CLINICAL PRACTICE

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Obstructive Sleep Apnea in Adults

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.*

A 58-year-old woman reports fatigue and sleepiness. Despite sleeping 7 to 8 hours nightly, she wakes unrefreshed. She has been told by her husband that she snores. She awakens nightly to urinate and typically falls promptly back to sleep. Recently, she has noted sleepiness while driving home from work. Her medical history includes obesity, hypertension, and type 2 diabetes mellitus. Her physical examination is notable for a body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) of 35 and a large tongue partially obscuring the soft palate. How would you evaluate and treat this patient?

THE CLINICAL PROBLEM

Obstructive sleep apnea is characterized by episodic sleep state–dependent collapse of the upper airway, resulting in periodic reductions or cessations in ventilation, with consequent hypoxia, hypercapnia, or arousals from sleep.[1] Many patients are unaware that their breathing is affected and may not visit a physician for evaluation. In addition, patients may not consider sleepiness a relevant topic to discuss with health care providers. Yet, the prevalence of obstructive sleep apnea is conservatively estimated to be 3% among women and 10% among men 30 to 49 years of age and 9% among women and 17% among men 50 to 70 years of age,[2] including an estimated 24 million persons in the United States who have not received a diagnosis.[3]

Risk factors for the disease are conditions that reduce the size of the resting pharynx or increase airway collapsibility. Obesity is the most important risk factor for obstructive sleep apnea.[4,5] Increased adipose tissue within the tongue and pharynx compromises upper-airway dimensions and makes the airway more prone to collapse during sleep. Obstructive sleep apnea has been reported to be present in more than 40% of persons with a BMI of more than 30 and in 60% of persons with metabolic syndrome.[6] Male sex is another important risk factor, although the scientific bases for the differences between sexes are unknown. Progesterone stimulation of upper-airway muscles and ventilation may contribute to the lower prevalence of obstructive sleep apnea among premenopausal women than among older women,[7] whereas higher androgen levels (e.g., as with use of androgen supplementation and polycystic ovarian disease) may increase muscle mass in the tongue and worsen obstructive sleep apnea.[8,9] The prevalence of obstructive sleep apnea is also substantially increased among persons with hypothyroidism or acromegaly.[10-12] Increased tonsillar and adenoid tissue and certain craniofacial abnor-

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KEY CLINICAL POINTS

OBSTRUCTIVE SLEEP APNEA IN ADULTS

- Obstructive sleep apnea is common and is an independent risk factor for motor vehicle accidents and cardiovascular disease.
- Home sleep apnea testing may be used to support, but not to rule out, the diagnosis of obstructive sleep apnea.
- Polysomnography is recommended in patients with a known or suspected history of stroke, a neuromuscular or pulmonary disorder with hypoventilation, or congestive heart failure or who are using opiates.
- Continuous positive airway pressure (CPAP) is considered first-line therapy for symptomatic or moderate-to-severe obstructive sleep apnea.
- The use of alternative therapies (mandibular-advancement devices and various surgical options) for patients who decline or are unable to use CPAP should be considered on a personalized basis, with respect to the nature of obstruction, patient-specific factors, and patient preferences.
- Recommended lifestyle modifications include weight-loss counseling in overweight and obese patients, avoiding medications and substances that promote relaxation of the upper airway (e.g., alcohol, benzodiazepines, and narcotics), and increasing awareness of and providing countermeasures for the risk of drowsy driving.

malities (retrognathia and maxillary insufficiency) may also confer a predisposition to obstructive sleep apnea.[1]

STRATEGIES AND EVIDENCE

The clinical approach to patients with obstructive sleep apnea should begin with an assessment of the likelihood of the disease, symptomatology, and relevant coexisting conditions in order to direct diagnostic testing. Once a diagnosis is made, treatment is guided by the severity of disease, symptoms, coexisting conditions, and the presence of exacerbating factors.

EVALUATION

Obstructive sleep apnea should be considered in all patients who report sleepiness. Because chronic sleepiness is common in the general population, other findings, as specified in Table 1, support pursuing evaluation for obstructive sleep apnea. It is important to note that not every patient with obstructive sleep apnea perceives sleepiness or has been told of snoring. Although higher BMIs markedly increase the risk of obstructive sleep apnea, some patients are of normal weight. Disease likelihood increases with specific medical disorders and conditions (Fig. 1). Screening questionnaires can be helpful in alerting providers to the likelihood of obstructive sleep apnea; a careful evaluation of sleep history, medical history taking, and physical examination are required to guide the need for further evaluation.[13] Evaluation should also include thorough consideration of coexisting conditions, as detailed below.

DIAGNOSIS

Traditionally, obstructive sleep apnea has been diagnosed with the use of overnight polysomnography in a clinical sleep laboratory to measure the frequency of obstructed breathing events — apneas and hypopneas — during sleep. Obstructive apneas are defined as near-complete (>90%) cessations in airflow for more than 10 seconds in sleep, despite ventilatory effort, and hypopneas are generally defined as reductions in airflow by more than 30% with concurrent reductions in oxyhemoglobin saturation by at least 3% or arousals from sleep.[14]

Collectively, the number of apneas and hypopneas per hour of sleep is termed the apnea–hypopnea index (AHI), in which the presence of obstructive sleep apnea is defined as an AHI of 5 or more events per hour. The AHI is used to categorize disease severity; persons with an AHI of 5 to 15, 16 to 30, or more than 30 events per hour are considered to have mild, moderate, or severe obstructive sleep apnea, respectively. The AHI is influenced by weight, sleeping position, age, alcohol and medications, fluid balance, and the conditions listed in Figure 1; thus, the AHI may vary over time and even across consecutive nights. Therefore, there are inherent limitations with using the AHI calculated from one night of sleep to categorize disease severity and long-term risks; measures of oxygen desaturation, such as the time spent with oxyhemoglo-

Table 1. Signs and Symptoms That Should Trigger Suspicion of Obstructive Sleep Apnea.

Sign or Symptom
Loud or irregular snoring
Daytime sleepiness
Unrefreshing sleep regardless of sleep duration
Increased fatigue when patient is sedentary
Nocturia
Choking and gasping in sleep
Dry mouth on awakening
Morning headaches
Body-mass index >30
Crowded oropharynx
Increased neck circumference (men, >17 in. [43.2 cm]; women, >15 in. [38.1 cm])

bin saturations of less than 90% and the lowest value of oxyhemoglobin saturation during sleep, may provide additional important information in this regard.

To meet the increased demands to diagnose obstructive sleep apnea and to reduce costs, simpler diagnostic tools that can be performed at home have been developed and validated. Home sleep apnea tests, the most commonly used portable in-home studies, do not measure sleep and thus cannot determine the AHI. Instead, these devices measure the respiratory-event index (REI), calculated as the frequency of breathing events (all apneas and any hypopneas with oxyhemoglobin desaturation of ≥4%) for the entire recording time with exclusion of events scored because of arousal. In poor sleepers and in persons with less pronounced arterial oxygen desaturations (e.g., young, thin persons and premenopausal women), these tests frequently underestimate the severity of obstructive sleep apnea. Ideally, home sleep apnea tests should be used in lieu of polysomnography only in persons in whom clinical suspicion is high for moderate-to-severe disease and in whom there are no conditions that confer a predisposition to nonobstructive sleep-disordered breathing (Fig. 1).[13] However, in areas where fewer resources are available, home sleep apnea testing may be the only option.

COEXISTING CONDITIONS

The AHI is associated with several coexisting conditions that warrant consideration. An AHI of more than 15 events per hour is associated with a decrement in psychomotor speed equivalent to 5 years of aging.[15] In addition, an inverse relationship exists between subjective measures of quality of life and the severity of the AHI.[15] Persons with untreated obstructive sleep apnea have three times the risk of motor vehicle accidents as the general population.[16]

Obstructive sleep apnea is also associated with an increased risk of cardiovascular disease. Among a population-based cohort of more than 6000 participants (age, >40 years), those with an AHI in the upper quartile (>11 events per hour) were more likely than those in the lower quartile (<1.4 events per hour) to have histories of hypertension, stroke, coronary artery disease, or heart failure, even after adjustment for BMI and other cardiovascular risk factors.[17] In a follow-up study, the AHI predicted incident hypertension.[18] Patients with obstructive sleep apnea, particularly those with an AHI of more than 30 events per hour, are also at increased risk for sleep-related dysrhythmias (e.g., sinus bradycardia and atrioventricular block) and nonsustained ventricular tachycardia.[19] Furthermore, hypoxemia in patients with obstructive sleep apnea probably drives parasympathetic activation and bradyarrhythmias[20] and is a predictor of cardiovascular outcomes, including sudden cardiac death.[21-23]

An AHI of 20 or more events per hour has been associated with an increase in an adjusted risk of stroke by a factor of four in men and a factor of two in women.[24] In addition, obstructive sleep apnea is associated with an increased risk of diabetes and glucose dysregulation, independent of obesity,[25] as well as increased levels of total cholesterol, low-density lipoprotein cholesterol, and triglycerides and decreased levels of high-density lipoprotein cholesterol.[26] In a 20-year longitudinal study, the presence of moderate-to-severe obstructive sleep apnea was associated with an increased adjusted risk of incident diabetes.[27] This same study also showed an increase in cancer mortality and all-cause mortality among men 40 to 70 years of age with an AHI of more than 30 events per hour.[27]

TREATMENT OPTIONS FOR OBSTRUCTIVE SLEEP APNEA

Currently, treatment is recommended for all patients with an AHI or REI of 15 or more events per hour, as well as for persons with an AHI or

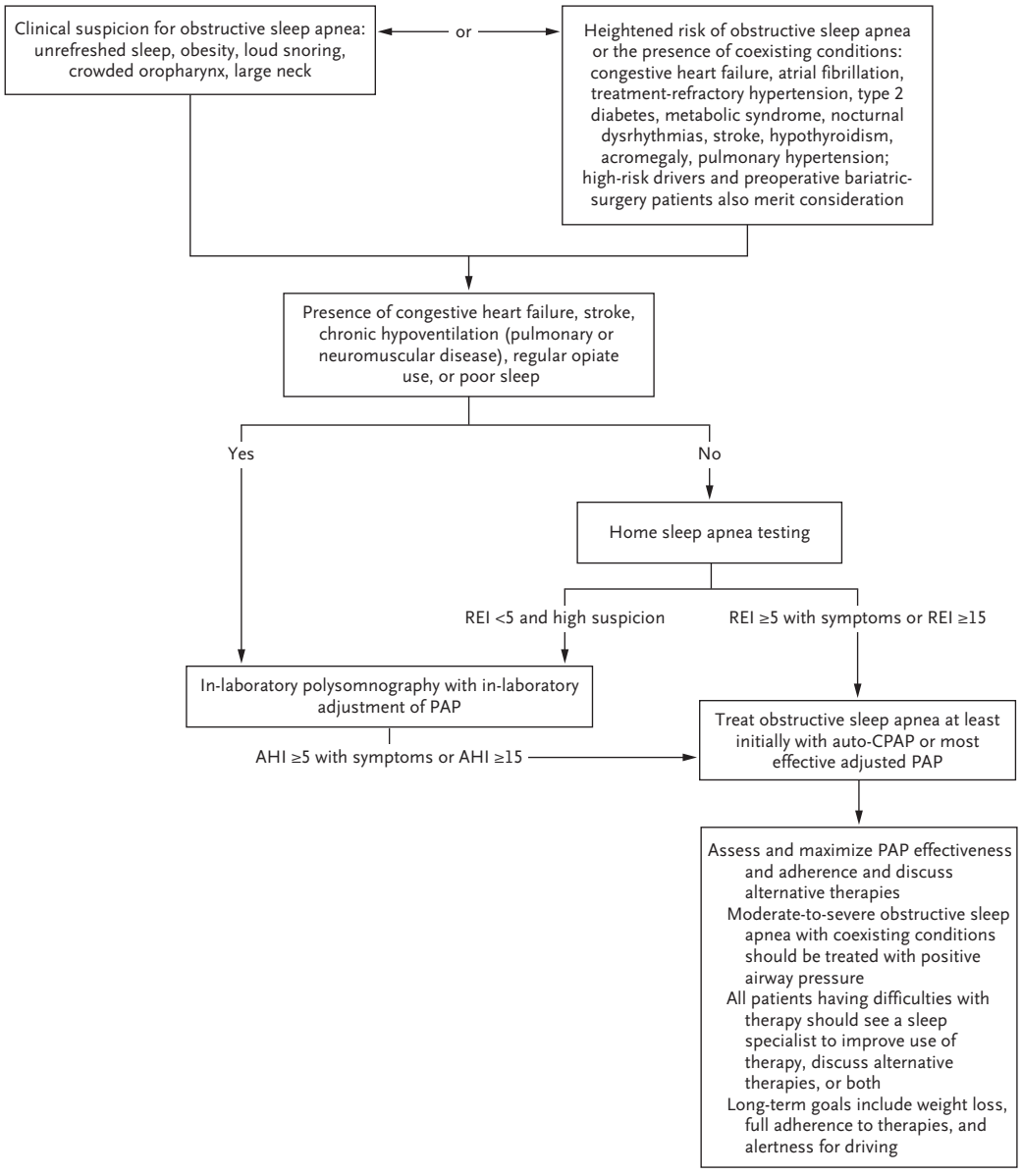

Figure 1. Diagnostic and Therapeutic Decision Making for Obstructive Sleep Apnea.

Obstructive sleep apnea should be considered in persons presenting with a strong clinical picture (upper left) and in those who have some symptoms suggestive of obstructive sleep apnea along with coexisting conditions that heighten the risk of obstructive sleep apnea or who have a disease or condition that has been associated with an increased prevalence of obstructive sleep apnea (upper right). Consideration of the likelihood of clinically significant disease and the absence of diseases that may confound the diagnosis is imperative to select the most appropriate diagnostic assay for obstructive sleep apnea. In patients with high clinical suspicion and without these conditions, a home sleep apnea test may be appropriate. Positive airway pressure (PAP), including continuous positive airway pressure (CPAP), is the frontline therapy for all patients with symptoms and those with moderate-to-severe disease. Patients who are unable to use PAP therapy may be candidates for oral mandibular-advancement splints, hypoglossal-nerve stimulation, or other surgical procedures. All patients must be regularly evaluated for effectiveness of therapy, weight loss, and risk of drowsy driving. The respiratory-event index (REI) is the number of respiratory events (all apneas and any hypopneas with oxyhemoglobin desaturation of ≥4%) per hour of monitored time. The apnea–hypopnea index (AHI) is the number of apneas and hypopneas per hour of sleep.

REI of 5 to 14 events per hour with symptoms of sleepiness, impaired cognition, mood disturbance, or insomnia or with coexisting conditions such as hypertension, ischemic heart disease, or a history of stroke. Therapies for obstructive sleep apnea have been designed to reduce the frequency of sleep-disordered breathing events (i.e., AHI and REI). The most effective therapy to reduce obstructive sleep apnea is positive airway pressure (PAP) applied with a tight seal to the nose or mouth (or both) serving to stent open the upper airway. Continuous positive airway pressure (CPAP) provides a constant level of positive pressure across inspiration and expiration. Although PAP is highly effective in reducing the AHI (to <5 events per hour in most patients) when assessed in the sleep laboratory, it requires tremendous effort on the patient's part to position the mask properly and maintain the machine and supplies. When adherence is defined as use for more than 4 hours per night for more than 70% of nights, PAP adherence rates of 75% have been reported[28]; a far smaller percentage of patients use PAP during all sleep. Variable-pressure approaches to PAP exist, including higher pressure during inspiration than during expiration, autoadjusting pressure in response to breath-to-breath airflow changes throughout the night, and lowered pressure just at the beginning of the expiratory phase; however, such approaches have not been shown to improve adherence rates. Small trials have shown that cognitive behavioral therapy or short-term use of a nonbenzodiazepine hypnotic drug (e.g., eszopiclone) at PAP initiation may increase nightly use of PAP.[29,30]

Patients with mild obstructive sleep apnea who decline or are unable to use PAP therapy may be candidates for an oral appliance to advance the mandible, positional therapy (avoiding a supine sleep position), or surgical correction of a collapsible pharynx. In a randomized, controlled trial, CPAP was shown to be more effective than a mandibular-advancement splint in reducing the AHI, but adherence was greater with the oral appliance.[31] Adjustable mandibular-advancement splints are recommended in patients with mild-to-moderate obstructive sleep apnea who are unable to use PAP; however, long-term use of the devices may alter dental occlusion.[32]

Surgical options have expanded for obstructive sleep apnea in the past several years. Radiofrequency reductive surgery of the tongue and soft palate has minimal effects on the AHI in controlled trials.[33] A systematic review, largely involving case series, suggests that uvulopharyngopalatoplasty and, in particular, maxillomandibular advancement surgical procedures may be beneficial in patients with mild or moderate obstructive sleep apnea and favorable anatomy.[33] Ideal candidates for these surgical procedures are nonobese persons with abnormalities in craniofacial pharyngeal structures (e.g., a hypoplastic mandible). A newer treatment option is hypoglossal-nerve stimulation during sleep to move the tongue forward and open the airway. Recently, a report involving a 5-year follow-up of a cohort of patients who underwent this procedure showed sustained effectiveness, with clinically relevant improvement (AHI of <20 events per hour and >50% reduction in the AHI) in 75% of the patients, and rare adverse events.[34]

LIFESTYLE CHANGES

Weight loss should be recommended to all overweight or obese patients with obstructive sleep apnea, including those using PAP, on the basis of data from randomized, controlled trials showing improvements in insulin sensitivity and serum triglyceride levels with combined therapy, relative to PAP alone.[35] Weight loss of more than 10 kg may resolve obstructive sleep apnea in more than 50% of persons with mild disease and improve cardiometabolic health.[36] Substantial improvement has been noted in obstructive sleep apnea after bariatric surgery,[37] although the magnitude of reduction in the AHI did not differ significantly from that associated with a nonsurgical weight-loss intervention in one randomized trial.[38] Medications and substances that relax muscles or suppress respiratory drive (e.g., alcohol, benzodiazepines, and opioids) may also exacerbate obstructive sleep apnea and should be minimized or avoided.

THE EFFECT OF TREATMENT ON CLINICAL OUTCOMES

Decisions regarding treatment of obstructive sleep apnea should include consideration of the effects on coexisting conditions. A randomized trial comparing effective and subtherapeutic PAP showed that effective CPAP markedly improved self-perception of health and vitality,[39] and a second study comparing CPAP and placebo showed

that CPAP reduced fatigue and daytime sleepiness.[40] An observational study showed that CPAP treatment of obstructive sleep apnea was associated with a substantial reduction in the risk of motor vehicle accidents, as compared with rates before treatment initiation, to a level similar to that of drivers without known obstructive sleep apnea.[16] CPAP may also improve cognitive performance, but data are inconsistent. A large, randomized, multisite trial comparing 6 months of CPAP with sham CPAP showed no meaningful difference across groups in three tests of basic executive function[41]; however, the average nightly use of a CPAP device was only 4 hours. In a subsequent analysis, adherence to therapy predicted improved psychomotor function.[42]

Therapy for obstructive sleep apnea positively influences some aspects of cardiovascular health. In a placebo-controlled crossover study involving men and women with an AHI of 15 or more events per hour, 24-hour systolic blood pressure was lower by 4 mm Hg in those who received CPAP than in those who received placebo.[43] Similar results were shown in patients with resistant hypertension[44] and in those with type 2 diabetes and hypertension.[45] Use of a mandibular-advancement splint has been shown to similarly reduce systolic pressure.[46]

However, the effects of treatment for obstructive sleep apnea on cardiovascular events remain uncertain. A randomized trial of CPAP (as compared with no CPAP) involving nonsleepy patients with an AHI of 20 or more events per hour showed no appreciable reduction in a composite end point of hypertension or cardiovascular events over a period of 4 years.[47] More recently, another randomized trial compared CPAP with usual care among persons with established cardiovascular disease and moderate-to-severe obstructive sleep apnea, without severe sleepiness, and showed no important effect of CPAP on the primary composite cardiovascular outcome or on any individual cardiovascular outcomes.[48] Relevant to both negative studies, sleepiness has been reported to be an independent risk factor for cardiovascular disease[49]; in addition, both studies were also limited by poor adherence to CPAP.

AREAS OF UNCERTAINTY

Adequately powered, randomized, controlled trials are needed to inform the effectiveness and limitations of newer diagnostics for obstructive sleep apnea, PAP devices, and alternative therapies. The role of CPAP and other therapies in the nonsleepy patient remains uncertain. Autoadjustable CPAP is being used, yet this therapy has not been tested as rigorously as CPAP. Finding ways to improve PAP adherence is critical. The potential role of pharmacotherapies in treating obstructive sleep apnea is uncertain. A small, placebo-controlled, crossover trial showed a reduction in the AHI with a combination of a noradrenergic agent and an antimuscarinic agent, but the trial involved only one night of therapy and did not assess other outcomes.[50] Socioeconomic and racial disparities in the diagnosis and treatment of obstructive sleep apnea and in clinical outcomes also require further study.

Thus far, diagnostic and therapeutic strategies have focused on the AHI, but the severity of oxyhemoglobin desaturation and event duration may vary widely among patients with similar AHIs and may influence outcomes. Data are needed to assess whether the effects of CPAP and other interventions on cardiovascular variables (e.g., 24-hour blood pressure or sympathetic drive) may be useful predictors of their effects on cardiovascular outcomes. Moreover, data are needed from long-term, randomized, controlled trials on the effects of treatment for obstructive sleep apnea, with good adherence, on cardiovascular and other disease outcomes. Studies are needed to better understand the extent and reversibility of cognitive impairments after initiation of therapy. Finally, most patients receive a diagnosis after years of symptoms of obstructive sleep apnea. Strategies to cost-effectively screen young adults for obstructive sleep apnea, before the onset of the condition, warrant study.

GUIDELINES

Specialized task forces that were charged by the American Academy of Sleep Medicine, American Thoracic Society, and the American College of Physicians have published recommendations for the evaluation and treatment of obstructive sleep apnea in adults, including the use of portable monitors for diagnosis and surgical options for therapy.[13,33,36,51,52] The recommendations in this article are consistent with the recommendations in these guidelines.

CONCLUSIONS AND RECOMMENDATIONS

The woman described in the vignette has a history and physical examination suggestive of obstructive sleep apnea. She has no medical conditions that preclude the use of home sleep apnea testing (e.g., chronic obstructive pulmonary disease or the use of opioid medications). Thus, this approach may be used to confirm the diagnosis, reserving polysomnography for a negative study. Because she is sleepy, she should be treated for an REI of more than 5 events per hour and treated with CPAP as first-line therapy. She should be advised regarding the importance of therapy and the benefits of weight loss. In addition, she should be counseled regarding the dangers of drowsy driving and to avoid sedating medications and alcohol. Close follow-up after initiation of PAP is warranted to maximize adherence to therapy; long-term assessment of improvements in the AHI and sleepiness with therapy should be evaluated at all follow-up visits, because both outcomes may change with age, weight fluctuations, and the status of associated coexisting conditions.

Dr. Veasey reports holding an issued patent (8,569,374) on NADPH oxidase inhibition pharmacotherapies for obstructive sleep apnea syndrome and associated conditions, licensed to the Trustees of the University of Pennsylvania; and Dr. Rosen, receiving grant support from Jazz Pharmaceuticals, ResMed, and Merck. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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