An Update on Obstructive Sleep Apnea

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Obstructive sleep apnea has become much more prevalent and is now considered the third most common respiratory condition affecting approximately 20 million Americans and an estimated 100 million people worldwide. It affects men, women and children alike. Obesity is thought to be one of the major contributors to the rise in cases. However, new technologies are starting to identify possible genetic links to the development of obstructive sleep apnea. Questionnaires and biometrics seem to be reliable methods to pre-screen people in an office setting, but the gold standard is still overnight, in-lab, polysomnography. Continuous positive airway pressure (CPAP) is the most effective treatment for all levels of severity of obstructive sleep apnea, but oral devices are also effective for mild-to-moderate cases. Novel treatments with oral suction devices, hypoglossal nerve stimulation, nasal expiratory positive airway pressure devices, and pharmaceuticals are all being investigated, but have shown mixed results in effectiveness. This article is an overview of Obstructive Sleep Apnea and a review of recent diagnostic and treatment options.

INTRODUCTION

Sleep is an opportunity for the body to conserve energy and restore its normal processes.[1]

The average American adult sleeps approximately 6.9 hours a night, which is less than the 7 - 9 hours recommended by many sleep experts.[2] While there are many reasons for lack of sleep, there is a growing concern over obstructive sleep apnea (OSA). OSA is defined as a recurrent cessation of breathing commonly from oropharyngeal collapse in adults[3] or enlarged tonsils and/or adenoids in children.[4]

OSA is increasing world wide and is now considered the third most common respiratory condition.[4] Concern for OSA is based on OSA's association with comorbid health conditions such as diabetes and hypertension, motor vehicle accidents among commercial drivers, and work related injuries and illnesses. These comorbidities have grave long term socioeconomic implications.

The insidious nature of OSA makes it sometimes difficult to recognize. The most commonly associated symptom is loud snoring,[5] but there are other symptoms also observed in people with OSA (Table 1).

Prevalence

It is estimated that OSA affects over 20 million Americans, and over 100 million people world wide.[6,7] The overall prevalence is estimated at 9 - 24% and affects men 2:1 over women.[4] Recent data estimates that approximately 2 - 4% of children also suffer from OSA in an even distribution between boys and girls.[8] While OSA can effect adults and children at any age, children seem to peak between 2 and 8 years old, which corresponds with peak tonsillar growth.[6,8]

The growing occurrence of OSA also has much to do with the obesity epidemic plaguing society. The prevalence of OSA ranges from 11 - 46% in obese women and 33 - 77% in obese males between 30 and 69 years old.[9] Between 25 and 45% of obese children have OSA compared with 1 to 3% of their normal-weight counterparts.[5]

Commercial drivers (CD) with OSA pose a particularly challenging and dangerous problem. As a profession CDs are at higher risk for OSA given the sedentary nature of their occupation coupled with a high prevalence of obesity due to poor eating habits and lack of exercise. It is estimated that 45 - 50% of CDs in the United States are obese.[10] This is significant because CDs with OSA have a 2 - 11 fold increased risk of being involved in a motor vehicle accident, and OSA is estimated to be present in 15 - 30% of CDs who have crashed.[10] Additionally, 29% of CDs have experienced almost falling asleep at the wheel and 18.3% have experienced a near miss due to falling asleep while driving.[11]

Studies have shown that CDs generally do not report their symptoms and diagnoses accurately because of the economic and occupational implications of an OSA diagnosis.[10] An anonymous survey of US truck drivers showed that over 20% of drivers reported falling asleep at traffic lights, casting further doubt about the validity of screening questionnaires used during medical exams due to the potential for denial or deception on the part of the driver.[10]

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OSA can cause a tremendous financial strain. There has been an increase in both direct and indirect medical costs due to OSA and its treatment in CDs, as well as nonfinancial costs such as loss of quality of life and premature death.[11] In general workers and commercial drivers with untreated OSA have more work disabilities, more work-related injuries, and higher rates of absenteeism and presenteeism compared to workers and drivers who do not have OSA.[11] It is estimated that individuals with sleep problems have a 1.62 % greater risk of injury and account for two thirds of the total financial costs on society once again compared to those workers who do not have OSA.[11]

Etiology

Multiple reasons exist as to why individuals suffer from OSA. Research conducted by Dongmei, MD and Jinmei, MD suggests that a first degree relative with OSA increases the risk for developing OSA by more than two-fold suggesting there may be a genetic component to the development of OSA.[4] Parish, MD's research further defines that there is no single sleep gene, and as such, sleep may be controlled or influenced by many genes.[12] Understanding the genetic basis of OSA is important to find new insights into its pathogenesis, the biologic basis for the disorder, and to develop new tests for the diagnosis of, and therapies for, patients with OSA.[12]

Changes in weight are inextricably liked to OSA. As little as a 10% weight gain can increase the apnea-hypopnea index (AHI) by 32%, conversely a weight loss of 10% will cause a reduction in AHI by 26%.[8] Current estimates suggest that about 58% of OSA cases can be attributed to excessive weight.[13]

The distribution of fat, particularly central/visceral obesity, is a more important risk factor versus fat size for OSA.[14,15] Studies have linked visceral obesity to the common OSA-related comorbidities (Table 2).[8,14,16]

In addition to obesity, several phenotypes associated with OSA have been identified. In children they include: adenotonsilar hypertrophy, craniofacial malformation, and primary muscular disorders.[17,18] In adults they are: passive critical closing pressure of the upper airway and arousal threshold (how easily a person is awakened from sleep). The higher the arousal threshold, the more likely a person will become hypoxic while sleeping because it will take a larger stimulus to awaken them. Additional adult phenotypes include: oropharyngeal muscle responsiveness and loop gain. Loop gain is the measurement of how quickly the body responds to changing levels of carbon dioxide in the blood to signal a need to awaken. The higher the loop gain the more carbon dioxide needed to cause a person to awaken from sleep.[19]

While these are the two most common etiologies, there are ongoing studies investigating other sources for the development of OSA as well.

SCREENING & DIAGNOSIS

Biometrics

Biometric indices are helpful in the screening process. Table 3 lists the measurements that should be taken at the initial visit and then subsequently followed during the treatment process. Additionally, assessment for long face syndrome (infraorbital darkening, mouth

TABLE 1:
Additional symptoms encountered in adult and pediatric OSA.[5]

Symptom	Adult	Child
Witnessed pauses in breathing while asleep	√	√
Fitful sleep quality	√	√
Fatique	√	√
Dry mouth	√	√
Morning headaches	√	√
Excessive daytime sleepiness	√	
Irritability		√
Behavioral problems		√
Learning difficulties		√
Motor vehicle accidents	√	√
Poor academic performance		√
Restless leg syndrome	√	

TABLE 2:
Common OSA-related comorbidities.[8,14,16]

Cardiovascular disease
Chronic obstructive pulmonary disease
Depression
Diabetes
Hypertension
Increased cancer risk
Neurocognitive disease
Stroke

TABLE 3:
Areas to obtain biometrics data from in screening for OSA.[19]

Blood pressure
Body mass index (increased risk if > 30 kg/m2)
Heart rate
Height
Neck circumference (increased risk if > 17" in men and 16" in women)
Weight

breathing, elongated midface and nasal atrophy) and facial morphology need to be evaluated.[19]

People with mandibular retrognathia (anterior prominence of the chin ≥ 2 mm behind a virtual line drawn from the vermillion border of the lip to the chin), Mallampati classification 3 or 4, and Friedman palate position of 3 or 4 are at increased risk for OSA.[19] While both Mallampati and Friedman classifications correlated positively with predicting OSA severity based on AHI, Friedman correlated more strongly with OSA severity.[20]

In addition to the adult risk factors, children with enlarged tonsils (grades 2 - 4), small maxillary dimensions, greater posterior facial height, reduced maxillary protrusion or shorter and flattened dental arches have additional risks for OSA.[21]

Questionnaires

Currently there are numerous screening questionnaires used to help predict the presence of OSA. The most popular screening questionnaires are the Epworth Sleepiness Scale (ESS), the STOP-Bang questionnaire (SBQ), the STOP questionnaire (SQ) and the Berlin questionnaire (BQ). These various questionnaires have been compared to each other in terms of sensitivity, specificity and the ability to predict the severity of OSA. While each one has its strengths and weaknesses, the SBQ appears to be the best overall choice for screening questionnaires.

The SBQ had superior sensitivity and area under the curve than the ESS, BQ and SQ.[22] The SBQ correlated not only with polysomnography, but also with hypoxia and poor sleep quality.[23] Additionally the SBQ has an excellent sensitivity and a low specificity (AHI ≥ 5/hour 94.9% and 50% respectively; AHI ≥ 15/hour 96.5% and 28.6% respectively; AHI ≥ 30/hour 97.7% and 17.9% respectively) and could predict the severity of OSA.[23]

Although the SBQ seems superior, there are advantages to the other questionnaires as well. Even though the ESS had limited value screening for OSA, it was able to identify the severity of OSA, and is the most commonly used questionnaire to prescreen patients.[22,24] The Berlin questionnaire had good sensitivity and specificity for diagnosing OSA and assessing its severity, but is a very long questionnaire to complete and has a complicated scoring system.[22]

Genetic Markers

New research is looking at genetic biomarkers for OSA. Studies have indicated that increased expression of cysteinyl leukotrienes and changes in glucocorticoid receptor expression and activity has been reported in the tonsils and adenoids of children with OSA.[21] Other research is suggesting that increased prevalence of the rs1054135 polymorphism of the FABP4 genomic sequence is also seen in children with OSA.[12,21] Additional researchers are looking at Kallirein-1 uromodulin, urocortin-3 and orosomucoid-1 in children as these genes have had high correlations with OSA.[4,25]

Inflammatory markers may also be useful to consider. Many investigators accept CRP as a marker of inflammation and its regulation is thought to be interlukin (IL)-6, IL-8, and IL-10

dependent, and is increased in the presence of hypoxemia in adults with OSA.[16,26,27]

Other promising genetic associations are genes with different alleles for apolipoprotein E4 (ApoE4), tumor necrosis factor (TNF), specifically the TNF polymorphism TNFA rs1800629 and TNF-⬚, as well as angiotensin-converting enzyme (ACE).[14]

Polysomnography

Although questionnaires are useful for initial quick screenings, and genetic biomarkers are an upcoming tool, the gold standard for the diagnoses of OSA is polysomnography (PSG). For those patients that require PSG, there are a few options available. The gold standard is still an in-lab overnight PSG test that is continuously monitored and read by a sleep specialist.

However, not all patients can afford the cost of an in-lab test, and in some cases in-lab testing is not available due to geographical considerations. In those cases, in-home testing may be available. There are advantages and disadvantages to in-home testing. Some advantages are: improved patient access, lower cost, and greater acceptability by patients.[18] Some of the disadvantages include: decreased reliability, diagnostic limitations, and the portable monitoring devices can vary according to number and types of signals, sensors used, methods of scoring, and the criteria used to define respiratory apneas.[18]

Classification

The agreed upon classification for OSA is based on the number of apneas, or a complete arrest of breathing, plus hypopnea (where the airway is severely obstructed but breathing is not arrested resulting in a 30% reduction in thoracoabdominal movement compared to baseline and ≥ 4% oxygen desaturation that lasts ≥ 10 seconds), a night divided by sixty.[3,6,14] This is defined as the apnea-hypopnea index (AHI) or respiratory disturbance index (RDI).[6] An AHI of < 5 events/hour is considered normal, 5 - 15 events/hour is mild, 15 - 30 events/hour is moderate and > 30 events/hour is considered severe.[16,18]

TREATMENT

The main goals in the treatment of OSA are: relief of clinical manifestations, restoration of sleep quality, reduction of respiratory events, and correction of nocturnal oxygen desaturations. This can be accomplished through many different therapeutic interventions. The gold standard of which is nightly use of nasal continuous positive airway pressure (CPAP) in adults, and adenoidectomy and tonsillectomy in children.[5,10]

However, recent developments have shown that there may be options other than CPAP for adults with mild or moderate OSA and for children where tonsillectomy and adenoidectomy does not resolve their OSA. These alternatives include: oral devices, upper airway surgery, positional therapy, nasal expiratory positive airway pressure (nEPAP), myofunctional therapies and electrical stimulators.[7,19,24,25]

In addition to the modality chosen, lifestyle modifications have been of tremendous benefit. These modifications include weight loss, smoking cessation, and avoidance of alcohol or neurorelaxant drugs within 4 - 6 hours of retiring.[8,24,25]

Oral Devices

Oral devices work in different ways, but generally they apply pressure to the jaw to prevent retroglossal collapse. Studies have shown that this method may be preferable over CPAP in individuals with mild-to-moderate OSA, or for those with severe OSA who cannot tolerate CPAP or refuse surgery.[24,28] The devices are commonly mechanical in order to advance the mandible and lift the palate, or to retain the tongue in an anterior position.[8,29]

A new technology is emerging that instead of applying positive pressure to the upper airway, applies gentle oral suction sufficient enough to anteriorly and superiorly displace the soft palate and tongue.[29,30] There is a lack of universal response though, which may be due to insufficient enlargement of the retropalate space or collapse of the airway at different sites, requiring further work to better delineate its applicability.[29,30] Side effects of this therapy include oral and dental discomfort and dry mouth.[29,31] Currently only 30 - 40% of patients using this device have had successful treatment of their OSA.[29,31]

Surgical Interventions

Surgery was once the primary and only method of treating OSA. The advent of CPAP has caused surgery to become a secondary consideration. Surgical interventions are broadly divided into procedures aimed at attempting to cure OSA via upper airway reconstruction, or interventions to improve CPAP adherence, e.g. nasal septoplasty or polypectomy.[8] Currently evidence supporting surgery is lacking, and the consensus among experts is that the best candidates for surgery are patients with known craniofacial structural abnormalities.[25]

Bariatric surgery is becoming recommended for any adult with a BMI ≥ 40 kg/m^2 or a BMI ≥ 30 kg/m^2 with significant comorbidities such as type 2 diabetes, hypertension, chronic kidney disease, cardiovascular disease or chronic obstructive pulmonary disease.[25]

Sleeping Position

It is estimated that up to 60% of individuals have positional OSA, which is defined as supine AHI greater than two times that of non-supine AHI.[25,31] The treatment for this can be changing the sleeping position from supine to a side-sleeping position. This can be achieved through a simple "tennis ball" tee shirt or more sophisticated items worn by patients to prevent them from sleeping on their backs.

Nasal Expiratory Positive Airway Pressure (nEPAP)

nEPAP is a unidirectional flow resistance device. nEPAP regulates flow through the nostrils creating expiratory flow resistance without affecting inspiratory resistance.[30] While it appears that nEPAP may be an alternative to traditional CPAP for those with mild OSA, it is contraindicated for those patients whose oxygen saturation is less than 75% for more than 25% of the first four hours of the study, or for 10% of the entire study. Additionally, if the patient has persistent nasal blockage nEPAP is contraindicated.[30] Current data suggested that approximated 35 - 50% of patients would benefit from this type of therapy.[31]

Electrical Stimulation

Patients with moderate-to-severe OSA may not have consistent clinical benefit from CPAP owing to poor adherence to treatment or anatomically from excessive airway collapsibility.[32] While not yet approved for clinical use, human studies have shown that hypoglossal nerve stimulation (HGNS) shows promise in the treatment of OSA; especially if the BMI is ≤ 32 kg/m^2.[30] The nocturnal activation of lingual muscles is a way to overcome sleep-related decrease in pharyngeal dilator muscle tone in order to maintain a patent airway through stimulation of the genioglossus muscle.[33] HGNS has been shown to improve airflow in a dose-dependent manner, and decreases pharyngeal collapsibility during sleep.[33] Additionally, electrical stimulation of the hypoglossal nerve evokes a functional response of the tongue muscles.[32] This causes an anterior displacement of the tongue further augmenting the increase in the orpharyngeal space.[32] Unfortunately, isolated activation of the tongue through transcutaneous or direct intra-muscular means has been shown to have limitations for treatment of OSA without concomitant activation of the muscle to dilate the pharynx.[33]

Pharmaceutical Treatment

There is emerging evidence that suggests arousals from sleep may contribute to the severity of OSA in that if there is a decrease in one's ability to be aroused from sleep when apneic events occur then the apnea could be more severe and last longer.[30,33] Pharmaceutical research is being conducted to increase the ability of someone to be aroused from sleep when apneic events occur. Evidence suggests that arousals destabilize the ventilator response to stimuli and it has been hypothesized that arousal thresholds could be raised pharmacologically causing sleep-stage stability.[30] Additional research has suggested that increasing upper airway muscle tone may help treat OSA as well.[33] Eszopiclone is the drug being investigated, and while the results are encouraging, the studies have not shown a statistically significant improvement in AHI so further investigation is warrented.[30]

Myofunctional Therapy

Myofunctional therapy is a treatment program that suggests training the upper airway muscles, similar to athletes training other body muscles, would help stabilize the upper airway to prevent collapse and thus treat OSA. Thus isotonic and isometric exercising of the lips, tongue, soft palate and lateral pharyngeal wall muscles has been suggested to have a positive influence on reducing upper airway collapse during sleep.[33] Treatment times vary from as little as 5 minutes twice daily four days a week to 10 minutes 3 - 5 times a day for 2 - 3 months.[19] Current literature demonstrates that myofunctional therapy could serve as an adjunct to other OSA treatments because it has been shown to decrease AHI by approximately 50% in adults and 62% in children.[19] These exercises can be taught by any provider familiar with them, but generally are taught by a pulmonologist or sleep physician. While there are no formal osteopathic manipulative therapy techniques for OSA, these myofunctional therapies could be a potential area for further Osteopathic specific research.

ADHERENCE

Many studies have defined acceptable compliance as consisting of at least 4 hours of usage for more than 70% of nights.[8] Unfortunately about 23% of patients on average (ranging from 7 - 74%) abandon treatment, mostly in the first year of usage.[28,30] It seems that the first few weeks are crucial to further adherence and that any support at this stage will have a positive impact on future compliance.[28] Studies suggest that motivational telephone interviews that enable patients to discuss their experiences with CPAP and having medical staff present to review the patient's goals and give advice to the patients, demonstrated that these patient's CPAP compliance was 1 hour more per night at 6 months and 2 hours more per night at 1 year, than patients who did not receive this intervention.[28]

Overall long term efficacy of mandibular advancement oral devices is fairly good (76% after 1 year and 62% after 4 years) showing AHI stability from 1 - 2 years after implementation in treatment responders.[29] Previously there was no method of determining compliance except for patients reporting their usage, which was quite good at 90% using the device more than 4 hours a night more than half the nights a week at 5 years.[29] Recent advances in technology have helped with the development in intra-oral temperature sensors and microsensor thermometers with on-chip integrated readout electronics to allow objective determination of compliance similar to CPAP devices.[29]

CONCLUSIONS

Since the discovery of OSA, researchers have been trying to develop new ways to diagnose and treat OSA earlier and easier. Screening with questionnaires such as STOP-Bang are aiding in this process, while advancements at the genetic level to develop reliable biomarkers are also looking promising.

The definitive diagnostic tool is still lab-based overnight PSG. New advances in technology are making home-based technology better, and in the cases of suspected mild-to-moderate OSA, have been proven as effective as in-lab studies. In areas where there is limited access to in-lab studies, the newer home-based technology is proving to be very useful.

CPAP remains the gold standard treatment modality for OSA, especially in severe cases. New and novel therapies are being developed and some of these therapies have been shown to be very promising. Oral devices in cases of mild-to-moderate OSA have proven to be just as effective as CPAP. Training of the muscles of the oropharynx and HGNS are showing promise, but further studies are needed to prove the effectiveness of these strategies before they will be considered mainstream treatment options. Surgical interventions are quickly becoming passé except in the cases of craniofacial abnormalities or as adjunctive treatment for severe OSA. Unfortunately, pharmaceutical options have not proven to be of any benefit at this time.

Ultimately, compliance with treatment is the biggest struggle with OSA. The importance of compliance with treatment must be enforced and compliance must be monitored closely. It is essential that patients understand that the associated comorbid conditions such as diabetes and hypertension are made worse in the presence of OSA. Treatment must occur nightly in order to help treat these other diseases and mitigate any additional potential complications. Therefore, studies have shown that patients requiring OSA do much better with a multidisciplinary approach aimed at providing positive reinforcement as well as encouraging weight loss in the obese patient.

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