Overview and Implications of Obstructive Sleep Apnoea

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ABSTRACT

Obstructive sleep apnoea (OSA) is a leading public health problem both in the developed and developing nations. However, awareness regarding diagnostic options, management and consequences of untreated OSA remains inadequate. In developing nations, the resources for adequate sleep medicine facilities are scarce. Therefore, there is a need for low cost, simple and accurate diagnostic and therapeutic modalities exists. Untreated OSA leads to excessive daytime sleepiness, diminished performance and an overall poor quality of life. The role of OSA in promoting insulin resistance, atherosclerosis, hypertension and a procoagulant state has now been established. Newer insights into the biochemical and genetic mediators of OSA have raised hopes regarding the development of a "cure". However, as of now, continuous positive airway pressure (CPAP) therapy remains the first-line treatment. Though its use improves the quality of life as well as metabolic derangements observed in OSA, patients' acceptance remains low. Its high cost and long-term use are also cumbersome. Newer modes of delivering CPAP, oral appliances and upper airway surgery are the other options available. It is hoped that their appropriate use to increase patients' compliance may improve the quality of life as well as provide a survival benefit.
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Key words: Obstructive sleep apnoea, Epidemiology, Risk factors, Pathogenesis, Consequences, Diagnosis, Continuous positive airway pressure, Surgery

INTRODUCTION

"Sleep is a reward for some, a punishment for others"
Issador Ducasse

Sleep disordered breathing (SDB) includes a spectrum of conditions, the most severe of which is obstructive sleep apnoea syndrome (OSAS). It is a potentially disabling condition characterised by disruptive snoring, repeated episodes of complete or partial pharyngeal obstruction during sleep resulting in nocturnal hypoxemia, frequent arousals and excessive daytime sleepiness.

Ever since Charles Dickens described a "Pickwickian stereotype", obstructive sleep apnea (OSA) has literally walked out of books to flourish around us in various under appreciated forms. Among adults, sleep apnea is more common than asthma. Recognised as a separate clinical entity nearly 35 years ago, OSA still remains a substantial but frequently ignored public health threat.

Apnoea is defined as complete cessation of nasal airflow for more than 10 seconds.[1] Hypopnoea is characterised by polysomnographic (PSG) variables as any one of the three,[1] namely, decrease in nasal airflow by more than 50% for more than 10 sec, decrease in nasal airflow by less than 50% with a more than 3% fall in oxygen saturation or a decrease in nasal airflow by less than 50% with electroencephalographic (EEG) evidence of arousal. As hypopnoeas lead to the same clinical consequences as apneas, the apnoea-hypopnoea index (AHI) is widely used for the diagnosis and the assessment of the severity of OSA.[1] The AHI or respiratory disturbance index (RDI) refers to the mean number of apnoeas or hypopneas per hour of sleep. An AHI of more than five on overnight PSG study is required for the diagnosis of OSA.[1] A respiratory event related arousal (RERA) is defined as increasing respiratory effort required to maintain a normal airflow culminating in an arousal on EEG. The OSAS requires a minimum presence of excessive daytime sleepiness.[1] The present classification of sleep disorders[2] is described in table 1.

EPIDEMIOLOGY

Several global epidemiological studies[3-12] have demonstrated a variable prevalence of OSAS (0.3 to 5.1%) (Table 2). In a recent summary pooling together three studies, it was estimated that 20% of adults with body mass index (BMI) in the range 25-28 have sleep apnoea based on a cut-off apnoea-hypopnoea index (AHI)>5 and 7% based on an AHI>15.[13] These estimates, however, are based on data from predominantly white

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Table 1. Current terminology for common sleep related breathing disorders

Primary central apnoea

Central sleep apnoea due to
Cheyne stokes breathing
High altitude periodic breathing
Drugs (barbiturates, morphine, sedative antihistaminics etc)
Medical conditions apart from Cheyne Stokes (hypothyroidism, renal failure, stroke, pregnancy etc)

Primary sleep apnoea of infancy

Obstructive sleep apnoea (OSA)

Sleep related non-obstructive alveolar hypoventilation; idiopathic

Congenital central alveolar hypoventilation syndrome

The American Sleep Disorders Association Arbitrarily Classifies OSA as
Mild OSA	AHI 5-15
Moderate OSA	AHI 15-30
Severe OSA	AHI $\geq$ 30

populations and may not be applicable to other racial groups. Major aetiological factors such as obesity and craniofacial anatomical predispositions are both genetically and environmentally influenced. Estimates of OSAS prevalence in Asian population are similar[12, 14, 15] (2-4%). It is likely that apart from obesity, other strong risk factors such as craniofacial features and ethnicity may be contributory to high prevalence of OSA in Asian population. Only two community-based prevalence studies have been done from India so far.[16, 17] The first conducted in a small sample of semi urban population in Delhi revealed that at least 13.7% and 3.8% of middle-aged Indian adults have OSA and OSAS, respectively.[16] Unpublished results from a recently completed community-based prevalence study covering a wide socio-economic base, the South Delhi Sleep Study (SDSS)[17] found the prevalence of OSA in middle-aged

urban adults to be 9.4% and that of OSAS to be 2.7 percent. The prevalence of OSA and OSAS in males was 13.4% and 4%, respectively while that in females was 5.6% and 1.5 percent. It was a two-stage study which screened 2505 subjects with a response rate of 62% (Table 3).

RISK FACTORS

Several factors have been hypothesised to have a role in the development and progression of OSA.[18,19] Some are not modifiable like ethnicity, age, gender while others like excess weight, alcohol, smoking, nasal congestion and postmenopausal status are highly prevalent.

Nonmodifiable Risk Factors

Age. The prevalence of OSA increases with age. In midlife and in elderly (>65 years) it is found to be 2 to 3 times higher than among the middle aged (35-64 years) men and women.[18] But this increase is not continual and there is a plateau in prevalence rate after 65 years of age.[18] It has been seen that there is little or no association of OSA with sleepiness, hypertension, or decrement in cognitive function in elderly, all of which are common correlates of OSA in middle ages. Association with BMI is weaker and prevalence of self-reported snoring is lesser as compared to middle age. There is a higher incidence of central sleep apnoea in elderly. Prevalence of OSAS in childhood varies between one percent to 1.8 percent.[18] In contrast to adults, there is an equal prevalence in either sex. Obesity is a less important risk factor for OSA in childhood. Daytime sleepiness is less commonly identified in children with OSA, but poor school performance is seen in 16% to 71% of them.

Table 2. Prevalence rates of sleep disorderd breathing in various international studies

Year	Author and Place	Study Design	Sample Size (n)	PSG (N)	Age (yr)	Estimated Prevalence (%)		
						HS	OSA	OSAS
1988	Gislason *et al* (Sweden)[3]	Population based	4,064	61	30-60	15	3	1.4
1993*	Young *et al* (Wisconsin, USA)[4]	Population based	3,513	624	30-60	36	9(F), 24(M)	2(F), 4(M)
1994	Bearpark *et al* (Australia)[5]	Population based	NA	294	40-65	22	26	3.1
1994	Olson *et al* (Australia)[6]	Population based	1,188	193	35-69	24	13.5	4.2
2001*	Bixler *et al* (Pennsylvania, USA)[8]	Population based	16,603	1,741	20-99	33	17	3.5
2001*	Duran *et al* (Spain)[9]	Population based	2,794	400	30-70	35	26(F), 28(M)	3.2

* = Studies with similar design and defining criteria; PSG = Polysomnography; N = No. of polysomnography studies done; HS = Habitual snorers, OSA = Obstructive sleep apnoea, OSAS = Obstructive sleep apnoea syndrome, NA = Not available, M = Males; F = Females.

Table 3. Prevalence rates of sleep disordered breathing in India

Year	Author and Place	Study Population (Questionnaire based)	PSG (N)	Age (yr)	Estimated Prevalence[†] %		
					HS	OSA	OSAS
2004	Udwadia *et al*[15] (Mumbai)	Male insurance claimers (658)	254	35-65	26.0	19.5	7.5
2006	Sharma *et al*[16] (New Delhi)	Community study (2150)	150	30-60	23.0	13.7	3.8
2007	Reddy[17] (New Delhi)	Community study (2505)	356	30-60	18.1	9.4	2.7

† = Estimations based on number of PSG studies done with extrapolation to the screened population; PSG = Polsomnography; N=No. of polysomnography studies, HS = Habitual snorers, OSA = Obstructive sleep apnoea, OSAS = Obstructive sleep apnoea syndrome

Adenotonsillar hypertrophy is an important treatable cause of sleep disorderd breathing (SDB) in children.[18]

Male gender. In majority of the population-based studies, male sex is a striking risk factor for OSA and a 2-3-fold greater risk of OSA has been reported for men compared with women.[19] The gender related protective effect decreases in postmenopausal women who are not receiving hormone replacement therapy. In addition to the lesser likelihood of women being evaluated and treated for OSA, effect of sex hormones, craniofacial morphology, pattern of fat deposition, differences in upper airway shape and genioglossal muscle activity during the awake state and control of ventilation, have been proposed to account for a higher male risk of OSA.[20] However, a reduction in the AHI on administration of estrogen and progesterone to men (or postmenopausal women) has not been demonstrated.[20] The effect of exposure to exogenous potential risk factors, such as occupational exposures or smoking, to explain the gender difference has also not been studied adequately till date. The observation that female patients with OSA have a poorer survival indicates that OSA is either probably diagnosed late in the course of the disease or is not treated aggressively enough in females.[19]

Ethnicity. Population-based studies[3-11] suggest that the prevalence of OSAS is higher in African-Americans as compared with Caucasians. It is hypothesised that other strong OSA risk factors, apart from obesity, such as craniofacial features that compromise the upper airway, that are more prevalent in certain ethnic groups might explain the comparable prevalence of OSA in diverse populations.

Anatomical abnormalities of the craniofacial region and upper airway. Several craniofacial, orthodontic skeletal or soft tissue structural abnormalities such as dysmorphisms related to mandibular or maxillary size and position (*e.g.,* a posteriorly placed mandible, a narrow posterior airway space), an enlarged tongue and soft palate, inferiorly placed hyoid bone, and narrowed nasal cavities, can result in a smaller or more collapsible upper airway, and an increased predisposition for the development of OSA.[21] Adenotonsillar hypertrophy in childhood can lead to abnormal growth patterns of the lower face and jaw (adenoidal facies) and may predispose to OSA in later life.[18]

Genetic predisposition. Apart from male sex the strongest genetic correlate, a number of genetic linkages have been found.[22, 23] Familial aggregation of OSA has been documented indicating a genetic basis for the causation of OSA.[24] Key contributory factors that influence OSAS, such as obesity, craniofacial and orthodontic abnormalities, ventilatory control, circadian rhythm and sleep regulation, have a complex genetic basis. However, it is difficult to disentangle environmental risk factors, including cultural differences in diet and lifestyle, from genetic factors. Data are available linking circulating nuclear factor-κB (NF-κB)-dependent genes, tumour necrosis factor-a (TNF-α), and interleukin-8 (IL-8) to OSA[23]. Patients with OSA have elevated circulating levels of TNF-α and it has also been demonstrated that OSA is associated with the TNF-α (-308A) gene polymorphism, which results in increased TNF-α production.[25]

Modifiable Risk Factors

Excess body weight. Results of most studies indicate that at least 60% to 70% of patients with obstructive sleep apnoea are obese.[3-17] Potential mechanisms to be considered include: *(1)* alteration in the upper airway structure, *(2)* alteration in the upper airway function, *(3)* alteration in the balance between ventilatory drive and the load and *(4)* obesity induced hypoxemia.

There is little controversy regarding the causal role of overweight in OSA but what is debated, is the magnitude of association, the importance of specific distribution of excess fat (general, central and neck obesity) in the body and the variability of response of OSA to excess weight. The present consensus is that neck fat distribution[26] and visceral fat[26] correlate more with OSA. A randomised study by Smith and co-workers[27] has shown that there occurs a 3% increase in AHI for each 1% increase in body weight. Data are also available from studies of surgical or dietary weight loss interventions where a consistent and substantial decrease in OSA severity following weight loss has been demonstrated.[28,29] While more than two-thirds of the patients with OSA are obese, population studies indicate that OSA is a considerable problem in non-obese individuals also.[13] Thus, when a non-obese patient presents with a clinical picture suggestive of OSA, the diagnostic possibility of OSA should not be simply dismissed because the patient is not obese.

Alcohol consumption. Alcohol consumption increases nasal and pharyngeal resistance and compromises breathing during sleep. Most studies including the MONICA II study[30] have shown a significant association of snoring and OSA with alcohol consumption but what is not clear is the effect of long-term alcohol use pattern, on the occurrence of the OSA.

Smoking. Smoking causes airway inflammation and increases airway oedema, thus contributing to OSA.[31] In the only epidemiological study to focus on the role of smoking in OSA, Wetter and co-workers found that, current smokers were three times more likely to have OSA than non-smokers.[32]

Nasal congestion. This is a potentially modifiable

condition which predisposes to airway collapse and hence OSA by increasing the pressure difference between atmospheric and intrathoracic space to maintain nasal breathing. It has been shown that the odds ratio for habitual snoring and chronic severe nasal congestion at night is 3.3.[33]

Menopause. Postmenopausal status has been shown to increase the risk of OSA.[20] The reasons are yet unclear but hormone replacement therapy has definitely improved OSA in postmenopausal women.[34]

Co-morbid Conditions

It is important to distinguish OSA from conditions, such as hypothyroidism and acromegaly that can be masquerading as OSA. Treatment of the primary condition may provide a substantial cure for OSA.[35] If the primary condition is not identified, this may result not only in a misdiagnosis but also a therapeutic misadventure. The OSA is associated with diabetes mellitus, hypertension, coronary artery disease, myocardial infarction, congestive heart failure, stroke and chronic renal failure. It is likely that the associations may reflect risk factors that are common to all these conditions and OSA. However, they may also reflect the role of OSA in the aetiology of these conditions.

PATHOPHYSIOLOGY

Peculiarly, man's best friend the dog (the bull dog) remains his sole companion from among the mammals to suffer from OSA. It appears the evolutionary blessings of airway modification for speech and upright

posture have constitutionally predisposed humans for OSA[36] (Figure 1).

State-dependent reductions in respiratory muscle activity are a normal phenomenon of sleep. Sleep apnea patients differ from normal subjects in the sleep dependent changes in respiratory drive to the upper airway and pump muscles and anatomy and biomechanical properties of the upper airway. The site of sleep dependent obstruction in OSA is usually in the retropalatal or the retroglossal regions or both.[37-39] The upper airway lumen is controlled by the net balance between the constrictors and dilators of the pharynx, which are in turn controlled by cranial motor nuclei (V, VII, X, XI and XII).[40] Sleep dependent changes in the firing rates of these motor nuclei are mediated through neurotransmitters, namely, serotonin, substance p, thyrotropin releasing hormone, noradrenaline, orexin, acetylcholine, glutamate are excitatory while glycine, γ-amino butyric acid GABA and enkephalin are suppressants.[41] The predominant and non-rapidly desensitising serotonin receptor subtype involved in excitation of hypoglossal motor neurons ($5HT_{2a}$) has also been implicated in vasoconstriction (systemic and pulmonary) and thromboembolism.[42, 43] Its stimulation has corrected sleep apnoea in animal models but side effects make it an unlikely therapeutic target. Other "orphan" receptors are under therapeutic evaluation. Neuronal function *per se* is also altered in OSA, through hypoxia and oxidative stress mediated damage of hippocampal motor neurons and upper respiratory neurons.[44, 45] Magnetic resonance spectroscopy (MRS) studies demonstrate altered neurometabolites (N-acetylaspartate, phosphorylcreatine, myoinositol) in hippocampus, and frontal lobe correlating with
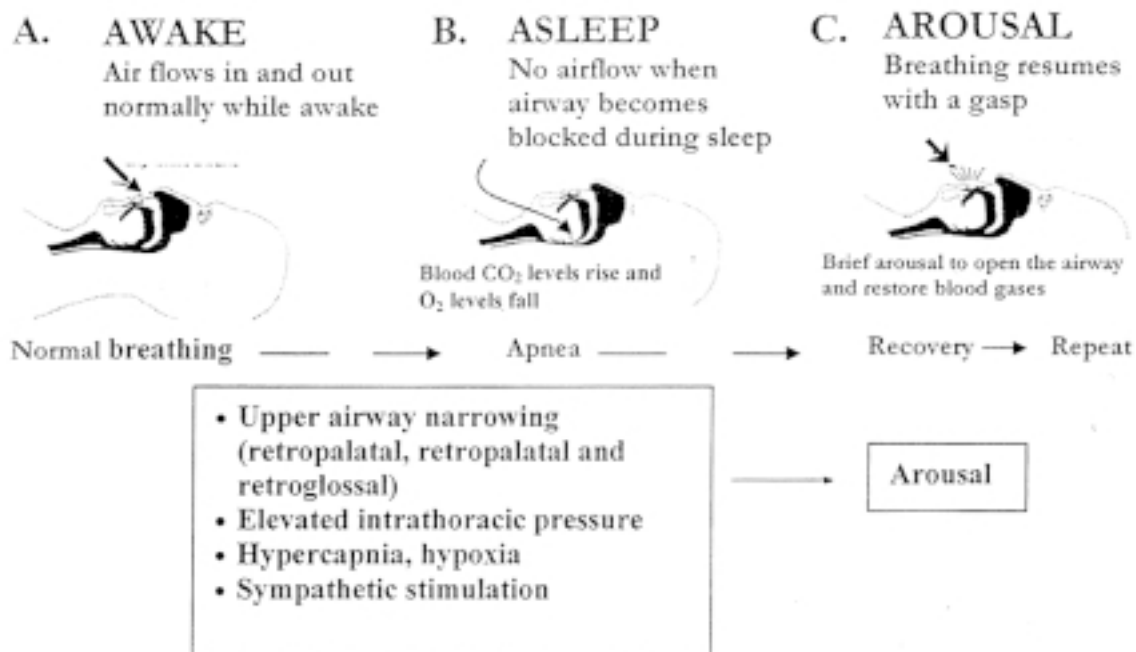

Figure 1. Pathophysiology of obstructive sleep apnoea.

increased cell damage.[46] The role of various upper airway reflexes in normal and OSA patients is also under evaluation. These reflexes might contribute significantly to upper airway activity in OSA patients who otherwise have compromised central neural drives.

Structural correlates of upper airway compromise in OSA include retrognathia, maxillary repositioning, intranasal obstruction, caudal displacement of hyoid bone, macroglossia, low-lying or enlarged soft palate, enlarged lymphoid tissue and brachycephalic posture.[47] Skeletal predispositions are multi-factorial with significant genetic influences that increase the likelihood of OSA in some subjects.[48] Soft tissue differences in the form of oedema and fatty infiltration also confer significant predispositions to OSA.[49] Neck size is the strongest of the obesity predictors for OSA and it correlates with increased dimensions of parapharyngeal fat pads.[50] A larger upper airway soft tissue volume in men may contribute to the increased prevalence of OSA in men. During wakefulness also OSA subjects demonstrate marked narrowing of the lateral airway walls and this region is distended in OSA patients treated with CPAP.

It is difficult to predict OSA severity reliably, solely on the basis of imaging or muscle activity alone. The biomechanics of the upper airway, altering compliance and collapsibility determines snoring and apnoea. The collapsible passage is formed by retropalatal and retroglossal regions. Airflow through this passage is influenced by variations in intra-luminal pressures, resistance and collapsibility, according to Starling's law. The airway (nasal) pressure at which flow ceases in this passage is termed as critical pressure (P_{crit}). Normal sleep decreases P_{crit} (-40cm H_2O to -15cm H_2O). Snorers have a P_{crit} closer to -6cm, persons with hypopnoea near -2cm and predominantly apneas occur when P_{crit} equals atmospheric pressure.[50] Nasal resistance contributes to severity of OSA by limiting maximal flow upstream to the collapsible passage and decreasing P_{crit}. On the contrary, positive airway pressure increases driving pressure, airflow and hence P_{crit}. The P_{crit} is also affected by length of the airway which is influenced by lung volume which is normally decreased in sleep and more so in OSA. Effect of supine positioning in aggravating apnoea is independent of its effect on lung volumes. Hysterical (shear stress dependent) properties of mucosa and folds also influence collapsibility. Muscle injury due to occasional high pressures and intermittent hypoxia may contribute to disease progression. The repeated systemic oxy-hemoglobin desaturations caused due to apnoea place a substantial oxidative burden on many physiologic systems contributing to the systemic disease associations of OSA.[51, 52]

CONSEQUENCES OF OSA

Apart from direct consequences of repetitive airway obstruction, the vicious cycle of hypoxia, sympathetic stimulation and arousal produces a significant oxidative load on all physiologic systems of the body. The damage is reflected initially in impaired endothelial function,[53] manifested through increased expressions of cell activators NF-κB,[52] adhesion molecules vascular endothelial growth factor (VEGF),[54] inflammatory mediators like cytokines and other markers high sensitivity-C reactive protein (hs-CRP), intercellular adhesion molecule-1 (ICAM-1), interleukins 6 and 18,[56] activated monocytes,[51] markers of apoptosis and remodeling. Patients with predisposing genetic polymorphisms are more prone to the deleterious effects of OSA, demonstrating accelerated progression of atherosclerosis.[25]

Hypertension

Population-based studies show that the prevalence of hypertension is greater in patients with OSA.[57] Studies in hypertensive subjects show a higher incidence of OSA.[58, 59] Data from the Wisconsin Sleep Cohort Study,[58] showed a dose response association between SDB at baseline and development of new onset hypertension four years later independent of other known risk factors [odds ratio (OR) for AHI <5, 5-15, >15 were 1.42, 2.03 and 2.89 respectively].[58] Further, in some studies CPAP therapy has been reported to reduce elevated blood pressure in hypertensive OSA subjects.[60] In OSA acute nocturnal surges in blood pressure occur due to chemoreflex mediated hypoxia induced sympathetic stimulation. These are potentiated in hypertensive subjects, increasing peripheral resistance. When the apnoea ends, changes in intrathoracic pressure increase the cardiac output, on a constricted vascular bed causing surges in blood pressure. "Carry over" of the elevated sympathetic tone leads to increased daytime blood pressures. Normotensive OSA patients without overt cardiovascular risk factors, have been shown to have decreased heart rate variability and increased blood pressure variability, which predispose to hypertension and endorgan damage. Chemoreceptor "resetting", tonic chemoreceptor activation occur even in normotensive patients with OSA. Endothelial dysfunction and remodeling may lead to increase wall lumen ratio and contribute to progression of hypertension (Table 4).

Heart Failure

Patients with systolic heart failure have a high prevalence of sleep apnoea predominantly central sleep apnoea (CSA).[61] Patients with diastolic dysfunction may have a higher prevalence of OSA.[61] Studies suggest that during the night the proportion of CSA goes on increasing, from the first to the last quarter.[61] Heart failure predisposes to OSA by increased soft tissue oedema, increased airway collapsibility and prolonged circulation times. Cardiac function is deranged in OSA

Table 4. Consequences of untreated obstructive sleep apnea

	Odds Ratio	Reference
Cardiovascular		
Prevalent HTN	1.4	Nieto et al[57]
Incident HTN	2.9	Peppard et al[58]
CAD	1.3	Shahar et al[59]
Stroke	4.5	Pozza et al[64]
CCF	2.4	Shahar et al[59]
Sudden death	#	Gami et al[76]
Neurocognitive		
Vehicle accidents	7	Teran-Sentos et al[89]
Metabolic effects		
Insulin resistance	#	IP et al[82]

#=Odds ratios were not provided, HTN=Hypertension, CAD=Coronary artery disease, CCF=Congestive cardiac failure

due to hypoxia, increased peripheral resistance (due to respiratory efforts), oxidative stress, increased atherosclerosis, and risk of arrhytmias. Treatment with CPAP therapy has been shown to increase stroke volume and improve functional status in patients with heart failure.[62] Thus, OSA in the backdrop of heart failure requires aggressive treatment.[63]

Cerebrovascular Disease

Breathing disorders consequent on a cerebrovascular attack, are more likely to cause primarily central sleep apnoea.[64] They are most likely to manifest in the initial hours after stroke,[65,66] but may aggravate pre-existing OSA. Prevalence of OSA is equally high in subjects with transient ischemic attacks,[66-68] suggesting against a causal association. The severity of obstructive events is independent of the type of stroke and localisation in the brain.[67] It is hypothesised that intermittent hypoxia along with its consequent sympathetic stimulation, hypertension and oxidative stress leads to disturbed autoregulation of cerebral blood flow, platelet activation and endothelial dysfunction which may precipitate a stroke in patients with OSA. The use of CPAP in the treatment of post-stroke OSA has been effective[69] in improving quality of life and abolishing apnoeas.

Pulmonary Artery Hypertension

Several studies show no difference between pulmonary hypertensive and normotensive subjects with OSA with respect to nocturnal oxygen saturation and AHI.[70, 71] This suggests that individual variation in pulmonary vascular sensitivity or factors other than OSA *per se*, may be responsible for pulmonary artery hypertension. Intriguingly, CPAP therapy has been shown to decrease pulmonary artery pressure in patients with OSA with either increased or with normal pulmonary artery pressures,[72, 73] which suggests that even "normal" may be elevated when compared with baseline.[74]

Arrhythmias

The most commonly associated arrhythmia with OSA is

sinus bradycardia with AV blocks (sinus arrest and complete heart block).[75] It is caused by increased vagal tone linked with apnoea severity. However in subjects with underlying cardiac disease, it can even precipitate tachyarrhythmias.[75] Recurrent sympathetic stimulation at the termination of an apnoea adds to the risk of fatal arrhythmias. Untreated OSA is an important under recognised cause of sudden cardiac death.[76] Treatment with CPAP therapy has been shown to abolish these triggered arrhythmias and is the first line treatment in patients with a compromised heart.

Insulin Resistance and Metabolic Syndrome

Animal studies have demonstrated the significant "stress" of intermittent hypoxia in disturbing the glucose-insulin axis.[77] Sleep fragmentation has also been demonstrated to disturb glucose tolerance in adults.[78] Sleep apnoea patients also have in addition, "visceral obesity" which contributes to their predisposition for insulin resistance. There have been conflicting reports from studies trying to assess the independent contribution of sleep apnoea to insulin resistance. Though similar methods of measurement, homeostatic model assessment for insulin resistance (HOMA-IR)[79-83] have been used in the studies, the confounding effects of obesity on insulin resistance can't be eliminated.[80, 84] Insulin resistance is a known risk factor for atherosclerosis. The OSA represents a stress that promotes insulin resistance and hence development of metabolic syndrome and finally atherogenesis as reflected in a number of studies which suggest association with OSA severity. Each additional apnoea or hypopnoea increases the fasting insulin level and HOMA-IR by about 0.5 percent.[82] Metabolic syndrome, the clustering of metabolic and morphological risk factors including insulin resistance is a well established risk factor for cardiovascular disease.[85, 86] Interaction of OSA with various vascular risk factors (called Syndrome Z) has long been recognised.[87] Though previous studies have shown an independent association between OSA and individual components of metabolic syndrome, the overall association of metabolic syndrome independent of obesity has been shown only recently.[84] However, the issue remains controversial and obesity may be a more significant factor in impairing metabolism.[80, 84] Comparative assessments of metabolic abnormalities and hs-CRP levels in carefully matched obese controls, non-obese controls and OSA patients have failed to reveal significant differences.[81, 88] Results from small cohort studies suggest that CPAP therapy which abolishes apnoeas and hypopnoeas also improves insulin resistance.[83]

Neurocognitive Sequelae of Obstructive Sleep Apnoea

Excessive sleepiness and impaired functioning can

seriously disturb the lives of patients with OSA. These patients have a seven times higher risk of automobile accidents.[89] Moreover, self-awareness about this possible hazard even among diagnosed patients is low.[90] Cognitive areas most frequently and reliably reported as being affected by OSA are general intelligence, attention, memory and executive and motor functioning.[91] Patients with OSAS suffer from excessive daytime sleepiness (EDS) due to: fragmented sleep and nocturnal hypoxemia. Recent work indicates that these two factors are differentially related to the neurocognitive deficits observed in OSAS. The EDS specifically relates to reduced attention and memory while hypoxemia specifically relates to reduced executive functioning reflected in impaired decision making.

CLINICAL PRESENTATION

Snoring and excessive daytime somnolence are the cardinal features of sleep apnoea syndrome. Prevalence of OSA has been reported to be 35% to 64% in habitual snorers.[13,16] The various symptoms of OSA patients are summarised in table 5. Hypoxemia, hypercapnia, and cor-pulmonale may complicate the late stages of the obstructive sleep apnoea syndrome, especially when obesity and chronic lung disease are present. Death can result from severe episodes of apnoea. Reference has already been made above to conditions, like hypo-thyroidism, acromegaly which may masquerade as OSA.[92]

Table 5. Clinical presentations in patients with obstructive sleep apnoea

Daytime Symptoms	Sleep Symptoms
Excess daytime sleepiness	Snoring
Cognitive and memory impairment	Choking
Executive dysfunction	Nocturnal polyuria
Erectile dysfunction	Restless sleep
Gastroesophageal reflux	Dryness of mouth
Morning headache	

DIAGNOSIS

An outline of the diagnostic approach to OSA is provided in figure 2. A high index of clinical suspicion is essential in detecting OSA, since patients' awareness regarding the problem is low (especially in mild and moderate cases). Often the patient seeks help for associated problems like hypertension, headaches, dry mouth, fatigue, erectile dysfunction etc. The differential diagnosis of OSA includes other sleep disorders, like narcolepsy, restless legs syndrome, nocturnal seizures and idiopathic hypersomnia. Narcolepsy characterised by "sleep attacks", cataplexy, and excessive daytime sleepiness can be readily differentiated by sleep latency testing. Restless legs syndrome (RLS) is a neurological disorder characterised by unpleasant sensations in the legs and an uncontrollable urge to move when at rest in an effort to relieve these feelings. The most distinctive or unusual aspect of the condition is that lying down and trying to relax activates the symptoms. More than 80% of the people with RLS also experience a more common condition known as periodic limb movement disorder. It is characterised by involuntary leg twitching or jerking movements during sleep that typically occur every 10 to 60 seconds, sometimes throughout the night. The symptoms cause repeated awakening and severely disrupted sleep. Patients are often unable to concentrate, have impaired memory, or fail to accomplish daily tasks. The diagnosis is based heavily on history and symptoms, hence should be kept in mind. Overnight polysomnography study may suggest a diagnosis of periodic limb movement disorder.

Assessment of Sleepiness

Subjective assessment. This involves the use of focused sleep questionnaires, validated in various studies and demonstrated to have a reasonably high sensitivity 74 percent to 86 percent.[93] In the Epworth Sleepiness Scale (ESS), the patient rates his or her propensity to fall asleep during eight situations ranging from lying down to rest, to sitting, to conversing. The likelihood of falling asleep is rated on a scale from 0 to 3, with 3 representing the highest likelihood of falling asleep. The total score ranges from 0 to 24, with a score of less than 7 considered within normal limits and a score of greater than 9 suggestive of sleep-disordered breathing. The Stanford Sleepiness Scale (SSS) rates subjective sleepiness on a scale from 1 to 7 with alert and wide awake as 1, a little foggy as 4 and almost asleep as 7. It is worthwhile to remember that sleep deprivation due to any cause can elevate the ESS or SSS scores.

Objective assessment

Multiple sleep latency test (MSLT). The MSLT is an objective test in which a patient is given four or five 20-minute opportunities to fall asleep at set intervals during the day (usually every two hours).[93] The tendency of a patient to fall asleep in a comfortable setting is measured. It is considered a reliable, validated measure of sleepiness, but does not correlate strongly with severity of OSA. The mean latency to sleep onset is helpful in differentiating patients with normal alertness, who have a mean sleep latency of more than five minutes, from those with excessive daytime sleepiness, whose mean latency is less than five minutes. The types of sleep that occur are also diagnostically useful. It is quite common in narcolepsy to observe two or more sleep-onset REM (SOREMs) periods in the five naps in a patient who otherwise had a normal night of sleep preceding the test. The MSLT is purported to be helpful
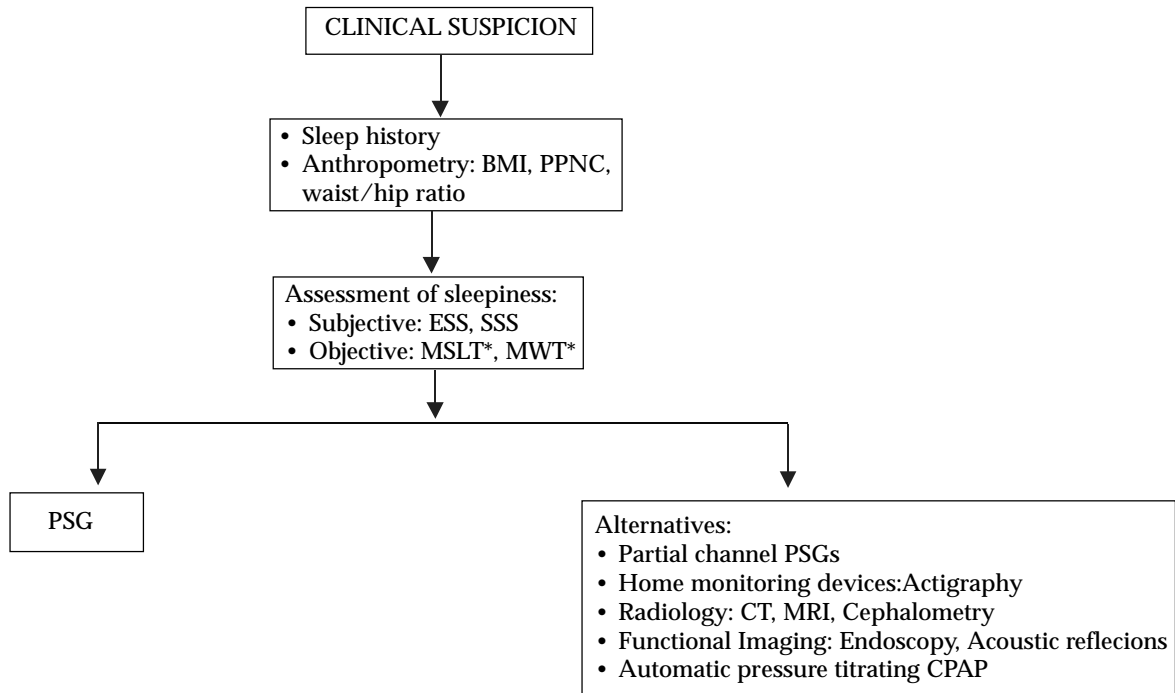
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┌──────────────────────┐
│  CLINICAL SUSPICION  │
└──────────────────────┘
            │
            ▼
┌─────────────────────────────────┐
│ • Sleep history                 │
│ • Anthropometry: BMI, PPNC,     │
│   waist/hip ratio               │
└─────────────────────────────────┘
            │
            ▼
┌─────────────────────────────────┐
│ Assessment of sleepiness:       │
│ • Subjective: ESS, SSS          │
│ • Objective: MSLT*, MWT*        │
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│   PSG   │
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┌───┐
│ Alternatives: │
│ • Partial channel PSGs   │
│ • Home monitoring devices:Actigraphy   │
│ • Radiology: CT, MRI, Cephalometry   │
│ • Functional Imaging: Endoscopy, Acoustic reflecions │
│ • Automatic pressure titrating CPAP   │
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Figure 2. Algorithm for diagnosis of obstructive sleep apnea.
*=Ideally MSLT, MWT should be performed after a full night sleep, mostly after the PSG; BMI = Body mass index; PPNC = Percent predicted neck circumference; ESS = Epworth sleepiness scale; SSS = Stanford sleepiness scale; MSLT = Multiple sleep latency test; MWT = Maintanence of wake test; PSG = Polysomnography; CT = Contrast tomography; MRI = Magnetic resonance imaging; CPAP = Continuous positive airway pressure.

in making a diagnosis of several other types of sleep disorders as well as in assessing the results of the treatment.

The MSLT has limitations, for example, it does not control for the mental state of the person tested and assumes the ability to fall asleep is directly associated with sleepiness, which may not always be the case. This test is optimally performed just after an overnight PSG, because disturbances in the quality or quantity of sleep the night before will influence the results obtained on the MSLT and may lead to a false-positive result.

Maintenance of wake test. It is similar in concept to the MSLT with the tendency to sleep being assessed on exposure to multiple stimuli.[93]

Polysomnography

Overnight PSG is required to make a diagnosis of OSA. The PSG consists of a modified electroencephalogram (EEG) to monitor brain activity, bilateral electro-oculogram (EOG) to monitor eye movement, submental and anterior tibialis electromyogram (EMG) to monitor limb activity, oral and nasal thermistors to monitor airflow, chest-wall and abdominal piezoelectric bands and intercostal EMG to monitor respiratory effort, ear or finger pulse oximetry to monitor arterial oxygen saturation (SaO_2), and V1 telemetry to monitor cardiac activity. Electrocardiography (ECG) may also be

included. Respiratory effort may be monitored by respiratory inductance plethysmography or esophageal manometry. Overnight PSG study provides data on the RDI, AHI, AI, and the lowest oxygen saturation (LSAT). Continuous esophageal and pharyngeal pressure measurements may be added to indicate respiratory effort and to help determine the site of obstruction. Night-to-night variability in PSG findings due to inter-observer differences in scoring, variability in sleeping position, alcohol ingestion, or nasal congestion may explain seemingly inconsistent results within individual patients and the lack of correlation between symptomatic improvement and sleep test results.[93]

In patients with OSA who are advised CPAP treatment, there is a need for a repeat PSG study for titration of appriopriate CPAP pressure for abolition of apnoeas and hypopnoeas. Often this separate PSG study is clubbed with the diagnostic PSG as a "split-night" study. The advent of auto-adjusting pressure titrating CPAP (A-CPAP) has enabled us to avoid the repeat overnight PSG and directly use the A-CPAP.[94] They have been used successfully for initial diagnosis also.[94]

Alternatives to overnight PSG. If, the estimated prevalence of sleep apnoea at 2 to 4 percent of middle-aged adults is accurate, then the material and manpower costs of full PSGs to diagnose all suspected cases would be prohibitive. Diagnostic approaches

which might be viewed either as alternatives to PSGs or as screening tests to better select patients for PSG include:[93]

1. Partial channel PSGs;
2. Partial night or daytime PSGs;
3. Portable sleep monitoring devices for use at home: actigraphy;[95]
4. Automatic pressure titrating CPAP based direct pressure titration study in suspected sleep apnoea patients for diagnosis and management;[95]
5. Radiology: imaging of the head and neck for anatomic abnormalities predictive of sleep apnoea: cephalometry, magnetic resonance imaging (MRI), acoustic reflections and computed tomography (CT) scans; and
6. Anthropomorphic measurements: such as neck circumference nasopharyngeal and laryngeal endoscopic measurements of both structure and function.

Prediction equations. Combinations of patient symptomalogy, anthropometry and demographic patterns have been modeled variously to arrive at prediction equations.[96-98] One such model developed and validated in subjects in New Delhi had a sensitivity, specificity, positive predictive value and negative predictive value of 91.3%, 68.5%, 70.5% and 92.3%, respectively.[98] The application of these models may help more efficient use of the already scarce sleep medicine facilities. Future incorporation of multiple airway parameters with mathematical modeling may increase accuracy.

TREATMENT

Lifestyle Modification

Weight reduction is undisputedly helpful in improving the severity of OSA. As referred previously there occurs a 3% increase in AHI for each 1% increase in body weight.[27] Weight reduction by as little as 3-5 kg has been shown to significantly decrease snoring, CPAP pressures and AHI.[28] However, this does not abolish OSA. Weight reduction is expected to ameliorate some of the risk for co-morbid conditions like CAD, hypertension, metabolic syndrome. Both sedative medications and alcohol have a depressant effect on the pharyngeal dilator muscles and increase respiratory resistance, aggravating OSA. In subjects with evidence of chronic or nocturnal nasal congestion, treatment with topical steroids, antihistamines and surgery may help in reducing severity of OSA. Decrease in nasal congestion also helps to improve CPAP compliance (Figure 3).

Pharmacological Treatment

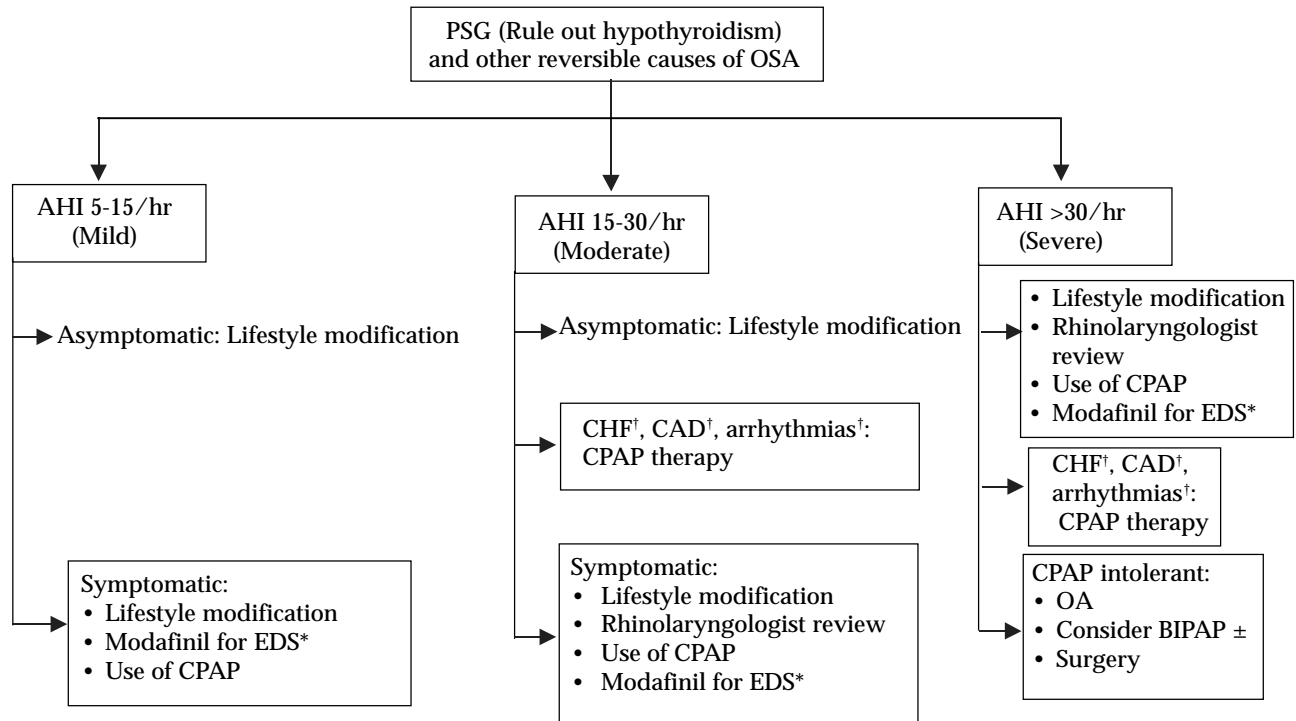A number of agents have been tried without success to

Figure 3. Algorithm for the management of obstructive sleep apnea.
PSG = Polysomnography; AHI = Apnea-hypoapnea index; CPAP = Continuous positive airway pressure; EDS = Excessive daytime sleepiness; CHF = Congestive heart failure; CAD = Coronary artery disease; OA = Oral appliances; * = Avoid in subjects with CHF, CAD and exercise caution in patients with LVH; † = Maximal benefit with CPAP; ± = high CPAP pressures,underlying lung disease; CHF = Congestive heart failure, CAD = Coronary artery disease.

ameliorate the excessive somnolence in OSA patients. The US FDA has approved the use of the wake promoting drug modafinil in improving alertness and subjective and objective sleepiness in patients with OSA.[99] The exact mode of action is unknown. It decreases the uptake of norepinephrine and dopamine, stimulates glutaminergic pathways and blocks "hypocretin" mediated pathways in the hypothalamus. It is contraindicated in patients with significant cardiac dysfunction. It has also shown a weight reducing effect across various studies, which may further benefit OSA patients.[100, 101] The starting dose is 200mg in the morning after waking and can be titrated upwards. Headache (11%) and nausea (12%) have been the commonest reported adverse effects.[99] More selective (R-enantiomer) molecules are also available.

Positive Pressure

Therapy with CPAP is the first-line treatment for OSA.[102] It delivers air at high flow (20-30 litres/min) through an interface to the upper airway, providing a constant mechanical splint (air at pressure) to prevent airway collapse during sleep, thus abrogating apnoeas and hypopnoeas.[103] This reduces intermittent hypoxia,[104, 105] respiratory effort, sympathetic stimulation,[105] arousals[105] and sleep fragmentation. Recent meta-analyses indicate that the treatment of OSA with CPAP therapy leads to significant improvement in daytime sleepiness and quality of life measures as well as reduced diastolic and systolic blood pressure.[102, 106] Currently, CPAP is recommended for any patient with symptoms, though maximum benefit has been observed in patients with AHI greater than 20 per hour.[107] It is the treatment of choice for severe OSA and in subjects with cardiovascular dysfunction.[106] Results of a recent study with CPAP therapy show a significant improvement in markers of early atherosclerosis in patients of mild to moderate OSA with no symptoms.[108] Though the overall magnitude of risk reduction is unknown, the indications for CPAP therapy may widen in the future. Retrospective cohort studies comparing compliance with CPAP use in patients with severe OSA suggest a reduction in mortality (85.5% *vs* 96.4%).[109, 110] Bullous lung disease and recurrent nasal/ear infections are relative contraindications. The theoretical risks of positive pressure; pneumoencephalus, increased intraocular pressure are rare. Despite its efficacy patient compliance is unsatisfactory ranging from 36% to 60% across studies.[102] Compliance failure due to discomfort can occur due to many reasons, like ill fitting face masks, claustruphobia and eustachian tube dysfunction.[102, 106] Interface designs for CPAP have been developed over the years in an effort to minimise the occurrence of such adverse effects and to improve compliance. The results of a meta-analysis suggest that nasal pillows or the Oracle oral mask may be useful alternatives when a patient is unable to tolerate conventional nasal masks.[111] The face mask can not be recommended as a first-line interface, but may be considered if nasal obstruction or dryness and uncontrolled air leakage from mouth limits the use of a nasal mask.[111] Appropriate pressure titration, proper masks, nasal decongestants and counselling should help. Humidified air at appropriate temperature (warmed or cooled) may help with nasal dryness. Newer respiration timed pressure delivery modes like A-CPAP and pressure relief CPAP are more comfortable. In contrast to the conventional fixed pressure (F-CPAP) in which the pressures remain constant throughout sleep, in A-CPAP the pressure delivered to the airway fluctuates with sleep. Apart from better patient comfort, the A-CPAP is significantly more effective in correcting the deranged metabolic parameters in OSA patients.[112] However, the A-CPAP is up to three times costlier than the conventional F-CPAP and patients should be given a trial of cheaper options, appropriate interface devices and counselling before prescribing an A-CPAP. The A-CPAP has been tried for primary diagnosis and management of suspected OSA patients, with acceptable results and may be beneficial in resource limited settings.[94, 113] Patients intolerant to CPAP may try uvulopalatopharyngoplasty or oral appliances.

Bilevel airway pressure therapy (BiPAP). The CPAP provides similar inspiratory and expiratory pressures, however, in BiPAP the inspiratory positive pressure (IPAP) is set to prevent upper airway closure and hypopnoea due to partial closure. The expiratory

Table 6. Surgical procedures for obstructive sleep apnoea

Surgery	Indication	Result
Septoplasty	Deformed septum	Improved CPAP tolerance
Nasal polypectomy	Airway obstruction	Improved CPAP tolerance
Adenoidectomy	Enlarged tonsils	Treats OSA (esp. children)
Uvulopalatopharyngoplasty	Debulking soft palate	Treats snoring, decreases AHI, long-term success rate 52.3%
Pillar procedure	Stabilises soft palate	Decreases snoring and AHI
Hyoid suspension	Enlarges hypopharyngeal airway	Helps moderate OSA, can cause dysphagia
MMA	Stepwise jaw reposition	In selected patients efficacy equals CPAP

CPAP = continous positive airway pressure; OSA = obstructive sleep apnoea; AHI = apnoea-hypopnoea index; MMA=Mandibular advancement genioglossus recession maxillary advancement

positive airway pressure (EPAP) serves to stabilise the collapsible airway at end expiration such that the patient can comfortably trigger the delivery of an IPAP. It provides ventilatory assistance with improved patient compliance. It can be particularly helpful in patients with high CPAP pressures and underlying lung diseases compromising oxygen transfer or increasing the work of breathing.[107]

Oral Appliances

The US FDA approves 16 devices for use in sleep apnoea. Oral appliances (OA) are now widely used as an alternative to CPAP therapy. They are designed to keep the upper airway open by either advancing the lower jaw forward or by keeping the mouth open during sleep. A recent meta-analysis found that OA should not be considered as the first choice therapy for OSA,[114] where symptoms and sleep disruption are severe. Although CPAP was clearly more effective at reducing the disruption to sleep, some people with OSAH may prefer using OA if they are found to be tolerable and more convenient than CPAP. When an active OA was compared with an inactive OA, there were improvements in daytime sleepiness and apnoea/hypopnoea severity. Also, OA may be more effective than corrective upper airway surgery.

Surgery

Continuous positive airway pressure provides at best a control for OSA. It is surgery alone which can provide a "cure". However, the role of surgery requires proper patient assessment and selection and is not for everyone.[114] Uvulopalatopharyngoplasty (UPPP) is the most common surgery performed for snoring. It has been shown to decrease OSA severity, more so in patients with retropalatal obstruction. This surgical procedure has an approximately 52.3% rate of long-term reduction of respiratory disturbance index (RDI) or AHI of greater than 50% of patients with mild or moderate sleep apnoea.[114, 115] Site-specific surgery, including maxillomandibular advancement, has been shown to be effective in selected patients with certain anatomical abnormalities. Tracheostomy is reserved for patients with severe OSA and cardiorespiratory compromise in whom positive airway pressure is neither tolerated nor effective. Table 6 provides a list of surgical procedures available for the treatment of symptomatic anatomical obstructions of the upper airway that contribute to or result in clinical OSA.[115]

Radiofrequency ablation of the soft palate and tongue base employs the administration of microwave radiofrequencies to the treated tissue of the soft palate and/or the tongue base with a needle-implanted probe. This modality has been predominantly used for the treatment of snoring by treating the soft palate. Mandibular advancement, genioglossus recession and

maxillary advancement (MMA) is successful for patients with base of tongue obstruction, severe OSAS, morbid obesity, and failure of other treatments.[116] With careful evaluation, results with MMA surgery equal those of nasal CPAP.[117] The Stanford Group[116] has outlined a specific surgical protocol that is phased and tailored to the specific anatomical abnormalities in each patient.

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