

Treatment of OSA: What (else) can it accomplish?

Treatment of obstructive sleep apnea improves daytime sleepiness, but does it improve other outcomes?

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PRACTICE RECOMMENDATIONS

► *Treat patients with symptomatic obstructive sleep apnea (OSA) with positive airway pressure (PAP) or oral appliances to reduce daytime sleepiness, improve quality-of-life scores, and modestly reduce blood pressure in patients with hypertension. (A)*

► *Consider recommending at least 4 hours of PAP every night for asymptomatic patients (those without daytime sleepiness) with severe OSA and other conditions, including resistant hypertension, atrial fibrillation, congestive heart failure, cognitive impairment, obesity, and stroke. (B)*

► *Do not screen asymptomatic patients for OSA. (C)*

Strength of recommendation (SOR)

- (A) Good-quality patient-oriented evidence
- (B) Inconsistent or limited-quality patient-oriented evidence
- (C) Consensus, usual practice, opinion, disease-oriented evidence, case series

Obstructive sleep apnea (OSA) is a common cause of daytime sleepiness, and severe OSA is a risk factor for hypertension, cardiovascular events, atrial fibrillation (AF), insulin resistance, cognitive impairment, motor vehicle crashes, adverse pregnancy outcomes, and overall mortality.¹⁻⁸ The hazard ratio for mortality for patients with severe OSA may be as high as 3.8.⁵

OSA is diagnosed by the apnea-hypopnea index (AHI), defined as the number of apnea or hypopnea events per hour as determined by polysomnography. An AHI score ≤ 5 is considered normal; > 5 to ≤ 15 is mild; > 15 to < 30 is moderate; and ≥ 30 is severe. Most studies of OSA treatment use reduction of AHI as the measure of treatment effectiveness, and several types of treatment improve AHI.

In family medicine, we generally want to know whether treatment of OSA will improve outcomes of significance to patients. A recent systematic review of evidence for the US Preventive Services Task Force found that it was unclear whether OSA treatment improved most health outcomes, including mortality, cardiovascular events, or motor vehicle crashes.⁶ Several other organizations have published guidelines regarding OSA treatment; these guidelines are reviewed in the TABLE.⁹⁻¹³

This article summarizes the current evidence surrounding the effect of treatment of OSA on outcomes of significance to patients. While multiple treatments have been advocated for patients with OSA, positive airway pressure (PAP) is the most widely used and studied and is recommended as standard treatment by most guidelines.⁹⁻¹³ Most available evidence about patient-oriented outcomes involves treatment with PAP; where there is evidence about the effect of other OSA treatments on a particular outcome, that evidence is also summarized.

Benefits of OSA treatment

Patients with OSA who have excessive daytime sleepiness can gain substantial symptomatic benefit from treatment of their OSA with PAP or oral appliances (OAs), and might benefit from

TABLE

Guidelines regarding obstructive sleep apnea⁹⁻¹³

Guideline	Recommendation	Grade
An official American Thoracic Society Clinical Practice Guideline: Sleep Apnea, Sleepiness, and Driving Risk in Noncommercial Drivers: An Update of 1994 Statement⁹ <i>Grade is based on the Grading of Recommendations, Assessment, Development, and Evaluation approach.</i>	Recommend CPAP for high-risk drivers (defined as drivers who have moderate-to-severe daytime sleepiness and a recent unintended motor vehicle crash or a near-miss attributable to sleepiness, fatigue, or inattention with confirmed OSA).	Strong recommendation, moderate-quality evidence
	For high-risk drivers with suspected or confirmed OSA, recommend avoiding stimulant medications for the sole purpose of reducing driving risk.	Weak recommendation, very low-quality evidence
Clinical Guideline for the Evaluation, Management and Long-term Care of Obstructive Sleep Apnea in Adults Adult Obstructive Sleep Apnea Task Force of the American Academy of Sleep Medicine¹⁰	CPAP is indicated for treatment of moderate-to-severe OSA.	Standard ^a
	CPAP is indicated for the treatment of mild OSA.	Option ^b
	CPAP is indicated for improving self-reported sleepiness.	Standard ^a
	CPAP is indicated for improving quality of life and as an adjunctive therapy to lower BP.	Option ^b
	Weight loss should be combined with primary treatment in overweight patients.	Option ^b
	Oral appliances are indicated for mild-to-moderate OSA in patients who prefer them to CPAP, do not respond to CPAP, or fail CPAP.	Guideline ^c
	Surgical therapy can be offered for mild OSA or as a secondary treatment when the outcome of PAP therapy is inadequate.	Consensus ^d
	Medications are not recommended for the treatment of OSA.	Standard ^a or Guideline, ^c depending on the medication
Continuous positive airway pressure for the treatment of obstructive sleep apnoea/hypopnoea syndrome Technology appraisal guidance [TA139] National Institute for Health and Care Excellence¹¹	CPAP is recommended for adults with moderate or severe symptomatic OSA.	<i>NICE does not grade individual recommendations. Technologies that are recommended by NICE must be funded by the United Kingdom National Health Service.</i>
	CPAP is only recommended for adults with mild OSA if they have symptoms that affect their quality of life AND other relevant treatment options have been unsuccessful or are considered inappropriate.	
Management of Obstructive Sleep Apnea in Adults: A Clinical Practice Guideline From the American College of Physicians¹² <i>Grade is based on the ACP Guideline Grading System.</i>	Encourage overweight and obese patients with OSA to lose weight.	Strong recommendation, low-quality evidence

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hypoglossal nerve stimulation or other surgical treatment. PAP is probably more effective than OAs in patients who use it ≥ 4 hours/night, but it is more difficult to comply with PAP.¹⁴

Evidence that treatment of asymptomatic OSA benefits other medical conditions is often conflicting. Given the low risk of treatment, it is reasonable to consider offer-

TABLE

Guidelines regarding obstructive sleep apnea⁹⁻¹³ (cont'd)

Guideline	Recommendation	Grade
Management of Obstructive Sleep Apnea in Adults: A Clinical Practice Guideline From the American College of Physicians¹² (cont'd)	CPAP should be used as initial therapy.	Strong recommendation, moderate-quality evidence
	Mandibular advancement devices should be used as alternative therapy to CPAP for patients who prefer them or who have adverse effects from CPAP.	Weak recommendation, low-quality evidence
Principles of practice parameters for the treatment of sleep disordered breathing in the elderly and frail elderly: the consensus of the International Geriatric Sleep Medicine Task Force¹³ <i>Grade is based on the Grading of Recommendations, Assessment, Development, and Evaluation approach.</i> <i>Note that all recommendations are considered at the expert consensus level.</i>	PAP should be used routinely for the treatment of SDB in older persons.	Strong
	In cases of PAP failure, oral appliance treatment is recommended in elderly SDB patients.	Weak
	PAP should be considered in patients with Alzheimer's or Parkinson's disease.	Strong
	PAP should routinely be used in patients with SDB and COPD.	Weak
	No surgical ear, nose, and throat procedure can be recommended as therapy for geriatric patients with OSA.	Weak
	Positional treatment cannot be recommended as treatment for OSA in the elderly.	Strong
	Laparoscopic Roux-en-Y gastric bypass surgery can be considered as supportive treatment in multimorbid severely obese patients in the intermediate elderly age group.	Weak
	Drugs used to treat dementia cannot currently be recommended for the treatment of SDB.	Weak

ACP, American College of Physicians; BP, blood pressure; COPD, chronic obstructive pulmonary disease; CPAP, continuous positive airway pressure; NICE, National Institute For Health and Care Excellence; OSA, obstructive sleep apnea; PAP, positive airway pressure; SDB, sleep disordered breathing.

^aStandard is a generally accepted patient-care strategy that reflects a high degree of clinical certainty; it implies the use of Level 1 evidence, which directly addresses the clinical issue, or overwhelming Level 2 evidence.

^bOption is a patient-care strategy that reflects uncertain clinical use and implies insufficient, inconclusive, or conflicting evidence or conflicting expert opinion.

^cGuideline is a patient-care strategy that reflects a moderate degree of clinical certainty; it implies use of Level 2 evidence or a consensus of Level 3 evidence.

^dConsensus recommendations reflect the shared judgment of the committee members and reviewers.

ing a trial of treatment, preferably with PAP, to asymptomatic patients with moderate-to-severe OSA and certain comorbidities, including obesity, resistant hypertension, high cardiovascular risk, congestive heart

failure (CHF), AF, diabetes that is difficult to control, and pregnancy. Such patients should be strongly encouraged to use PAP ≥ 4 hours/night, and should be advised that benefits may not be immediately apparent.

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Patients with OSA who have excessive daytime sleepiness can gain substantial symptomatic benefit from treatment with positive airway pressure or oral appliances.

Treatment of OSA improves daytime sleepiness

Daytime sleepiness is typically measured with the Epworth Sleepiness Scale (ESS), a self-administered questionnaire assessing a person's level of drowsiness and propensity to fall asleep in 8 different daytime situations. Each situation is scored between 0 (would never doze) and 3 (high chance of dozing), with the scores then totaled to provide an overall score between 0 and 24. A score > 10 is considered abnormal.

Treatment of OSA with either PAP or OAs significantly improves ESS scores, with PAP being more effective.¹³ The difference appears to widen in patients with greater daytime sleepiness; in other words, patients with greater daytime sleepiness will gain even greater benefit from PAP, both overall and when compared with OAs.¹⁵

One randomized trial of an intensive lifestyle modification program for patients with OSA failed to show improvement in the ESS in the intention-to-treat analysis, but did demonstrate a 2.4-point greater reduction in ESS scores in those patients who successfully followed the program (achieving weight loss).¹⁶

Surgical treatments for OSA, such as uvulopalatopharyngoplasty or maxillary advancement, have been shown in some (but not all) studies to improve ESS scores; the different types of surgical treatment and the heterogeneity of studies prevents estimation of effect size.¹⁷ A meta-analysis of case series studies of hypoglossal nerve stimulation reported a mean improvement of 4.5 points on the ESS;¹⁸ comparison with other interventions is lacking.

Improved quality of life

Both PAP and OAs have been shown to improve sleep-related quality of life in patients with OSA. However, while the improvement is statistically significant, the effect size is small.¹⁴ That could be said of a study by Lewis et al.¹⁹ These researchers randomized patients with moderate-to-severe OSA and known coronary artery disease (CAD) or at least 3 risk factors for CAD to receive PAP, nocturnal oxygen, or lifestyle education.¹⁹ The patients randomized to receive PAP improved vitality scores by only 3.6 points on a 100-point scale; this was significantly better statistically than the improvement achieved by those ran-

domized to lifestyle education. Smaller improvements were noted in depression, social function, and general health. Patients who had more daytime sleepiness at baseline had greater improvements in function.¹⁹

Cognitive function findings are mixed

In a systematic review published in 2004, Aloia et al⁴ found measurable impairments on neuropsychological tests of global cognitive functioning, attention/vigilance, executive functioning, memory, psychomotor function, and constructional abilities in patients with OSA. The results of treatment studies (all but 1 using PAP) were mixed. No studies showed improvement in psychomotor speed or language, and studies disagreed on whether treatment produced benefits in global cognition, attention, or executive functions.⁴

Findings of more recent studies remain mixed. A 3-month Spanish trial of PAP in older adults with severe OSA showed improvement in 2 of 4 neuropsychological tests of cognitive function; this was a secondary outcome measure.²⁰ The PREDICT trial in the United Kingdom demonstrated a reduction in daytime sleepiness but no improvement in cognitive function in PAP-treated older adults with OSA but without dementia over a 1-year period.²¹

In contrast, a French long-term study of adults ages ≥ 65 years with severe (but not necessarily symptomatic) OSA showed better maintenance of memory performance; these results must be interpreted with caution, however, because the study was not randomized, controlled, or blinded, and the results were not adjusted for potential confounders.²² The severity of OSA may influence the impact of PAP treatment on cognitive function.

The prevalence of OSA in patients with dementia is high, and more severe dementia is associated with more severe OSA.²³ Although it is intuitive that disrupted sleep may worsen cognitive function, and that treatment could improve it, minimal benefit on cognitive function was shown by neuropsychological testing in patients with Alzheimer's disease and OSA treated with continuous positive airway pressure (CPAP) vs sham CPAP in 1 small short-term randomized trial.²³

In another study of patients with Alzheimer's disease, this time an observational (nonrandomized, non-controlled, single-

blind) study of patients who also had severe symptomatic OSA, researchers followed the patients for 3 years and found a significant delay in median annual cognitive decline of 1.5 points per year on the Mini-Mental Status Examination in patients treated with PAP compared with those who did not receive PAP treatment.²⁴

Hypertension: Small but positive results

A meta-analysis of PAP use in patients with OSA and resistant hypertension (defined as inadequate control while taking at least 3 antihypertensive agents or control requiring at least 4 agents) documented significant blood pressure (BP) lowering, with a pooled estimate of -7.21 mm Hg systolic and -4.99 mm Hg diastolic.²⁵ The decrease in BP was demonstrated in both sleepy and non-sleepy subjects.

Multiple studies have shown a small reduction in BP readings (generally about 2 mm Hg) with PAP treatment in nonresistant hypertensive patients with OSA who are sleepy.²⁶ Conversely, the literature is mixed on whether treatment of non-sleepy patients with OSA reduces BP. One long-term study demonstrated a small (1.89 mm Hg systolic, 2.19 mm Hg diastolic) BP reduction effect of PAP in non-sleepy subjects with OSA.²⁷ Similarly, research has shown mandibular advancement devices to lower BP in patients with OSA, in a range similar to that achieved with PAP.²⁸ Whether very small reductions in BP improve important clinical outcomes such as stroke or heart disease is unknown.

CV risk: Again, findings are mixed

The SAVE study is the largest randomized investigation of the effect of treatment of OSA with PAP for secondary prevention of cardiovascular events.²⁹ The trial involved 2717 adults with cardiovascular disease, moderate-to-severe OSA, and minimal sleepiness, and had as its primary composite endpoint death from cardiovascular causes, myocardial infarction (MI), stroke, hospitalization for unstable angina, heart failure, or transient ischemic attack. Patients with severe daytime sleepiness or severe hypoxemia were excluded. The study found no difference between PAP and usual care in the primary outcome, despite a significant reduction in the AHI from a mean of 29 at baseline to 3.7 with PAP treatment.

Similarly, a randomized controlled trial (RCT) of 725 patients with non-sleepy OSA failed to show a reduction in cardiovascular events or in the development of hypertension.³⁰ Peker et al³¹ randomized 244 adults with recently revascularized coronary artery disease and OSA without daytime sleepiness to auto-titrating CPAP or usual care and did not find a statistically significant difference in revascularization, MI, stroke, or cardiovascular mortality; however, those patients who were compliant with CPAP for ≥ 4 hours/night did have a statistically significant reduction in the combined endpoint.

In contrast, a trial of patients with first-ever stroke and moderate-to-severe OSA who were randomized to early nasal CPAP or usual care demonstrated better 5-year cardiovascular survival for the patients in the CPAP group, and a trend toward better cardiovascular event-free survival.³² Degree of daytime sleepiness was not stated in this study.

A recent meta-analysis of RCTs failed to find a reduction in major adverse cardiovascular events (MACE) in patients with moderate-to-severe OSA treated with PAP.³³ In this study, subgroup analysis documented benefit in patients who were adherent with PAP for ≥ 4 hours/night. A larger meta-analysis, however, did not find a reduction in MACE even in the adherent subgroup.³⁴

AF and OSA: An interesting relationship

OSA is an independent risk factor for AF, approximately doubling the risk.³⁵ A review of 10,132 patients with AF (1841 with OSA) in a large observational study demonstrated no difference in outcomes of all-cause mortality, first hospitalization, major bleeding, or major cardiovascular events in OSA patients who were or were not treated with PAP. The PAP-treated patients did have a slightly lower (16% vs 18%) risk of worsening of AF over 2 years.³⁶ Overall, AF patients with OSA had more symptoms and higher admission rates, but no difference in overall mortality or MACE. Observational studies have suggested that PAP treatment of OSA facilitates maintenance of normal sinus rhythm after cardioversion and after ablation.³⁷

CHF: Results look promising

In one small study, 24 patients with heart failure with reduced ejection fraction who were



The prevalence of OSA in patients with dementia is high, and more severe dementia is associated with more severe OSA.

➤ Offer a trial of treatment with PAP to asymptomatic patients with moderate-to-severe OSA and comorbidities, such as obesity, resistant hypertension, CHF, atrial fibrillation, and diabetes.

optimally medically treated were randomized to receive PAP or sham PAP for 1 month.³⁸ The treatment group demonstrated reduced systolic BP, reduced end systolic dimension, and significant improvement in ejection fraction from $25 \pm 2.8\%$ to $33.8 \pm 2.4\%$.

OSA Tx improves insulin sensitivity

OSA is associated with impaired glucose tolerance, and PAP treatment of OSA has been documented to improve insulin sensitivity.^{39,40} An efficacy study utilizing PAP in a laboratory setting for 8 hours/night demonstrated significant reduction in fasting blood sugar and a reduction in the dawn phenomenon (an increase in early morning fasting glucose as a result of rebound from hypoglycemia during sleep).³⁹ A 2015 meta-analysis of short-term studies also showed improvement in insulin sensitivity in OSA patients treated with PAP, but failed to find any reduction in A_{1C} or in body mass index.⁴⁰

All-cause mortality: Difference in findings between short- and long-term studies

Yu et al's³⁴ meta-analysis of 10 RCTs involving 7266 participants found no difference in mortality in treated (vs no treatment or sham treatment) OSA patients. This was true even in the more adherent subgroup. These studies were relatively short-term, with the longest mean follow-up being 68 months.

However, several longer-term population-based studies have suggested that OSA treatment improves all-cause mortality. An 18-year follow-up of a Wisconsin cohort documented dramatically increased mortality in patients with severe sleep apnea; mortality was even higher when patients treated with PAP were removed from the analysis, suggesting that PAP treatment was protective, mainly for cardiovascular death.⁵

A Danish registry documented that patients treated with CPAP had higher rates of comorbidities before and during treatment; when these comorbidities were controlled, men ages ≥ 60 years had improved survival when treated with CPAP. There was no survival benefit in women.⁴¹

A recent analysis—the Sleep Heart Health Study—followed patients with obesity and severe OSA for a mean of 11.1 years and calculated a hazard ratio for all-cause mortality associated with prescribed PAP therapy of 0.58 (95% confidence interval [CI], 0.35–0.96)

after propensity matching.⁴² The difference in mortality appeared 6 to 7 years after PAP therapy was prescribed. This delay may explain the failure of shorter-term studies to demonstrate evidence of benefit.

OSA Tx reduces motor vehicle crashes

Drowsy driving is widely accepted as a risk for motor vehicle crashes. Successful treatment of OSA with PAP has been shown to improve driving performance on a driving simulator.⁴³ An analysis of 15 studies similarly demonstrated a significant reduction in driving accidents (incident rate ratio [IRR] = 0.45) and in near-miss accidents (IRR = 0.23) in patients with OSA treated with CPAP.⁴⁴

Pulmonary hypertension: OSA Tx lowers pulmonary arterial pressure

Patients with OSA have higher than expected rates of pulmonary arterial hypertension—as high as 22%—documented by pulmonary artery catheterization findings.⁴⁵ A meta-analysis of studies that examined the effect of PAP in patients with OSA and coexisting pulmonary hypertension but without other overt pulmonary or cardiac disease found significant reductions in pulmonary artery pressure.⁴⁶ Whether this finding translates into improved patient-oriented outcomes is unknown.

OSA and pregnancy outcomes

A national cohort study demonstrated that OSA is an independent risk factor for multiple adverse pregnancy outcomes, including gestational diabetes, hypertensive disorders in pregnancy, intrauterine growth retardation, and stillbirth.⁷ OSA was also associated with the rare serious adverse outcomes of congestive heart failure, cardiomyopathy, and pulmonary embolism.⁷ There is little evidence to date with which to determine whether treatment of OSA improves outcomes, but PAP treatment is documented to be safe in pregnant women.⁸ **JFP**

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Strongly encourage patients to use PAP ≥ 4 hours/night and to recognize that benefits may not be immediately apparent.