Review Article

Obstructive Sleep Apnoea: Prevalence, Consequences, Pathophysiology & Treatment

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Abstract

Obstructive sleep apnoea (OSA) is a common disorder characterized by repetitive narrowing or collapse of the pharyngeal airway during sleep. The disorder is associated with major comorbidities including excessive daytime sleepiness and increased risk of cardiovascular disease. The underlying pathophysiology is multifactorial and may vary considerably between individuals. The primary objective of this article is to review the diagnosis, pathophysiology and treatment of OSA as well as several of the comorbidities commonly associated with the disorder.

Key words: Obstructive sleep apnoea, Polysomnography, Continuous positive airway pressure, Sleep

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Introduction and Definition

Obstructive sleep apnoea (OSA) is characterized by repeated narrowing or collapse of the upper airway during sleep. Episodes of complete airway collapse or airway narrowing are often associated with oxygen desaturation and terminated by an arousal from sleep.[1] Individuals with OSA frequently have excessive daytime sleepiness (somnolence) due to sleep fragmentation from these repetitive arousals.

OSA is diagnosed using polysomnography (Figure 1), which provides objective measures of the stages of sleep as well as breathing pattern. Polysomnography incorporates measurements of electroencephalogram (brain activity), left and right electrooculograms (eye movement), submental electromyogram (chin muscle activity), tibial electromyogram (leg muscle activity), electrocardiogram (heart activity), abdominal and thoracic movement (respiratory effort), nasal and oral airflow, nasal pressure, oxygen saturation, body position and sound intensity. The time spent in each sleep stage can be defined, as well as the pattern of progression between stages to provide information on sleep architecture. The arousal index (number of arousals per hour of sleep) is used to quantify the degree of sleep fragmentation. Oximetry, nasal airflow (nasal pressure), oral airflow and abdominal and thoracic movement are used to identify disordered breathing events. Periods of apnoea (complete airway collapse) and hypopnoea (airway narrowing) are determined based on an abolition (in the case of an apnoea) or reduction (in the case of a hypopnoea) in airflow (Figure 1). The most current definitions describe an apnoea as ≥90% decrease in airflow lasting for more than 10s; a hypopnoea as a reduction in airflow of ≥30% or a reduction in airflow but accompanied by a ≥4% oxygen desaturation, also lasting more than 10s.[2] The severity of OSA is determined by the Apnoea-hypopnoea Index (AHI), which is defined as the number of apnoeas or hypopnoeas per hour of sleep. OSA is defined as 'mild' if the AHI is between 5 and 15; 'moderate' if the AHI is between 15 and 30; and 'severe' if the AHI is >30 events per hour. A clinical diagnosis of OSA syndrome (OSAS) is made if an individual has an AHI > 5 and they report excessive daytime somnolence

Prevalence of OSA

In a national sleep poll (questionnaire-based) in the United States of America [3], undertaken in 2005, 6% of individuals reported having apnoeas overnight, which had been witnessed by others with 26% of the overall population meeting the criteria for being a high risk of having OSA. Duran et al. [4], in a study investigating the prevalence of OSA in the general population, also found that 6% of individuals reported having witnessed apnoeas during sleep. In addition, approximately 30% of individuals report habitual snoring [4,5], a hallmark of OSA.

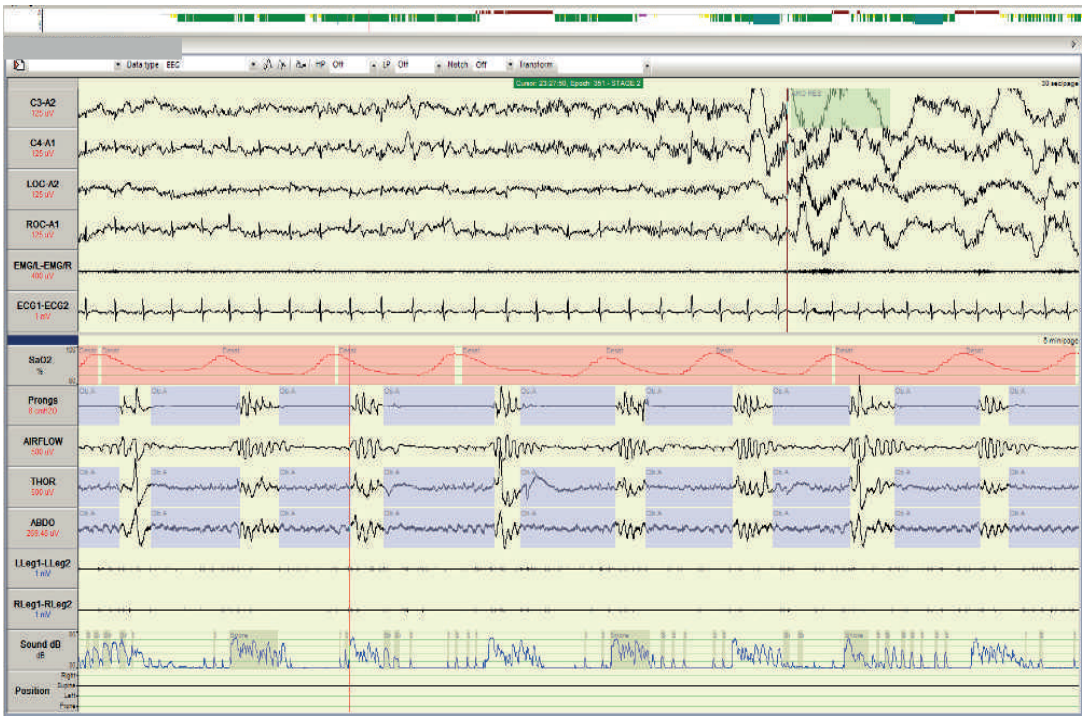

Figure 1. A section of recording taken during a polysomnographic study on an OSA patient. The top panel depicts 30s of monitoring (a 30 second epoch), the bottom panel, 5 minutes (a 5 minute epoch). The vertical red lines indicate coinciding timepoints between the two panes.

A summary of the whole night (sleep hypnogram) is shown at the top of the image (marked with an arrow): yellow periods = stage N1, green = stage N2; blue = stage N3; red = rapid eye movement (REM) sleep. The red line in the hypnogram also indicates the coinciding timepoints in the two panes below. The hypnogram shows a preponderance of stage N2 sleep ("light" sleep) and frequent awakenings throughout the night. This is characteristic of patients with OSA.

The recording channels depicted from top to bottom are as follows: C3-A2 = left central electroencephalogram (C3, brain activity) referenced to the right mastoid reference (A2); C4-A1 = right central electroencephalogram (C4, brain activity) referenced to the left mastoid reference (A1); ROC-A1 = right electrooculugram (ROC, eye movement) referenced to the left mastoid reference (A1); LOC-A2 = left electrooculugram (LOC, eye movement) referenced to the right mastoid reference (A2); L-EMG /R-EMG = left and right submental electromyogram (EMG, chin muscle activity); L-ECG/R-ECG = left and right electrocardiogram (ECG, heart activity); SaO2 = oxygen saturation measured with pulse oximetry; Prongs = nasal pressure signal; Airflow = nasal and oral airflow measured with a thermistor; Thorax = respiratory effort (thoracic chest wall motion); Abdo = respiratory effort (abdominal motion); LEG-L = left leg electromyogram; LEG-R = right leg electromyogram; Sound = snoring intenstity (decibels); and Position = body position.

The top panel shows that the individual is in stage N2 sleep. The bottom panel shows that the patient is having repeated disordered breathing events (obstructive apnoeas), each being accompanied by a transient arousal from sleep (top panel). Note the nasal pressure ("prongs") fluctuations, respiratory effort changes (in thorax and abdominal signals) and oxygen desaturations (red blocks) indicating apnoeas (purple blocks). Note also the respiratory arousal (green block) associated with an apnoea.

Large population based studies using polysomnography report the prevalence of OSA in men to be 4 to 5%.[4-6] The prevalence of OSA in females is lower than that in males and estimated to be 2 to 2.5%.[5,6] A review of the population-based epidemiology studies has estimated that the prevalence of OSAS, that is OSA with daytime impairment, in Western countries is approximately 5%.[7]

The prevalence of OSA reported by previous studies is likely to be underestimated as obesity is the most significant risk factor for OSA and the prevalence of obesity throughout developed countries has increased significantly in recent years [8,9], undoubtedly increasing the prevalence of OSA in the general population.

Consequences of OSA

Fragmented sleep

Increasing severity of OSA is associated with inefficient sleep with decreased sleep time, a reduced proportion of REM sleep [10, 11] and an increase in the number of arousals overnight coincident with obstructive respiratory events.[10] Sleep fragmentation is a hallmark of OSA due to an increased number and frequency of arousals from sleep in response to repetitive upper airway occlusion and is at least partly responsible for the other performance and health-related problems associated with OSA.

Daytime sleepiness and impaired quality of life

People with OSA are sleepier than those without, regardless of whether sleepiness is assessed objectively

by laboratory-based measures of sleep latency or subjectively by sleep symptom questionnaires. Excessive sleepiness is associated with increased morbidity including decreased productivity and increases in vehicular and work-related accidents.[12] Daytime sleepiness rapidly decreases after treatment for OSA with continuous positive airway pressure (CPAP).[13]

OSA patients have significantly lower general health and health-related quality of life than those without OSA.[14, 15] The level of impairment is directly related to the extent of sleep fragmentation indicating that poor sleep quality may be the most significant factor in determining quality of life in OSA patients.[16] Treatment for OSA with CPAP restores quality of life measures to levels similar to that reported in normal healthy individuals.[16]

Cognitive consequences

OSA has been associated with a wide range of cognitive impairments including deficits in vigilance, memory, psychomotor performance, attention and executive function.[17,18] The current belief is that these neurocognitive impairments are due to intermittent hypoxia [17, 19] and/or sleep fragmentation.[20]

Intermittent hypoxia has been reported to significantly affect sleepiness, memory, and executive function.[21, 22] In OSA, these changes have been attributed to decreases in grey matter and fiber integrity in brain regions that regulate memory and executive functions [23] such as the frontal lobe and hippocampus.[24, 25]

Sleep fragmentation may impact cognition via its effects on attention rather than executive function.[20, 26] There is a strong similarity between cognitive deficits seen in OSA and those seen in healthy individuals who have been experimentally deprived of sleep.[26] Such sleep-deprived individuals show increased daytime sleepiness and reduced activity in the prefrontal and posterior parietal cortices and in the thalamus.[27] These functional, central neural changes have been associated with reductions in attention and vigilance.[28] Sleep fragmentation might also mediate the cognitive deficits seen in OSA via dysfunction in neural networks, especially in the frontal lobes.[21] It is possible that these neurobehavioral sequele do not completely return to normal with therapy.[24]

Metabolic consequences

OSA is associated with alterations in metabolic function including decreased glucose tolerance and increased insulin resistance.[29, 30] Several studies have reported a relationship between insulin resistance, AHI and sleep-related hypoxemia.[29,30] These associations appear to be independent of obesity.[29, 30] Recently, increasing severity of OSA has been linked to poor glucose control in type II diabetics.[31]

Metabolic syndrome is a term used to describe the clustering of several proatherogenic factors including hypertension, dyslipidemia and impaired glucose tolerance.[32] OSA patients are reported to be 9 times more likely to have metabolic syndrome, independently of obesity, than those without it.[32] Recently, Sharma et al.[33] in a double-blind, placebo-controlled study showed that treatment of OSA with CPAP has significant benefits on the metabolic profile of individuals with OSA, decreasing the frequency of metabolic syndrome, decreasing total cholesterol, low density lipoprotein and plasma triglycerides as well as increasing high density lipoprotein levels.

The precise mechanism for metabolic dysfunction in individuals with OSA is unknown, however there are several possibilities. Firstly, untreated OSA patients have increased sympathetic nerve activity which is anti-insulin in its effects.[34] Secondly, sleep disruption and sleep deprivation and the associated sleep loss may be associated with detrimental changes in glucocorticoid regulation and abnormal glucose tolerance.[35] Finally, hypoxia may independently impair glucose metabolism.[36]

Cardiovascular consequences

Cardiovascular disease is reported to be the most common cause of death in OSA patients.[37] Individuals with OSA have up to an 11-fold increased risk of cardiovascular complications such as hypertension, ischaemic heart disease and cardiovascular disease.[38-40]

Severe OSA can cause significant sleep-related hypoxemia, pulmonary hypertension and right heart failure.[41-43] OSA increases left ventricular afterload, aggravating left ventricular failure.[42, 44] Treating OSA with CPAP in already treated heart failure patients results in further improvements in heart function.[44] While the exact mechanism for the association between OSA and cardiovascular disease remains undefined it is possible that increased generation of reactive oxygen species with exposure to chronic intermittent hypoxia and initiation and amplification of the inflammatory process in OSA may play an important role.[45] Support for this hypothesis comes from studies in healthy individuals showing that repeated exposure to intermittent hypoxia leads to increased sympathetic outflow, sustained daytime elevation in blood pressure, and decreased baroreflex function.[46]

All cause mortality

Several studies have reported a significantly increased risk of death from any cause in OSA patients compared to normal individuals, even when cardiovascular risk factors are accounted for.[47,48] Two studies, in Busselton (Australia) and Wisconsin (USA), using well-defined and long-standing general population cohorts have studied all-cause mortality in OSA patients compared to individuals without OSA.[49, 50] Both studies reported a significantly greater all-cause mortality in individuals with moderate-severe OSA than in individuals with no OSA. This increase appears to be at least partly reversible as treatment of OSA with CPAP results in reductions in mortality.[37, 47]

Mechanisms of pharyngeal collapse in OSA

The human upper airway (pharynx) can be thought of

as a collapsible tube. The presence of bony structures and soft tissues increase extra-luminal pressure on the tube and can predispose it to collapse. In contrast, the upper airway dilator muscles act to maintain patency via reflex pathways from the central nervous system and from receptors within the upper airway itself. The mechanisms underlying increased collapsibility of the upper airway in OSA are thought to be multifactorial in nature, but simplistically can be considered to be due to changes in the mechanical loads placed on the upper airway by surrounding structures (anatomical mechanisms) and/or to changes in dynamic neuromuscular responses (neurogenic mechanisms) to upper airway obstruction during sleep.

Anatomical mechanisms

Anatomical changes to the upper airway may be an important determinant of upper airway collapsibility during sleep.[51] Conditions such as tonsillar hypertrophy[52], acromegaly[53], retrognathia[54], and other changes in mandibular structure [55]have been associated with OSA, likely due to anatomy-related narrowing of the upper airway.

Ethnic differences in craniofacial structures are thought to underlie the different prevalence estimates of OSA among different ethnic groups for a given obesity level.[56] For example, Ip et al.[57] reported prevalence rates among Chinese men to be similar to white American males, however the mean BMI of the Chinese men was lower than that of the Americans, suggestive of a role for craniofacial structure in the pathogenesis of OSA.

Obesity, one of the major risk factors for development of OSA[6] is usually accompanied by increased neck circumference and fat deposition around pharyngeal structures.[58] These changes increase the load on the upper airway, reduce its cross sectional area and potentially contribute to the OSA pathogenesis. Fat deposition around the neck may be particularly important, with neck circumference being independently related to OSA severity, even when BMI is accounted for.[59, 60] OSA patients have increased pharyngeal fat deposits compared to age, BMI and neck circumference matched control subjects [61] and these have been associated with an increase in AHI.[62] A decrease in AHI has been reported with weight loss-related reductions in these fatty deposits.[62] It is likely that fat deposition around the neck and pharynx precipitates OSA by a direct compressive effect on the airway lumen.

Central obesity is also related to OSA, with studies reporting a relationship between AHI and waist circumference, an indirect measure of abdominal obesity[63], and intra-abdominal and subcutaneous abdominal fat.[64] Central obesity is likely to increase upper airway collapsibility through reductions in lung volume (functional residual capacity)[58] which is accentuated with sleep onset.[65] Such a decrease in lung volume may affect upper airway collapsibility via a decrease in caudal forces (traction) applied to the trachea and pharynx.[66, 67]

Neurogenic mechanisms

Skeletal muscle activity, including that of the upper airway dilator muscles, normally decreases with sleep onset. This decrease is particularly problematic in predisposed individuals as it can lead to sleep-related pharyngeal collapse. Increased baseline levels of upper airway dilator muscle during wakefulness in individuals with OSA is thought to represent a neuromuscular compensatory mechanism for a smaller or more collapsible airway.[68] This compensatory augmentation of activity is lost at sleep onset, permitting upper airway collapse to ensue.[68]

The mechanisms underlying the increase in wakeful muscle activity are thought to be central or reflex in origin and may include increases in wakeful drive to the dilator muscles and/or activation of the upper airway negative pressure reflex. This latter reflex is modulated by pharyngeal and laryngeal pressure sensors and causes an increase in upper airway dilator muscle activity when negative intrathoracic pressure is transmitted to the pharynx during inspiratory efforts.[69, 70]

It is also possible that neural pathways to and from the pharynx are impaired in OSA, predisposing to obstruction. There are several lines of evidence to support such a contention. Firstly, two-point discrimination and vibration sensation thresholds in the upper airway are impaired in OSA patients compared to normals[71], an impairment which is partially reversible with CPAP therapy for OSA. Secondly, OSA patients have histopathologic changes to upper airway muscles compared to normal individuals.[72,73] This may indicate a process of dennervation and degeneration of upper airway muscles in OSA patients. Such changes may result from trauma induced by repetitive collapse and re-opening of the upper airway during sleep. It is also possible that obesity-related hormones and cytokines such as leptin could impair neuroanatomical interactions necessary for stable breathing and increase the frequency of OSA.[58]

Treatment of OSA

The most common treatments for OSA include weight loss, CPAP therapy, mandibular advancement splint therapy and surgical therapy.

Weight loss

OSA is related to obesity.[3,7,74,75] Studies investigating the effect of surgical weight loss (i.e. bariatric surgery) on OSA report dramatic decreases in AHI [76,77] and arousal index and improvements in sleep architecture, daytime sleepiness and quality of life.[76] Likewise, studies investigating the effect of weight loss by diet modification report significant decreases in AHI[75, 78-80] the number of oxygen desaturations [79-81], arousal index [81], improvements in metabolic status [81] and daytime sleepiness.[79, 80] In addition, weight loss results in a decrease in upper airway collapsibility.[79, 82] With sufficient weight loss, the requirement for CPAP may be abolished and/or the therapeutic pressure requirement decreased.[76, 77]

The mechanism by which weight loss decreases the severity of OSA most likely relates to a decrease in neck and pharyngeal fat, decreasing the compressive forces on the upper airway. Central fat loss may also play an important role due to improved lung volumes and increased tension on the pharynx via caudal traction mechanisms. Indeed, the change in AHI after dietary weight loss has been shown to be strongly associated with waist circumference.[83]

Continuous positive airway pressure

CPAP involves administration of air under pressure to the upper airway via a nose or face mask. This provides a pneumatic splint for the upper airway preventing narrowing or collapse of the airway walls during sleep.[84] CPAP has been shown to reduce obstructive events, significantly improve both objective and subjective measures of daytime somnolence [85,86] and fatigue[87] and also improve sleep quality as it consolidates sleep and returns oxygen saturation and arousal indices to within normal limits.[88]

CPAP has been shown to reverse many of the complications associated with OSA: reducing risk of cardiovascular events (fatal and non fatal) or disease [38, 39]; reducing systolic and diastolic blood pressure[89]; reducing night time mean arterial pressure [89]; reducing signs of atherosclerosis[90]; improving metabolic function[33,91,92] and returning quality of life to that of individuals without OSA.[16] Its proven efficacy for reducing AHI and daytime symptoms makes CPAP the mainstay therapy for OSA.

An important determinant of therapy effectiveness is patient compliance, with hours of CPAP use related to the degree of improvements in Epworth Sleepiness Score, multiple sleep latency score, cognitive function and daytime functioning.[93] Treatment compliance with CPAP is reported to be between 31 and 80% [94,95], and is largely dependent on patient education and follow-up. Compliance in recent years has improved with the development of humidifiers, expiratory pressure relief, and improved nasal and oro-nasal interfaces. While it may be expected that patient compliance should improve with use of auto titrating positive pressure devices, a meta-analysis of 9 studies comparing the effectiveness of auto titrating positive airway pressure and traditional CPAP[96] showed that while mean pressure overnight was significantly lower with the auto titrating device, post-treatment AHI, subjective sleepiness and adherence were similar with both treatment modalities. This finding suggests that the mode of pressure delivery may not be a significant determinant of adherence to therapy.

Mandibular advancement splint

Mandibular advancement devices (MAD) are widely used as an alternative to CPAP therapy. They are designed to maintain upper airway patency by advancing the mandible and anteriorly displacing the tongue[97], increasing the size of the upper airway[98] thereby reducing its collapsibility during sleep.[99] Anterior displacement of the mandible and tongue may have neuromuscular, as well as anatomical, effects on the upper airway as MADshave been shown to increase the activity of upper airway dilator muscles which would stiffen the airway wall and decrease its propensity for collapse.[100]

In individuals with mild-moderate OSA, MAD therapy has been shown to decrease subjective daytime sleepiness[101,102] and objective daytime sleepiness.[102] Subjective and objective measures of snoring are also improved with MAD therapy[101,102], as are overnight oxygen saturation measures.[99,102] MAD therapy significantly decreases objective measures of OSA severity[99, 101, 102], with reported decreases in AHI of approximately 50%[101,102] and associated improvements in sleep architecture.[101-103]

Between 30 and 65% of patients achieve complete treatment success with MAD therapy.[99,101,102] Decreases in AHI of between 2 and 35 events per hour have been reported [86, 99, 101, 102] suggesting that issues such as design and degree of mandibular advancement, and patient selection are critical to its efficacy. The therapy appears most suited to those with mild to moderate OSA.

CPAP has a higher treatment success rate[104], decreases AHI by a greater amount[86,103,104] and normalises sleep architecture to a greater degree[86,103] than MAD therapy. When successful at decreasing AHI, both treatments are effective at improving daytime sleepiness.[86,103]

Surgery

The aim of surgical treatment of OSA is to increase upper airway size, make the airway less collapsible and prevent further obstruction. Surgical treatment has been separated into two phases, outlined below.

Phase I surgical therapy

Phase I surgery is the most conservative approach and addresses palatal and tongue base obstruction.

Uvulopalatopharyngoplasty (UPPP) is an example of phase I surgery and is the most common surgical procedure for the treatment of OSA. UPPP involves palate shortening with tonsillectomy and lateral pharyngoplasty and has been shown to improve quality of life[105] and daytime sleepiness, with a decrease in AHI of 33% [106] and up to 40% of patients being successfully treated (i.e. >50% fall in AHI and an AHI <20 events.hr-1).[107] However, the benefits of UPPP appear to deteriorate over time.[108]

Temperature controlled radio-frequency tissue ablation (TCRFTA) is used to induce a sub-mucosal thermocoagulation lesion in the tongue. Subsequent wound healing leads to fibrosis and tissue contraction. TCRFTA decreases AHI by 34%[106], however the therapy success rate is low, being approximately 20%. Further, the longevity of beneficial effects is unclear, as some individuals relapse and worsen after 2 years.[109]

Genioglossus advancement surgery involves a small window being made in the lower jaw. This bony window along with its attachment to the genioglossus muscle is pulled forward and down, then fastened to

the outside of the lower jaw.[110,111] The increased tension on the genioglossus may be sufficient to maintain airway patency at the level of the tongue base during sleep. Hyoid suspension surgery requires anterior movement of the hyoid complex and has been shown to increase upper airway cross sectional area.[110]

These surgical procedures can be performed in isolation or combined to increase treatment success. For example, combining UPPP with genioglossus advancement; hyoid suspension or radiofrequency treatment increases treatment success to 50 to 76% [112, 113] compared to 40% with UPPP alone.[107]

Recent developments in surgery for snoring and OSA include non-invasive procedures which can be performed under local anaesthesia such as soft palate implants which stiffen the palate. These implants have been shown to reduce snoring, daytime sleepiness and AHI in both habitual snorers and individuals with mild to moderate OSA.[114,115] However, the reported changes in AHI are relatively small. [106, 114, 115]

Phase II surgical treatment

Phase II surgery involves the surgical advancement of the mandible and/or maxilla and has been used to successfully treat OSA in individuals with and without craniofacial abnormalities.[116] Mandibular advancement advances the suprahyoid and tongue muscles [117] whereas maxillary advancement advances the velopharyngeal muscles.[118] Combined, these procedures significantly increase posterior air space and decrease airway collapsibility.[119] The procedure has been reported to decrease AHI, improve oxygen saturation, decrease stage N1 and stage N2 sleep and increase stage N3 sleep, decrease arousal index and improve fatigue and daytime sleepiness.[106,120,121] The magnitude of these changes is reported to be equivalent to that achieved with successful CPAP therapy.[120, 121]

Despite the high success rate, the pain and risk of complications associated with surgery and the proven efficacy of treatments such as CPAP therapy have meant that these relatively complex surgical procedures are not widely used in the treatment of individuals with OSA.

Hypoglossal Nerve Stimulation

Reduced upper airway muscle activity during sleep is fundamental to the pathogenesis of OSA. The hypoglossal nerve innervates multiple upper airway muscles, most importantly the genioglossus muscle which is considered to be the major upper airway dilator. Stimulation of the hypoglossal nerve results in contraction of the genioglossus muscle, moving the tongue in an anterior direction, thereby opening the airway and preventing collapse. Building on early work by Eisele et al.[122] and Schwartz et al.[123], several recent studies have investigated the efficacy of hypoglossal nerve stimulation as a treatment for OSA. These studies have reported significant increases in airflow [124], decreases in AHI and OSA symptoms and have shown this to be a safe and effective treatment for OSA.[125,126]

Summary

OSA is a highly prevalent sleep disorder, the pathophysiology of which is not yet fully understood. It is associated with significant health and safety risks as well as markedly decreased quality of life. Therapy, particularly CPAP is extremely effective in improving symptoms and other adverse health effects.

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