull the soft palate anteriorly and stabilize the tongue to reduce airway obstruction during sleep.[71]

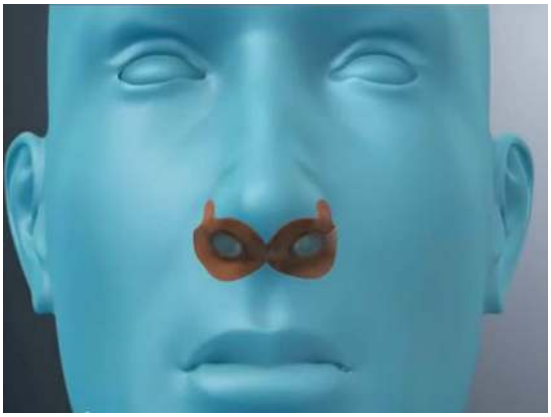

Figure 3.—Nasal expiratory positive airway pressure (nEPAP) device (Provent Sleep Apnea Therapy, Ventus Medical Inc., Belmont, CA, USA).

A recent study evaluated 26 men and 20 women with a baseline AHI of 38.7±27.5 events/hour who were undergoing OPT system treatment (ApniCure, Inc, Redwood City, CA, USA). As the application of the device was generally well tolerated without any serious adverse events, and significantly reduced AHI (24.6±25.7 events/hour ($P<0.001$), the Authors concluded that OPT can improve OSA in some subjects identifiable by PSG.[72] A multicentre study has, instead, shown that a fall in the AHI score below 10 (which should be the goal of the treatment) is achieved in only one-third of patients treated.[70] Due to non-conforming results, further investigations are required to assess the potential benefits of this evolving technology for individuals with OSA.

Non-airway pressure therapies

Oral appliances

For patients with primary snoring and mild to moderate OSA as well as for those with more severe OSA who do not tolerate PAP therapies, oral appliance therapy (OAT) has become an increasingly popular, efficacious option.[70] Mandibular advancement devices (MADs) are currently the most common class of oral appliances used to treat OSA, and custom-made MADs are preferred and recommended over prefabricated ones.[73, 74] MADs, which attach to both the upper and lower dental arches, are intended to protrude and stabilize the mandible, thereby increasing the cross-sectional airway dimension preventing UA collapse during sleep. Some studies have reported favorable results within a short time period with less snoring and obstructive sleep apneas.[75, 76] Aarab *et al*. reported a dose- dependent AHI improvement depending on the degree of mandibular advancement.[77] MADs may cause transitory and very mild side effects, including excessive salivation, dry mouth and gingivitis; more persistent side

effects include arthralgia, teeth pain and occlusal changes.[78]

One systematic review/meta-analysis [79] and three randomized controlled trials (RCTs) [80-82] compared the clinical effectiveness of CPAP to oral devices in treating moderate to severe OSA. Generally speaking, the results showed that CPAP had better efficacy, defined as a significant reduction in AHI, than oral devices. It is, however, possible that this major benefit may be offset by patient's higher compliance to oral devices which, in turn, can lead to real life clinical effectiveness.

The importance in identifying subjects that might benefit from OAT has recently led to efforts to develop objective, standardized criteria (*i.e*., anthropometric and/or polysomnographic measurements) that can predict the outcomes of patients undergoing MAD therapy. De Corso *et al*. investigated the use of DISE combined with a bimanual advancement maneuver as a tool to predict oral devices' outcomes in a group of patients with mild to moderate OSA. In 35 out of the 65 patients recruited (53.8%), improvement of airway patency obtained following the advancement maneuver was significant and those patients were considered eligible for oral device application. After three months of treatment, the Authors found a significant improvement in: the mean Epworth Sleepiness Scale (ESS) Index [(7.35±2.8 *versus* 4.1±2.2 (P<0.05)], the mean AHI [(21.4±6 events/hour *versus* 8.85±6.9 (P<0.05)] and the mean ODI [(18.6±8 events/hour to 7±5.8 (P<0.05)].[75]

When no dentition is present, tongue retaining devices can be therapeutic alternatives to MADs. These oral appliances do not use dentition to advance tissues, but a suction bulb holds the soft tissue tongue in a more advanced position thus increasing the dimension of the UA. Although tongue retaining devices are less common and apparently less successful, their utilization has resulted in a significant reduction in the AHI.[83]

Following the publication of a growing number of studies, the AASM and the American Academy of Dental Sleep Medicine Working Group recently published an update on the role of OAT in the management of OSAS [84] outlining the following recommendations:

— it is preferable to prescribe oral appliances, rather than no therapy, for adult patients who request treatment of primary snoring (without OSA);

— when OAT is prescribed for an adult patient with OSA, a custom-made, titratable appliance should be preferred over non-custom oral devices;

— it is preferable to prescribe oral appliances rather than no therapy, for adult patients with OSA who are intolerant of CPAP therapy or who prefer alternative therapy;

— it is preferable that a qualified dentist be assigned to monitoring management of OAT— rather than no follow-up — to assess dental related side effects or occlusal changes and to reduce their incidence;

— sleep physicians should conduct follow-up sleep testing to monitor and if possible to improve treatment efficacy in patients fitted with oral appliances.

Positional therapy

According to many studies, "position dependence" for OSA patients is assumed if the Respiratory Disturbance Index (RDI) is double in supine sleeping position compared with other positions.[47] The adverse effect of the supine position on snoring and OSA is theoretically linked to the impact of gravity which predisposes the soft tissues in the UA to fall backwards, thus narrowing the cross-sectional airway dimension. It has, in fact, been shown that a base of tongue or epiglottis obstruction is visualized more frequently during DISE in patients with positional or position-dependent OSA (POSA) in comparison to patients with OSA.[85]

Positional therapy (PT) [86] consists in the use of various techniques/devices preventing the patient from assuming a supine position; these include an upright sleep posture, positional alarms, verbal instructions, tennis ball technique, vests, or special pillows; there is little evidence of any one of these is more ef-

fective over the others.[83] PT has been demonstrated to have a significant influence on snoring and OSA severity, and a recent study by Permut *et al*. showed that PT (in this case, a bulky mass was strapped to the patient's back) had the same effect as CPAP in normalizing the AHI in patients with a mild to moderate POSA. Only patients with a non-supine AHI of <5 were however included in the study and the long-term effect was not evaluated.[87] According to a recent meta-analysis, despite a positive impact, PT provides less effective results than CPAP in patients with POSA as far as relevant respiratory outcomes, including AHI and oxygen saturation level are concerned.[88]

Due to controversial study results, PT has not yet found its way into commonly prescribed diagnostic routines and methods, and it has been largely neglected in clinical application despite the fact that approximately 30 % of patients with OSA have position-dependent OSA.[89] Recently, however, new methods and devices have been devised to prevent a sleeper from moving into a supine sleeping position. Part of the new generation of PTs, the Sleep Position Trainer (SPT), which consists in a small, lightweight device placed in a pocket of a neoprene strap attached around the patient's chest, has been recently introduced. The device uses a three-dimensional digital accelerometer to determine body-position and provides vibrations with increasing intensity at varying frequencies when supine position is assumed and until the body position changes.[90] One study reported that the SPT was found to be a highly efficacious, well-tolerated treatment for POSA patients, resulting in diminished subjective sleepiness and improved sleep-related quality of life (QoL) after utilization for 1 month, without negatively affecting sleep efficiency.[90] Van Maanen *et al*. reported that use of PST can diminish the percentage of supine sleep and subjective sleepiness and improve sleep related QoL in patients with mild to moderate POSA with sustained effects for over 6 months.[91]

Electric stimulation of the upper airway

Some have hypothesized that electric stimulation (ES) of UA muscles could be a potential approach for patients who can/do not tolerate PAP, the first-line therapy for symptomatic individuals. ES therapy addresses the problem of inadequate UA muscle activation in oropharyngeal collapse during sleep, rather than the anatomy-passive mechanical properties treated by CPAP, site-selective surgery, or oral appliances, thereby representing a conceptually novel treatment procedure.[92] Although animal and human studies have shown that of the hypoglossal electric nerve stimulation (HNS), activating the genioglossus muscle improves UA patency,[93] ES has been commercially developed as a therapy for OSA, using both non-invasive and invasive methods, only over the past 10-12 years. Recent studies on HNS have aroused new hope in the potential of this approach in treating OSA.

Non-invasive methods

Submental transcutaneous electrical stimulation

The first study on transcutaneous ES performed by Miki *et al*. produced promising results.[94] The study was carried out on six OSA patients who were studied in the supine position during all-night sessions with and without electrical stimulation of the genioglossus. Using an apnea demand-type stimulator, electrical pulses of 0.5 ms (repetition rate, 50 Hz) and 15 to 40 V were delivered through bipolar electrodes (10 mm in diameter) attached to the skin of the submental region when apnea lasted more than 5 s, and was stopped immediately after breathing resumed or after 10 s at the longest. The treatment led to a significant reduction in the apnea index and the apnea time per total sleep time. Other investigators were, however, unable to confirm these positive results and until now no studies on non-invasive ES in OSA have been evaluated by randomized controlled trials. The complex, variable stimulation settings linked to its use

make standardization and treatment optimization quite difficult, causing the procedure to be considered controversial.[5] Pengo *et al* recently published the first randomized sham-controlled trial of transcutaneous ES in OSA patients and reported a significant improvement in ODI in the active treatment group compared to sham stimulation group [(19.5 (11.6-40.0)/hour vs 26.9 (17.5-39.5)/hour); P=0.026).[95] The Authors concluded that inconsistent results in the literature could be explained by a lack of standardization. Future trials will need to screen for likely 'responders' and to test the feasibility and effectiveness of this method in routine clinical practice.

HNS

A number of recent studies have investigated the use of electrical stimulators targeting the distal branch of the hypoglossal nerve innervating the genioglossus muscles [96, 97] in order to increase tongue muscle tone and to cause a slight protrusion of the body of the tongue.

Novel technologies by the ImThera Medical and Inspire companies have been available in Europe since 2013. With regard to the United States, the pivotal clinical trial on Inspire System therapy was completed in late 2013 and gained Food and Drug Administration (FDA) approval in April 2014. Both technologies are based on intraoperative placement of an electrode on more distal branches of the hypoglossal nerve; activation using an Inspire device is synchronized with the inspiratory phase of respiration sensed by intrathoracic pressure, ideally triggered by its fall with inspiration.[94]

A recent review by Certal *et al*. which evaluated the efficacy of HNS in improving AHI, ODI, and residual excessive daytime sleepiness, determined by ESS,[98] demonstrated a statistically significant improvement in all three outcomes examined after 12 months of treatment. None of the studies included found any serious adverse events. The results of the Stimulation Therapy for Apnea Reduction (STAR) trial, a 36-month study investigating an OSA cohort [99] including 116 participants showed that 74% of patients met the a priori definition of success with the primary outcomes of AHI, reduced from the median value of 28.2 events per hour at baseline to 8.7 and 6.2 at 12 and 36 months, respectively. Similarly, self-reported outcomes improved from baseline to 12 months and were maintained at 36 months. Soft or no snoring reported by bed partner increased from 17% at baseline to 80% at 36 months, leading to the conclusion that long-term 3-year improvements in objective respiratory and subjective QoL outcome measures were maintained with rare adverse events. Safiruddin *et al*. [100] evaluated the effect of stimulation on retropalatal and retrolingual dimension during DISE compared to wakefulness to assess mechanical changes in response to UA stimulation. During wakefulness, a therapeutic level of stimulation increased the retropalatal area by 56.4% (P=0.002) and the retrolingual area by 184.1% (P=0.006); during DISE, the same stimulation increased the retropalatal area by 180.0% (P=0.002) and retrolingual area by 130.1% (P=0.008). 'Responders' to HNS had larger retropalatal enlargement with stimulation than 'non-responders' and UA stimulation increased both the retropalatal and retrolingual areas. Further studies are needed to evaluate and compare HNS with other conventional therapies (*i.e*., CPAP, OAT, and other surgical procedures).

Conclusions

The review has shown that PSG is no longer a prerequisite for diagnosing OSA and that technological advances have produced a variety of effective devices and procedures to evaluate and treat patients at all stages of disease. In the future, inflammatory and oxidative stress biomarkers will probably be able to provide further data to facilitate early diagnosis and staging of OSA patients. Being able to differentiate patients with regard to the mechanism under-

lying airway obstruction will also contribute to facilitating a tailored therapeutic approach that will further enhance the care and management of these patients. In addition, DISE could be able to localize the site(s) of UA collapse and aid in the selection of candidates for surgery and/or for the use of customized oral appliance devices. UA electric stimulation will, if further studies confirm promising preliminary results, broaden the spectrum of treatment for patients with non-anatomical traits.

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