SLEEP APNEA

INTRODUCTION

Obstructive sleep apnea (OSA) is a condition of repetitive upper airway collapse/obstruction during sleep that causes alternating periods of hypoxia and arousal. It affects many adults – and children, too – and people with OSA suffer from far more than insomnia and daytime sleepiness: OSA is a very common disorder that is thought to cause a wide range of serious health problems and be a major contributor to adult morbidity and mortality, and mild sleep apnea has a tendency to worsen over time.

OBJECTIVES

When the student has completed this module, he/she will be able to:

1. Identify a basic definition of OSA.
2. Identify a commonly used screening tool used to help detect and diagnose OSA.
3. Identify two physical characteristics that are associated with OSA.
4. Provide a definition for the apnea-hypoxia index.
5. Identify the sleeping laboratory test that is used to confirm a diagnosis of OSA.
6. Identify three risk factors that increase an individual's chances of developing OSA.
7. Identify one possible physiological basis for the damage caused by OSA.
8. Identify three complications/health problems associated with OSA.
9. Identify one drug that may be helpful in treating OSA.
10. Identify the therapy that is considered the mainstay of treatment for OSA.
11. Name one lifestyle alteration that may be helpful in treating OSA.
12. Name one class of device that may be helpful in treating OSA.

EPIDEMIOLOGY

Approximately 12 million Americans have obstructive sleep apnea (OSA), but this figure is almost certainly an underestimate.[1] However, estimating the true incidence of this disorder may depend on definitions and the criteria used: one important study noted that 24% of men and 9% of women aged 30 to 60 had OAS, but not all of these people had significant impairment.[2] Other sources estimate that OSA affects 1% to 4% of the middle-aged male population and half that number of women.[3] and that 1 in 5 white adults with a body mass index (BMI) of 25-28 kg/m^2 has a mild form of the disease.[4] Regardless of the true incidence, it is clear that even if we accept as true the *lowest* estimate of the how many people have the disease, OSA is very common and a very serious public health problem.

DIAGNOSING OBSTRUCTIVE SLEEP APNEA

Diagnosing OSA begins with an interview that focuses on the patient's sleep pattern and habits. The **Epworth Sleepiness Score** is a commonly used questionnaire that can help determine whether or not someone has OSA.[5]

How often are you likely to doze off or fall asleep in the following situations, in contrast to feeling just tired? This refers to your usual way of life in recent times. Even if you have not done some of these things recently, try to work out how they would have affected you. Use the following scale to choose the most appropriate number for each situation:

0 = would never doze
1 = slight chance of dozing
2 = moderate chance of dozing
3 = high chance of dozing

Sitting and reading
Watching TV
Sitting, inactive in a public place (e.g., theater or a meeting)
As a passenger in a car for an hour without a break
Lying down to rest in the afternoon when circumstances present
Sitting and talking to someone
Sitting quietly after lunch without alcohol
In a car, while stopped for a few minutes in traffic

Patients can also be asked if they have an inability to concentrate, excessive daytime sleepiness, memory loss, mood swings, or fatigue, or if he/she – or their partner – notices if the patient snores loudly or stops breathing during sleep. The presence of risk factors (these will be discussed in another section) should be noted.

There are some physical characteristics that are associated with OSA and increased upper airway resistance.[6]

- Retrognathia (abnormal posterior positioning of one or both jaws, usually the mandible; in layman's terms, a receding chin)
- Deviated nasal septum
- Enlarged uvula
- Enlarged base of tongue
- Neck circumference larger than 43 centimeters
- Enlarged tonsils
- Narrow pharyngeal space

If the patient is strongly suspected to have OSA, the next step would be to perform a **polysomnogram** in a sleep laboratory. The polysomnogram measures pulse oximetry, heart rate, respiratory rate, airway pressure, ECG, EEG, limb movement, electro-oculography, electromyography, and plethysmography.[7] The clinician takes particular note of the number of apneas (cessation of air flow for at last 10 seconds) and hypopneas (reduction of air flow by at least 50% with a reduction in oxygen saturation of at least 3%) and determines the **apnea-hyponpea index** (AHI).

Learning Break: The AHI measures the number of apneic and hyponeic incidents in one hour. Five to 14 an hour defines mild sleep apnea, 15-29 defines moderate sleep apnea, and over 30 defines severe sleep apnea.[8]

Learning Break: The consensus definition of OSA is an AHI of 5 or greater with evidence of disturbed or unsatisfying sleep, daytime sleepiness, or other daytime symptoms, or when the AHI is 15 or higher.[9]

RISK FACTORS FOR OBSTRUCTIVE SLEEP APNEA

There are risk factors that are clearly increase the chances of developing OSA and there are others that are suspected, but have not been not proved, to be risk factors.

- Obesity: Obesity is considered to be one of the strongest risk factors for developing OSA.[10] Even an increase of one standard deviation in BMI may possibly increase the risk of developing OSA by four-fold[11] and one author found that a 10% change in body weight increased the AHI by more than 30%.[12] The relationship between obesity and OSA is complex, and there are multiple possible reasons – physical, neurological, metabolic – for the strong association between obesity and OSA. Excess fat deposits around the neck may narrow the upper airway, although this is not always the case,[13] and the airways of people who are obese are more collapsible than those of people with of normal weight.[14] People who are obese have lower lung volume, and this has been shown to decrease upper airway size and stiffness.[15] There has also been speculation that some of the neuromuscular mechanisms that control upper airway patency during sleep may be altered when body weight is increased, although there is no proof for this.[16] Metabolic reasons that could link obesity to OSA include increased leptin levels (leptin is a hormone that reduces appetite) that can reduce the body's response to elevated carbon dioxide levels,[17] and elevations in pro-inflammatory cytokines can affect neuromuscular control of the upper airway.[18]
- Gender: Men are much more likely to develop OSA than women, but it isn't clear why this is so.[19]
- Ethnicity: African Americans and Asians are at a greater risk for OSA for a given BMI.[20]
- Genetics: OSA may be, in part, an inherited condition. One author notes that about 40% of the genetic variance in AHI can be explained by obesity. There are in other people who have a strong family association of OSA but are not obese, there are thus other factors causing the disease, but these have not been identified.[21]
- Smoking: Smoking appears to double the risk of developing OSA.[22]

PATHOPHYSIOLOGY

OSA has been studied extensively for many years, but even after all of the effort that has been devoted to understanding OSA, many of the most basic questions about the disease have not been answered. Specifically:

- It is known what happens – physically – during the periods of airway collapse and obstruction, *but it is not known why they happen.*
- It is known that there are conditions/risk factors that are the causes of OSA, *but it is not known why or how these risk factors cause the disease and how much they each contribute to the pathogenesis of the disease.*
- It is known that OSA is a cause of cardiovascular morbidity and mortality, stroke, diabetes, and other disease states, *but it is not clearly understood how OSA causes these pathological processes.*

Learning Break: Some researchers have theorized that OSA causes reperfusion injuries. Patients suffer hypoxemia when they are apneic and during the compensation phase of reoxygenation that happens after these hypoxemic events, reactive oxygen species are generated that damage tissues.[23]

Learning Break: The intermittent hypoxemia of OSA can also, possibly, cause a generalized state of low level inflammation which can accelerate the development of atherosclerosis.[24]

COMPLICATIONS

OSA has been linked to serious pathologies of the heart, brain, cardiovascular system, kidneys, liver, and endocrine system. OSA can also have a significant impact on someone's psychological, social, and professional life.

- Stroke: OSA and stroke are strongly associated. Several authors have noted that OSA was noted to be present in approximately 60% of stroke victims as opposed to 4% of middle-aged adults,[25] and the presence of the disease greatly increases the possibility of suffering a stroke, even after even after risk factors such as age, hypertension, etc., have been accounted for.[26,27,28.29] This may be due to an increase in fibrinogen levels that can cause hypercoaguability,[30] reduced cerebral blood flow, and an increase in atherogenesis, but it is most likely that there are multiple mechanisms at work, e.g., neural, metabolic, hemodynamic, inflammatory, etc.[31,32]
- Diabetes: Type II diabetes has been noted to be more prevalent in patients with sleep-disordered breathing – patients with an AHI of greater than 15 had a 3 to 4 more times prevalent in patients with an AHI of less than 5 - and this association is evident even when risk factors for diabetes have been taken into account.[33] There is also a lot of evidence that OSA can increase glucose intolerance and insulin resistance, conditions which are precursors to the development of diabetes mellitus,[34,35] and this association appears to be independent of obesity and other (parts) of the metabolic syndrome.[36,37]

Learning Break: There is strong evidence that OSA causes diabetes. It is not known why this happens, but it is probably due to hypoxia, oxidative stress, or inflammation.[38])

- Cardiovascular disease: Cardiovascular disease and OSA are intimately associated. OSA increases the risk of morbidity and mortality from cardiovascular disease:[39] in some studies, nonfatal and fatal cardiovascular events were almost twice as common in people with OSA compared to a population without OSA.[40,41] Atherosclerosis has been shown to affect people with OSA who have no other risk factors for the disease,[42] and OSA has been associated with an increased incidence of hypertension,[43,44] arrhythmias,[45] and heart failure.[46,47]

Learning Break: No one knows for sure why OSA can cause cardiovascular disease, but the most likely reasons are increased sympathetic activity, oxidative stress (caused by reactive oxygen species generated by the decline in oxygen levels and subsequent reoxygenation, a similar process to the reperfusion injury process), and inflammation.[48,49]

- Hypertension: OSA has been definitely linked with hypertension.[50] OSA can increase the 24 hour mean blood pressure by as much as 10 mm Hg, and this could – potentially – increase the risk of suffering a myocardial infarction by 20% and the risk of suffering a stroke by 40%.[51]
- Renal disease: Sleep apnea and end-stage renal disease are strongly associated, but it is not known if one causes the other.[52]
- Liver disease: Kallwitz et al found that in people who are obese and have non-alcoholic fatty liver disease (a relatively common problem in this population), alanine aminotransferase levels were elevated and fibrosis.[53]
- Impairment of quality of life can be a serious problem for people with OSA, and the level of impairment seems to correlate directly with the severity of the disease.[54] Memory, the ability to concentrate, and general intellectual function have been shown to be adversely affected by OSA, and

PHARMACOLOGICAL TREATMENT

Lifestyle changes, mechanical devices, and surgery can all help people who suffer from OSA. However, these therapies all have drawbacks and do not work for everyone, and drug therapy has been used to treat OSA.

Unfortunately, pharmacological treatment of OSA has, to this point, not been very successful in relieving symptoms, treating the underlying causes, or preventing the disease, and treatment of OSA with drugs is only an adjunct.[55,56]
However, given the potential health complications and the effects OSA can have on someone's lifestyle, trying drug therapy may be a reasonable approach.

- Corticosteroid nasal sprays and decongestants: Many patients with OSA have allergic rhinitis, and this can cause nasal obstruction and increase airflow resistance. Two studies have shown that corticosteroid nasal sprays can lower AHI and decrease the incidence of desaturation and arousal episodes during sleep.[57,58]

  There is only one study that examined the use of nasal decongestants for treating OSA, and these drugs were not successful.[59]

- Nicotine: Nicotine can dilate the muscles in the upper airway. One author reported it to be helpful in treating OSA, but most of the evidence indicates that it disrupts patients' sleep patterns.[60]
- Opiod antagonists: These drugs stimulate ventilation, but although it was found that in patients with OSA who were given naltrexone the number of AHIs decreased, the patient's sleep patterns (e.g., total REM sleep, decrease in total sleep time, etc.) were adversely affected.[61]
- Methylxanthine derivatives: These drugs (e.g., aminophylline, theophylline, caffeine) stimulate ventilation by inhibiting the activity of adenosine, a nucleoside that can act a respiratory depressant, and by increasing the contractility of the diaphragm. The methylxanthine derivatives have been used for treating OSA but they have serious side effects, and their use would be contraindicated in many people with OSA because of concomitant medical conditions that are common in this patient population. Also, the studies involving these drugs have been small and the results have been inconsistent.[62]
- Sex hormones: Sex hormones, e.g., estrogen, progesterone, have been used to treat OSA – particularly in post-menopausal women – but these drugs either did not work at all or improved some sleep parameters while worsening others.[63]
- Thyroid hormone: OSA is more common in people with hypothyroidism, but treating these patients with thyroid replacement has produced results that are typical of most of the experience with drugs and OSA; thyroxine has worked for some patients but not others.[64,65]
- Tricyclic antidepressants and serotonergic drugs: Brownell [66] found that tricyclic antidepressants did not significantly help patients with OSA, but in another study, protriptyline decreased the amount of apneic events and oxygenation was improved.[67] The serotonergic drugs have attracted attention as a possible treatment for OSA because serotonin has a function – one that is not completely understood – in upper airway dilation. However, a recent review of the data did not support the use of serotonergic drugs as a treatment for OSA.[68]
- Physostigmine: The neurotransmitter acetylcholine affects respiratory efforts during rapid eye movement (REM) sleep. Physostigmine inhibits the activity of acetylcholinesterase, and it may be that physostigmine, by increasing the amount and activity of acetylcholine at nerve endings, may be beneficial for patients with OSA, and there is some evidence that this drug, and others of its class, can help the OSA population.[69]
- Carbonic anyhdrase inhibition: Carbonic anhydrase is an enzyme involved in the breakdown of carbon dioxide and carbonic acid. Acetazolamide produces a metabolic acidosis by inhibiting the activity of carbonic anhydrase, and chemoreceptors that are sensitive to pH changes in the blood respond to this acidosis by increasing central respiratory drive. There is not a lot of published literature about using acetazolamide to treat OSA, but the studies available indicate it may be helpful.[70,71]

SURGICAL TREATMENT FOR OSA

Positive airway pressure (PAP) is usually the preferred treatment for people with OSA,[72] but even though PAP can be very effective, this effectiveness is limited by the inability of many patients to tolerate PAP therapy.[73] For these people, surgery may be an option. However, surgery should not be the *first* option.[74]

Learning Break: The success rate of surgery for OSA is unpredictable and less than the success rate of PAP,[75] but for some patients it may be the only option.

Surgery for OSA reduces airway obstruction in either the nose, oropharynx (palate), or hypopharynx (base of tongue) that may be contributing to/causing OSA.

- Nasal surgery: Septorhinoplasty,septoplasty, and turbinectomy (using various methods) may help patients with OSA.[76,77] These procedures rarely cure OSA, but they may help patients to tolerate PAP.
- Uvulectomy
- Pillar procedure: The Pillar procedure uses three inserts in the soft palate to stffen the soft palate and reduce the possibility that this structure will contribute to airway obstruction during sleep.
- Uvulopalatopharyngoplasty: Uvulopalatopharyngoplasty (UPPP) enlarges the retropalatal airway. A tonsillectomy is performed, the posterior and anterior lateral paharyngeal pillars are trimmed, and the posterior portion of the palate, and the uvula are excised.
- Uvulopalatal flap: The uvulopalatal flap (UPF) is a simpler procedure and is often performed in preference to a UPPP because it is a simpler operation with fewer complications. In this procedure, the uvula is partially removed and retracted superiorly, and part of the pharyngeal wall is removed.
- Mandibular osteotomy with genioglossus advancement: This procedure involves advancing a section of bone in the mandible, allowing for advancement and stabilization of the genioglossus muscle of the tongue and resulting in anterior displacement of the tongue.
- Thyrohyoid suspension: By making an incision in the midline of the neck and advancing the hyoid bone anteriorly and inferiorly in relation to the thyroid cartilage, the base of the tongue will be drawn forward and less likely to fall back against the pharyngeal wall.
- Maxillary-mandibular advancement: The maxillary-mandibular advancement moves the upper and lower jaws forward, also moving forward the tissues of the tongue and soft palate, opening up the airway. This procedure is the most aggressive treatment for OSA, but if it is performed correctly on the appropriate patients, the success rate is quite high.[78]
- Tracheotomy: This procedure cures OSA, but it is only used if the patient is morbidly obese, has severe craniofacial abnormalities, or has severe OSA.[79]

Learning Break: As mentioned earlier, surgery may be the only option for some patients with OSA, and it can be helpful, but there is little evidence of the effectiveness of many of these procedures.[80]

POSITIVE PRESSURE AIRWAY THERAPY

Positive airway pressure (PAP) has long been the mainstay of therapy for treating OSA and is still considered the standard of care.[81] Patients are fitted with a mask that covers the nose and mouth, a mask that covers only the nose, or nasal prongs. The PAP unit works by pushing a continuous flow of air at a prescribed pressure to keep the airway open. There are PAP devices that deliver a constant level of pressure and there are others, called autotitration PAP, that lower the mean delivered pressure and titrate the delivered pressure to adjust to changing pressure requirements, and may be easier to tolerate. In addition there is a type of PAP device called the bi-level PAP. Bi-level PAP delivers a higher inspiratory pressure and a lower expiratory pressure. This mode of delivering PAP is used for patients that cannot tolerate continuous pressure PAP.[82]

There has been some controversy over the effectiveness of PAP.[83] However, there is a very large amount of evidence that has shown that PAP improves quality of life, reduces the incidence of traffic accidents, may decrease the incidence of cardiovascular disease associated with OSA, and may lower blood pressure.[84,85] Unfortunately, although PAP can be very helpful for patients with OSA, compliance with PAP therapy is often a problem.[86] Approximately 50% of patients who start treatment with PAP stop using it within a year,[87] objecting to the discomfort and inconvenience. The most common side effects of PAP therapy are dry mouth, rhinitis, sinus congestion, nasal congestion, and nosebleeds.

LIFESTYLE CHANGES FOR TREATING OSA

Lifestyle changes can be used to treat OSA. Smoking, alcohol, and caffeine can worsen OSA, so these should be avoided or used in moderation. Perhaps the most important change a patient make is to lose weight. There is some controversy regarding how effective weight loss can be,[88,89] not all patients with OSA are obese, and weight loss may not work for all patients with OSA.[90] But there is a large amount of evidence that clearly indicates that weight loss can be a very effective treatment for OSA.[91]

ORAL APPLIANCE THERAPY

As mentioned previously, PAP is the most effective treatment for OSA, but it can be difficult for patients to tolerate and the compliance rate is not good.

Oral appliances are a good alternative. They are inexpensive, relatively unobtrusive, portable, and they do not require a power source. The obvious question is do they work, and there is good evidence that they do,[92] and they can be used for patients with all degrees of severity of the disease; the success rate – as measured by the AHI – has been estimated to be 60-65%, and the compliance rate is generally better than that of PAP devices.[93] There is also evidence that these devices can help prevent some of the complications that are associated with OSA. There are adverse effects such as headaches, dry mouth, dental pain, gum irritation, and changes in the alignment of the jaw

Oral appliances are classified as *mandibular advancement splints* or *tongue-retaining devices* (TRDs). The mandibular advancement devices are placed in contact with the dental arches and they protrude the mandible. TRDs use suction to keep the tongue

protruded while the patient sleeps. Both types are trying to accomplish the same goal: improve the patency of the airway by increasing the dimensions of the airway and making it less susceptible to collapse.[94,95]

SUMMARY

OSA is a widespread public health problem, but many people who do not work in medical professions are not aware of how common the disease is and the extensive morbidity and mortality it can cause. OSA has also been shown to cause long-term sick leave and permanent disability,[96] and the economic burden of the disease is measured in billions of dollars.[97] It seriously affects quality of life, impairs higher intellectual function, and significantly increases mortality rates.[98,99] Unfortunately, although the problem is widespread, most people with OSA have not been diagnosed and therefore are not receiving treatment: one author estimated that 93% of females and 82% of males with OSA are undiagnosed.[100] OSA can also be difficult to diagnose. There are craniofacial feature that can predict the presence of OSA and there are screening questionnaires and clinical tests, but except in cases of severe OSA, none of these has been shown to have the desired level of accuracy and reproducibility.[101,102] The good news is that noninvasive and relatively well tolerated treatments *are* available, and that therapy, if compliance if good, can effectively treat OSDA and prevent complications.[103]

SUMMARY

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