PAKISTAN CHEST SOCIETY
STRIVING FOR PULMONARY CARE

Clinical Practice Guidelines

OBSTRUCTIVE SLEEP APNEA

Pakistan Chest Society-2020

GUIDELINES ON

Obstructive Sleep Apnea

March 2020

PAKISTAN CHEST SOCIETY

PAKISTAN
CHEST SOCIETY
STRIVING FOR PULMONARY CARE

Obstructive Sleep Apnea Guideline Working Group

Dr. Muhammad Irfan Malik (Chairman working group)
MBBS. FCPS (Pulm)
Associate Professor Department of Pulmonology.
AMC/ Lahore General Hospital.
Lahore, Pakistan

Prof. Kamran Cheema,
MD, DABIM, Pulmonology, Critical Care, Sleep Medicine
Professor and Head of Pulmonary & Critical Care Department
Services Hospital,
Lahore, Pakistan

Dr Hashir Majid
MD, DABIM, Pulmonology, Critical Care, Sleep Medicine
Consultant Pulmonologist
Aga Khan University Hospital,
Karachi, Pakistan

Dr Hafiza Shafia Naz
MBBS, FCPS (Pulm)
Senior Registrar
Department of Pulmonology.
Sheikh Zayed Medical College / Hospital.
Rahim Yar Khan, Pakistan

PCS GUIDELINES COMMITTEE

Prof. Muhammad Irfan (Chairman)
Prof. Nisar Ahmed Rao
Prof Mukhtiar Zaman Afridi
Prof. Ali Bin Sarwar Zubairi
Prof. Sadia Ashraf
Prof Talha Mahmud
Dr Maqbool A Langove

Message By The President Pakistan Chest Society (PCS)

Obstructive sleep apnea (OSA) is a common and progressive chronic condition characterized by frequent episodes of upper airway collapse during sleep. It is responsible for a high number of comorbidities and increased mortality, including a rise in the rate of sudden cardiac death. Unfortunately, OSA now affects millions of people worldwide.

The 20th century witnessed some progress in uncovering the mysteries of obstructive sleep apnea which continues in this 21st century. Concomitantly, the awareness about the importance of sleep and its disorders has increased. Recent years have brought many significant changes in the field of sleep apnea and snoring, this aims to cover various aspects like pathogenesis, at-risk populations, clinical scenarios and management

Despite the numerous advancements in knowledge regarding the pathogenesis and clinical consequences of the disorder a great majority of those affected remain undiagnosed. Simple queries of the patient or bed-partner for the symptoms and signs of the disorder, namely loud snoring, observed apneas, and daytime sleepiness, would help identify those in need of further diagnostic evaluation.

I feel much delighted on excellent efforts of the relevant working group in bringing about this excellent guiding tool. It is the first guideline on Sleep apnea from Pakistan and PCS is proud of having such wonderful colleagues who imparted their share in bring out this guideline. This guideline will provide an overview of OSA, comprehensive and up-to-date knowledge regarding the diagnostic aspects of obstructive sleep apnea in adults and subsequent therapeutic measures, making this publication a useful aid to postgraduates, physicians, clinicians and pulmonologists concerned with the management of this disease.

PROF. DR. NISAR AHMED RAO

President,

Pakistan Chest Society

Message By The Chairman Guidelines Committee, Pakistan Chest Society (PCS)

It is a matter of great pleasure, pride and satisfaction that the first clinical practice guideline on **Obstructive Sleep Apnea** has been published by PCS**.** Governing Council of PCS has mandated the Guideline committee to develop evidence based guidelines for important pulmonary diseases. Besides this document, guidelines on Asthma, Non-invasive ventilation, Preoperative Pulmonary Risk Assessment, COPD and guideline on smoking Cessation have already been developed and will distributed during the 14th Biennial Chest Con 2020 in Karachi. It is very encouraging to note that PCS has been consistently working on developing and updating guidelines. These guidelines provide a highly valuable resource for the trainees and practicing physicians.

Obstructive sleep apnea (OSA) is a sleep disorder that involves cessation or significant decrease in airflow in the presence of breathing effort. It is the most common type of sleep-disordered breathing and is characterized by recurrent episodes of upper airway collapse during sleep. These episodes are associated with recurrent oxyhemoglobin desaturations and arousals from sleep. For people with sleep apnea, the combination of disturbed sleep and oxygen starvation may lead to hypertension, heart disease and mood and memory problems. This guideline provides a highly valuable resource for the trainees and practicing physicians involve in management of sleep related breathing disorders specially the obstructive sleep apnea.

Finally, I would like to acknowledge the hard work of Dr. Irfan Malik and other members of the working group who has prepared this very informative document and the members of PCS guideline committee for reviewing the document. PCS remain committed to always endeavor for the achievement of the best possible clinical practice.

Prof. Muhammad Irfan

Chairman Guidelines Committee, PCS

PREFACE:

Firstly, I thank Allah Almighty for showering His countless blessings upon me and empowered me and my team to accomplish the very big task of compiling the first PCS guidelines on obstructive sleep apnea. This is very important to notify here that only limited set ups of Pakistan have established the polysomnography services so these guidelines are made to motivate other centers for providing this brilliant service. We have tried our level best to reflect all local experiences and international recommendations for obstructive sleep apnea. Later on we have planned to cover other aspects of sleep disordered breathing like central sleep apnea and obesity hypoventilation syndrome etc. in next reviews. I appreciate the co-operation of my team to support in designing these guidelines. OSA is increasingly prevalent in both adults and children in modern society. The National Commission on Sleep Disorders Research in the United States estimated that minimal SDB (RDI >5) affects 7 – 18 million people and that relatively severe cases (RDI > 15) affect 1.8 – 4 million people. SDB remains undiagnosed in approximately 92% of affected women and 80% of affected men. The male–to-female ratio in community-based studies is 2-3:1.

It is definitely a brilliant opportunity for us to be the pioneer of making the first ever guidelines of OSA in Pakistan. All members of my team have tried their level best to put their concentrated efforts in making this national guideline which can facilitate every reader to take maximum benefit from this document and utilize the information provided in a best possible way. We have tried to cover all aspects of obstructive sleep apnea including its epidemiology, pathophysiology, risks, etiology, diagnostic modalities and scores and its management protocols.

I am very grateful to my all teachers to polish my capabilities and my family members for their wonderful encouragement and continuous support to fulfil my commitment. We must also pay our full regard to all our sleep apnea patients who enabled us to gain a very good experience on this vast topic of sleep medicine. and to apply our concrete knowledge and updated information in making this document. So that it will be a continuous source of learning for all the readers to gain maximum benefit to expand their knowledge in this specialized field. May we all learn to take sleep medicine to its wonderful peaks in Pakistan.

Dr. Muhammad Irfan Malik

INTRODUCTION:

Definitions and Classification:

Sleep-related breathing disorders are characterized by abnormal respiration during sleep. They are divided into three major groups: Obstructive Sleep Apnea (OSA) Syndrome, Central Sleep Apnea (CSA) Syndromes, and Sleep-related Hypoventilation/Disorders. .

The sleep apnea syndromes are characterized by intermittent absence or reduction of airflow during sleep. The difference between OSA and CSA centers on the presence or absence of airway obstruction and ventilatory effort. In CSA, the airway remains patent while there is no ventilatory effort; in OSA, both airway obstruction and respiratory effort are present.

The hallmark of Sleep-related Hypoventilation Disorders is elevation of carbon dioxide levels for a significant duration during sleep. When there is sustained oxygen desaturation during sleep, in the absence of CO2 monitoring, a diagnosis of Sleep-related Hypoxemic Disorder is sometimes utilized.

This guideline pertains to Obstructive Sleep Apnea Syndrome.

Epidemiology:

Obstructive Sleep Apnea Syndrome is the most common sleep-related breathing disorder. It is more prevalent in males and in the obese.

It is important to differentiate Obstructive Sleep Apnea Syndrome from a sleep study confirmation of obstructive events during sleep. A “positive” sleep study refers to any study with more than five obstructive respiratory events per hour of sleep. Obstructive Sleep Apnea Syndrome refers to a positive sleep study in addition to a constellation of symptoms (especially daytime sleepiness) related to sleep related breathing disorder. Hence, although the estimated prevalence of patients with abnormal obstructive events during sleep is approximately 20 to 25 percent in males and 5 to 10 to in females in North America (Wisconsin cohort, Pennsylvania), the actual prevalence of the syndrome is lower: between 3–7% of middle-aged men and 2–5% of women.

Pathophysiology:

OSA is characterized by recurrent collapse of the pharyngeal airway during sleep despite ongoing breathing efforts.

Factors which enhance collapsibility - e.g. conditions associated with a narrowed cross-sectional diameter of the airway (obesity, retrognathia, micrognathia, macroglossia etc.), poor muscle tone

of the airway (advancing age, neurological and congenital disorders), increased upper airway resistance (male airway) – hence predispose individuals to develop OSA.

Other factors, including arousal threshold, upper airway anatomy, upper airway muscle drive, and stability of the respiratory control system can also affect the severity of OSA in a patient. The underlying pathogenesis may also vary by age: younger patients are more likely to have alterations in ventilatory control, whereas older patients are more likely to have predominant upper airway collapsibility.

The airway collapse in OSA leads to intermittent reduction or complete cessation of airflow and is associated with disturbances in gas exchange (eg, hypercapnia and hypoxemia), fragmented sleep and sympathetic nervous system activation. These in turn cause deleterious metabolic and cardiovascular consequences, such as myocardial infarction, stroke, congestive heart failure, arrhythmias and insulin resistance etc.

RISK FACTORS FOR OSA:

Table:1

Structural risk factors	Non-structural risk factors
Innate anatomic variations (facial elongation, posterior facial compression)	Obesity
Retrognathia and micrognathia	Central fat distribution
Mandibular hypoplasia	Male sex
Brachycephalic head form (associated with an increased AHI in whites but not in African Americans)	Age
Inferior displacement of the hyoid	Postmenopausal state
Adenotonsillar hypertrophy, particularly in children and young adults	Alcohol use
Pierre Robin, Down, Marfan, and Prader-Willi Syndromes	Sedative use
High, arched palate (particularly in women)	Smoking
	Habitual snoring with daytime somnolence
	Supine sleep position
	Rapid eye movement (REM) sleep

Table 1: structural and non-structural risk factors for obstructive sleep apnea.[2]

1. Age: OSA prevalence increases from young adulthood to seventh decade and then reaches to a plateau.
2. Gender: 2-3 times more common in males than females.
3. Obesity: OSA prevalence increases as the BMI and associated markers (neck circumference, waist-to-hip ratio) increase. Particularly severe obesity BMI more than 40 kg/m^2 carries a risk for concomitant obesity hypoventilation syndrome (OHS). Patients with OHS have high rates of awake hypoventilation in addition to high rates of comorbid OSA.

4. Craniofacial and upper airway abnormalities: These abnormalities include abnormal maxillary or short mandibular size, wide craniofacial base, tonsillar hypertrophy and adenoid hypertrophy. These factors are best recognized in Asian patients.
5. Other risk factors: Nasal congestion confers a two-fold increase risk of OSA. Smoking also increases the risk of OSA as current smokers are 3 times more likely to have OSA than past or never smokers. Menopausal women have increased risk of OSA. Patients of OSA also report of having family history of snoring or OSA. Genetic basis accounts for about one fourth of OSA prevalence.
6. Medical conditions: Certain medical conditions increase the risk of OSA. These include pregnancy, End-stage renal disease, Congestive Heart Failure, Chronic Lung disease, post-traumatic stress disorder, Stroke and transient ischemic attacks, Acromegaly, Hypothyroidism, Poly Cystic Ovarian Syndrome (PCOS).

CLINICAL FEATURES:

A constellation of signs and symptoms can be suggestive of OSA; however, it should be noted that there is no specific clinical feature that is pathognomonic for the disease.

Symptoms: Common symptoms exhibited by OSA patients are listed in table 2 below.

Table:2

DURING SLEEP	WHILE AWAKE
Loud snoring / snorting	Daytime sleepiness
Witnessed apneas by bed partner	Non-restorative sleep
Awakening with choking	Lack of concentration
Nocturnal restlessness	Cognitive deficits
Vivid, strange or threatening dreams	Changes in mood
Gastro-esophageal reflux	Morning headaches
Insomnia with frequent awakening	Dry mouth
Nocturia	Impotence or decreased libido
Hyper-salivation	
Teeth-grinding	
Diaphoresis	

Table 2: symptoms of obstructive sleep apnoea syndrome. Adapted from Riha, 2010, with permission from the publisher

The classical presentation described for patients with OSA is one of snoring, witnessed apneas and daytime somnolence. While this is common in the obese, middle-aged male, it is important to remember that women may present with more subtle mood disturbances and that their snoring or apneas may have been missed by less vigilant male partners.

Certain conditions are associated with a higher incidence of obstructive sleep apnea (table 3). Their presence should alert the clinician to assess for the possibility of undiagnosed OSA, including post-menopausal state in women, history of refractory hypertension or asthma, lone atrial fibrillation, hypothyroidism, acromegaly, polycystic ovarian syndrome, cigarette-smoking and chronic nasal congestion.

Signs: When evaluating for OSA, the clinician should be alert to the presence of certain physical characteristics that are associated with an increased risk of the disease (table 3). These include:

- Obesity: Body mass index (BMI) more than 30 kg/m^2. The correlation with OSA is stronger with central obesity, indicated by a waist circumference of 40 inches for men and 38 inches for women, and a waist-hip ratio of 0.595 and 0.575 respectively.
- Crowded airway: craniofacial features that predispose to narrowing of the upper airway and OSA include retrognathia, micrognathia, malocclusion, high and arched hard palate, macroglossia, elongated and low-lying uvula, enlarged tonsils and adenoids, lateral peritonsillar narrowing, reduced nasal valve patency due to nasal septal deviation and/or nasal polyps, hypertrophied nasal turbinates. A modified Mallampati class III or IV airway is considered a risk factor for OSA.
- Large neck circumference: Collar sizes of above 17 inches for men and 16 inches for women are associated with a higher incidence of OSA.

Table:3

SIGNS TO LOOK ON EXAMINATION
• Obesity BMI more than 30 kg/m2
• Large neck circumference more than 40 cm
• Reduced nasal patency
• Small mandible, small maxilla
• Dental malocclusion
• Macroglossia
• Retrognathia (back set jaw)
• Enlarged tonsils
• Adenoid hypertrophy

• Elongated or low-lying uvula
• High or narrow hard palate
• Crowded airway

Table 3: Clinical features of obstructive sleep apnoea syndrome. BMI: body mass index. Adopted from RIHA, 2010, with permission from the publisher.

Patients at high risk for OSA:

- Obesity
- Congestive heart failure
- Atrial Fibrillation
- Nocturnal arrhythmias
- Pulmonary Hypertension
- Treatment Refractory Systemic Hypertension
- Cerebrovascular accidents
- Type 2 diabetes
- Bariatric surgery candidates
- Commercial pilots and truck-drivers

CONSEQUENCES:

The association with cardiovascular, cerebrovascular and metabolic disorders implies that OSAS contributes to increased morbidity and mortality in the general population. Undiagnosed OSAS results in higher medical costs, even a single road side accident due to sleepiness caused by OSAS can incur considerable health costs. Other consequences include:

- Untreated OSA is associated with considerable morbidity and mortality.
- Cardiovascular morbidity: OSA, especially moderate-to-severe OSA, is associated with systemic hypertension, pulmonary hypertension, coronary artery disease, cardiac arrhythmias, heart failure sudden cardiac death, venous thromboembolism and stroke. Use of PAP therapy diminishes these risks, particularly in those under the age of 65 years.
- Impaired daily function: OSA is associated with excessive daytime sleepiness, inattention and fatigue which may impair daily function.
- Impaired cognition and psychiatric disturbances: OSA may induce cognitive deficits. These patients have two fold higher risk of depression and sexual dysfunction.

- Drowsy driving and motor vehicle crashes: Motor vehicle crashes are two to three times more common among patients with OSA than without OSA. OSAS is associated with a large increase in the risk of motor vehicle accident, with a relative risk of 3.7. These patients should be counseled to avoid activities that require vigilance and alertness. Successful OSA treatment improves stimulator performance and decreases motor vehicle crashes.
- Metabolic syndrome and type 2 diabetes: In patients with metabolic syndrome, OSA has been independently associated with increased glucose and triglyceride level, insulin resistance and type 2 diabetes as well as markers of inflammation. Proposed mechanism for this include oxidative stress caused by intermittent hypoxemia and sympathetic activation.
- Nonalcoholic fatty liver disease: Patients with OSA have an increased prevalence (two to three fold) of NAFLD particularly those with severe OSA.
- Perioperative complications: Patients with OSA may be at greater risk for perioperative complications such as postoperative acute respiratory failure, cardiac events and intensive care unit transfers.
- Mortality: Patients with untreated severe OSA (AHI more than 30 events/ hour) have two to three fold increased risk of all-cause mortality compared with individuals without OSA, independent of other risk factors.

DIAGNOSTIC TESTING FOR ADULT SLEEP APNEA PATIENT CLINICAL PRACTICE GUIDELINE:

OSA is a chronic disease that rarely resolves except with substantial weight loss or successful corrective surgery. As with other chronic diseases, periodic follow-up by a qualified clinician (e.g physician or advanced practice provider) is necessary to confirm adequate treatment, assess symptom resolution, and promote continued adherence to treatment

Patients with untreated OSA may be at increased risk of developing cardiovascular disease, including difficult-to control blood pressure, coronary artery disease, congestive heart failure, arrhythmias and stroke. OSA is also associated with metabolic dysregulation, affecting glucose control and risk for diabetes. Undiagnosed and untreated OSA is a significant burden on the healthcare system, with increased healthcare utilization seen in those with untreated OSA, highlighting the importance of early and accurate diagnosis of this common disorder.

Recognizing and treating OSA is important for a number of reasons. The treatment of OSA has been shown to improve QOL, lower the rates of motor vehicle accidents, and reduce the risk of the chronic health consequences of untreated OSA mentioned above. There are also data supporting a decrease in healthcare utilization and cost following the diagnosis and treatment of OSA. However, there are challenges and uncertainties in making the diagnosis and a number of questions remain unanswered. Therefore, when OSA is suspected, a comprehensive sleep evaluation is important to ensure appropriate diagnostic testing is performed to address OSA, as well as other comorbid sleep complaints. The diagnosis of OSA involves measuring breathing during sleep.

The third edition of the International Classification of Sleep Disorders (ICSD-3) defines OSA as a PSG-determined obstructive respiratory disturbance index (RDI) ≥ 5 events/h associated with the typical symptoms of OSA (e.g., unrefreshing sleep, daytime sleepiness, fatigue or insomnia, awakening with a gasping or choking sensation, loud snoring, or witnessed apneas), or an obstructive RDI ≥ 15 events/h (even in the absence of symptoms). In addition to apneas and hypopneas that are included in the AHI, the RDI includes respiratory effort-related arousals (RERAs).

The scoring of respiratory events is defined in The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications, Version 2.3 (AASM Scoring Manual). However, it should be noted that there is variability in the definition of a hypopnea event. The AASM Scoring Manual recommended definition requires that changes in flow be associated with a 3% oxygen desaturation or a cortical arousal, but allows an alternative definition that requires association with a 4% oxygen desaturation without consideration of cortical arousals. Depending on which definition is used, the AHI may be considerably different in a given individual

Due to the high prevalence of OSA, there is significant cost associated with evaluating all patients suspected of having OSA with PSG (currently considered the gold standard diagnostic test). Further, there also may be limited access to in laboratory testing in some areas. HSAT, which has limitations, is an alternative method to diagnose OSA in adults, and may be less costly and more efficient in some populations

There are four levels of sleep studies as shown in table4.

Table:4

Level of study	Characteristics	Comments
Level 1	Attended in-laboratory full polysomnography (typically consists of EEG, EOG, chin EMG, airflow, respiratory effort, SaO_2, EKG, leg EMG, and body position)	Gold standard for the diagnosis of OSA
Level 2 (comprehensive portable polysomnography)	Unattended full polysomnography (monitors same parameters as Level 1 study including EEG, EOG, chin EMG, airflow, respiratory effort, SaO_2, EKG, leg EMG, and body position)	Validity of results may be limited by insufficient sleep time, absence of REM sleep, or absence of sleep in the supine position.
Level 3 (cardiorespiratory sleep studies, or modified portable sleep-apnea testing)	Cardiopulmonary studies consisting of 4 or more parameters (eg, airflow, SaO_2, respiratory effort, EKG, or body position)	Useful when there is a high pretest likelihood of OSA, Levels 1 or 2 studies are not readily available, and delay in testing is unacceptable. Might be useful for follow-up evaluation following therapy of patients previously diagnosed with OSA
Level 4 (continuous single or dual bioparameter recording)	Monitoring using only one or two parameters (eg, SaO_2, airflow or snoring)	Poor specificity, and sensitivity Not recommended for diagnosis of OSA

CLINICAL PRACTICE RECOMMENDATIONS:

Diagnostic testing for OSA should be performed in conjunction with a comprehensive sleep evaluation and adequate follow-up

OSA is one of many medical conditions that may be the cause of sleep complaints and other symptoms. Therefore, diagnostic testing for OSA is best carried out after a comprehensive sleep evaluation. The clinical evaluation for OSA should include a thorough sleep history and a physical examination that includes the respiratory, cardiovascular, and neurologic systems. The examiner should pay particular attention to observations regarding snoring, witnessed apneas, nocturnal choking or gasping, restlessness, and excessive sleepiness. It is also important that other aspects of a sleep history be collected, as many patients suffer from more than one sleep disorder or present with atypical sleep apnea symptoms. In addition, medical conditions associated with increased risk for OSA, such as obesity, hypertension, stroke, and congestive heart failure should

be identified. The general evaluation should serve to establish a differential diagnosis, which can then be used to select the appropriate test(s). Follow-up, under the supervision of a sleep medicine physician, ensures that study findings and recommendations are relayed appropriately; and that appropriate expertise in prescribing and administering therapy is available to the patient.

This pathway should include the following elements: a focused evaluation of sleep apnea performed by a clinical provider, and use of tools or questionnaires that capture clinically important information that is reviewed by a sleep medicine physician prior to testing. Following testing, a comprehensive sleep evaluation and follow up under the supervision of a sleep medicine physician should be completed.

- **Polysomnography is the standard diagnostic test for the diagnosis of OSA in adult patients in whom there is a concern for OSA based on a comprehensive sleep evaluation.**

Misdiagnosing patients can lead to significant harm due to lost benefits of therapy in those with OSA, and the prescription of inappropriate therapy in those without OSA. As discussed in the recommendations below, sleep apnea-focused questionnaires and clinical prediction rules lack sufficient diagnostic accuracy, and therefore direct measurement of SDB is necessary to establish a diagnosis of OSA. PSG is widely accepted as the **gold standard test** for diagnosis of OSA. Further, this test has traditionally been used as the gold standard for comparison to other diagnostic tests, including HSAT (Home Sleep Apnea Testing). Besides the diagnosis of OSA, PSG can identify co-existing sleep disorders, including other forms of sleep-disordered breathing. In some cases, and within the appropriate context, the use of HSAT as the initial sleep study may be acceptable, as discussed in the recommendations below. However, PSG should be used when HSAT results do not provide satisfactory post-test probability of confirming or ruling out OSA.

Recommendation 1: We recommend that clinical tools, questionnaires and prediction algorithms not be used to diagnose OSA in adults, in the absence of polysomnography or home sleep apnea testing. (STRONG)

Clinical prediction algorithms may be used in sleep clinic patients with suspected OSA, but are not necessary to establish the need for PSG or HSAT and further are not sufficient to substitute

for PSG or HSAT. In non-sleep clinic settings, these tools may be more helpful to identify patients who are at increased risk for OSA, but this was beyond the scope of this guideline.

Evaluation with a clinical tool, questionnaire or prediction algorithm may be less burdensome to patients and clinicians than HSAT or PSG; however, their low levels of accuracy make them poor diagnostic tools.

Berlin Questionnaire: The Berlin Questionnaire consists of eleven questions divided into three categories to classify the patient as high or low risk for OSA

Overall, the Berlin Questionnaire produced a large number of false negative results, thereby limiting its utility as an instrument to diagnose patients with OSA. Specifically, when assessing the performance of the Berlin Questionnaire in identification of subjects with an AHI cutoff of ≥ 5, the pooled sensitivity was 0.76 (95% CI: 0.72 to 0.80), while the pooled specificity was 0.45 (95% CI: 0.34 to 0.56).

Furthermore, the questionnaire had suboptimal accuracy, ranging from 56% to 70%; accuracy became progressively more compromised with consideration of higher OSA severity thresholds

The quality of evidence for the use of the Berlin Questionnaire was low after being downgraded due to either heterogeneity, indirectness, or imprecision.

Epworth Sleepiness Scale: The Epworth Sleepiness Scale (ESS) is a self-reported questionnaire involving eight questions to assess the propensity for daytime sleepiness or dozing.

The overall results indicate that the ESS had a large number of false negative results limiting its utility for the diagnosis of OSA. When considering an AHI of ≥ 5, the ESS revealed a range of sensitivity of 0.27–0.72 and specificity of 0.50–0.76. The ESS demonstrated an accuracy ranging from 51% to 59% for the AHI ≥ 5 cutoff. Therefore, the ESS had a high number of false negative results (range of 244 to 635 per 1,000 patients; assuming a prevalence of 87%).

STOP-BANG Questionnaire: The STOP-BANG questionnaire is an OSA screening tool consisting of four yes/no questions and four clinical attributes

The overall findings reveal that the STOP-BANG questionnaire had high sensitivity, but low specificity for the detection of OSA. These findings became more pronounced when higher levels of OSA category cutoffs were considered.

Benefits Versus Harms: These clinical tools, questionnaires and prediction algorithms carry the risk of not capturing the diagnosis of OSA when indeed OSA is present. Given the downstream effects of false negative diagnostic results, this would translate into high levels of OSA-related decrements in QOL, morbidity, and mortality due to undiagnosed and untreated OSA. On the other hand, false positive results would result in unnecessary testing and treatment for sleep apnea. Therefore, the TF determined that the potential harms outweigh the potential benefits of using clinical tools, questionnaires and prediction algorithms alone to diagnose OSA

Home Sleep Apnea Testing for the Diagnosis of Obstructive Sleep Apnea in Adults

Recommendation 2: We recommend that polysomnography, or home sleep apnea testing with a technically adequate device, be used for the diagnosis of OSA in uncomplicated adult patients presenting with signs and symptoms that indicate an increased risk of moderate to severe OSA. (STRONG)

Recommendation 3: We recommend that if a single home sleep apnea test is negative, inconclusive or technically inadequate, polysomnography be performed for the diagnosis of OSA. (STRONG)

Remarks: The following remarks are based on specifications used by studies that support these recommendation statements:

An uncomplicated patient is defined by the absence of: 1. Conditions that place the patient at increased risk of non-obstructive sleep-disordered breathing (e.g., central sleep apnea, hypoventilation and sleep related hypoxemia). Examples of these conditions include significant cardiopulmonary disease, potential respiratory muscle weakness due to neuromuscular conditions, history of stroke and chronic opiate medication use. 2. Concern for significant non-respiratory sleep disorder(s) that require evaluation (e.g., disorders of central hypersomnolence, parasomnias, sleep related movement disorders) or interfere with accuracy of HSAT (e.g., severe insomnia). 3. Environmental or personal factors that preclude the adequate acquisition and interpretation of data from HSAT.

An increased risk of moderate to severe OSA is indicated by the presence of excessive daytime sleepiness and at least two of the following three criteria: habitual loud snoring, witnessed apnea or gasping or choking, or diagnosed hypertension. HSAT is to be administered under the supervision of a sleep medicine physician. A single HSAT recording is conducted over at least one night. A technically adequate HSAT device incorporates a minimum of the following sensors:

nasal pressure, chest and abdominal respiratory inductance plethysmography, and oximetry; or else PAT with oximetry and actigraphy. For additional information regarding HSAT sensor requirements, refer to The AASM Manual for the Scoring of Sleep and Associated Events. A technically adequate diagnostic test includes a minimum of 4 hours of technically adequate oximetry and flow data obtained during a recording attempt that encompasses the habitual sleep period.

Finally, use of HSAT to diagnose OSA has been shown to provide adequate clinical outcomes and efficiency of care when performed with adequate clinical and technical expertise, using specific types of HSAT devices, in an appropriate patient population, and within an appropriate management pathway. Use of HSAT in other contexts may not provide similar benefit, and therefore the recommendations for the use of HSAT are limited. On the other hand, unstudied or understudied contexts could exist in which HSAT may provide benefit to a patient.

CPAP Adherence: Six RCTs evaluated CPAP adherence (mean hours of use per night); meta-analysis found no significant difference between the two assessment pathways. When determining adherence by number of nights with greater than 4 hours of use, meta-analysis of five RCTs found a clinically insignificant trend towards increased CPAP adherence in the HSAT arm versus the PSG arm. The quality of evidence for CPAP adherence was moderate to high across different AHI cutoffs after being downgraded due to imprecision. The TF determined that the overall quality of evidence across AHI cutoffs was high.

Benefits Versus Harms: Use of HSAT may provide potential benefits to patients with suspected OSA. Such benefits could include convenience, comfort, increased access to testing, and decreased cost. HSAT can be performed in the home environment with fewer attached sensors during sleep. The availability of HSAT for diagnosis may improve access to diagnostic testing in resource-limited settings, or when the patient is unable to leave the home or healthcare setting for testing. In addition, HSAT may be less costly when used appropriately. These benefits must be weighed against the potential for harm. Harms could result from the need for additional diagnostic testing among patients with technically inadequate or inconclusive HSAT findings, or from misdiagnosis and subsequent inappropriate therapy or lack of therapy.

A single HSAT recording encompassing multiple nights may have potential advantages or drawbacks relative to only a single night of recording. For example, if multiple-night HSAT improved accuracy or resulted in fewer inconclusive or inadequate studies, patient outcomes or costs might improve. On the other hand, the potential for multiple-night recordings to increase cost and patient inconvenience must be considered. Insufficient evidence exists to support routine performance of more than a single night's recording for HSAT.

Diagnosis of Obstructive Sleep Apnea in Adults with Comorbid Conditions

Recommendation 4: We recommend that polysomnography, rather than home sleep apnea testing, be used for the diagnosis of OSA in patients with significant cardiorespiratory disease, potential respiratory muscle weakness due to neuromuscular condition, awake hypoventilation or suspicion of sleep-related hypoventilation, chronic opioid medication use, history of stroke or severe insomnia.

Summary

This recommendation is based on the limited data available regarding the validity of HSAT in patients with significant cardiorespiratory disease, neuromuscular disease with respiratory impairment, suspicion of hypoventilation, opioid medication use, history of stroke, or severe insomnia. The overall quality of evidence was very low due to imprecision, indirectness, and risk of bias.

PSG is the gold standard method for the diagnosis of OSA and other forms of sleep-disordered breathing. HSAT has not been adequately validated or demonstrated to provide favorable clinical outcomes and efficient care in the above patient populations, and may result in harm through inaccurate assessment of sleep-disordered breathing.

Benefits Versus Harms: Certain patient populations are at increased risk of having forms of SDB other than OSA (e.g., CSA, hypoventilation, and hypoxemia). These forms of SDB can cause significant morbidity and mortality if left untreated. HSAT has not been validated to diagnose some of these types of SDB (CSA, hypoventilation); therefore, the use of HSAT in populations at increased risk for SDB other than OSA increases the likelihood of not detecting these breathing disorders, which could lead to inadequate treatments, increased long-term healthcare costs, morbidity and mortality. In addition, the accuracy of HSAT has not been validated in patients with severe insomnia where it may be compromised leading to similar outcomes. Though the cost of

diagnostic PSG is higher than HSAT, however the benefits of increased accuracy, use of appropriate therapy, and improved clinical outcomes outweigh this factor. There are, however, instances where PSG cannot be performed for practical reasons (hospitalization, inability of patient to leave home setting or participate in PSG), and use of HSAT may be reasonable, as the alternative is to not addressing SDB at all.

DIAGNOSIS OF OBSTRUCTIVE SLEEP APNEA IN ADULTS USING A SPLIT-NIGHT VERSUS A FULL-NIGHT POLYSOMNOGRAPHY PROTOCOL

Recommendation 5: We suggest that, if clinically appropriate, a split-night diagnostic protocol, rather than a full-night diagnostic protocol for polysomnography be used in the diagnosis of OSA. (WEAK)

This recommendation is based on a split-night protocol that initiates CPAP titration only when the following criteria are met: (1) a moderate to severe degree of OSA is observed during a minimum of 2 hours of recording time on the diagnostic PSG, AND (2) at least 3 hours are available for CPAP titration.

A split-night study may be preferred relative to full-night PSG and PAP titration studies due to the convenience and cost savings of completing a diagnostic and titration study during one rather than two separate PSG studies. However, this needs to be balanced with the consequences of potentially inconclusive diagnostic or titration portions of the sleep study. If the diagnostic portion is inconclusive, a second PSG is needed. If the titration portion is inconclusive, a second PAP titration study, or the use of auto adjusting PAP may be needed. Based on clinical judgment, the majority of well-informed patients would choose the split-night protocol over a full-night protocol, when clinically appropriate and feasible, and that the benefits of a split-night diagnostic protocol in such circumstances outweigh the potential harms

Benefits Versus Harms: The split-night protocol, in comparison to a full-night baseline assessment followed by a separate PAP titration, has the potential to provide the needed diagnostic information and effective CPAP settings within the same recording. Potential disadvantages of the split-night study include insufficient diagnostic sampling (e.g., limited REM sleep time and limited supine time in those with difficulty initiating sleep), and insufficient time to ascertain appropriate CPAP treatment settings. Based on clinical judgment, the TF determined that there is low certainty that the benefits of a split-night study in comparison to full-night studies exceed the harms.

Patients' Values and Preferences:

When comparing the split-night study to the full-night study, existing data are consistent and demonstrate a high level of reproducibility of the standard AHI metric and effective identification of the optimal CPAP pressure. These data also suggest that the two approaches lead to similar follow-up CPAP adherence

REPEAT POLYSOMNOGRAPHY FOR THE DIAGNOSIS OF OBSTRUCTIVE SLEEP APNEA IN ADULTS

Recommendation 6: We suggest that when the initial polysomnogram is negative and there is still clinical suspicion for OSA, a second polysomnogram be considered for the diagnosis of OSA. (weak)

Summary

There was limited evidence from which to assess the efficacy of performing a repeat PSG when the initial PSG is negative. The recommendation is based on evidence from comparisons of a single-night PSG to two-nights of PSG for the diagnosis of OSA. These studies found no consistent differences overall in AHI scores, but potentially significant minorities of patients had results that were different in clinically meaningful ways on the two nights. The certainty in the evidence regarding night-to-night variability of AHI from the meta-analysis started as high, but there was limited evidence from which to assess the efficacy of single-night PSG versus two-night PSG in terms of diagnostic accuracy and clinical outcomes.

Benefits Versus Harms: A second night of PSG in symptomatic patients allows for the diagnosis of OSA in 8% to 25% of patients with initial false negative studies. Establishing a diagnosis of OSA in these patients allows for treatment that leads to improved symptom control (e.g., less daytime sleepiness), better QOL, and potentially decreased cardiovascular morbidity over time. However, routinely repeating a PSG in patients with an initial negative PSG has potential downsides. There is a risk that repeat testing could lead to false positive cases being identified, and unnecessarily treated. In addition, the routine use of a 2-night study protocol would cause inconvenience to the patient, increased utilization of resources and healthcare costs, and perhaps even delays in the care of other patients awaiting PSG. However, due to the increased likelihood of diagnosing symptomatic patients, and based on their clinical judgment, the TF determined that the benefits of a second PSG outweigh the harms; though the certainty that the benefits outweigh the harms is low.

For patients scheduled for upper airway surgery for snoring, there is currently insufficient evidence to determine if the diagnostic evaluation of OSA can decrease peri-operative risk and improve surgical outcomes. Because it has been established that questionnaires cannot be used to diagnose OSA, many sleep experts have followed previous guidelines recommending diagnostic testing to evaluate for OSA prior to performing surgery for snoring. Further research to evaluate this protocol would be useful.

While PSG remains the gold standard for the diagnosis of OSA, it involves cumbersome sensors and devices that, if minimized and less obtrusive, could make PSG more tolerable for patients. Newer technology that is less intrusive and more comfortable may influence patient preferences regarding diagnostic approaches. Split-night PSG testing, which may improve the efficiency of PSG, has not been adequately studied. The quality of evidence regarding split-night sleep studies is low and additional research is needed to better determine its overall impact on patient outcomes. Past research often utilized outmoded testing methodology (e.g., they did not use nasal pressure cannulas) or outdated scoring criteria, limiting its relevance. There is also a lack of data on the utility of split-night testing in patients with significant underlying cardiopulmonary disease. Finally, the cost-effectiveness of split-night studies warrants further exploration

MANAGEMENT OF OSA:

Obstructive sleep apnea should be managed with a multi-faceted approach, focusing on 1)patient education 2)adjunctive measures including weight management, behavioral changes and 3)specific treatment for the disease.

1) PATIENT EDUCATION:

Patient education should be an integral component of OSA management.
The sleep specialist should have a detailed discussion on the risk factors, pathophysiology, natural course, clinical consequences and treatment options of OSA with all patients. The discussion should be tailored to the individual, focusing on patient related factors such as weight, co-morbid conditions, expectations, and should be based on the severity of their OSA as quantified by objective, accurate sleep testing. Patient education is associated with better compliance with OSA treatment with positive airway pressure, decreased disturbance related to PAP therapy and improved overall quality of life in OSA patients on PAP. Hence, a multi-disciplinary approach for education, involving the sleep specialist, primary care physician and ancillary health staff, should be actively pursued.

2) GENERAL ADJUNCTIVE MEASURES:

Weight and behavior management should be part of the general management of OSA patients.

Weight Management

Weight loss should be part of the management of overweight patients with OSA.

70 % patients are obese. OSA Prevalence in obese men & women is about 40%.
Higher BMI is associated with higher prevalence.

10% increase in body weight = 30% increase in OSA severity

OSA patients who are overweight or obese (BMI equal or greater than 25 kg/m2) should be encouraged to lose weight. Those whose weight is in the acceptable range should be encouraged to maintain their weight and counseled against weight gain.

Weight loss, via "medical" (lifestyle changes with dietary intervention coupled with exercise) or surgical means, can lead to a diminution in the severity of OSA, with improvement in Apnea Hypopnea Index and oxygen desaturation. In addition, weight loss has significant further health benefits in overweight individuals, related to the association between cardiovascular, metabolic and malignant diseases and obesity.

Conversely, weight gain is associated with a worsening of the severity of sleep disordered breathing. OSA patients who are within their acceptable weight range should be commended and encouraged to maintain their weight.

Weight loss should not be used as the primary treatment for significant OSA.

The complete cure rate of OSA with dietary intervention and weight loss alone is low. A significant proportion of OSA patients continue to have residual obstructive respiratory events despite losing weight. Hence, weight loss alone cannot be recommended as the primary therapy for OSA. However weight loss do have some impact on reduction of AHI. 1% reduction in weight loss is associated with 3% change in AHI. 10% reduction leads to 26% reduction in AHI and more effective in patient with BM1 > 35mg/kg2

A repeat titration study may be considered in OSA patients with a significant weight change.

PAP requirements can change with a significant alteration in a patient's weight. This may lead to a different PAP requirement for the patient. When auto-titrating PAP (APAP) therapy is being used for treatment, the machine will automatically adjust delivered PAP to meet the new requirements (unless the required PAP falls out of the machine's set limits); however, for patients on fixed CPAP, a repeat titration study (or switch over to an APAP) may be needed, to ascertain ideal PAP for treatment.

Behavior Management

Sedatives, narcotics and hypnotics, including alcohol, should be used with caution or avoided in OSA patients

Drugs that have the potential to induce respiratory depression should be used with extreme caution in patients with OSA. A few trials have not shown significant deterioration of OSA severity (as measured by the oxygen desaturation and apnea-hypogea indices) with these medicines; however, these were mostly small scale studies of short duration and less than robust methodology. Minimum oxygen saturations, however, were found to be lower with some of the sedative/hypnotic and opiates.

Alcohol use is associated with the risk of developing OSA and is known to worsen existing OSA. Smoking and Alcohol should be avoided also Sedative hypnotics, barbiturates and narcotic should be avoided as they contribute to upper airway dysfunction.

Patients should not drive or operate heavy machinery when sleepy or tired

Untreated OSA patients are more prone to motor vehicle collisions and workplace accidents than those without OSA. OSA should be treated to decrease the risk of these accidents and patients should be advised against driving or operating heavy vehicles, especially, if they are tired or sleepy.

Side sleeping can be considered as adjunctive therapy for OSA in certain situations

Obstructive respiratory events worsen in the supine posture during sleep. Side sleeping leads to improvement in respiratory disturbance indices. However, the reduction in obstructive events with postural therapy is variable, and, hence, is generally not recommended as sole treatment for significant OSA.

Body Positioning

Sleeping with head and trunk elevated 30 to 60 degree improve respiratory disturbance. 30 degree elevation improves better than lateral Position.

3) AIRWAY-SPECIFIC TREATMENT MEASURES:

Indications for treatment

Moderate to severe OSA should be treated

OSA, especially untreated moderate and severe sleep apnea (an apnea-hypopnea or respiratory disturbance index of 15/hour or more), is a significant risk factor for cardiovascular morbidity and

mortality. A consistent association between OSA and cardiovascular diseases, such as systemic arterial hypertension, coronary artery disease, heart failure, arrhythmias and strokes, has been observed across multiple studies. Treatment of OSA in this population is hence strongly recommended.

Treatment of mild OSA should be considered if associated with functional impairment or co-morbid cardiovascular or mood disorders

PAP therapy brings about improvement in excessive sleepiness and sleep-related quality of life. Impairment in sleep and daytime functioning linked with snoring, nocturnal choking, sleep disturbances, nocturia, morning headaches, daytime fatigue and lost productivity are alleviated with PAP treatment. Other than cardiovascular disease, OSA has also been linked with metabolic disorders, depression, and impairment of cognition and functioning. Treatment of OSA, even when mild, should be considered when accompanied by these comorbid conditions or symptoms.

Positive Airway Pressure Therapy for OSA

PAP should be considered first-line therapy for OSA in most patients

Positive airway pressure is effective in treating OSA. It is superior to oral appliances in treating moderate to severe OSA and is associated with less morbidity when compared to the surgeries that are most successful for OSA treatment. As such, it should be considered as first-line therapy for most OSA patients.

However, there is a significant proportion of patients who are unwilling to use or unable to tolerate PAP therapy. In these situations, alternative treatment - such as oral appliances, especially for mild OSA; surgery and hypoglossal nerve stimulation device for more severe disease - should be used.

CPAP or autoPAP are recommended over BiPAP in the routine initial treatment of OSA

Bilevel positive airway pressure (BPAP) is perceived to be more comfortable than CPAP because it lowers pressures during expiration, making it easier for patients to exhale. However, this has not been objectively demonstrated, with similar adherence rates to CPAP when compared to BPAP for OSA. Moreover, CPAP was found to be equivalent to BPAP in improving quality of sleep, sleep-related quality of life, excessive sleepiness and lowering of AHI.

Newer CPAP devices, with their modified pressure profile technology which lowers positive airway pressure during exhalation, mostly nullify the advantage of BPAP over CPAP; in addition, they are less costly than BiPAP. However, in situations where higher PAP are needed (typically above 20 cmH2O), which are beyond the capability of most CPAP or APAP machines to generate, BPAP is needed for therapy. BiPAP may also have a role in patients who are unable to adhere to CPAP or APAP therapy.

APAP and CPAP have been found to have similar efficacy and clinical outcomes in treating OSA. Either can be used when initiating treatment for OSA. CPAP is generally cheaper than APAP, whereas APAP is advantageous in situations where there might be a change in pressure

requirement for OSA treatment, e.g. weight change, alcohol consumption, different body positioning, nasal blockage.

PAP therapy can be initiated at home with an autoPAP or with CPAP after an in-lab PAP titration. It should be noted that this recommendation does not apply to patients with certain coexisting medical problems (e.g. heart failure, COPD, BMI > 40): in-lab PAP titration is suggested in these scenarios prior to starting home PAP.

Factors that cause patient discomfort with PAP therapy should be addressed

Nasal blockade or dryness, poor mask fit and air leak related to use of PAP interface can lead to patient discomfort and potentially affect adherence. These factors should be inquired about and addressed if present during follow-up visits.

The use of a heated humidifier with PAP has been shown to improve nasopharyngeal symptoms and improve patient comfort. These symptoms include oropharyngeal and nasal dryness, nasal congestion and discharge, epistaxis, microsomia, sinus pain or headaches, sore throat and dysphonia. Use of heated humidifier (HH) should be considered in patients reporting such complaints. A trial of nasal steroids can also be considered in patients exhibiting these symptoms. It should be noted, however, that HH use has not been associated with better adherence to PAP therapy.

Mask selection is important in ensuring a good fit and seal, minimizing discomfort and air leak. Use of nasal PAP interface improves patient comfort and, potentially, adherence rates when compared to Oro-nasal masks.

Oral Appliances for OSA

Oral appliances can be used for treatment of mild to moderate OSA

Oral appliances (OAs) increase the cross-sectional diameter of the upper airway and improve its patency by either advancing the jaw (mandibular repositioning device) or preventing posterior collapse of the tongue (tongue retaining device).
These devices also improve the muscle tone of the upper airway, thereby decreasing collapsibility.

OAs are not as effective in treating OSA as PAP therapy. They decrease obstructive respiratory events to a lesser extent than PAP; however, this diminution is generally sufficient for successful treatment of mild to moderate OSA. OAs can hence be used as primary therapy in this population of OSA patients, especially if patients are intolerant to PAP or prefer alternate treatment. Generally, adherence to OAs is better than that for PAP therapy.

Oral appliances for OSA patients should be custom-made by a qualified dentist

OAs should be customized, and preferably, titratable. Patients should be evaluated by a dental professional who is qualified to assess and treat patients with OSA. Patients need to be evaluated whether they will benefit from OA (a thorough examination of oral structures, temporo-mandibular joints and surrounding tissue needs to be undertaken by the dentist to determine candidacy) prior to the manufacture of customized OAs.

Adequacy of treatment by oral appliances should be ascertained by follow-up sleep testing and periodic follow-up

A follow-up sleep test (in-lab or at home) should be performed with the OA in place once the device has been titrated to its final, optimal fit. This is to ensure that the OA is achieving its desired therapeutic effect. Patients should also be followed periodically by the sleep specialist and dental professional to ensure that the device is fitting well and for adequacy of treatment and resolution of symptoms.

Surgery for OSA

Airway surgery can be considered for OSA patients intolerant of other modalities

More than twenty-five surgical modalities have been utilized for OSA treatment. Results are quite variable for different procedures. Only tracheostomies and maxilla-mandibular advancement have shown consistently successful results. Due to the associated morbidity and small risk of mortality with these procedures, they are generally reserved for patients with severe OSA who have failed or cannot tolerate PAP or other modalities. Multi-level surgery, radiofrequency ablation and palatal implants have variable success rates and can be tried in milder OSA. As surgery is associated with potentially higher rates of morbidity and mortality, it is considered as second line therapy behind PAP and oral appliances.

Patients undergoing airway surgery for OSA should have a follow up sleep study

Due to the variable success rates and cases of relapse after surgery, follow-up objective testing, to ascertain cure, is recommended after a reasonable period to allow healing. Typically, testing is performed a few weeks after the procedure. Patients should also be monitored clinically for recurrence of symptoms.

Hypoglossal Nerve Stimulation for OSA

Hypoglossal nerve stimulator device can be used in a selected group of patients

Patients with moderate-to-severe OSA who are intolerant to PAP therapy can be treated with an implantable hypoglossal nerve stimulator (HNS) device. Patients most likely to benefit from HNS are those with a BMI < 35 kg/m^2, an AHI between 20-50 events/hour (with a non-supine AHI > 10 events/hour), and non-concentric retro-palatal airway collapse on drug-induced sleep endoscopy. Obstructive respiratory and oxygen desaturation events decrease by about two-third with HNS use, with an average decrease in AHI by 21 events/hour of sleep. HNS should be placed by an operator experienced in performing this procedure.

References:

1. Buchanan A, Cohen R, Looney S, Kalathingal S, Rossi S D. Cone-beam CT analysis of patients with obstructive sleep apnea compared to normal controls. Imaging Science in Dentistry 2016; 46: 9-16 http://dx.doi.org/10.5624/isd.2016.46.1.9

2. https://www.erswhitebook.org/chapters/sleep-breathing-disorders/

3. Saraç S, Afşar GÇ, Oruç Ö, Topçuoğlu ÖB, Saltürk C, Peker Y. Impact of Patient Education on Compliance with Positive Airway Pressure Treatment in Obstructive Sleep Apnea. Med Sci Monit. 2017 Apr 13;23:1792-1799.

4. Hu ST, Yu CC, Liu CY, Tsao LI. The effects of integrated nursing education on quality of life and health-related outcomes among obstructive sleep apnea patients receiving continuous positive airway pressure therapy. Sleep Breath. 2017 Dec;21(4):845-852.

5. Mitchell LJ, Davidson ZE, Bonham M, O'Driscoll DM, Hamilton GS, Truby H. Weight loss from lifestyle interventions and severity of sleep apnoea: a systematic review and meta-analysis. Sleep Med. 2014;15(10):1173-1183.

6. Greenburg DL, Lettieri CJ, Eliasson AH. Effects of surgical weight loss on measures of obstructive sleep apnea: a meta-analysis. Am J Med. 2009;122(6):535-542.

7. Buchwald H, Avidor Y, Braunwald E, et al. Bariatric surgery: a systematic review and meta-analysis. JAMA. 2004;292(14): 1724-1737.

8. Newman AB, Foster G, Givelber R, Nieto FJ, Redline S, Young T. Progression and regression of sleep-disordered breathing with changes in weight: the Sleep Heart Health Study. Arch Intern Med. 2005;165:2408–13

9. Foster GD, Borradaile KE, Sanders MH, et al. A randomized study on the effect of weight loss on obstructive sleep apnea among obese patients with type 2 diabetes: the Sleep AHEAD study. Arch Intern Med. 2009;169(17):1619-1626. 34.

10. Tuomilehto H, Seppä J, Uusitupa M, Tuomilehto J, Gylling H; Kuopio Sleep Apnea Group. Weight reduction and increased physical activity to prevent the progression of obstructive sleep apnea: a 4-year observational postintervention follow-up of a randomized clinical trial [corrected]. JAMA Intern Med. 2013;173(10):929-930. 36.

11. Tuomilehto HP, Seppa JM, Partinen MM, et al. Lifestyle intervention with weight reduction: first-line treatment in mild obstructive sleep apnea. Am J Repir Crit Care Med. 2009;179(4):320-327. 37.

12. Kuna ST, Reboussin DM, Borradaile KE, et al. Long-term effect of weight loss on obstructive sleep apnea severity in obese patients with type 2 diabetes. Sleep. 2013;36(5):641-649A.

13. Lankford DA, Proctor CD, Richard R. Continuous positive airway pressure (CPAP) changes in bariatric surgery patients undergoing rapid weight loss. Obes Surg. 2005 Mar;15(3):336-41.

14. Mason M, Cates CJ, Smith I. Effects of opioid, hypnotic and sedating medications on sleep-disordered breathing in adults with obstructive sleep apnoea. Cochrane Database Syst Rev. 2015 Jul 14;(7):CD011090.

15. Simou E, Britton J, Leonardi-Bee J. Alcohol and the risk of sleep apnoea: a systematic review and meta-analysis. *Sleep Med*. 2018;42:38–46.

16. Scanlan MF, Roebuck T, Little PJ, Redman JR, Naughton MT. Effect of moderate alcohol upon obstructive sleep apnoea. Eur Respir J. 2000 Nov;16(5):909-13.

17. Ellen RL, Marshall SC, Palayew M, et al. Systematic review of motor vehicle crash risk in persons with sleep apnea. J Clin Sleep Med. 2009;5:573–81.

18. Garbarino S, Guglielmi O, Sanna A, Mancardi GL, Magnavita N. Risk of Occupational Accidents in Workers with Obstructive Sleep Apnea: Systematic Review and Meta-analysis. *Sleep*. 2016;39(6):1211–1218.

19. Strohl KP, Brown DB, Collop N, et al. An official American Thoracic Society Clinical Practice Guideline: sleep apnea, sleepiness, and driving risk in noncommercial drivers. An update of a 1994 Statement. *Am J Respir Crit Care Med*. 2013;187(11):1259–1266.

20. Ayas N, Skomro R, Blackman A, et al. Obstructive sleep apnea and driving: A Canadian Thoracic Society and Canadian Sleep Society position paper. *Can Respir J*. 2014;21(2):114–123.

21. Menon A, Kumar M. Influence of body position on severity of obstructive sleep apnea: a systematic review. ISRN Otolaryngol. 2013;2013:670381. Published 2013 Oct 8.

22. Punjabi NM, Caffo BS, Goodwin JL, Gottlieb DJ, Newman AB, O'Connor GT, Rapoport DM, Redline S, Resnick HE, Robbins JA, Shahar E, Unruh ML, Samet JM. Sleep-disordered breathing and mortality: a prospective cohort study. PLoS Med. 2009 Aug;6(8):e1000132.

23. Gottlieb DJ, Yenokyan G, Newman AB, O'Connor GT, Punjabi NM, Quan SF, Redline S, Resnick HE, Tong EK, Diener-West M, Shahar E. Prospective study of obstructive sleep apnea and incident coronary heart disease and heart failure: the sleep heart health study. Circulation. 2010 Jul 27;122(4):352-60.

24. Redline S, Yenokyan G, Gottlieb DJ, Shahar E, O'Connor GT, Resnick HE, Diener-West M, Sanders MH, Wolf PA, Geraghty EM, Ali T, Lebowitz M, Punjabi NM. Obstructive sleep apnea-hypopnea and incident stroke: the sleep heart health study. Am J Respir Crit Care Med. 2010 Jul 15;182(2):269-77.

25. Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. N Engl J Med. 2000 May 11;342(19):1378-84.

26. Cadby G, McArdle N, Briffa T, Hillman DR, Simpson L, Knuiman M, Hung J. Severity of OSA is an independent predictor of incident atrial fibrillation hospitalization in a large sleep-clinic cohort. Chest. 2015 Oct;148(4):945-952.

27. Giles TL, Lasserson TJ, Smith B, White J, Wright JJ, Cates CJ. Continuous positive airways pressure for obstructive sleep apnoea in adults: a Cochrane Collaboration Review. Etobicoke, Canada: John Wiley & Sons, Ltd; 2008. Issue 4, 1–103.

28. Rotenberg BW, Vicini C, Pang EB, Pang KP. Reconsidering first-line treatment for obstructive sleep apnea: a systematic review of the literature. J Otolaryngol Head Neck Surg. 2016;45:23.

29. Gay PC, Herold DL, Olson EJ. A randomized, double-blind clinical trial comparing continuous positive airway pressure with a novel bilevel pressure system for treatment of obstructive sleep apnea syndrome. Sleep. 2003;26(7):864–869.

30. Powell ED, Gay PC, Ojile JM, Litinski M, Malhotra A. A pilot study assessing adherence to auto-bilevel following a poor initial encounter with CPAP. J Clin Sleep Med. 2012;8(1):43–47.

31. Reeves-Hoche MK, Hudgel DW, Meck R, Witteman R, Ross A, Zwillich CW. Continuous versus bilevel positive airway pressure for obstructive sleep apnea. Am J Respir Crit Care Med. 1995;151(2 Pt 1):443–449.

32. Galetke W, Anduleit N, Richter K, Stieglitz S, Randerath WJ. Comparison of automatic and continuous positive airway pressure in a night-by-night analysis: a randomized, crossover study. Respiration. 2008;75(2):163–169.

33. Senn O, Brack T, Matthews F, Russi EW, Bloch KE. Randomized short-term trial of two autoCPAP devices versus fixed continuous positive airway pressure for the treatment of sleep apnea. Am J Respir Crit Care Med. 2003 Dec 15;168(12):1506-11.

34. Ip S, D'Ambrosio C, Patel K, et al. Auto-titrating versus fixed continuous positive airway pressure for the treatment of obstructive sleep apnea: a systematic review with meta-analyses. Syst Rev. 2012;1:20.

35. Patil SP, Ayappa IA, Caples SM, Kimoff RJ, Patel SR, Harrod CG. Treatment of Adult Obstructive Sleep Apnea with Positive Airway Pressure: An American Academy of Sleep Medicine Clinical Practice Guideline. J Clin Sleep Med. 2019 Feb 15;15(2):335-343

36. Rotenberg BW, Murariu D, Pang KP. Trends in CPAP adherence over twenty years of data collection: a flattened curve. J Otolaryngol Head Neck Surg. 2016;45(1):43.

37. Saraç S, Afşar GÇ, Oruç Ö, Topçuoğlu ÖB, Saltürk C, Peker Y. Impact of Patient Education on Compliance with Positive Airway Pressure Treatment in Obstructive Sleep Apnea. Med Sci Monit. 2017;23:1792–1799.
38. Budhiraja R, Parthasarathy S, Drake CL, Roth T, Sharief I, Budhiraja P, Saunders V, Hudgel DW. Early CPAP use identifies subsequent adherence to CPAP therapy. Sleep. 2007 Mar;30(3):320-4.
39. Aloia MS, Arnedt JT, Stanchina M, Millman RP. How early in treatment is PAP adherence established? Revisiting night-to-night variability. Behav Sleep Med. 2007;5(3):229-40.
40. Kribbs NB, Pack AI, Kline LR, et al. Objective measurement of patterns of nasal CPAP use by patients with obstructive sleep apnea. Am Rev Respir Dis. 1993;147(4):887–895.
41. 4Soudorn C, Muntham D, Reutrakul S, Chirakalwasan N. Effect of Heated Humidification on CPAP Therapy Adherence in Subjects With Obstructive Sleep Apnea With Nasopharyngeal Symptoms. Respir Care. 2016 Sep;61(9):1151-9.
42. Mador MJ, Krauza M, Pervez A, Pierce D, Braun M. Effect of heated humidification on compliance and quality of life in patients with sleep apnea using nasal continuous positive airway pressure. Chest. 2005 Oct;128(4):2151-8.
43. Charakorn N, Hirunwiwatkul P, Chirakalwasan N, Chaitusaney B, Prakassajjatham M. The effects of topical nasal steroids on continuous positive airway pressure compliance in patients with obstructive sleep apnea: a systematic review and meta-analysis. Sleep Breath. 2017 Mar;21(1):3-8.

44. Borel JC, Tamisier R, Dias-Domingos S, Sapene M, Martin F, Stach B, Grillet Y, Muir JF, Levy P, Series F, Pepin JL; Scientific Council of The Sleep Registry of the French Federation of Pneumology (OSFP). Type of mask may impact on continuous positive airway pressure adherence in apneic patients. PLoS One. 2013 May15;8(5):e64382.
45. Rowland S, Aiyappan V, Hennessy C, Catcheside P, Chai-Coezter CL, McEvoy RD, Antic NA. Comparing the Efficacy, Mask Leak, Patient Adherence, and Patient Preference of Three Different CPAP Interfaces to Treat Moderate-Severe Obstructive Sleep Apnea. J Clin Sleep Med. 2018 Jan 15;14(1):101-108.
46. Chan AS, Sutherland K, Schwab RJ, Zeng B, Petocz P, Lee RW, Darendeliler MA,Cistulli PA. The effect of mandibular advancement on upper airway structure in obstructive sleep apnoea. Thorax. 2010 Aug;65(8):726-32.
47. Sutherland K, Vanderveken OM, Tsuda H, Marklund M, Gagnadoux F, Kushida CA, Cistulli PA. Oral appliance treatment for obstructive sleep apnea: an update. J Clin Sleep Med. 2014 Feb 15;10(2):215-27.
48. Schwartz M, Acosta L, Hung YL, Padilla M, Enciso R. Effects of CPAP and mandibular advancement device treatment in obstructive sleep apnea patients: a systematic review and meta-analysis. Sleep Breath. 2018 Sep;22(3):555-568.
49. Ramar K, Dort LC, Katz SG, Lettieri CJ, Harrod CG, Thomas SM, Chervin RD. Clinical Practice Guideline for the Treatment of Obstructive Sleep Apnea and Snoring with Oral Appliance Therapy: An Update for 2015. J Clin Sleep Med. 2015 Jul 15;11(7):773-827.
50. Ramar K, Dort LC, Katz SG, Lettieri CJ, Harrod CG, Thomas SM, Chervin RD. Clinical Practice Guideline for the Treatment of Obstructive Sleep Apnea and Snoring with Oral Appliance Therapy: An Update for 2015. J Clin Sleep Med. 2015 Jul 15;11(7):773-827.
51. Strollo PJ Jr, Soose RJ, Maurer JT, de Vries N, Cornelius J, Froymovich O, Hanson RD, Padhya TA, Steward DL, Gillespie MB, Woodson BT, Van de Heyning PH, Goetting MG, Vanderveken OM, Feldman N, Knaack L, Strohl KP; STAR Trial Group. Upper-airway stimulation for obstructive sleep apnea. N Engl J Med. 2014 Jan 9;370(2):139-49.
52. Strollo PJ Jr, Gillespie MB, Soose RJ, Maurer JT, de Vries N, Cornelius J, Hanson RD, Padhya TA, Steward DL, Woodson BT, Verbraecken J, Vanderveken OM, Goetting MG, Feldman N, Chabolle F, Badr MS, Randerath W, Strohl KP; Stimulation Therapy for Apnea Reduction (STAR) Trial Group. Upper Airway Stimulation for Obstructive Sleep Apnea: Durability of the Treatment Effect at 18 Months. Sleep. 2015 Oct 1;38(10):1593-8.
53. Kompelli AR, Ni JS, Nguyen SA, Lentsch EJ, Neskey DM, Meyer TA. The outcomes of hypoglossal nerve stimulation in the management of OSA:A systematic review and meta-analysis. World J Otorhinolaryngol Head Neck Surg. 2018 Sep 25;5(1):41-48.