JAMA | Review

Diagnosis and Management of Obstructive Sleep Apnea
A Review

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IMPORTANCE Obstructive sleep apnea (OSA) affects 17% of women and 34% of men in the US and has a similar prevalence in other countries. This review provides an update on the diagnosis and treatment of OSA.

OBSERVATIONS The most common presenting symptom of OSA is excessive sleepiness, although this symptom is reported by as few as 15% to 50% of people with OSA in the general population. OSA is associated with a 2- to 3-fold increased risk of cardiovascular and metabolic disease. In many patients, OSA can be diagnosed with home sleep apnea testing, which has a sensitivity of approximately 80%. Effective treatments include weight loss and exercise, positive airway pressure, oral appliances that hold the jaw forward during sleep, and surgical modification of the pharyngeal soft tissues or facial skeleton to enlarge the upper airway. Hypoglossal nerve stimulation is effective in select patients with a body mass index less than 32. There are currently no effective pharmacological therapies. Treatment with positive airway pressure lowers blood pressure, especially in patients with resistant hypertension; however, randomized clinical trials of OSA treatment have not demonstrated significant benefit on rates of cardiovascular or cerebrovascular events.

CONCLUSIONS AND RELEVANCE OSA is common and the prevalence is increasing with the increased prevalence of obesity. Daytime sleepiness is among the most common symptoms, but many patients with OSA are asymptomatic. Patients with OSA who are asymptomatic, or whose symptoms are minimally bothersome and pose no apparent risk to driving safety, can be treated with behavioral measures, such as weight loss and exercise. Interventions such as positive airway pressure are recommended for those with excessive sleepiness and resistant hypertension. Managing asymptomatic OSA to reduce cardiovascular and cerebrovascular events is not currently supported by high-quality evidence.

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Obstructive sleep apnea (OSA) is characterized by recurrent episodes of partial or complete collapse of the upper airway during sleep, resulting in reduced (hypopnea) or absent (apnea) airflow lasting for at least 10 seconds and associated with either cortical arousal or a fall in blood oxygen saturation. OSA is present in approximately 25% of adults in the US and is a major cause of excessive sleepiness, contributing to reduced quality of life, impaired work performance, and increased motor vehicle crash risk.[1,2] OSA is associated with an increased incidence of hypertension, type 2 diabetes mellitus, atrial fibrillation, heart failure, coronary heart disease, stroke, and death.[3-6] OSA can be diagnosed with either home- or laboratory-based sleep testing, and effective treatments are available. This review provides an update on the epidemiology, pathophysiology, diagnosis, and management of OSA.

Discussion and Observations

Methods

We searched PubMed and Cochrane databases for English-language studies of the epidemiology, diagnosis, and management of adult OSA published from January 2010 to February 2020, and manually searched the references of selected articles for additional relevant articles. Emphasis was given to the selection of randomized clinical trials, systematic reviews, meta-analyses, and clinical practice guidelines and to articles with relevance to a general medical readership.

Epidemiology

The presence and severity of OSA are typically quantified by the apnea-hypopnea index (AHI), defined as the number of apneas plus hypopneas per hour of sleep (or hour of recording for home tests). The prevalence of OSA varies depending on the definition of hypopneas. Using the conservative definition, requiring a 4% decline in blood oxygen saturation to define hypopnea, the Wisconsin Sleep Cohort Study estimated that 17.4% of women and 33.9% of men in the US aged 30 to 70 years had at least mild OSA, defined as an AHI of 5 to 14.9 events per hour of sleep, while 5.6% of women and 13.0% of men had moderate (AHI of 15-29.9) or severe (AHI ≥30) OSA.[7] The prevalence of OSA increased by approximately 30% between 1990 and 2010, with absolute increases of 4.2% in women and 7.5% in men.[7] The prevalence of

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OSA increases with age and is approximately twice as common in men as in women. In the US, the prevalence of OSA is approximately 26.6% in men and 8.7% in women among individuals aged 30 to 49 years and approximately 43.2% in men and 27.8% in women among individuals aged 50 to 70 years.[7] This cohort was 96% non-Hispanic white.[7] A somewhat higher prevalence of OSA was reported by the Jackson Heart Sleep Study, which estimated that OSA prevalence among African American adults aged 50 to 80 years was 53.6%, with moderate to severe OSA in 20.4% of individuals.[8] In the Multi-Ethnic Study of Atherosclerosis, the prevalence of OSA in adults aged 54 to 93 years exceeded 60%, with moderate to severe OSA present in 30.3% of white individuals, 32.4% of African American individuals, 38.2% of Hispanic individuals, and 39.4% of participants of Chinese descent.[9] A similar prevalence of OSA exists in other high-income countries.[10-13] OSA is associated with overweight and obesity. Among individuals aged 30 to 49 years with a body mass index (BMI) less than 25, the prevalence of OSA among men is 7.0% and among women is 1.4%, compared with 44.6% among men and 13.5% among women with a BMI of 30 to 39.9.[7] The association of OSA with obesity and male sex diminishes with age.[7,14]

Pathophysiology

OSA is characterized by repetitive partial or complete collapse of the upper airway during sleep, resulting in episodic reduction (hypopnea) or cessation (apnea) of airflow despite respiratory effort. Contraction of upper airway dilator muscles is necessary to maintain airway patency during inspiration. The most important upper airway dilator muscle is the genioglossus muscle, which contracts with each inspiration to prevent posterior collapse of the tongue, assisted by the levator and tensor palatini muscles (advancing and elevating the soft palate) and the geniohyoid and stylopharyngeus muscles (opposing medial collapse of the lateral pharyngeal walls).[3] Most people with OSA have a narrow upper airway, typically caused by fat deposition in the parapharyngeal fat pads and pharyngeal muscles[15,16] or abnormalities in craniofacial structure (**Figure 1**). These abnormalities include both clinically evident anatomic abnormalities, such as micrognathia and retrognathia, or subtle radiographic findings, such as inferior positioning of the hyoid bone and shorter mandibular and maxillary length, which result in a small maxillomandibular volume.[2,17] The relative contribution of soft tissue and bony abnormalities to OSA differs among individuals and between populations; for example, for the same severity of OSA, Caucasian individuals tend to be more overweight, while Chinese individuals have more craniofacial bony restriction.[18] In the presence of a small pharyngeal airway, upper airway collapse is prevented when an individual is awakened by the activity of pharyngeal dilator muscles. A decrease in both basal and compensatory dilator muscle tone during sleep permits airway collapse.[3,19]

Obstructive apneas and hypopneas result in large changes in intrathoracic pressure, intermittent hypoxemia, and arousal from sleep (**Figure 2**). Although these arousals generally do not wake the patient, this sleep fragmentation is the primary cause of excessive sleepiness in individuals with OSA. Intermittent hypoxemia, particularly with concomitant hypercapnia, activates the sympathetic nervous system and is the major contributor to both acute and chronic elevation of blood pressure (**Figure 3**).[3,4] Increased catecholamine levels decrease insulin sensitivity and, in animal models, promote pancreatic beta-cell apoptosis, suggesting a possible mechanism underlying the association of OSA with type 2 diabetes mellitus,[20] which persists after adjustment for demographic factors and BMI.[21] Repetitive episodes of hypoxemia increase reactive oxygen species, which may further contribute to vascular disease, metabolic abnormalities, and inflammation.[3]

Clinical Presentation

The most common symptom of OSA is unrefreshing sleep, with excessive sleepiness reported by up to 90% of patients with OSA referred to sleep clinics[22,23] (**Table 1**). Patients may also report fatigue, tiredness, or lack of energy.[24] In some studies, these symptoms are more common than sleepiness.[24] Excessive sleepiness is reported by 15% to 50% of people with OSA identified through general population screening.[7,12,13,25] While some patients experience awakenings accompanied by gasping or choking, awakenings without accompanying symptoms are more typical. A systematic review concluded that on history and physical examination, nocturnal gasping or choking is the most reliable indicator of OSA, while snoring is not specific.[26] A population study reported nocturia at least 2 times per night in 37.4% of individuals with an AHI of at least 20 per hour compared with 25.6% of those with an AHI of less than 20 per hour (adjusted odds ratio, 1.64 [95% CI, 1.03-2.55]).[27] Chronic morning headache (occurring at least half of days) is twice as common in individuals with OSA as in the general population.[28] These headaches, characterized by a bilateral pressure sensation, resolve within hours of awakening and are of unknown etiology. Nocturnal gastroesophageal reflux is approximately twice as common in patients with OSA as in the general population.[29] Difficulty falling asleep is unlikely to be caused by OSA.[30] Typical signs of OSA include habitual snoring, present in 50% to 60% of those with OSA, and witnessed apneas during sleep, present in 10% to 15% of those with OSA. The latter is twice as common as in those without OSA.[11,14,31] Recent studies estimate the prevalence of OSA at 73% to 82% in individuals with resistant hypertension,[32,33] 76% to 85% in individuals with atrial fibrillation,[34,35] 65% to 85% in individuals with type 2 diabetes,[36] 71% in individuals with stroke,[37] and 71% to 77% in patients undergoing bariatric surgery.[38,39]

Assessment and Diagnosis

Because of the high prevalence of OSA and patients often not reporting sleep problems to clinicians, the review of systems should include asking about snoring, breathing pauses at night, and excessive fatigue or sleepiness during the day (**Box**). Questionnaires available for assessing OSA risk include the Berlin Questionnaire,[40] developed for use in the primary care setting, and the STOP-Bang questionnaire,[41] developed for preoperative screening. The Epworth Sleepiness Scale[42] is widely used in both clinical practice and research to assess sleepiness, but has low sensitivity for OSA[43] (**Table 2**). There are no physical examination findings specific to OSA, although it is approximately twice as common in individuals who are overweight and 4 times as common in individuals with obesity compared with individuals without overweight or obesity.[7,10,12,13] Examination of the upper airway may identify anatomic abnormalities, such as tonsillar hypertrophy, macroglossia, or retrognathia, but normal upper airway examination findings do not exclude OSA. If the clinical evaluation suggests OSA, diagnostic confirmation requires overnight testing.

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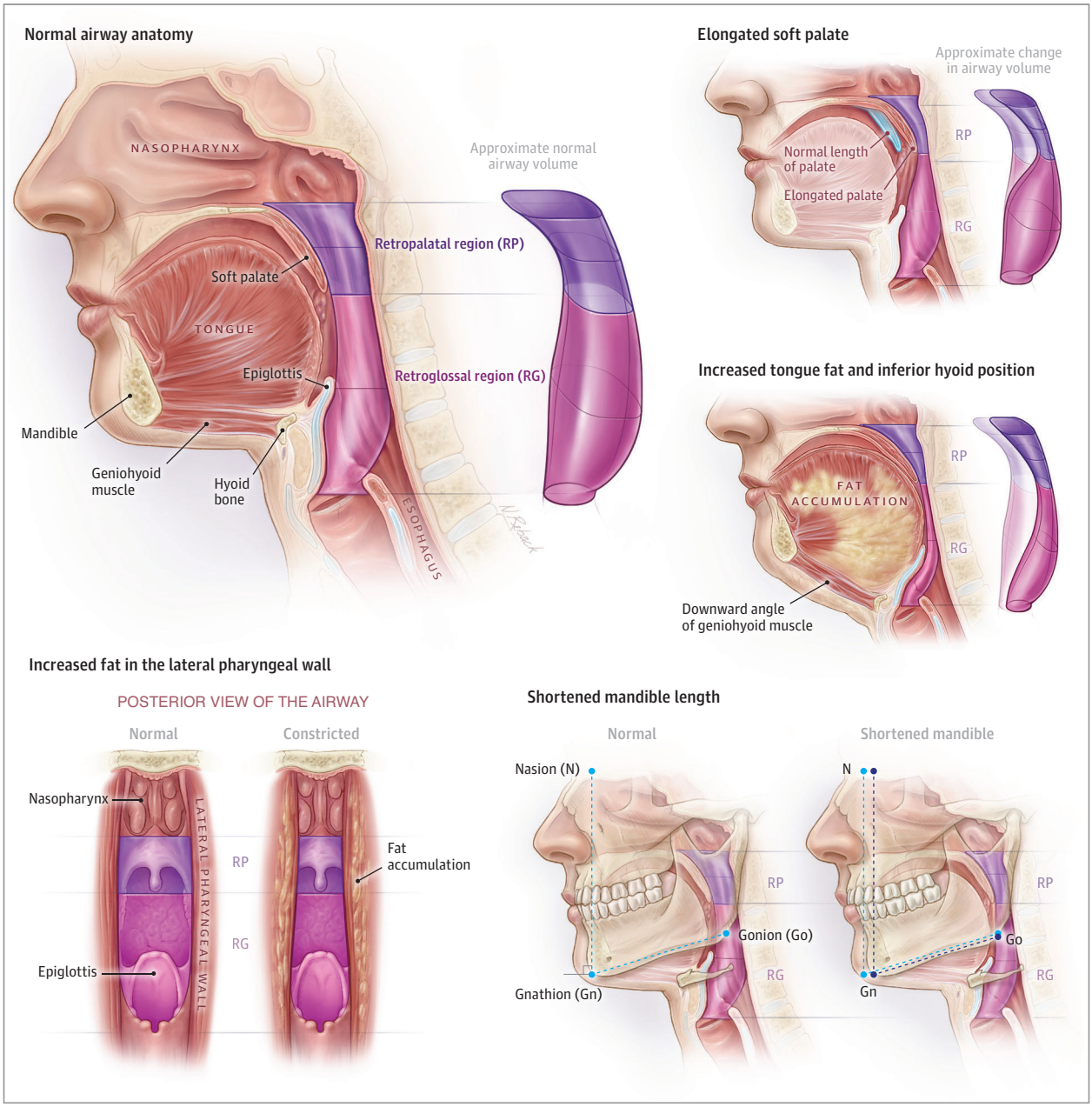
Figure 1. Anatomic Features Contributing to Obstructive Sleep Apnea (OSA)



Narrowing of the upper airway is common in patients with OSA. This can result from a long soft palate, enlargement of the tongue and pharyngeal wall, and a more inferior and posterior position of the hyoid bone, commonly due to fat deposition, or from skeletal features including mandibular retrognathia and a shorter mandibular or maxillary length.

Testing for OSA is recommended in any patient with unexplained excessive sleepiness, fatigue, or unrefreshing sleep. Testing should be considered in patients with unexplained nocturia, nocturnal gastroesophageal reflux, morning headache, or frequent nocturnal awakenings, particularly in the setting of snoring, witnessed nocturnal apneas, or overweight body habitus. Because of the absence of a clear treatment benefit in people without symptoms, the US Preventive Services Task Force does not recommend screening for OSA in asymptomatic people (Box).[45] However, screening may be appropriate in individuals whose occupation involves driving[46] or in patients with resistant hypertension.

The standard diagnostic test is laboratory-based polysomnography, during which both sleep and respiratory parameters are monitored (Table 2 and Figure 2).[47] A typical laboratory-based polysomnogram includes measures of (1) airflow through the nose using a nasal cannula connected to a pressure transducer or through the nose and mouth using a thermal sensor; (2) respiratory effort using thoracic and abdominal inductance bands; (3) oxygen hemoglobin

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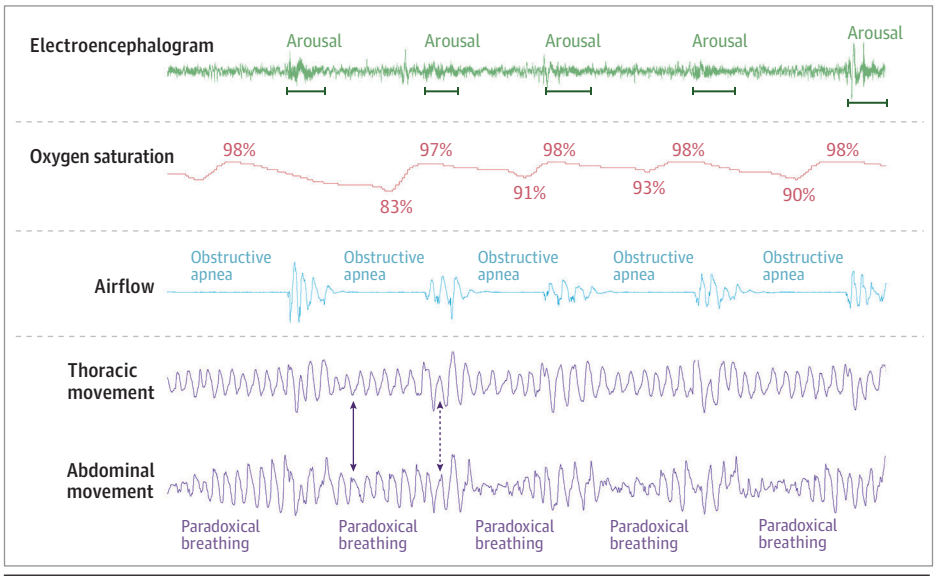
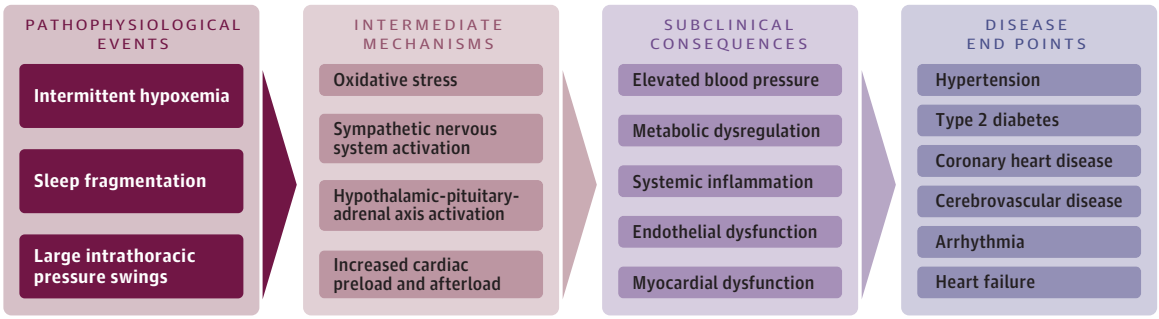
Figure 2. Polysomnogram Demonstrating Physiological Effects of Obstructive Apnea



A 5-minute polysomnographic tracing of obstructive sleep apnea events. With each obstructive apnea, the absence of airflow is accompanied by out-of-phase movement of the thorax and abdomen (solid arrow), known as *paradoxical breathing*, and by a decrease in oxygen saturation. Because oxygen saturation is measured by pulse oximetry at the finger, the nadir oxygen saturation is delayed relative to the apnea due to lung-to-finger circulation time. Electroencephalogram arousals terminate the obstructive events, with resumption of normal breathing (dotted arrow) and restoration of oxygen saturation to normal levels. Transition back to sleep after each arousal is associated with collapse of the upper airway and recurrent obstructive apnea.

Figure 3. Putative Causal Mechanisms of Obstructive Sleep Apnea–Related Cardiovascular and Metabolic Disease



Obstructive sleep apnea results in 3 proximate pathophysiological events: intermittent hypoxemia, sleep fragmentation, and large swings in intrathoracic pressure. These events initiate a cascade of interacting processes that contribute to adverse health outcomes. Intermittent hypoxemia, particularly in the presence of hypercapnia, causes elevation of sympathetic nervous system activity that persists during wakefulness. Arousal from sleep, due to increased respiratory effort against an obstructed airway and to hypoxemia and hypercapnia, also contributes to sympathetic activity and activation of the hypothalamic-pituitary-adrenal axis. Intermittent hypoxemia and reoxygenation result in production of reactive oxygen species. Both sympathetic activity and oxidative stress contribute to blood pressure elevation, metabolic dysregulation, systemic inflammation, and endothelial dysfunction. These abnormalities are likely precursors of clinical hypertension, type 2 diabetes, and coronary and cerebrovascular disease. Large intrathoracic pressure swings, which result from respiratory efforts against an obstructed upper airway, increase cardiac preload and afterload that, together with the effects of sympathetic activity, oxidative stress, inflammation, and gas exchange abnormalities, may contribute to heart failure and cardiac rhythm disturbances.

saturation by finger pulse oximetry; (4) snoring using a microphone affixed over the trachea or by filtering out low-frequency signals from the nasal cannula-pressure transducer system; (5) sleep stage and arousal using electroencephalogram, electrooculogram, and chin electromyogram; (6) electrocardiogram findings; (7) body position; and (8) leg movement. Laboratory-based testing is labor-intensive and inconvenient for the patient. The Medicare cost of laboratory-based testing is $621, approximately 5 times the cost of home sleep apnea testing.[48]

Home sleep apnea testing is increasingly used to diagnose OSA, and consists of measures of airflow, respiratory effort, and oxygen saturation, but not measures of sleep or leg movements. The sensors are self-applied by the patient at home following instruction from a technologist or via an instructional video. Home sleep apnea testing has both high sensitivity (79% [95% CI, 71%-86%]) and specificity (79% [95% CI, 63%-89%]) (Table 2), with values for area under the receiver operating characteristic curve exceeding 0.85.[44,45,49] However, in patients with a high prior probability of disease, as many as 25% to 50% of study results negative for OSA were false-negative.[50,51] Therefore, in patients with unexplained sleepiness and a high clinical suspicion of OSA, a negative home study result should be followed by laboratory-based polysomnography to exclude OSA and evaluate alternative causes of sleepiness. This approach to OSA diagnosis is accurate and cost-effective (Box).[45,52,53] Although practice guidelines recommend home sleep apnea testing only in the setting of a high prior probability of OSA and absence of significant cardiorespiratory disease or insomnia, high diagnostic accuracy has also been demonstrated in patients with only moderate suspicion of OSA or with comorbid obstructive lung disease or heart failure.[49,54,55]

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Table 1. Risk Factors and Clinical Features of Obstructive Sleep Apnea

Characteristic	Measure[a]
Risk factors	**Odds ratio**
Weight	
Overweight vs normal weight	2.3-3.4
Obese vs normal weight	4.0-10.5
Male sex (vs female)	1.7-3.0
Age (per 10-y increment)	1.4-3.2
Postmenopausal state in women	2.8-4.3
Enlarged upper airway soft tissues (eg, tonsils, adenoids, tongue)	Unknown
Craniofacial abnormalities (eg, retrognathia, micrognathia)	Unknown
Clinical symptoms and signs	**Prevalence, %**
Excessive sleepiness, fatigue, or unrefreshing sleep	73-90
Snoring most nights	50-60
Witnessed breathing pauses, choking, or gasping during sleep	10-15
Nocturia (2 or more times per night)	30
Nocturnal gastroesophageal reflux	50-75
Morning headache	12-18

[a] Odds ratios reflect the range of values reported from population-based cohort studies, excluding extreme values. Prevalence estimates are from population- or clinic-based patient samples referenced in the text.

OSA severity is typically quantified using the AHI. Based on expert consensus, an AHI less than 5 events per hour is considered normal, 5 to 14.9 is considered mild, 15 to 29.9 is considered moderate, and at least 30 is considered severe OSA.[56] Differences in how hypopneas are defined affect the AHI value,[57] and a lack of consistency in event definition complicates the interpretation of sleep test results and highlights the importance of considering symptoms and comorbid illnesses when making treatment decisions.

Treatment

Effective treatments for OSA include behavioral measures, medical devices, and surgery (**Table 3**). Behavioral measures include abstinence from alcohol, avoiding supine sleep position, regular aerobic exercise, and weight loss. In patients with positional OSA (ie, elevated AHI predominantly in the supine position), restricting sleep to side or prone position may be sufficient treatment.[58] There is no standard definition of positional OSA, although a commonly used definition includes an AHI that is at least 50% lower when sleeping nonsupine than when sleeping supine. Weight loss improves OSA[59,60] and should be recommended for all patients with overweight or obesity in conjunction with other therapies. It may be considered as the sole initial treatment in asymptomatic or minimally symptomatic patients. Lifestyle interventions, bariatric surgery, and weight loss medication are each associated with improved OSA severity.[61-63] In the Sleep AHEAD (Action for Health in Diabetes) study, 264 patients with overweight or obesity with type 2 diabetes mellitus and OSA were randomized to undergo a lifestyle intervention consisting of weight loss through diet and exercise or a diabetes education control. At the 1-year follow-up, the lifestyle intervention resulted in a 10.2-kg greater reduction in weight and a 9.7–event per hour greater reduction in AHI.[61] There is no apparent threshold amount of weight loss needed to improve OSA severity; greater weight loss is associated with greater benefit.[61-63]

Box. Commonly Asked Questions About Obstructive Sleep Apnea (OSA)

What is the most sensitive and specific question for identifying OSA?

"Do you snore" is the most sensitive and "Do you stop breathing during sleep" is the most specific question to identify a patient at risk for OSA.

Does every patient with overweight or obesity need to be referred for a sleep study?

Although overweight and obesity are strong risk factors for OSA, not every patient with overweight or obesity needs to undergo a sleep study. However, they should be questioned for OSA-related signs and symptoms. Most asymptomatic patients do not need to be referred for a sleep study.

Do patients need to spend a night in the sleep laboratory for diagnosis and management of OSA?

For most patients in whom OSA is suspected, the diagnosis can be made with a home sleep apnea test, in which a sleep apnea monitor is worn overnight in the patient's home. If OSA is confirmed by the home test, positive airway pressure (PAP) therapy can usually be initiated at home using an automatic titrating PAP device. If there is a high suspicion for OSA and the home test findings are negative for OSA, laboratory-based polysomnography should be recommended.

What are the benefits of managing OSA?

Daytime sleepiness, fatigue, quality of life, and blood pressure have all been documented to improve with management of OSA. Current evidence suggests that treatment does not reduce the risk of cardiovascular disease, stroke, or metabolic abnormalities in asymptomatic patients.

What should a patient with OSA do if they need to have surgery?

Patients with known OSA should inform all clinicians involved in their perioperative care, including their surgeon and anesthesiologist, of their OSA diagnosis. Patients using PAP should continue this therapy in the perioperative period. Patients with known or suspected OSA should be monitored closely during the perioperative period, and the use of opiate analgesics should be minimized or avoided if possible.

Are there nonsurgical alternatives for patients who are unable to tolerate PAP therapy?

Mandibular advancement devices, weight loss, exercise, avoiding sleep in the supine position, and abstaining from alcohol can be beneficial for patients who are unable to tolerate PAP therapy. There are no medications currently approved for the management of OSA.

Exercise may improve OSA independently of weight loss.[64-67] There is a dose-dependent association of exercise with lower prevalence of OSA. Compared with individuals who were not engaging in vigorous exercise, the odds ratio for moderate to severe OSA was 0.62 for individuals who exercised 1 to 2 hours per week, 0.39 for those who exercised 3 to 6 hours per week, and 0.31 for those who exercised at least 7 hours per week, after adjustment for age, sex, body habitus, and daytime sleepiness.[64] In small randomized clinical trials of patients with moderate to severe OSA, exercise was associated with a 24% to 34% decrease in OSA severity without significant weight change.[65-67] The mechanism of this weight-independent benefit is unclear. Fat redistribution, reduced nighttime fluid resorption from the legs, increased pharyngeal muscle strength, and improved sleep quality are potential mechanisms.

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Table 2. Methods to Identify Obstructive Sleep Apnea (OSA)

Metric	Description	Additional information	Sensitivity, %[a]	Specificity, %[a]
Questionnaire				
Berlin Questionnaire	Eleven items grouped in 3 domains: snoring/apneas, fatigue/sleepiness, and obesity/hypertension. Range, 0-3; 0 indicates the lowest risk and 2-3 indicate high risk of OSA.	Developed for assessing sleep apnea risk in the primary care setting.	77 (73-81)	44 (38-51)
STOP-Bang questionnaire	Eight items assess snoring, sleepiness, apneas, hypertension, obesity, neck girth, age, and sex. Range 0-8; 0 indicates the lowest risk of OSA.	Developed for sleep apnea screening in the preoperative setting.	90 (86-93)	36 (29-44)
Epworth Sleepiness Scale	Self-administered assessment of sleep tendency in 8 common situations. Range 0-24; 0 indicates the least sleepy and greater than 10 indicates excessive sleepiness.	Widely used for assessing sleepiness and response of sleepiness to therapy; not useful in screening for OSA.	47 (35-59)	62 (56-68)
Sleep Testing				
Polysomnography	Monitors electroencephalogram, eye movements, and chin muscle tone to assess sleep-wake state and thoracic and abdominal excursion, oronasal airflow, and pulse oximetry to identify apneas and hypopneas. Measures number of apneas plus hypopneas per hour of sleep.	Criterion standard for diagnosis of OSA; permits diagnosis of sleep disorders other than sleep apnea; cost is high relative to HSAT.		
Home sleep apnea testing (HSAT)	Multiple available devices; most include monitoring of airflow, respiratory effort, and oximetry; some use nonstandard measures, such as peripheral arterial tonometry. Measures number of apneas plus hypopneas per hour of recording.	Lower cost and greater convenience compared with polysomnography; false-negative results possible; unable to diagnose disorders other than sleep apnea.	79 (71-86)	79 (63-89)
Oximetry	Overnight recording of blood oxygen saturation. Measures number of 3% or 4% desaturation events per hour of recording.	Inexpensive and convenient; false-negative results possible; cannot distinguish OSA from central sleep apnea; can document resolution of hypoxemia with treatment of OSA.	7-100	15-100

[a] Sensitivity and specificity for diagnosis of moderate to severe OSA (apnea-hypoxia index [AHI] ≥15) using laboratory-based polysomnography as the criterion standard. Data for questionnaires[43] and HSAT[44] are presented as mean (95% CI), where a positive result is a score of 2 or 3 on the Berlin Questionnaire, a score of at least 3 the STOP-Bang questionnaire, a score of at least 11 on the Epworth Sleepiness Scale, and an AHI of at least 15 on the HSAT. Data for oximetry are presented as the range of reported values.[45]

Positive airway pressure (PAP) is the primary therapy for individuals with symptomatic OSA of any severity. PAP devices deliver pressure to the airway through a mask worn over the nose or the nose and mouth. This pressure acts as a splint to prevent airway collapse during inspiration. PAP normalizes AHI in more than 90% of patients while wearing the device.[68,69] Benefit depends on adherence to therapy, with more hours of use per night associated with greater symptom improvement[70] and greater blood pressure reduction.[33] Although arbitrary, adequate adherence is commonly defined as use for at least 4 hours per night for at least 5 nights per week, a standard that is used by the Center for Medicare & Medicaid Services to authorize continued reimbursement for PAP after the initial 90 days of therapy. In a 2019 report of more than 2.6 million patients who started PAP therapy between 2014 and 2017, this level of adequate adherence was achieved by 75% of patients within the first 90 days of treatment.[71] Overall, PAP was used on 93% of nights for a mean (SD) of 6.0 (2.0) hours per night.[71] Approximately 65% to 80% of patients who start PAP therapy continue using it after 4 years.[72,73] Factors that improve PAP adherence include education about risks of OSA and the expected benefits of PAP therapy; monitoring of PAP use with reinforcement and support for technical problems; and behavioral interventions, including cognitive behavioral therapy and motivational enhancement therapy. Each of these factors increases PAP adherence by more than 30 minutes per night, with mean effects as large as 80 minutes per night for behavioral interventions.[74] Monitoring PAP adherence is facilitated by the ability of most newer PAP devices to transmit adherence data via cellular networks for remote viewing. Early PAP devices delivered a fixed positive pressure and required laboratory-based pressure titration to identify optimal treatment pressure. Automatic titrating PAP devices, which monitor airflow and adjust pressure in response to changes in flow, have facilitated initiation of PAP therapy without a titration study, reducing costs and increasing convenience without significant difference in efficacy or adherence to therapy between laboratory-based titration and automatic titration.[68] However, automatic titration may not be appropriate for individuals in which central sleep apnea is common (eg, individuals with chronic heart failure) or nocturnal hypoxemia for reasons other than sleep apnea is possible. Bilevel PAP devices, which deliver a higher pressure during inspiration than during expiration, may be useful in conditions characterized by hypoventilation but are neither more effective nor better tolerated than fixed-pressure or automatic titrating PAP devices.

Oral appliances (mandibular repositioning devices) are effective treatment options, particularly for individuals with mild to moderate OSA (Box).[69,75] These devices consist of plates made to fit the upper and lower teeth. Positions of these plates can be adjusted, allowing advancement of the mandible relative to the maxilla, resulting in increased upper airway volume and,

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Table 3. Primary Treatments for Obstructive Sleep Apnea (OSA)

Treatment	Description	Advantages	Disadvantages and adverse effects
Behavioral interventions			
Weight loss	Weight loss via lifestyle interventions (also effective for OSA when achieved via medication or bariatric surgery)	Can have positive effects on multiple cardiovascular and metabolic diseases	Difficult to achieve for many patients; takes time to achieve; not efficacious in all patients
Exercise	Aerobic exercise	Contributes to weight loss; can have positive effects on multiple cardiovascular and metabolic diseases	May be difficult for patients with significant musculoskeletal or cardiopulmonary illness
Sleep position restriction	Avoidance of supine sleep position; positioning pillows or devices can help maintain side sleep position	No cost for self-positioning; pillows and devices are inexpensive	Applicable only to patients with positional OSA; difficult for some patients, particularly those with discomfort lying on their side
Medical devices			
Positive airway pressure (PAP)	Pressure generated by the device is delivered via a mask worn over the nose or both nose and mouth; pressure may be continuous or bilevel and may be automatic titrating or delivered at a preset pressure	Efficacious in most patients, regardless of disease severity, level of airway collapse, or body weight; improves sleepiness, quality of life, and blood pressure	Poor tolerance in approximately one-third of patients; minor adverse effects, such as mucosal dryness, nasal congestion, and skin irritation, are common
Mandibular repositioning devices (oral appliances)	Fabricated to fit the upper and lower teeth, these devices provide adjustable forward advancement of the mandible during sleep	Well tolerated by many patients who are intolerant of PAP	Lower efficacy than PAP in most patients, especially in those with severe OSA or class 2 or 3 obesity; requires adequate dental and periodontal structure; can cause temporomandibular joint discomfort and occlusal abnormalities due to tooth movement
Surgical procedures			
Uvulopalatopharyngoplasty (UPPP) and related soft tissue procedures	Involves resection of the uvula and a portion of the soft palate; other soft tissue procedures focus on reducing volume of the lateral pharyngeal walls or base of tongue to increase pharyngeal volume	Extensively studied; results in improvement in OSA severity in many patients; adherence to therapy is ensured	Lower efficacy than PAP in most patients; effectively manages airway collapse only at the level of the velopharynx; postoperative pain is common; small risk of velopharyngeal insufficiency; relapse can occur with weight gain
Maxillomandibular advancement	LeFort I maxillary and bilateral mandibular osteotomies with forward fixation of the facial skeleton	Highly efficacious regardless of disease severity, level of airway collapse, or body weight; adherence to therapy is ensured	Complex surgical procedure involving bony structures with recovery time of 2 to 10 weeks; potential complications include malocclusion, poor cosmetic result, and facial numbness or paresthesia
Tracheostomy (rarely used)		Curative in most patients with OSA, regardless of disease severity, level of airway collapse, or body weight; adherence to therapy is ensured	Unacceptable cosmetic result; effect on speech; need for long-term tracheostomy care
Hypoglossal nerve stimulation	Surgically implanted electrode stimulates the hypoglossal nerve to enhance tongue protrusion and stabilize the upper airway during inspiration	Highly effective and well tolerated in select patients (body mass index <32 and absence of concentric collapse of the retropalatal airway on drug-induced sleep endoscopy)	Expensive compared with alternative therapies; potential complications include temporary tongue weakness and tongue soreness and discomfort from stimulation

consequently, reduced airway collapsibiliity.[76,77] A 2015 meta-analysis of 34 randomized clinical trials found that these devices were associated with a mean reduction in AHI of 13.6 (95% CI, 12.0-15.3) events per hour.[75]

Surgical modification of the upper airway is suitable for select patients and is often recommended for symptomatic patients unable to tolerate PAP therapy.[78] Although tracheotomy was used to manage severe OSA prior to the availability of PAP therapy, and was effective because it bypassed airway obstruction, it is now rarely used to manage OSA. The most common surgical procedures for managing OSA modify upper airway soft tissue, including palate, tongue base, and lateral pharyngeal walls. The most extensively studied procedure is uvulopalatopharyngoplasty, which involves resection of the uvula and part of the soft palate. While most studies are nonrandomized case series,[79] 2 randomized trials found that uvulopalatopharyngoplasty reduced AHI significantly more than an observation control.[80,81] In the larger of these trials (32 individuals who underwent surgery and 33 control individuals), surgery was associated with a mean reduction in AHI from 53.3 to 21.1 events per hour, with no significant change in the control group.[80] Selection criteria for this procedure are not clearly established, although most studies excluded patients with a BMI greater than 35. Other procedures include lateral wall pharyngoplasty and tongue reduction procedures. The bony structures of the face can also be modified to manage OSA. The best-studied procedure is maxillomandibular advancement, in which the upper airway is enlarged via LeFort I maxillary and bilateral mandibular osteotomies with forward fixation of the facial skeleton by approximately 10 mm. A meta-analysis of 45 studies including 455 patients who underwent pre- and posttreatment sleep studies found that maxillomandibular advancement surgery was associated with a mean reduction of 80% in AHI, consistent with a mean (SD) change of −47.8 (25.0) events per hour.[82]

Hypoglossal nerve stimulation is a newer surgical procedure that increases pharyngeal dilator muscle tone during sleep. The only device currently approved by the US Food and Drug Administration involves unilateral placement of an electrode on the medial branch of the hypoglossal nerve to enhance tongue protrusion, a pressure sensor placed between internal and external intercostal muscles to detect inspiratory effort, and a small neurostimulator implanted in the chest wall that triggers the hypoglossal electrode in response to respiratory effort. In the Stimulation Therapy for Apnea Reduction (STAR) trial of this device, the treatment reduced median AHI from 29.3 to 9.0 events per hour (median [interquartile

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range] change, −17.3 [−26.4 to −9.3] events/h) and benefits were sustained after 5 years of therapy.[83,84] Participants in the STAR trial had an AHI of 20 to 50 events per hour and a BMI less than or equal to 32, and were excluded if they had central sleep apnea, positional OSA, severe cardiopulmonary or neuromuscular disease, or complete concentric collapse of the upper airway on drug-induced sleep endoscopy. Bilateral hypoglossal nerve stimulation is also effective for managing OSA,[85] and transcutaneous stimulation is under investigation.[86] While hypoglossal nerve stimulation appears efficacious and well tolerated in select patients, it requires a surgical procedure and is more costly than PAP and oral appliances.

Pharmacologic therapies tested in individuals with OSA include drugs proposed to increase airway muscle tone, increase ventilatory drive, or raise the arousal threshold. Most of these therapies have been studied in single, small trials of fewer than 75 participants, often with single-night dosing, and none has clearly established efficacy.[87] Because reduced noradrenergic drive contributes to decreased genioglossus tone during nonrapid eye movement sleep and active muscarinic inhibition contributes to pharyngeal hypotonia during rapid eye movement sleep, a 2019 study evaluated the combination of the norepinephrine reuptake inhibitor atomoxetine and the antimuscarinic oxybutynin. In this randomized, crossover, single-dose study of 20 patients with a median AHI of 28.5 and median BMI of 34.8, combination therapy reduced AHI by a median (interquartile range) of 15.9 (7.3-35.3) events per hour compared with placebo.[88] In a randomized trial of 73 patients with similar OSA severity, the cannabinoid receptor agonist dronabinol reduced mean (SD) AHI by 12.9 (4.3) after 6 weeks of therapy.[89] Although promising, these treatments remain under investigation.

Supplemental oxygen is not recommended for individuals with OSA because it may prolong respiratory pauses and worsen hypercapnia. Oxygen therapy does not improve AHI or sleep architecture in most patients with OSA,[90] although there may be a subset of oxygen-responsive patients with a less collapsible airway and greater ventilatory instability than the average individual with OSA.[91] However, long-term data on the efficacy of oxygen in these patients are not available, and supplemental oxygen is not recommended for managing OSA. Recent studies reported conflicting results regarding the effect of nocturnal supplemental oxygen on blood pressure control. One study found no association of oxygen with blood pressure when used as a primary therapy for OSA,[92] while another found that after withdrawing effective PAP therapy, participants treated with supplemental oxygen had a 6.6-mm Hg lower blood pressure increase (95% CI, 1.9-11.3) compared with participants treated with a sham (air) control.[93]

Treatment for individuals with OSA should be prescribed for symptomatic patients, specifically those with unexplained excessive sleepiness or fatigue, because OSA treatment improves sleepiness and quality of life. A 2019 meta-analysis found that in patients with OSA, PAP was associated with a decline in the Epworth Sleepiness Scale score by 2.7 (95% CI, 2.2-3.3) points, compared with controls.[68] PAP was also associated with improved mental and physical quality of life, as measured by the Medical Outcomes Study Short Form-36 questionnaire, with improvement in the vitality scale score of 4.6 (95% CI, 2.0-7.2), compared with control individuals.[68] Although not evaluated in randomized trials, OSA treatment may reduce motor vehicle crashes. After treatment with PAP, the risk ratio for motor vehicle crash in a meta-analysis of 10 studies of 1741 patients with OSA was 0.28 (95% CI, 0.18-0.43) compared with pretreatment risk,[68] with a reduction in crash incidence from 7.6 to 2.5 accidents per 1000 drivers per year in a 2015 study.[94] In commercial truck drivers with OSA, the rate of preventable crashes per 1 million miles driven was 7.0 in those not adherent to PAP therapy and 1.4 in those adherent to therapy.[95] Treatment should also be considered for patients with unexplained nocturia, morning headaches, frequent nighttime awakenings, or nocturnal gastroesophageal reflux.

Asymptomatic OSA

The benefit of treating individuals with asymptomatic OSA is unclear. Managing OSA with PAP in patients with hypertension is associated with a 2- to 3-mm Hg reduction in 24-hour systolic and diastolic blood pressure.[68] Blood pressure lowering is greater at night and in those with resistant hypertension.[68,96]

Additional research is needed to identify other subgroups of asymptomatic patients with OSA who may benefit from treatment. A 2019 meta-analysis of observational studies reported that, for individuals with OSA, treatment with PAP therapy, compared with controls, was associated with a lower rate of major adverse cardiovascular and cerebrovascular events (risk ratio, 0.46 [95% CI, 0.32-0.66]) and all-cause mortality (risk ratio, 0.40 [95% CI, 0.24-0.69]) than no OSA treatment.[68] However, these observational studies are susceptible to bias. Because untreated patients in these studies had refused or were nonadherent to therapy, healthy user bias is likely. Randomized clinical trials showed no effect of PAP on reducing rates of myocardial infarction, stroke, or mortality in individuals with OSA.[97] The Sleep Apnea Cardiovascular Endpoints (SAVE) study randomized 2717 patients with either cardiovascular or cerebrovascular disease and moderate to severe OSA to receive PAP therapy or usual care. Participants were excluded if they were excessively sleepy. Over a mean follow-up of 3.7 years, the composite primary end point of myocardial infarction; stroke; cardiovascular death; or hospitalization for heart failure, acute coronary syndrome, or transient ischemic attack occurred in 17.0% of participants in the PAP group and 15.4% in the usual care group (hazard ratio [HR], 1.10 [95% CI, 0.91-1.32]).[98] In the Impact of Sleep Apnea Syndrome in the Evolution of Acute Coronary Syndrome (ISAACC) study, 1264 patients hospitalized with acute coronary syndrome with moderate to severe OSA, but not excessive sleepiness, were randomized to receive PAP therapy or usual care. Over a median follow-up of 3.4 years, the composite primary end point of cardiovascular death; myocardial infarction; stroke; or hospitalization for heart failure, unstable angina, or transient ischemic attack occurred in 16% of participants in the PAP group and 17% of participants in usual care group (HR, 0.89 [95% CI, 0.68-1.17]).[99]

These randomized trials have been criticized for low PAP adherence, with mean (SD) use per night of 3.3 (2.3) hours in the SAVE study and 2.8 (2.7) hours in the ISAAC study.[98,99] However, no benefit was observed in participants using PAP therapy for 4 or more hours per night (SAVE: HR, 0.80 [95% CI, 0.60-1.07] compared with a propensity-matched subset of the usual care group; ISAACC: HR, 0.94 [95% CI, 0.65-1.36] compared with usual care). The null result of these studies may reflect the exclusion of patients with excessive sleepiness, because sleepiness may identify those patients with OSA at increased vascular disease risk.[100-102]

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Benefits of therapy for patients with asymptomatic OSA and atrial fibrillation are also unclear. Observational studies suggested a 35% to 40% absolute reduction in atrial fibrillation recurrence in the year following cardioversion or pulmonary vein isolation in treated compared with untreated patients with OSA.[103] However, these studies were susceptible to bias, and there are no adequately powered published randomized clinical trials.

Some observational studies find a higher rate of perioperative cardiac and pulmonary complications in patients with OSA (Box).[104] Patients at high risk for OSA should have close postoperative monitoring and continued PAP use in the perioperative period if previously prescribed, and prescription of opioids should be limited. Preoperative sleep testing and treatment are of uncertain benefit.[105]

Prognosis

OSA treatment usually improves sleepiness and associated behavioral impairment. The degree of improvement is associated with adherence to therapy. Optimal response is observed when PAP therapy is used more than 6 hours per night.[70] Residual sleepiness is observed in approximately 9% to 20% of patients with OSA who use PAP for at least 6 hours per night.[70,106,107] This is not higher than in the population of individuals without OSA[11,25] and, thus, is likely due to causes other than OSA, such as sleeping fewer than the recommended minimum of 7 hours per night.[108] Chronic neurodegenerative residua of sleep fragmentation or intermittent hypoxemia have been demonstrated in animal models and might contribute to persistent sleepiness, but whether this occurs in humans is uncertain. Therefore, although wake-promoting agents, such as modafinil and solriamfetol, are approved to manage residual sleepiness in patients with OSA, they should only be used after other causes of excessive sleepiness have been excluded. Treatment with either PAP or oral appliances is not curative. Lifelong treatment is typically needed in the absence of weight loss sufficient to cause disease remission. Surgical interventions do not depend on adherence, although OSA may recur or worsen with subsequent weight gain.

Limitations

This review has some limitations. First, it was restricted to English-language publications and was developed primarily from published systematic reviews, meta-analyses, and clinical practice guidelines. Second, the literature search may have missed some relevant publications. Third, not all aspects of OSA were discussed. Fourth, high-quality data are lacking for some covered topics.

Conclusions

OSA is common and the prevalence is increasing. Daytime sleepiness is among the most common symptoms, but many patients with OSA are asymptomatic. Patients with OSA who are asymptomatic, or whose symptoms are minimally bothersome and pose no apparent risk to driving safety, can be treated with behavioral measures, such as weight loss and exercise. Interventions such as PAP are recommended for those with excessive sleepiness and resistant hypertension. Treating individuals with asymptomatic OSA to reduce cardiovascular and cerebrovascular events is not currently supported by high-quality evidence.

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