

REVIEW ARTICLES

Treatment of Adult Obstructive Sleep Apnea With Positive Airway Pressure: An American Academy of Sleep Medicine Systematic Review, Meta-Analysis, and GRADE Assessment

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Introduction: The purpose of this systematic review is to provide supporting evidence for the clinical practice guideline for the treatment of obstructive sleep apnea (OSA) in adults using positive airway pressure (PAP).

Methods: The American Academy of Sleep Medicine commissioned a task force of experts in sleep medicine. A systematic review was conducted to identify studies that compared the use of PAP with no treatment as well as studies that compared different PAP modalities. Meta-analyses were performed to determine the clinical significance of using PAP in several modalities (ie, continuous PAP, auto-adjusting PAP, and bilevel PAP), to treat OSA in adults. In addition, meta-analyses were performed to determine the clinical significance of using an in-laboratory versus ambulatory strategy for the initiation of PAP, educational and behavioral interventions, telemonitoring, humidification, different mask interfaces, and flexible or modified pressure profile PAP in conjunction with PAP to treat OSA in adults. Finally, the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) process was used to assess the evidence for making recommendations.

Results: The literature search resulted in 336 studies that met inclusion criteria; 184 studies provided data suitable for meta-analyses. The data demonstrated that PAP compared to no treatment results in a clinically significant reduction in disease severity, sleepiness, blood pressure, and motor vehicle accidents, and improvement in sleep-related quality of life in adults with OSA. In addition, the initiation of PAP in the home demonstrated equivalent effects on patient outcomes when compared to an in-laboratory titration approach. The data also demonstrated that the use of auto-adjusting or bilevel PAP did not result in clinically significant differences in patient outcomes compared with standard continuous PAP. Furthermore, data demonstrated a clinically significant improvement in PAP adherence with the use of educational, behavioral, troubleshooting, and telemonitoring interventions. Systematic reviews for specific PAP delivery method were also performed and suggested that nasal interfaces compared to oronasal interfaces have improved adherence and slightly greater reductions in OSA severity, heated humidification compared to no humidification reduces some continuous PAP-related side effects, and pressure profile PAP did not result in clinically significant differences in patient outcomes compared with standard continuous PAP.

Keywords: obstructive sleep apnea, OSA, positive airway pressure, PAP

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INTRODUCTION

Obstructive sleep apnea (OSA) is a common sleep disorder affecting 26% of the United States adult population¹ and is associated with adverse health outcomes including excessive sleepiness, impaired quality of life (QOL), increased motor vehicle crashes (MVC), and cardiovascular events.^{2,3} Despite the advent of an array of treatment options, positive airway pressure (PAP) remains the primary treatment modality for OSA since the approach was introduced in 1981.⁴ Since the publication of the previous American Academy of Sleep Medicine (AASM) PAP practice parameters,^{5–7} the scientific literature on the effects of PAP on clinical outcomes in adults with OSA has grown substantially. Research on improving PAP adherence, a major barrier to maximizing the effectiveness of PAP therapy, and advancements in device technology to improve patient comfort have continued to evolve. The objective of this systematic review is to examine the clinical utility of

PAP to treat OSA in adults given these recent advancements in technology and knowledge. The AASM commissioned a task force (TF) of content experts to conduct this review. This review is intended to provide supporting evidence for the new clinical practice guideline on the use of PAP for the treatment of OSA in adults,⁸ and to replace the previously published AASM systematic review on the use of PAP treatment for sleep-related breathing disorders.⁹ This review addresses the initial management of patients with OSA without major medical comorbidities. This review does not address the initiation and management of PAP in patients with obesity hypoventilation syndrome, sleep-related hypoventilation, or those with concurrent forms of OSA and central sleep apnea. Prior reviews provided evidence in support of previously published AASM practice parameters regarding the efficacy of various modes of PAP therapy for central sleep apnea and hypoventilation syndromes,^{10,11} and are not considered in the scope of this review.

BACKGROUND

OSA is a common sleep disorder affecting 26% of adults, with 10% estimated to have moderate to severe disease.¹ Untreated OSA is associated with multiple adverse health outcomes including daytime sleepiness and decreased QOL as well as increased risk of MVC, systemic hypertension, diabetes, coronary artery disease, stroke, atrial fibrillation, congestive heart failure, and mortality.¹ OSA is defined by repetitive upper airway collapse and arousals from sleep, traditionally quantified with testing during sleep by the apnea-hypopnea index (AHI), respiratory disturbance index (RDI) or respiratory event index (REI). Common risk factors for OSA include obesity, advanced age, male gender, post-menopausal status in women, race, and craniofacial dysmorphisms.¹ Obesity is a prominent risk factor for OSA as demonstrated by reductions in OSA severity with weight loss interventions^{12,13} and the concurrent rise in the prevalence of OSA as obesity rates have risen.¹ Specifically, recent data from the Wisconsin Sleep Cohort estimate that 17% of men and 9% of women aged 50 to 70 years have at least moderate to severe OSA.¹ Furthermore, individuals of African American, Asian, or Hispanic race/ethnicity are at higher risk for OSA compared with similarly-aged Caucasians.^{14,15}

An important and well-recognized direct consequence of OSA is excessive daytime sleepiness, which can interfere with productivity both at home and in the workplace, and has been associated with an increased risk of MVC.¹⁶ OSA has been associated with QOL impairment, based upon global questionnaires like the Short Form of the Medical Outcomes Survey (SF-36), as well as those more specific to sleep-related domains, such as the Functional Outcomes of Sleep Questionnaire (FOSQ), Quebec Sleep Questionnaire (QSQ), and the Calgary Sleep Apnea Quality of Life Index (SAQLI). Although results have varied, studies have also found associations between OSA and impaired cognition, with more consistent deficits in executive function and vigilance.¹⁷

OSA is also associated with a number of systemic disorders. It is strongly linked with cardiovascular diseases such as congestive heart failure, stroke, atrial fibrillation and ischemic heart disease, and may have a causal role in the development of systemic hypertension.¹⁸ Although the evidence is conflicting and sometimes confounded by obesity, OSA has been shown to impair insulin sensitivity and predict incident type 2 diabetes mellitus (T2DM).¹⁹

The pathogenic role of upper airway collapse was initially described in the 1960's,^{20,21} and for more than a decade tracheostomy was the only effective treatment. PAP has become the primary therapy used to treat adult OSA across the spectrum of disease severity. Continuous positive airway pressure (CPAP) therapy as a treatment modality was first described in 1981.⁴ This form of treatment applied a constant pressure throughout the respiratory cycle to splint the airway open. Subsequently, bilevel PAP (BPAP), a modality which delivers a higher inspiratory PAP (IPAP) relative to the expiratory PAP (EPAP) was also found to be effective in the treatment of OSA. A theoretical advantage of BPAP was that a lower EPAP could be applied that would increase tolerance to PAP treatment of OSA. With advancements in technology, flow sensors were integrated into

PAP devices to assess the presence of obstructive breathing events. Computer algorithms were then developed and incorporated into CPAP devices to dynamically increase CPAP when obstructive breathing events were detected, and to periodically reduce the delivered pressure when no events were detected for some period of time, ie auto-adjusting PAP (APAP). Auto-adjusting computer algorithms were subsequently developed for BPAP (auto-BPAP). APAP in the ambulatory setting is increasingly being utilized as an alternative to traditional in-laboratory PAP titrations for the initiation and continued treatment of OSA.

Regardless of these technological advancements, the continuous application of PAP during sleep when the airway is vulnerable to collapse is critical. To maximize clinical benefit, most clinicians recommend utilization of PAP therapy for the entire sleeping period, though lesser utilization may have benefits for some individuals. Although PAP use for at least 4 hours during sleep per a 24-hour period is commonly used to clinically define minimal acceptable levels of adherence, current evidence suggests a continuous dose-response relationship between hours of use and therapeutic response.^{22,23}

Given challenges in optimizing PAP adherence, approaches to making PAP more comfortable are desirable. Technological advances in PAP therapy have occurred over time to promote patient comfort and potentially improve adherence to treatment. A variety of mask interfaces available continues to evolve with design advances in nasal masks, nasal pillows, full face masks, and oral masks. This greater variety of mask configurations has allowed for better individualization of the interface to a patient to reduce leak and improve comfort. PAP manufacturers have also addressed the common side effect of nasal dryness by designing in-line humidifiers, which were first passive but now include heated systems. These have become standard to include with PAP therapy in many markets. The current generation of PAP devices also integrates modified pressure profiles and is offered as a standard feature. This option transiently lowers the treatment pressure during expiration, with some systems also modifying the inspiratory pressure profile, to increase patient comfort without compromising airway patency. Prior to the development of modified pressure profile technologies, BPAP was and continues to be used for similar reasons.

Given evidence that patients overestimate their usage of PAP, objective adherence monitoring has been another major advance in PAP technology. Initially, based on a meter built into the machine,²⁴ the development of removable cards to record PAP usage increased the ability of providers to track patient adherence. Internet-based applications combined with built-in modems now allow for remote monitoring of usage. The adoption of adherence requirements for insurance coverage by many payors has made objective adherence monitoring a standard of care in the United States.

Because device improvements have only had a modest impact on adherence,²⁵ more attention is being given to educational and behavioral interventions to improve patient adherence. Observational data have demonstrated that increased knowledge of OSA and its long-term impacts, as well as the beneficial effects of PAP predict adherence, raising interest in

Table 1—PICO questions.

1. In adult patients with OSA, does CPAP versus no treatment improve AHI/RDI/REI, daytime sleepiness, neurocognitive function, quality of life, sleep quality, mood, and motor vehicle crashes?
2. In adult patients with OSA, does PAP versus no therapy improve left ventricular ejection fraction, blood pressure control, and glucose control (hemoglobin A1c; fasting glucose)?
3. In adult patients with OSA, does PAP versus no therapy reduce cardiovascular event rates (incident hypertension, myocardial infarction, coronary revascularization procedures, stroke, atrial fibrillation, sudden death, hospitalization for heart failure, and cardiovascular mortality), all-cause hospitalization, and all-cause mortality?
4. In adult patients with OSA, does initiation of PAP based on an in-laboratory versus ambulatory APAP-based strategy improve AHI/RDI, adherence to PAP therapy, sleepiness, and quality of life?
5. In adult patients with OSA, does APAP versus CPAP improve AHI/RDI, adherence, sleepiness, neurocognitive function, and quality of life, and reduce side effects?
6. In adult patients with OSA, does BPAP or auto-BPAP versus CPAP improve AHI/RDI, adherence to PAP therapy, sleepiness, neurocognitive function, and quality of life, and reduce side effects?
7. In adult patients with OSA, does the addition of modified pressure profile PAP to PAP therapy improve adherence to PAP therapy, sleepiness, and quality of life, and reduce side effects?
8. In adult patients with OSA, does oral CPAP versus nasal (nasal mask versus intranasal) CPAP versus oronasal CPAP improve AHI/RDI, adherence to PAP therapy, sleepiness, and quality of life, and reduce side effects?
9. In adult patients with OSA, does humidified PAP versus standard PAP improve adherence to PAP therapy, sleepiness, quality of life, and reduce side effects?
10. In adult patients with OSA, do educational or behavioral interventions versus no intervention prior to or during PAP treatment improve adherence to PAP therapy, sleepiness, and quality of life?
11. In adult patients with OSA, do interventions guided by monitoring of OSA and PAP parameters during PAP treatment versus no monitoring improve adherence to PAP therapy, sleepiness, and quality of life, and reduce side effects?

AHI = apnea-hypopnea index, APAP = auto-adjusting positive airway pressure, BPAP = bilevel positive airway pressure, CPAP = continuous positive airway pressure, OSA = obstructive sleep apnea, PAP = positive airway pressure, PICO = Patient, Population or Problem, Intervention, Comparison, and Outcomes, RDI = respiratory disturbance index, REI = respiratory event index.

educational interventions.²⁶ Similar data suggest that decisions about PAP usage are made very early after treatment initiation suggesting any such intervention needs to be delivered early to maximize effect.²⁷ Based on efficacy in changing behaviors in other conditions and settings such as sleep behaviors in insomnia, abstinence in addiction disorders, and medication adherence in chronic medical diseases, there has been interest in developing behavioral interventions such as cognitive behavioral therapy or motivational enhancement to improve PAP adherence. A major challenge, however, has been developing an intervention intensive enough to be effective, but not so expensive as to reduce feasibility in clinical practice. In this milieu, the use of telemonitoring of adherence has gained substantial interest. By identifying those patients who are having the greatest difficulties in real-time, interventions can be individually tailored and quickly deployed to those who will benefit the most.

Finally, the overall concerns of rising healthcare costs have impacted the delivery of OSA care. More patients are being diagnosed based on home sleep apnea tests and in this setting the use of APAP has the potential to allow for rapid initiation of treatment at lower costs in the uncomplicated patient. These devices detect flow and/or impedance and based on manufacturer-specific algorithms, adjust pressure in real-time in an effort to deliver the lowest pressure needed to maintain airway patency.^{28,29} While originally developed to improve comfort, the technology has increasingly been utilized as an alternative to in-laboratory PAP titration. Long-term use of APAP has the potential benefit of obviating adjustments in pressure settings over time in response to changes in OSA severity. However, as

the algorithms are designed to continually lower pressure until respiratory events return, there is the potential for incomplete treatment of OSA.²⁹

With these key issues in mind, this systematic review provides a comprehensive update of the latest evidence for the use of PAP to treat adult patients with OSA.

METHODS

Expert Task Force

The AASM commissioned a TF composed of both board-certified sleep medicine specialists and experts with proficiency in the use of PAP in adults with OSA to develop this systematic review. The TF was required to disclose all potential conflicts of interest (COI) per the AASM's COI policy prior to being appointed to the TF, and throughout the research and writing of this paper. In accordance with the AASM's COI policy, TF members with a Level 1 conflict were not allowed to participate. TF members with a Level 2 conflict were required to recuse themselves from any related discussion or writing responsibilities. All relevant COI are listed in the disclosure statement.

PICO Questions

PICO (Patient, Population or Problem, Intervention, Comparison, and Outcomes) questions were developed based on a review of the existing AASM practice parameters on the use of PAP and a review of systematic reviews, meta-analyses, and guidelines published since 2005. The AASM Board of

Table 2—Critical outcomes by PICO question.

Outcomes	PICO Question										
	1	2	3	4	5	6	7	8	9	10	11
Sleepiness	✓			✓	✓	✓	✓	✓	✓		✓
Adherence to PAP therapy				✓	✓	✓	✓	✓	✓	✓	✓
Quality of life	✓			✓	✓	✓	✓	✓	✓	✓	✓
Side effects							✓		✓		✓
Blood pressure control		✓									
Cardiovascular events			✓								
All-cause mortality			✓								

PAP = positive airway pressure, PICO = Patient, Population or Problem, Intervention, Comparison, and Outcomes.

Directors approved the final list of PICO questions presented in **Table 1** before the literature search was performed. To develop the PICO questions, the TF identified commonly used PAP interventions and alternative approaches and strategies for the implementation of PAP in the treatment of adults with OSA. The TF then developed a list of patient-oriented, clinically relevant outcomes to determine whether CPAP, compared to no treatment, alternative PAP modes, and concurrent strategies designed to enhance acceptance and use of PAP for OSA treatment should be recommended for clinical practice. The TF rated the relative importance of each outcome to determine which outcomes were critical for decision-making. A summary of these “critical” outcomes by PICO is presented in **Table 2**. Several additional clinical outcomes considered of importance for the clinical management of OSA and related comorbidities were also examined including the AHI/RDI/REI, hemoglobin A1c, fasting glucose, blood pressure, left ventricular ejection fraction (LVEF), neurocognitive function, MVC, hospitalizations, cardiovascular events, and mortality.

The TF set a clinical significance threshold for each outcome to determine whether the mean changes in the outcomes assessed were clinically significant. The clinical significance threshold was defined as the minimum level of improvement in the outcome of interest that would be considered clinically important to clinicians and patients. Outcomes which met the clinical significance threshold but were not statistically significant resulted in reductions in the grading of the evidence quality and reduced the strength of the recommendation. A summary of the clinical significance thresholds for the clinical outcome measures is presented in **Table 3**. Clinical significance thresholds were determined based on a TF literature review of commonly used thresholds. Where no clearly established threshold values could be determined, the TF used the literature review, clinical judgment, and experience to establish a clinical significance threshold based on consensus.

Literature Searches, Evidence Review and Data Extraction

The TF performed an extensive review of the scientific literature to retrieve articles that addressed the PICO questions. Separate literature searches were performed by the AASM research staff for each PICO question using the PubMed and Embase databases (see **Figure 1**). The key terms, search limits,

and inclusion/exclusion criteria specified by the TF are detailed in the supplemental material. Randomized controlled trials (RCTs) and observational studies that were cited in the prior AASM PAP practice parameters^{5,7} were included for data analysis only if they met the current inclusion criteria.

The initial literature search of English publications in PubMed and Embase was performed in October 2013 and was limited to RCTs. A second literature search was performed in April 2015 using broader search terms to identify additional articles in PubMed and Embase from October 2013 to April 2015 (see supplemental material). This search was conducted using broader search terms in an effort to capture more relevant articles than the initial PICO-targeted searches. In addition, for PICO questions 1 (MVC only), 3, and 8, where the evidence based on RCTs was low or not available, the TF also searched for observational studies with both an intervention and control group relevant to the specific PICO. A third literature search limited to PubMed was performed in September 2016 to identify studies that were published since the second literature search to update the body of evidence for the review. A fourth search also limited to PubMed was conducted in February 2018 to update the evidence prior to publication. These searches identified a total of 1,447 unique articles. Lastly, the TF reviewed previously published guidelines, systematic reviews, and meta-analyses to spot check for references that may have been missed during the prior searches. The TF identified 65 additional articles for a total of 1,512 articles that were screened for inclusion/exclusion in the guideline.

The TF set inclusion and exclusion criteria, which are presented in the supplemental material and summarized in **Figure 1**. All abstracts were reviewed based on inclusion/exclusion criteria by two TF members. Any discrepancies between the reviewers were discussed and resolved by the Chair. A total of 184 studies were determined to be suitable for meta-analysis and/or grading.

Meta-Analysis

Meta-analysis was performed on outcomes of interest, when possible, for each PICO question. Comparisons of CPAP to no treatment and the comparative efficacy of alternative types of PAP devices used to treat OSA in adult patients were performed. For the purposes of our analyses, PAP devices were categorized into the following categories: CPAP, APAP, BPAP,

Table 3—Summary of clinical significance thresholds for outcome measures.

Outcome Measure	Clinical Significance Threshold* †	Outcome Measure	Clinical Significance Threshold* †
AHI/RDI/REI	≥ 15 events/h ³⁰⁻³²	Sleep quality	
Adherence to PAP therapy	0.5 h/night; 10% patient use > 4 h/night ^{32,33}	Pittsburgh Sleep Quality Index	3 points ⁴⁶
Self-reported sleepiness		Blood pressure	
Epworth Sleepiness Scale	2 points ³⁵⁻³⁷	24-hour mean	1 mmHg ^{47,48}
Objective sleepiness		Systolic blood pressure	–
MWT	2 minutes ³⁸⁻⁴⁰	24-hour	2 mmHg ^{47,48}
OSLER	2 minutes ³⁸⁻⁴⁰	Nighttime	2 mmHg ^{47,48}
MSLT	1 minute ³⁸⁻⁴⁰	Daytime	2 mmHg ^{47,48}
OSLER, MWT combined	0.2 SMD ⁴¹	Diastolic blood pressure	–
MWT, OSLER, MSLT combined	0.2 SMD ⁴¹	24-hour	1 mmHg ^{47,48}
Quality of life		Nighttime	1 mmHg ^{47,48}
FOSQ	1 point ³³	Daytime	1 mmHg ^{47,48}
SAQLI	1 point ³³	Mood	
SF-36	–	HADS depression	2 points ^{49,50}
Physical component summary	3 points ⁴²	HADS anxiety	2 points ^{49,50}
Mental component summary	3 points ⁴²	Cardiovascular Events	Risk ratio of 0.8 ⁵¹
Vitality summary	12.5 points ⁴³	All-cause mortality	Risk ratio of 0.8 ⁵¹
QSQ	–	Left ventricular ejection fraction	4% ⁵²
Daytime sleepiness	1.8 points ⁴⁴	Fasting glucose	0.6 mmol/L ⁵³
Diurnal symptoms	2.0 points ⁴⁴	Hemoglobin A1c	0.3% ^{54,55}
Nocturnal symptoms	1.5 points ⁴⁴	Neurocognitive function	0.2 SMD ⁴¹
Emotions	1.1 points ⁴⁴	All-cause hospitalizations	Risk ratio of 0.9 ⁵⁶
Social interactions	2.5 points ⁴⁴	Motor vehicle crashes	Risk ratio of 0.9 ⁵⁷⁻⁵⁹
FOSQ, SAQLI, and/or QSQ combined	0.2 SMD ⁴¹	Side effects	Odds ratio of 0.9
EQ-5D	0.08 points ⁴⁵		

* = references used to inform task force consensus. † = the clinical significance thresholds are for comparison of posttreatment effects between two different treatments. AHI = apnea-hypopnea index, EQ-5D = European Quality of Life-5D, FOSQ = Functional Outcome of Sleep Questionnaire, HADS = Hospital Anxiety and Depression Scale, MSLT = Multiple Sleep Latency Test, MWT = Maintenance of Wakefulness Test, Osler = Oxford Sleep Resistance Test, QSQ = Quebec Sleep Questionnaire, RDI = respiratory disturbance index, REI = respiratory event index, SAQLI = Calgary Sleep Apnea Quality of Life Index, SF-36 = Short Form - 36 item, SMD = standardized mean difference.

and modified pressure profile PAP. Mask interfaces were categorized as nasal PAP, nasal pillow PAP, oral PAP, and oronasal PAP. Education and behavioral interventions were categorized as education, education plus troubleshooting, and behavioral interventions. Telemonitoring was defined as the remote monitoring of PAP parameters such as PAP usage, residual OSA severity, excessive mask leaks, and PAP settings, during treatment initiation and follow-up. Treatment delivery strategies were categorized as home APAP-initiated (ambulatory) or in-laboratory initiated CPAP and treatment with APAP or fixed CPAP. There was insufficient evidence to perform meta-analyses for some outcome measures and comparisons within some of the PICO questions, including side effects data.

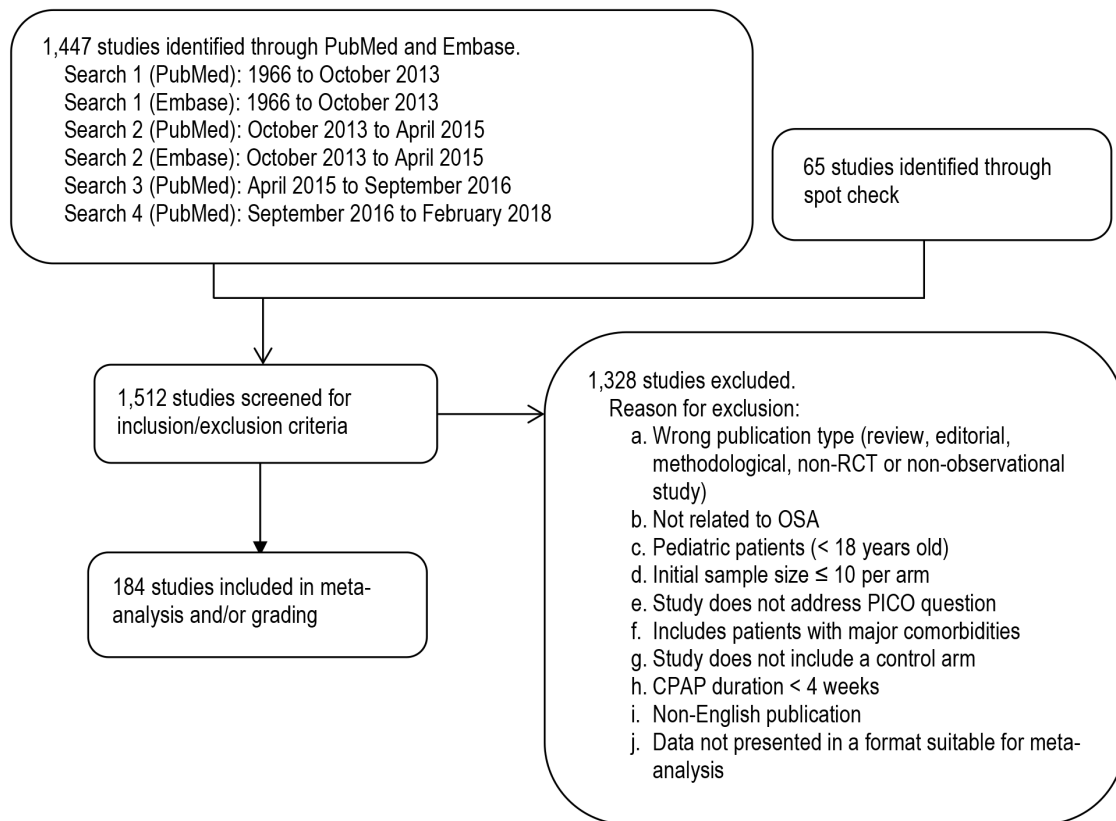
Meta-analysis was performed using Review Manager 5.3 software by pooling data across studies for each outcome measure. Posttreatment data were used for meta-analysis, except where change values were determined to be more meaningful to the reader (eg, blood pressure [BP], LVEF, neurocognitive outcomes, and driving proficiency). Standardized mean differences (SMD) were used for outcomes when the TF determined

interpretation of effect size would be more clinically meaningful than posttreatment or change values (eg, combined Maintenance of Wakefulness Test [MWT] and Oxford Sleep Resistance Test [OSLER], combined FOSQ, QSQ, and SAQLI, neurocognitive measures, and driving simulator outcomes). The pooled results for each continuous outcome measure are expressed as the mean difference or standardized mean difference between the intervention and comparator. The pooled results for dichotomous outcome measures are expressed as the odds ratio or risk ratio between the intervention and comparator. All analyses were performed using a random effects model with results displayed as a forest plot. Interpretation of clinical significance for the outcomes of interest was conducted by comparing the mean difference in effect of each treatment approach to the clinical significance threshold (see **Table 3**).

GRADE Assessment for Developing Recommendations

The assessment of evidence quality was performed according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) process.⁶⁰ The TF assessed

Figure 1—Evidence base flow diagram.



CPAP = continuous positive airway pressure, OSA = obstructive sleep apnea, PICO = Patient, Population or Problem, Intervention, Comparison, and Outcomes, RCT = randomized controlled trial.

the following four components to determine the direction and strength of a recommendation: quality of evidence, balance of beneficial and harmful effects, patient values and preferences, and resource use, as described below.

1. Quality of evidence – based on an assessment of the overall risk of bias (randomization, blinding, allocation concealment, selective reporting), imprecision (95% confidence interval relative to the clinical significance threshold), inconsistency (I^2 cutoff of 50%), indirectness (study population), and risk of publication bias (funding sources), the TF determined their overall confidence that the estimated effect found in the body of evidence was representative of the true treatment effect that typical adult patients with OSA would see. The overall quality of the evidence was based on outcomes that the TF deemed critical for decision making.
2. Benefits versus harms – based on the meta-analysis (if data were available), analysis of any harms/side effects reported within the accepted literature, and the clinical expertise of the TF, the TF determined if the beneficial outcomes of the intervention outweighed any harmful side effects.
3. Patient values and preferences – based on the clinical expertise of the TF members and any data published on the topic relevant to patient preferences, the TF

determined if patient values and preferences would be generally consistent across the majority of patients, and if patients would use the intervention based on the relative harms and benefits identified.

4. Resource use – based on the clinical expertise of the TF members, the TF judged resource use to be important for determining whether to recommend the use of a specific PAP device type or approach to patient care over another for the treatment of adults with OSA.

A summary of each GRADE domain is provided after the detailed evidence review. As this guideline focuses on providing recommendations on the indications for PAP therapy in adult patients with OSA, rather than the use of specific components or accessories of the PAP device, recommendations for PICOs 7–9 (**Table 1**) were not included. A summary of the systematic review and meta-analyses of the evidence for these PICO questions can be found in the “Additional Considerations” section, as these factors are still important for clinicians to consider in the context of their individual patient’s circumstances when initiating PAP therapy.

Public Comment and Final Approval

A draft of the guideline and systematic review was made available for public comment for a two-week period on the AASM website. The TF took into consideration all the comments

received and made decisions about whether to revise the draft based on the comments. The revised guideline and systematic review were submitted to the AASM Board of Directors for subsequent approval. This review reflects the state of knowledge at the time of publication and will be reviewed and updated as new information becomes available.

THE USE OF POSITIVE AIRWAY PRESSURE

The aims of the current literature reviews and data analyses were focused on addressing 11 questions pertaining to the use of PAP to treat OSA in adults. Below are detailed summaries of the evidence identified in the literature searches and the statistical analyses performed by the TF. Each evidence summary is accompanied by a discussion of the quality of evidence, balance of benefits and harms, patient values and preferences, and resource use considerations that contributed to the development of the recommendations provided in the accompanying clinical practice guideline.⁸

Continuous Positive Airway Pressure Therapy Versus No Therapy

This section addresses PICO questions 1–3 (see **Table 1**) and resulted in three recommendations (see Recommendations 1–3 in the companion clinical practice guideline).⁸ A total of 80 RCTs^{34,36,61–132} and 15 non-randomized studies^{133–152} investigated the use of PAP to improve one or more of the following outcomes: OSA severity, sleepiness, QOL, sleep quality, mood, neurocognitive function, MVC, blood pressure, left ventricle ejection fraction, fasting glucose, hemoglobin A1c, incident cardiovascular events, and incident mortality. Participants in the studies were from clinic-based populations and were predominantly male, obese, with moderate to severe OSA and self-reported sleepiness. RCTs were reviewed for all outcomes with the exception of MVC, for which non-randomized studies were reviewed. Both RCTs and non-randomized studies were reviewed for the outcomes of incident cardiovascular events and incident mortality. For the RCTs, participants were randomized to a control intervention utilizing sham CPAP, conservative measures or no intervention, sham surgery, placebo tablet, or nasal dilator strips. For each outcome, important differences in patient population or study design from the general description above are noted below. Several meta-analyses were performed to assess the efficacy of PAP for the treatment of OSA in adults as compared with no therapy. The meta-analyses are provided in the supplemental material, **Figure S1** through **Figure S57**. Summary of Findings tables are provided in the supplemental material, **Table S1** through **Table S3**. A summary of the evidence for each outcome is provided below.

OSA Severity

The efficacy of PAP in reducing OSA severity in adults was evaluated using a meta-analysis of studies that reported on the AHI or RDI. For this analysis, the two measures were considered equivalent. All studies were RCTs, with 3 studies using a randomized, cross-over design.^{61,65,84} Participants were

randomized to CPAP or a control intervention. The control interventions utilized included sham CPAP ($n = 5$),^{34,66,74,84,93} conservative measures (advice on weight loss or good sleep habit counseling), no intervention ($n = 3$),^{78,82,92} sham surgery ($n = 1$),⁹⁰ placebo tablet ($n = 1$),⁶⁵ and nasal dilator strips ($n = 1$)⁶¹. The duration of intervention was at least 1 month (range: 1–6 months).

A meta-analysis of 11 RCTs^{34,61,65,66,74,78,82,84,90,92,93} demonstrated a clinically significant mean difference in OSA severity of -23 events/h (95% CI: -29 to -18 events/h) with PAP (see supplemental material, **Figure S1**). An additional meta-analysis of these studies comparing OSA severity before and after CPAP treatment demonstrated a clinically significant mean reduction in OSA severity of -29 events/h (95% CI: -37 to -20 events/h) or an AHI reduction of 86% with PAP (see supplemental material, **Figure S2**). The mean pretreatment AHI was 32.7 ± 12.6 events/h and the posttreatment AHI was 4.1 ± 5.6 events/h. Overall, the analyses support the conclusion that CPAP is effective in reducing OSA severity as measured by the AHI or RDI, across the spectrum of OSA severity. The quality of evidence for OSA severity was high.

Sleepiness

Meta-analyses on sleepiness outcomes were performed analyzing both self-reported sleepiness as determined by the Epworth Sleepiness Scale (ESS) and objective sleepiness as determined by the Multiple Sleep Latency Test (MSLT), MWT, and the OSLER. Participants were self-reportedly sleepy with the exception of 5 studies that recruited non-sleepy participants evaluated after at least 1 month of intervention (range: 4–12 months follow-up).^{63,76,85,106,112} Seven studies recruited participants with concomitant hypertension^{36,63,68,86,100,106,112} and one study⁸⁹ recruited participants with concomitant T2DM. The control intervention employed was predominantly sham PAP or no PAP with one study⁸⁵ using nasal dilator strips, one study¹¹² using sleep hygiene and counseling, and one study³⁶ asked participants to continue with their normal medication.

A meta-analysis of 38 RCTs^{34,61–90,106,112,114–116,150,153} demonstrated a clinically significant reduction in self-reported sleepiness of -2.4 points in the ESS score (95% CI: -2.8 to -1.9 points) in participants on PAP compared to controls (see supplemental material, **Figure S3**). A sub-analysis of the 5 studies^{63,85,86,106,112} recruiting only non-sleepy participants with OSA demonstrated an ESS reduction of -1.0 points (95% CI: -0.7 to -1.4 points) that the TF judged to not be clinically significant. A meta-analysis of 7 RCTs using the MWT or OSLER sleep latency to assess objective wakefulness demonstrated a clinically significant SMD in objective sleepiness of 0.5 (95% CI: 0.2 to 0.8) with the use of PAP^{65,71,73,76,77,81,89} (see supplemental material, **Figure S4**). In contrast, a meta-analysis of 7 RCTs^{63,64,69,70,82,85,91} using the MSLT to assess objective sleepiness demonstrated no clinically significant difference in sleep latency with the use of PAP (see supplemental material, **Figure S5**). Overall, the analyses support the conclusion that treatment of OSA with CPAP results in clinically significant improvements in self-reported sleepiness and the ability to maintain wakefulness, particularly in sleepy patients with OSA. The overall quality of evidence for sleepiness was high.

Quality of Life

The efficacy of PAP in improving sleep-related QOL in adults with OSA was evaluated using meta-analyses combining studies that reported on the FOSQ ($n = 8$),^{34,63,65,72,82–84,90} and the SAQLI ($n = 5$),^{36,78,81,87,89} In addition, meta-analyses were also performed for the SF-36 component summary scores, specifically the mental component score ($n = 12$),^{36,63,64,71,76,78,83,87,90,116,150,151} the physical component score ($n = 11$),^{63,64,70,76,78,83,87,90,116,150,151} and the vitality score ($n = 8$)^{36,64,71,78,83,87,150,151} to assess the efficacy of PAP to improve general QOL.

The studies were performed with participants who had moderate to severe OSA and/or were self-reportedly sleepy, with the exception of one study that recruited non-sleepy participants with mild to moderate OSA⁶³ and two studies^{71,72} that specifically recruited participants with mild OSA and symptoms of sleepiness. All studies were RCTs, with 5 studies^{64,65,71,72,84} using a randomized, cross-over design. Participants were randomized to PAP or a control intervention. Sham PAP ($n = 8$),^{34,63,76,83,84,87,89,150} conservative measures (advice on weight loss or good sleep habit counseling) or no intervention ($n = 6$),^{36,78,82,116,150,151} placebo tablet ($n = 4$),^{64,65,71,72} and sham surgery ($n = 1$)⁹⁰ were utilized as control interventions. The length of the intervention was at least 1 month (range: 1–48 months follow-up).

The meta-analyses for QOL are presented in the supplemental material, **Figure S6** through **Figure S9**. A total of 19 RCTs investigated the efficacy of PAP to improve QOL in adults with OSA.^{34,36,63–65,71,72,76,78,81–84,87,89,90,116,150,151} Meta-analysis of some measures of QOL demonstrated a clinically significant difference with PAP while others did not. A meta-analysis of 8 RCTs^{34,63,65,72,82–84,90} reporting on FOSQ and 5 RCTs^{36,78,81,87,89} reporting on SAQLI demonstrated a clinically significant SMD of 0.3 (95% CI: 0.1 to 0.5). Meta-analyses of RCTs reporting on QOL using the SF-36 physical component summary score,^{63,64,71,76,78,83,87,90,116,150,151} the mental component summary score,^{36,63,64,71,76,78,83,87,90,116,150,151} and the vitality score^{36,64,71,78,83,87,150,151} demonstrated no clinically significant improvement in QOL using PAP. Overall, the analyses suggest that PAP is effective in improving sleep-related QOL, but not overall QOL in adults with OSA. The quality of evidence for QOL ranged from moderate to high, depending on the measure employed, and was downgraded due to imprecision.

Blood Pressure (All Participants)

A total of 26 RCTs measured BP before and after PAP therapy.^{36,63–66,68,75,79,82,86,89,94–98,100–102,104,105,112,116,117,120,148} Of these, 5 specifically recruited hypertensive participants,^{68,86,100,112,148} and 5^{79,97,98,117,120} focused on resistant hypertension (participants treated with ≥ 3 antihypertensive medications). The majority of RCTs studied mixed populations of normotensives and hypertensives, many of whom were treated with antihypertensive drugs. Three trials recruited only normotensive participants.^{72,94,95} Most RCTs did not specify sleepiness status a priori, however, a few RCTs were limited to non-sleepy^{63,86,112} or sleepy^{94,101} participants, with most studies^{63,86,112} primarily based on the ESS. Trial participants were often concurrently treated with anti-hypertensive agents at study enrollment, but medication use was not explicitly considered in participant

selection or outcome assessment. Several control conditions were utilized, ranging from sham PAP,^{63,66,68,75,86,89,94,100–102,104,120} to usual care,^{36,82,97,98,112,116,148} to an oral placebo tablet^{64,65} to no treatment while maintaining antihypertensive medications^{79,95,96,105,117} for comparison to PAP. The intervention duration ranged from 1 month to 1 year. Many studies utilized 24-hour (or 48-hour) ambulatory BP measurements, considered to be the most accurate method to diagnose hypertension and the best predictor of future cardiovascular risk.¹⁵⁴ Some studies utilized office or lab-based measurements limited to the daytime hours^{67,82} and one study³⁶ utilized home daytime measurements.

Meta-analyses were performed on several measures of BP including: nighttime systolic and diastolic BP; daytime systolic and diastolic BP; 24-hour systolic and diastolic BP; and 24-hour mean BP (see supplemental material, **Figure S10** through **Figure S33**). Studies that did not describe a systematic method of BP ascertainment were excluded from the meta-analyses.

For the entire participant sample, meta-analysis demonstrated that PAP therapy was associated with a clinically significant reduction in nighttime systolic blood pressure (SBP) and diastolic blood pressure (DBP) of -4.2 mmHg (95% CI: -6.0 to -2.5 mmHg), and -2.3 mmHg (95% CI: -3.7 to -0.9 mmHg), respectively (see supplemental material, **Figure S10** and **Figure S11**). Clinically significant reductions in daytime SBP and DBP of -2.8 mmHg (95% CI: -4.3 to -1.2 mmHg) and -2.0 mmHg (95% CI: -3.0 to -0.9 mmHg), respectively were observed (see supplemental material, **Figure S12** and **Figure S13**). In addition, PAP therapy was also associated with a clinically significant reduction in 24-hour SBP and DBP of -1.5 mmHg (95% CI: -2.3 to -0.7 mmHg) and -1.6 mmHg (95% CI: -2.2 to -0.9 mmHg), respectively (see supplemental material, **Figure S14** and **Figure S15**). Lastly, a meta-analysis demonstrated a clinically significant reduction in 24-hour mean BP of -2.6 mmHg (95% CI: -3.9 to -1.4 mmHg) with PAP therapy (see supplemental material, **Figure S16**).

As described above, many trials studied heterogeneous populations with respect to characteristics that may differentially influence the BP-lowering response to PAP therapy. For example, most studies described a minimum requirement for moderate to severe OSA, while only two^{63,95} specified severe OSA defined by an AHI > 30 events/h. Two studies included participants with an AHI of 5–30 events/h,^{64,65} and none exclusively recruited participants with mild OSA (AHI of 5–15 events/h). Nightly PAP adherence was variable and commonly in the range of what most clinicians would deem suboptimal. One study suggested greater BP reduction with increased CPAP adherence.¹⁵⁵ However, whether this reflects the effect of PAP treatment or patient adherence with therapies in general, remains unclear. Some trials^{63,95} used fixed CPAP titrated during PSG in the sleep laboratory and some^{36,94} used APAP, while others^{68,97} used CPAP derived from a night on APAP. Distinguishing between these modes may be important in light of some studies suggesting differential effects of CPAP and APAP on BP.^{156,157}

The BP reductions associated with RCTs of PAP therapy found in these meta-analyses, if sustained, would result in substantial reductions in long-term cardiovascular risk.¹⁵⁸ The TF only considered the impact of PAP versus no treatment on BP in

adults with OSA and did not compare PAP to antihypertensive drugs, which has been considered in some recent trials.^{159,160}

Overall, the analyses suggest that PAP use reduces BP in adults with OSA, particularly in participants with moderate to severe OSA. The quality of evidence for BP in all participant types with OSA ranged from moderate to high, depending on the time and type of BP measured, and was downgraded due to imprecision.

Blood Pressure (Resistant Hypertensive Participants)

A total of 5 of the 27 RCTs reported on the effects of PAP therapy on BP in participants with OSA and comorbid resistant hypertension at baseline.^{79,97,98,117,120} Participants had predominantly moderate to severe OSA. Meta-analyses demonstrated the mean estimate of the effect of PAP therapy were clinically significant reductions in nighttime SBP and DBP (−3.3 mmHg [95% CI: −6.1 to −0.4 mmHg] and −2.2 mmHg [95% CI: −4.4 to 0.0 mmHg], respectively), daytime DBP (−1.1 mmHg [95% CI: −3.4 to +1.1 mmHg]), and 24-h SBP and DBP, (−2.2 mmHg [95% CI: −5.1 to +0.8 mmHg], and −2.1 mmHg [95% CI: −4.1 to 0.0 mmHg], respectively) with CPAP therapy but not a clinically significant reduction in daytime SBP (see supplemental material, **Figure S17** through **Figure S22**).

Overall, the analyses suggest that PAP use reduces nighttime and 24h blood pressure in adults with predominantly moderate to severe OSA and resistant hypertension. The quality of evidence for BP in resistant hypertensive participants with OSA was moderate due to imprecision.

Blood Pressure (Hypertensive Participants)

A total of 5 of the 27 RCTs reported on the effects of PAP therapy on BP in participants with OSA and comorbid hypertension at baseline.^{68,86,100,112,148} Participants had predominantly moderate to severe OSA. Meta-analyses demonstrated clinically significant reductions in nighttime SBP and DBP of −3.9 mmHg [95% CI: −6.5 to −1.4 mmHg] and −3.0 mmHg [95% CI: −5.3 to −0.8 mmHg], respectively (see supplemental material, **Figure S23** and **Figure S24**). Clinically significant reductions in daytime SBP and DBP of −2.7 mmHg [95% CI: −4.9 to −0.5 mmHg], and −2.4 mmHg [95% CI: −3.9 to −0.9] respectively, were observed (see supplemental material **Figure S25** and **Figure S26**). In addition, PAP therapy was also associated with clinically significant reductions in 24-hour SBP and DBP of −2.5 mmHg [95% CI: −4.3 to −0.8 mmHg] and −2.2 mmHg [95% CI: −3.4 to −1.0 mmHg] with PAP therapy, respectively (see supplemental material, **Figure S27** and **Figure S28**). Lastly, meta-analysis demonstrated a clinically significant reduction in 24-hour mean BP of −2.2 mmHg [95%CI: −3.6 to −0.7 mmHg], (see supplemental material, **Figure S29**).

Overall, the analyses suggest that PAP use reduces BP in adults with OSA and hypertension. The quality of evidence for BP in hypertensive participants was moderate due to imprecision.

Blood Pressure (Normotensive Participants)

A total of 3 of the 27 RCTs reported on the effects of PAP therapy on BP in normotensive participants at baseline.^{72,94,95} Meta-analyses demonstrated no clinically significant reduction

in daytime or nighttime SBP and DBP (see supplemental material, **Figure S30** through **Figure S33**). However, one study demonstrated a clinically significant reduction in 24-hour DBP of −1.4 mmHg [95% CI: −3.2 to 0.4 mmHg] with PAP therapy.⁷²

Overall, the analyses suggest that PAP use does not reduce blood pressure in normotensive adults with OSA. The quality of evidence for BP in normotensive participants was low due to very high imprecision.

Cardiovascular Events

The TF reviewed both RCT and non-randomized data regarding the effects of PAP on cardiovascular event rate. Six RCTs assessed the impact of PAP therapy on cardiovascular event rate, which were variably defined by composite outcomes.^{36,81,106–108,116} The studies recruited participants with at least moderate OSA severity (AHI > 15–20 events/h), middle to older age, predominantly male and overweight to obese, followed for an average of 3 to 5 years. Studies of participants examining incident cardiovascular events¹⁰⁶ and recurrent cardiovascular events^{107,108,116} were included for analysis. The largest trial to date showed no clinically significant impact of CPAP therapy on secondary prevention in adults with established cardiovascular disease.¹¹⁶ The meta-analysis also did not demonstrate a clinically significant reduction in the rate of cardiovascular events occurring with the use of PAP (see supplemental material, **Figure S34**).

Eleven non-randomized studies assessed the impact of PAP on cardiovascular event rate.^{133,134,136–141,143–145} Most studies included participants that were male, middle-aged, overweight to obese with predominantly moderate to severe OSA, and mean follow-up time ranged from 1 to 10.1 years. A notable exception was one study that reported on women only.¹⁴⁷ The majority of studies measured composite outcomes of fatal and non-fatal cardiovascular events,^{134,136–140,143–145} while two studies^{133,141} were limited to incident arrhythmias. Two studies were also limited to participants with heart failure.^{142,146} Meta-analysis of 11 non-RCTs^{133,134,136–141,143–145} demonstrated a clinically significant reduction in cardiovascular events with a risk ratio of 0.5 (95% CI: 0.3 to 0.7) with the use of PAP (see supplemental material, **Figure S35**).

The vulnerability of non-randomized studies to bias is worth highlighting, as reliance on such studies often contributes to downgrading of recommendations. Comorbidities among study cases and controls are often imbalanced and may be difficult to control for. In many instances, the control groups were comprised of participants who refused PAP therapy,^{134,143} raising questions of adherence with other medical therapies that may impact outcomes. Non-systematic ascertainment of study participant characteristics, and the outcomes typical of non-randomized studies, may be biased in the data abstraction process.¹⁶¹ Furthermore, non-randomized studies are much more prone to publication bias. Finally, since many of the studies were published more than a decade ago, including the largest,¹⁴³ it is unknown what impact interim advances in cardiovascular disease therapies may have on the benefit of treating OSA with PAP.

One area of controversy in reconciling the discrepant findings between the non-randomized studies and RCTs is that, in

general, PAP adherence was lower in the RCTs than in the non-randomized studies. Whether the greater effect of PAP on lowering cardiovascular event rate in non-randomized studies reflects a beneficial effect of a higher adherence to CPAP or alternatively, a non-specific effect of being adherent with other medical treatments or healthier lifestyles remains to be answered.¹⁶² Furthermore, whether greater PAP use would have demonstrated a beneficial impact on cardiovascular event reduction is unknown, but was suggested in secondary analyses performed in several studies.^{106,108,116} Two reasons for the lower adherence in RCTs may be the inclusion of less symptomatic/sleepy participants and exclusion of participants with the most severe disease¹¹⁶—given that symptoms and OSA severity are predictors of PAP adherence.¹⁶³ In addition, the benefits of PAP on cardiovascular event risk may be greater in more symptomatic and more severe disease, which are the groups that were excluded from the RCTs.

The quality of evidence for cardiovascular event rate ranged from low to moderate, based on the types of studies pooled for meta-analysis, and was downgraded due to study type and imprecision.

All-Cause Mortality

The TF reviewed both RCT and non-randomized data regarding the effects of PAP on all-cause mortality. Four RCTs assessed the impact of PAP therapy on all-cause mortality.^{106–108,116} The studies recruited participants with at least moderate OSA severity (AHI > 15–20 events/h), middle to older age, predominantly male and overweight to obese, followed for an average of 3 to 5 years. cardiovascular prevention studies^{106,107, 108,116} were included for analysis. The largest trial to date showed no clinically significant impact of CPAP therapy on mortality in adults with established cardiovascular disease.¹¹⁶ The meta-analysis did not demonstrate a clinically significant reduction in all-cause mortality with the use of PAP (see supplemental material, **Figure S36**).

Nine non-randomized trials reported on mortality associated with the use of PAP versus control conditions in participants with or without heart failure (see supplemental material, **Figure S37**).^{137–140,142–144,146,147} A meta-analysis of these studies demonstrated a clinically significant reduction in risk with a risk ratio of 0.40 (95% CI: 0.24 to 0.69). When studies were stratified into subgroups based on the presence or absence of heart failure, meta-analyses demonstrated clinically significant reductions in the risk ratio for mortality of 0.2 (95% CI: 0.1 to 0.5) and 0.4 (95% CI: 0.2 to 0.7) for heart failure^{142,146} and no heart failure participants,^{137,139,143,144,147} respectively (see supplemental material, **Figure S38** and **Figure S39**).

Like the evidence review for cardiovascular events, the analyses are inconclusive regarding the effects of PAP in reducing all-cause mortality in adults with OSA, in part related to differences in patient populations studied and PAP adherence between randomized and non-randomized studies. The quality of evidence for mortality was low due to study type and imprecision.

Overall Quality of Evidence

The outcomes of sleepiness, sleep-related QOL, and blood pressure were determined by the TF to be critical for

decision-making. The overall quality of evidence for recommendation 1, based on the critical outcome of sleepiness, was high. The overall quality of evidence for recommendation 2, based on the critical outcome of sleep-related QOL, was moderate due to imprecision. The overall quality of evidence for recommendation 3, based on the critical outcome of BP, was moderate due to imprecision.

Benefits Versus Harms

The potential benefits of CPAP based on the meta-analyses performed include reduction in OSA severity, improvement in patient symptoms, particularly sleepiness, sleep-related QOL, MVCs, and reduction in BP. The potential for cardiovascular and mortality benefits cannot be ruled out. These potential benefits should be considered in the context of the potential harms of CPAP. Direct side effects that have been reported with the use of PAP are presented in the supplemental material, **Table S16**.⁹ These side effects can result in sleep disruption and poor sleep quality thereby reducing patient adherence to CPAP, and should be carefully monitored and managed by a clinician. There are also some concerns about the development of treatment-emergent central sleep apnea associated with PAP in general, however, patient harm has yet to be demonstrated. The TF judged that the potential benefits of CPAP outweighed the harms in those patients with excessive daytime sleepiness, other symptoms impairing sleep-related QOL, or with hypertension.

Patient Values and Preferences

The TF judged that the majority of sleepy patients and most patients with reduced sleep-related QOL with OSA of any severity would consider a trial of PAP therapy given the rapid reversibility of side effects. The TF recognizes that individual patients, despite their symptoms, may choose not to pursue CPAP treatment due to concerns about side effects. A balanced discussion between a patient and their clinical provider about the consequences of excessive sleepiness and other OSA symptoms, the benefits and harms of CPAP, and consideration of alternative therapies such as weight loss, positional therapy, oral appliance therapy or surgical interventions, can help guide individual treatment decisions.

The TF also judged that most patients with OSA and hypertension would want their OSA treated to help reduce BP as the benefits may include reduction in cardiovascular risk. Patients experiencing symptoms of OSA (eg, excessive sleepiness) may be more accepting of CPAP therapy, with the possibility of secondary benefits related to cardiovascular risk reduction. Non-sleepy patients with OSA, however, may have a more nuanced view of whether to pursue treatment of OSA, particularly given the efficacy of alternative antihypertensive treatments. The TF recognizes that some non-sleepy patients will place a high value on any intervention that potentially reduces long-term cardiovascular events, including CPAP therapy.

The meta-analysis of non-sleepy OSA participants, demonstrated a statistically but not clinically significant reduction in ESS. However, given the limitations of the ESS in assessing sleepiness,^{164,165} patients with OSA who are non-sleepy or minimally symptomatic as assessed by the ESS, may experience clinically important improvements in sleepiness. As such, the

clinician assessment of sleepiness should not be solely based on the ESS. For patients with a normal ESS but other signs of sleepiness, a short-term therapeutic trial of CPAP may be reasonable to assess symptomatic benefits. For other non-sleepy patients, based on the ESS, the uncertainty of any cardiovascular benefit, may lead them to decline treatment of OSA, regardless of their OSA severity. For example, some RCTs that selectively recruited non-sleepy participants demonstrated no benefits in BP^{63,86,106} or cardiovascular risk reduction^{106,108} with CPAP. Given the absence of high-quality evidence for the use of PAP to treat non-sleepy adults with OSA, conservative management of OSA in non-sleepy patients, with monitoring for development of OSA symptoms over time may be appropriate.

Resource Use

In general, cost-effectiveness analyses have demonstrated that CPAP is a cost-effective therapy compared to no therapy. In one systematic review performed by the Canadian Agency for Drugs and Technologies in Health,¹⁶⁶ two studies^{167,168} were identified demonstrating the cost effectiveness of CPAP. The first study¹⁶⁷ demonstrated an incremental cost-effectiveness ratio (ICER) of CDN\$15,915 per quality-adjusted life year (QALY) with CPAP therapy while another study¹⁶⁸ performed for the National Institute of Health and Clinical Excellence (NICE) in the United Kingdom demonstrated an ICER for CPAP therapy compared to dental devices or lifestyle advice that ranged from £4,413–£20,585 depending on the OSA severity. The TF judged that resource use is justified for CPAP for the treatment of OSA in adults to improve patient sleepiness and sleep-related QOL. The TF did not identify cost-effectiveness studies regarding PAP therapy and outcomes related to blood pressure. Hypertension is highly prevalent, affecting nearly one-third of the United States adult population. Depending upon patterns of provider recognition, perceived value, and patient acceptance, resource use may be substantial. Cost analyses are therefore needed. In light of comparative trials highlighting the efficacy of antihypertensive medications in those with OSA, as well as potential synergy with PAP therapy, modeling of this relationship in such analyses will be important.

Other Outcomes

The TF considered several other outcomes to be important but not critical for decision-making for the development of the recommendations. These outcomes included neurocognitive function, mood, MVC, fasting glucose, hemoglobin A1c, LVEF, and incident hospitalizations. A summary of the findings for each of these outcomes is presented below.

Neurocognitive Function

For neurocognitive outcomes, two experts outside of the TF were consulted to assist grouping of neurocognitive tests into appropriate domains, which was finalized through a consensus process. The efficacy of PAP in improving neurocognitive function in adults with OSA was evaluated using meta-analyses of studies that reported on several sub-domains of executive function (shifting, updating, and fluid reasoning) and the domains of processing speed, attention and vigilance, memory, and intelligence (see supplemental material, **Tables**

S17). A total of 9 RCTs investigated the efficacy of PAP for improvement in neurocognitive function as measured across these domains.^{63,65,70,71,81,82,90,114,115} Two studies recruited elderly participants (age ≥ 65 years).^{81,114} One study⁷¹ recruited sleepy participants with mild OSA and one study⁶³ recruited non-sleepy participants with mild to moderate OSA. None of the studies selectively enrolled participants with concurrent mild cognitive impairment or dementia. However, one study of participants with predominantly severe OSA had baseline impairments in short-term memory and executive function compared to a historical control group matched on age and educational background.¹¹⁴ Sham PAP (n = 1),⁶³ conservative measures (advice on weight loss or good sleep habit counseling) (n = 3),^{81,82,114} and placebo tablet (n = 3)^{65,70,71} were utilized as control interventions. The intervention lasted for at least 1 month (range: 1–12 months follow-up).

Meta-analyses performed to assess neurocognitive function are presented in the supplemental material, **Figure S40** through **Figure S46**. The meta-analyses demonstrated no clinically significant differences between PAP and control groups in any of the domains of neurocognitive function tested, which included executive function, processing speed, attention and vigilance, memory, and intelligence.

Overall, the analyses suggest that CPAP does not appear to improve neurocognitive function in adults with OSA. The quality of evidence for neurocognitive function ranged from low to high and was downgraded due to imprecision in certain domains.

Mood

The efficacy of PAP in improving mood, specifically anxiety and depression, in adults with OSA was evaluated using meta-analyses of 5 studies that reported on the Hospital Anxiety and Depression Scale (HADS anxiety and HADS depression).^{70,71,81,116,130} The studies identified for the systematic review did not specifically recruit participants with comorbid anxiety or depression.

Three studies were performed with participants who had moderate to severe OSA and were self-reportedly sleepy,^{70,81,130} one study recruited minimally sleepy participants with mild to moderate OSA,¹¹⁶ and one study⁷¹ recruited participants specifically with mild OSA and symptoms of sleepiness. Two studies recruited only older participants.^{81,130} All studies were RCTs, with 2 studies using a randomized, cross-over design.^{70,71} Participants were randomized to CPAP or a control intervention. No intervention (n = 3)^{81,116,130} or placebo tablet (n = 2)⁷² were utilized as controls. The length of the intervention was for at least 1 month (range: 1–4 years follow-up).

Meta-analyses of the HADS anxiety scale and HADS depression scale scores demonstrated no clinically significant improvements in mood using CPAP; however, the studies did not specifically enroll participants with anxiety or depression at baseline (see supplemental material, **Figure S47** and **Figure S48**). The quality of evidence for depression and anxiety was high.

Motor Vehicle Crashes

The efficacy for CPAP in improving MVC in adults with OSA was evaluated using meta-analyses examining the relative risk reduction of obstacles hit during driving simulation

in 4 RCTs^{63,70,71,82} and MVC in ten non-randomized studies^{118,119,121–123,125–128,132} (see supplemental material, **Figure S49** through **Figure S51**).

In studies that used driving simulator data and had control participants with untreated OSA, all but one study⁶³ was performed with participants that were self-reportedly sleepy. One study⁶³ recruited non-sleepy participants with mild to moderate OSA and one study⁷¹ recruited participants specifically with mild OSA with symptoms of sleepiness. Sham CPAP (n = 1),⁶³ conservative measures (advice on weight loss or good sleep habit counseling) (n = 2),^{82,85} and placebo tablet (n = 3)^{64,70,71} were utilized as control interventions. The duration of the intervention was for at least 1 month (range: 1–6 months follow-up) in the RCTs. Meta-analyses of RCTs did not demonstrate a clinically significant reduction in obstacles hit or percent obstacles hit using a driving simulator (see supplemental material, **Figure S49** and **Figure S50**). Extrapolation of results from driving simulators to real world driving should be made with caution given variations in simulators and protocols for testing and differences in participant motivations when driving in simulated versus real world conditions.

For studies examining MVC risk reduction, the TF included 10 non-randomized studies with pre- and post-CPAP assessment of MVC by self-report or objective reports and performed a meta-analyses on these studies.^{118,119,121–123,125–128,132} Participants had predominantly moderate to severe OSA and were self-reportedly sleepy,¹¹⁹ ESS or another tool,^{118,121,125,127,128,132} or data^{122,123} was not reported. Most studies compared participants for a period pre-CPAP intervention to post-CPAP intervention. Two studies compared changes in MVC in participants with OSA before and after CPAP to a non-OSA control group followed over time to control for secular trends,^{118,123} while one study¹²² compared changes in MVC to participants with OSA declining CPAP use also followed over time. All studies included were of non-commercial motor vehicle operators. A separate AASM TF has reviewed data from studies of commercial motor vehicle drivers.¹⁶⁹ Outcome assessment was through self-report,^{119,121,125,127,128,132} data from transportation offices,^{122,123} or data¹¹⁸ from auto insurers. Follow-up varied ranging up to 2 years before enrollment to 6 years after (range 2–6 years) or prospective follow-up after enrollment between 6–12 months.

Meta-analyses of the 10 non-randomized studies^{118,119,121–123,125–128,132} comparing participants with OSA before and after CPAP treatment demonstrated a mean crash rate risk ratio of 0.3 (95% CI: 0.2 to 0.4) (see supplemental material, **Figure S51**), which was considered to be clinically significant. Overall, the analyses suggest that CPAP use results in a reduction in crash rates in adults with OSA as assessed by both objective MVC data and self-report from questionnaires. The quality of evidence for MVC ranged from low to moderate. The quality of evidence from RCTs for the use of PAP to reduce MVC was downgraded due to imprecision and was moderate. The quality of evidence from observational studies for the use of PAP to reduce MVC was low and was downgraded due to study design.

Fasting Glucose and Hemoglobin A1c

A total 8 RCTs assessed fasting glucose before and after 6 to 12 weeks of PAP therapy in primarily obese, male participants

with at least moderate to severe OSA.^{67,74,88,89,93,129,131,153} Five studies included participants without diabetes,^{67,74,88,93,153} 3 studies^{89,129,131} included participants with T2DM, and one study recruited participants from an obesity surgery clinic.¹⁵³ All of the trials individually failed to demonstrate a clinically significant reduction in fasting glucose with PAP (see supplemental material, **Figure S52**). Despite the lack of improvement in fasting glucose levels, there have been several trials in those without diabetes suggesting CPAP therapy for comorbid OSA may reduce insulin resistance.^{170–172} Whether this translates into a reduction in risk of incident T2DM is unclear.

The efficacy of PAP in reducing HbA1c in adults with OSA was evaluated using a meta-analysis of 4 RCTs.^{89,129,131,153} The studies were performed in primarily clinic-based populations. Participants in three of four studies had T2DM and were predominantly male, obese, with moderate to severe OSA.^{89,129,131} One study recruited severely obese participants without T2DM with severe OSA.¹⁵³ Three of the four studies recruited participants that as a group were not self-reportedly sleepy based on the ESS.^{129,131,153} The mean baseline HbA1c ranged from 5.7 to 8.5%. Participants were randomized to CPAP or a control intervention, which included either sham CPAP⁸⁹ or usual care^{129,131,153} for diabetes management. Participant follow-up ranged from 3–6 months. Of the four studies, only one showed a significant reduction in HbA1c.¹²⁹ A meta-analysis of the four studies did not demonstrate a clinically significant improvement in HbA1c with PAP (see supplemental material, **Figure S53**). Mean CPAP use across participants in three of the four studies ranged from 3.6–5.4 h/night.^{89,129,131} Whether interventions that lead to greater PAP use could demonstrate an improvement in glycemic control remains unknown.¹⁷³

Overall, the TF judged that analyses do not support that PAP reduces fasting glucose or HbA1c in adults with OSA with or without T2DM. The quality of evidence for the efficacy of PAP to reduce fasting glucose and hemoglobin A1c was high in finding no clinically significant reduction.

Left Ventricle Ejection Fraction

Eight RCTs measuring LVEF by echocardiography or radionuclide ventriculography compared the efficacy of PAP versus control conditions (see supplemental material, **Figure S54** through **Figure S56**).^{93,94,99,102,109,110,113,124} Studies on participants with heart failure^{99,102,109,110} recruited from cardiology or heart failure clinics while studies of participants without heart failure^{93,94,113} recruited primarily from sleep clinics. Participants were largely male, between the age of 50–60, obese, with severe OSA, and the intervention lasted for at least 1 month (mean 2.7 months; range: 1 to 6-month follow-up). Either sham PAP^{93,94,102,110} or no PAP^{99,109,113} was employed as the control intervention.

Meta-analysis of all participants in these studies showed no clinically significant improvement in LVEF.^{93,94,99,102,109,110,113,124} When limited to participants with heart failure, a meta-analysis of 5 RCTs demonstrated no clinically significant improvement in LVEF.^{99,102,109,110,124} In addition, a meta-analysis of the 3 RCTs that were conducted in participants without heart failure demonstrated no clinically significant improvement in LVEF.^{93,94,113}

Overall, the analyses suggest that PAP does not result in clinically significant improvements in LVEF in adults with

OSA either with or without comorbid heart failure. The quality of evidence for LVEF was moderate due to imprecision.

Hospitalization

Two non-randomized studies reported on all-cause hospitalizations associated with PAP versus control conditions.^{135,140} A meta-analysis of these studies did not demonstrate a significant reduction in hospitalizations associated with PAP therapy compared with control conditions (see supplemental material, **Figure S57**). Overall, the analyses did not support that CPAP reduced the risk of hospitalization in adults with OSA, although very few studies were identified that met criteria for analysis. The quality of evidence for hospitalizations was very low due to study type and imprecision.

APAP at Home Versus In-Laboratory PAP Titration for Initiation of PAP

This section addresses PICO question 4 (see **Table 1**) and resulted in one recommendation (see Recommendation 4 in the companion clinical practice guideline).⁸ A total of 10 RCTs were identified that compared initiation of PAP using home APAP versus an in-laboratory PAP titration in improving one or more of the following outcomes: AHI/RDI, adherence to PAP therapy, sleepiness, and QOL.^{35,174–182} Participants were predominantly middle-aged males with sleepiness and moderate to severe OSA. Studies included only participants with high clinical suspicion of moderate to severe OSA. Most studies reviewed excluded participants with the following comorbidities or conditions: congestive heart failure, chronic opiate use, significant lung disease such as chronic obstructive pulmonary disease, neuromuscular disease, history of uvulopalatopharyngoplasty, sleep-related oxygen requirements, or expectation for nocturnal arterial oxyhemoglobin desaturation due to conditions other than OSA, including hypoventilation syndromes and central sleep apnea syndromes. For the in-laboratory titration protocol, 6 studies used only full night in-laboratory titration and 4 studies used a combination of full night and split-night in-laboratory titration. Most participants in these studies using home APAP had mask fittings and education on PAP use at a sleep center. Some studies also offered daytime nap acclimatization. Follow-up by trained staff early during the treatment period was common. All studies used the home APAP device in auto-adjustment mode for a brief period (2–7 nights) and then switched to a fixed pressure (90th or 95th percentile). Several meta-analyses were performed to assess the impact of home APAP versus in-laboratory PAP titration for the initiation of OSA treatment. The meta-analyses are provided in the supplemental material, **Figure S58** through **Figure S61**. A Summary of Findings table is included in **Table S4** of the supplemental material. A summary of the evidence for each outcome is provided below.

OSA Severity

The impact of PAP in reducing OSA severity in adults with OSA who initiated PAP using home APAP was evaluated using a meta-analysis of 3 RCTs that reported on the AHI.^{174,178,179} Participants were randomized to in-laboratory CPAP titration versus home APAP followed by conversion to a fixed CPAP

pressure based on PAP monitoring data, with outcomes assessed after at least 6 weeks of treatment (range 6 to 12 weeks). The meta-analysis demonstrated no clinically significant difference in residual OSA severity (see supplemental material, **Figure S58**) when PAP was initiated using home APAP compared to in-laboratory titration.^{174,178,179} Residual OSA severity was obtained from the in-laboratory PSG^{178,179} or from the PAP device¹⁷⁴ in these studies.

Overall, the analysis demonstrated similar effects on OSA severity in adults with OSA when PAP is initiated via home APAP or in-laboratory PAP titration. The quality of evidence for OSA severity was high.

Adherence

Adherence to PAP in adults with OSA, after initiation of PAP using home APAP versus an in-laboratory titration, was evaluated using a meta-analysis of 10 RCTs that reported on adherence.^{35,174–182} Participants were randomized to a home-based pathway that included APAP versus an in-laboratory CPAP titration with outcomes assessed after at least 1 month of treatment (range 1 month to 6 months). The meta-analysis demonstrated no clinically significant difference in PAP adherence when comparing treatment initiation using home APAP versus in-laboratory titration (see supplemental material, **Figure S59**).

Overall, the analysis demonstrated similar levels of PAP adherence in adults with OSA with PAP initiation by either home APAP or in-laboratory titration. The quality of evidence for adherence was high.

Sleepiness

The impact of PAP initiation using APAP versus an in-laboratory titration for the treatment of self-reported sleepiness in adults was evaluated using a meta-analysis of 9 RCTs that reported on the ESS.^{35,174–180,182} Participants with high clinical suspicion for OSA and without comorbid conditions were randomized to home APAP versus in-laboratory CPAP titration with outcomes assessed after at least 1 month of treatment (range 1 month to 3 months). The meta-analysis demonstrated no clinically significant difference in self-reported sleepiness when PAP therapy was initiated using home APAP compared to an in-laboratory titration (see supplemental material, **Figure S60**).

Overall, the analysis suggests that initiation of therapy using home APAP compared to an in-laboratory titration in adults with OSA results in similar effects on sleepiness. The quality of evidence for sleepiness was high.

Quality of Life

Meta-analyses of RCTs that reported on the SAQLI,^{178,180,182} FOSQ,^{175,176,180} and SF-36 component summary scores^{175,180} were performed to assess the impact of PAP initiation using home APAP versus an in-laboratory titration on QOL. Participants were randomized to a home-based pathway that included APAP versus in-laboratory CPAP titration with outcomes assessed after 3 months. A meta-analysis combining 2 RCTs measuring sleep-related QOL with FOSQ,^{175,176} 2 RCTs measuring sleep-related QOL with SAQLI,^{178,182} and one RCT¹⁸⁰ measuring both FOSQ and SAQLI demonstrated no clinically

significant difference in sleep-related QOL when comparing PAP initiation using home APAP versus an in-laboratory titration (see supplemental material, **Figures S61**). Two RCTs^{175,180} demonstrated no clinically significant difference in general QOL as assessed by the SF-36 mental component summary, physical component summary, and vitality scores when comparing home APAP versus an in-laboratory titration (see supplemental material, **Table S4**).

Overall, the analysis suggests that PAP initiation in adults with OSA using a home APAP or in-laboratory titration have similar effects on both sleep-related and general QOL. Overall, the quality of evidence for QOL was moderate. The quality of evidence for the SF-36 physical and mental component summary scores was low due to very high imprecision. The quality of evidence for SF-36 vitality was high. The quality of evidence for combined FOSQ and SAQLI was moderate.

Side Effects

No studies were identified that reported on side effects of either strategy.

Overall Quality of Evidence

The outcomes of adherence to PAP therapy, sleepiness, and QOL were determined by the TF to be critical for decision-making. The overall quality of evidence was high.

Benefits Versus Harms

The potential benefits of PAP initiation using home APAP over in-laboratory titration are a reduced time to initiation of therapy, particularly in areas with limited laboratory resources, reduced time away from home, lower overall cost, and greater access to care. Despite the greater cost-effectiveness of home-based APAP initiation,^{175,177,179} out-of-pocket costs to patients may be lower with either split or whole-night in-laboratory PAP titration due to payor coverage policies in certain instances. The potential harms of initiating therapy with APAP at home after adequate patient education is provided are difficulties in identifying and immediately addressing problems related to mask fit or leak. However, similar issues could occur with an in-laboratory titration approach once the patient is using PAP in the home setting. In such instances, initiating therapy with APAP at home may delay or obscure recognition of these conditions and reduce adherence to therapy. There was no evidence of poor treatment efficacy (based on AHI) or reduced PAP adherence in the home APAP arm and the side effects of PAP that have been reported were deemed by the TF as likely independent of PAP initiation strategy. There are some concerns about the development of treatment-emergent central sleep apnea associated with PAP in general, however, patient harm has yet to be demonstrated. Nevertheless, the TF determined that the potential benefits of PAP initiation using either APAP at home or in-laboratory PAP titration in adults outweigh the potential harms and burdens of doing neither.

Patient Values and Preferences

Both review of available data and clinical expertise of the TF was used to assess patient values and preferences. Only one randomized trial was identified that assessed patient

preference of an ambulatory/home pathway versus an in-laboratory diagnostic and treatment pathway.¹⁷⁸ In that study, 62% of participants randomized to the in-laboratory pathway would have preferred home management, compared to 6% of participants in the ambulatory group who would have preferred in-laboratory based management.

The TF considered issues of patient access for home APAP and in-laboratory PAP titration. From a logistical standpoint, home APAP setup requires one step after diagnosis of OSA—a visit to educate on APAP use and provision of the APAP device. In-laboratory PAP titration typically requires two steps—one visit for the titration study and another for PAP education and provision of the PAP device. However, there are some situations where a single visit may suffice such as when a split-night study is performed, or immediate dispensation of equipment is available at the laboratory. Regional variations in the time to get scheduled for an additional sleep study for PAP titration and navigating the healthcare system for PAP setup after titration can be substantial, which would generally favor home APAP. On the other hand, in some regions, the health care system creates barriers that make APAP difficult to implement and may take longer to perform than an in-laboratory titration strategy followed by PAP setup. The motivation to address OSA symptoms is greatest when patients first seek OSA evaluation. Behavior change theory informs clinicians that overcoming some level of ambivalence and motivation to begin treatment varies depending on other life challenges competing for attention (eg, job or family demands, other health issues). Delays in initiating PAP therapy can substantially increase chances of loss to follow-up or poor adherence due to loss of engagement and motivation.

The TF also recognized that clinicians may need to consider patient burdens associated with in-laboratory CPAP titration or home APAP. For example, with respect to in-laboratory CPAP titration, some patients may find it difficult to spend a night away from home due to shiftwork, child-care or adult-care responsibilities, or transportation challenges between home and the testing facility that make APAP at home more convenient. In contrast, for some patients with issues of comprehension, anxiety or physical limitation, in-laboratory CPAP titration may be more favorable as a sleep technologist can provide education and other intervention during this initial introduction to PAP therapy.

Given this discussion, the TF determined that the majority of well-informed patients would most likely choose the more convenient, accessible, and cost-effective intervention, particularly when adequate education on PAP with mask fittings and daytime acclimatization by trained staff are available. Determination of which strategy is ideal for an individual patient should be based on patient preferences and abilities, the sleep clinician's judgement, anticipated or known previous difficulty with PAP treatment, and availability of resources and cost of each strategy in a particular region.

Resource Use

Six studies evaluated cost,^{35,175,177,179–181} of which three^{35,180,181} reported a slightly reduced cost for a combined home-based diagnostic and treatment pathway, and three^{175,177,179} reported a lower cost for home APAP compared to in-laboratory titrations. The cost reduction ranged from 25–84% in favor of treatment

arms including APAP in the home. Of note, one study¹⁸⁰ demonstrated lower cost using a home-based pathway compared to the laboratory pathway where > 50% of the studies were split-night studies. While in-laboratory titration costs include infrastructure and overnight staffing, resources for education and training of patients are required for APAP initiation. The availability of resources and cost of each strategy may vary by region. The TF judged that resource use is justified for home APAP titration in the initiation of therapy for patients without significant comorbidities with established diagnoses of OSA, while recognizing that in some regions due to patient access and patient preference that in-laboratory CPAP titration may be a more effective use of resources.

APAP Versus CPAP

This section addresses PICO question 5 (see **Table 1**) and resulted in one recommendation (see Recommendation 5 in the companion clinical practice guideline).⁸ A total of 26 RCTs were identified that investigated the effects of ongoing treatment with APAP compared with fixed CPAP in reducing side effects and improving one or more of the following outcomes: AHI/RDI, adherence to PAP therapy, sleepiness, QOL, and neurocognitive function.^{156,179,183–206} Participants were predominantly male, with previously untreated moderate to severe OSA and no major medical comorbidities. Participants were randomized to CPAP versus APAP for at least 1 month up to a maximum of 6 months (median 2 months). In the studies reviewed, participants with conditions that increased the risk of central sleep apnea (eg, congestive heart failure or opiate use), hypoventilation syndromes (eg, significant lung disease such as chronic obstructive pulmonary disease), neuromuscular disease, sleep-related oxygen requirements or the expectation of nocturnal arterial oxyhemoglobin desaturations, or a history of uvulopalatopharyngoplasty (which potentially could affect inspiratory airflow patterns and the response of some APAP algorithms) were usually excluded. Thus, results of meta-analyses should not be extrapolated to participants with OSA and these comorbidities or situations. For each outcome, important differences in participant population or study design from the general description reported above are provided. Meta-analyses were performed to assess the effects of APAP compared with CPAP in improving several clinical outcomes. Results of these meta-analyses are provided in the supplemental material, **Figure S62** through **Figure S74**. Side effect data were not sufficiently standardized to permit meta-analysis, but a description of side effect findings is provided. A Summary of Findings table is provided in the supplemental material, **Table S5**. A summary of the evidence for each outcome is provided below.

OSA Severity

A meta-analysis of 21 RCTs that reported on OSA severity was performed (see supplemental material, **Figure S62**).^{156,179,183,184,187,188,191,193–197,199–204,206–208} Residual OSA severity was obtained in a majority of studies from PSG recordings on treatment, while several studies reported OSA severity from the PAP device microprocessor.^{193,199,200,202,205,206} Meta-analyses demonstrated no clinically significant differences in residual AHI between APAP and CPAP.

Overall, the analysis supports the conclusion that CPAP and APAP in adults with OSA have similar effects on OSA severity as measured by the AHI or RDI, across the spectrum of OSA severity. The quality of evidence for this outcome was high.

Adherence

Adherence to APAP versus CPAP was evaluated using meta-analyses of 23 studies (see supplemental material, **Figure S63** through **Figure S65**).^{156,179,183–196,198,199,202–206} A meta-analysis of all 23 RCTs demonstrated no clinically significant difference in average hours of use in adults with OSA treated with APAP compared to CPAP. In addition, a meta-analysis of 6 of these studies demonstrated no clinically significant difference in percent of nights PAP was used.^{186,189,191,192,206,208} Furthermore, a meta-analysis of 2 RCTs demonstrated that the difference in the percent of nights PAP therapy was used > 4 hours with APAP versus CPAP was not clinically significant.^{185,193}

Overall, the analyses support the conclusion that adherence to APAP and CPAP in adults with OSA is similar. The quality of evidence for this outcome ranged from moderate to high, being downgraded due to imprecision.

Sleepiness

The efficacy of APAP versus CPAP for the treatment of sleepiness in adults with OSA was evaluated using meta-analyses of 19 studies^{179,183–199,202} that reported on the ESS, 4 studies^{193,196,199,200} that reported on the OSLER, and 2 studies^{197,201} that reported on the MWT. Meta-analyses of studies reporting ESS and combining studies reporting either the OSLER or MWT demonstrated no clinically significant mean differences in self-reported or objective sleepiness (see supplemental material, **Figure S66** and **Figure S67**).

Overall, the analyses support the conclusion that APAP and CPAP in adults with OSA have similar effects on daytime sleepiness. The overall quality of evidence for sleepiness ranged from moderate to high and was downgraded due to imprecision.

Quality of Life

Meta-analyses of studies that reported on the SAQLI,^{198,200} the FOSQ,^{188,202} and SF-36 component summary scores^{190,193,196,199,205,208} were performed to evaluate the efficacy of APAP compared to CPAP in improving QOL in adults with OSA. Meta-analyses demonstrated no clinically significant differences in QOL as measured by the combined SAQLI/FOSQ, or by the SF-36 physical component summary, mental component summary, or vitality scores (see supplemental material, **Figure S68** through **Figure S71**).

Overall, the analyses support the conclusion that APAP and CPAP in adults with OSA have similar effects on sleep-related and general QOL. The overall quality of evidence for QOL ranged from moderate to high and was downgraded due to imprecision.

Neurocognitive Function

Two RCTs studied participants' attention span using the psychomotor vigilance test (PVT).^{188,199} Participants were randomized to APAP versus CPAP in a parallel design for 6 months.¹⁸⁸

or in a cross-over study¹⁹⁹ for 6 weeks per arm. Meta-analyses of these studies demonstrated no clinically significant differences in attention as measured by either mean reaction time or lapses on the PVT (see supplemental material, **Figure S72** and **Figure S73**).

Overall, the analyses support the conclusion that APAP and CPAP in adults with OSA have similar effects on attention. The quality of evidence for neurocognitive function was moderate due to imprecision.

Side Effects

The efficacy of APAP versus CPAP in reducing PAP-related side effects in adults with OSA was evaluated. However, data were not reported in a sufficiently standardized format to perform a meta-analysis. A total of 11 studies reported data on side effects,^{179,183,186,188,191,193–196,198,205} with 6 of the studies^{179,183,188,191,195,196} reporting no clinically significant differences in side effects between APAP and CPAP. A total of 5 studies reported differences in side effects between APAP and CPAP.^{186,193,194,198,208} In 4 of these studies,^{186,193,198,208} there was less pressure discomfort with APAP than CPAP, and in at least 2 of the studies, less nasal irritation^{186,205} or machine noise^{193,205} with APAP than CPAP. On the other hand, in one study more discomfort due to pressure variation with APAP was noted.¹⁹⁴

Overall, differences in side effects between APAP and CPAP in adults with OSA were minor and were judged by the TF to not be clinically significant (see supplemental material, **Table S5**). The TF noted that in clinical practice, side effects may differ between APAP and CPAP for individual patients, and that a trial of the alternate modality may be warranted when treatment intolerance due to side effects occurs. The overall quality of evidence for side effects was low due to imprecision and heterogeneity.

Overall Quality of Evidence

The outcomes of adherence to PAP therapy, sleepiness, and QOL were determined by the TF to be critical for decision-making. The overall quality of evidence was moderate due to imprecision.

Benefits Versus Harms

A potential benefit of APAP over CPAP is the ability to automatically adjust therapeutic pressures as OSA severity changes with weight fluctuations, nighttime alcohol consumption, body position, seasonal variations (eg, upper respiratory tract infections), and changes in upper airway anatomy. Potential disadvantages of APAP, which may be observed for some patients, include sleep disruption from pressure fluctuations or the return of sleep disordered breathing events when the PAP level is lowered by internal device algorithms. Furthermore, inappropriate or inadvertent increases in pressure may result in the development of treatment-emergent central sleep apnea or periodic breathing in certain patients, however, patient harm has yet to be demonstrated. The present meta-analyses demonstrated no clinically significant differences in most of the critical outcomes assessed between APAP and CPAP, and no substantial harm was identified for APAP compared with CPAP. Thus, the TF judged that the balance of benefit versus

harm does not strongly favor either intervention. The TF therefore concluded that either APAP or CPAP should be used to treat adult OSA.

Patient Values and Preferences

Patient preference for APAP compared with CPAP was assessed in a total of 9 RCTs.^{183,184,187,189,191–193,198,199} The proportion of participants favoring APAP (see supplemental material, **Figure S74**) varied considerably between studies, with no consistent pattern of preference emerging. Based on this variability in patient preference between studies, the similarity of clinical outcomes with APAP versus CPAP, and variations in economic considerations and health care access, patients should discuss with their sleep clinician which form of PAP is best suited to their individual needs.

Resource Use

The TF did not perform a systematic review to identify cost-effectiveness studies of APAP versus CPAP devices. However, in some regions of the world, market and other factors may lead to differences in cost between APAP and fixed CPAP (as discussed in the section on APAP at home versus in-laboratory PAP titration for initiation of PAP for the treatment of adults with OSA), which may therefore impact the feasibility of APAP-based treatment. Over the long-term, APAP therapy may reduce costs due to reduced need for patient visits and in-laboratory titrations as pressure requirements change over time. However, the magnitude of any hypothetical costs savings has not been studied.

BPAP Versus CPAP

This section addresses PICO question 6 (see **Table 1**) and resulted in one recommendation (see Recommendation 6 in the companion clinical practice guideline).⁸ A total of 5 RCTs compared the use of BPAP to CPAP to improve one or more of the following outcomes: AHI, adherence to PAP therapy, sleepiness, neurocognitive function, QOL, and reduction of side effects.^{209–213} Participants were predominantly male, middle aged, referred to sleep clinics without concomitant medical or psychiatric disorders with moderate to severe OSA, randomized to CPAP versus BPAP for durations of either 1 month, 3 months, or 12 months of PAP use. Only one study included participants who had previously showed nonadherence with CPAP (< 4 h/night),²⁰⁹ whereas the other 4 studies included PAP naïve participants.^{210–213} The average therapeutic pressure reported in the studies was ~10 cm H₂O and none of the studies specifically selected participants with high PAP requirements. Four of the studies implemented modified pressure profile technology.^{209–211,213} Two studies employed the use of auto-BPAP.^{211,213} One study employed the use of flexible BPAP.²⁰⁹ One study employed the use of a novel BPAP device.²¹⁰ This device was modified so that the inspiratory pressure was slightly reduced near the end of inspiration, and the expiratory pressure slightly reduced near the beginning of expiration. One study employed the use of standard BPAP.²¹² All 5 studies titrated CPAP and BPAP pressure levels during an attended laboratory study.^{209–213} Meta-analyses were performed to assess the effects of BPAP compared with CPAP in improving AHI, PAP

adherence, and daytime sleepiness (see supplemental material, **Figure S75** through **Figure S77**). There were insufficient data available to perform meta-analyses for QOL, neurocognitive function, or side effects; however, data from individual studies were reviewed. A Summary of Findings table is presented in the supplemental material, **Table S6**. A summary of the evidence for each outcome is provided below.

OSA Severity

The efficacy of BPAP compared to CPAP in reducing OSA severity in adults with OSA was evaluated in a meta-analysis of 2 RCTs.^{210,213} Participants were randomized to BPAP versus CPAP for a duration of 1 month or 3 months of PAP use. Meta-analysis of the 2 RCTs^{210,213} did not demonstrate a clinically significant difference in residual AHI with treatment using BPAP compared to CPAP (see supplemental material, **Figure S75**). The mean difference in residual AHI between BPAP and CPAP was -2.2 events/h (95% CI: -5.1 to 0.7 events/h).

Overall, the analyses suggest that BPAP compared to CPAP in adults with OSA similarly reduces AHI in adults with OSA. The quality of evidence for OSA severity was low due to imprecision and potential publication bias from industry funding.

Adherence

Adherence to BPAP compared to CPAP for the treatment of adult OSA was evaluated using a meta-analysis of 4 studies²¹⁰⁻²¹³ in PAP naïve participants and one study²⁰⁹ in CPAP nonadherent participants that reported on adherence. Participants were randomized to BPAP versus CPAP for at least 4 weeks up to a maximum of 1 year of PAP use. The meta-analysis demonstrated no clinically significant difference in adherence with BPAP compared with CPAP (see supplemental material, **Figure S76**) in the 4 studies that used BPAP as the first line therapy.²¹⁰⁻²¹³ The study using BPAP with a modified pressure profile as a rescue therapy in participants nonadherent to CPAP after ≥ 2 weeks demonstrated a clinically significant increase in the point estimate adherence of 0.8 h/night (95% CI: -0.03 to 1.6 h/night) in the BPAP compared to the CPAP group, although the precision was very low.²⁰⁹

Overall, the analyses suggest that BPAP conferred no clinically significant advantage over CPAP in adults with OSA in improving adherence, except potentially as rescue therapy for participants' nonadherent to CPAP. The quality of evidence for adherence was low due to imprecision and potential publication bias from industry funding.

Sleepiness

The efficacy of BPAP compared to CPAP for the treatment of sleepiness in adults with OSA was evaluated using a meta-analysis of 3 RCTs that reported on the ESS.^{210,211,213} Participants were randomized to BPAP versus CPAP for a duration of 1 month²¹⁰ or 3 months^{211,213} of PAP use. The meta-analysis demonstrated no clinically significant difference in self-reported sleepiness in adults with OSA treated with BPAP compared to CPAP (see supplemental material, **Figure S77**). However, the studies demonstrated that both BPAP and CPAP use improve self-reported sleepiness compared to before initiation of treatment.

Overall, the analyses suggest that BPAP compared to CPAP in adults with OSA similarly reduces sleepiness. The quality of evidence for self-reported sleepiness was low due to potential publication bias from industry funding and imprecision.

Quality of Life

There were insufficient data available to perform a meta-analysis of the impact of BPAP compared to CPAP on QOL in adults with OSA. However, the TF reviewed available data from 2 RCTs that reported on the FOSQ.^{209,210} Participants were randomized to BPAP versus CPAP for a duration of 1 month²¹⁰ and 3 months²⁰⁹ of PAP use. One of the studies examined the effects of BPAP compared to CPAP on QOL in participants previously intolerant of CPAP, while the other study recruited participants naïve to PAP, thus they were not combined for meta-analysis. Neither study^{209,210} demonstrated a clinically significant difference in QOL between BPAP and CPAP as assessed by the FOSQ (see supplemental material, **Table S6**).

Overall, the analyses suggest that BPAP compared to CPAP in adults with OSA results in similar effects on sleep-related QOL. The quality of evidence for sleep-related QOL was very low due to imprecision and potential publication bias from industry funding.

Side Effects

There were insufficient data available to perform a meta-analysis of side effects. Side effects have been reported with the use of both BPAP and CPAP. These include but are not limited to nasal dryness or irritation, dry mouth, sore throat, sinus infection, and poor sleep quality. These side effects can impact patient adherence with PAP and should be carefully monitored. Participants in the one RCT of CPAP versus BPAP that reported side effects followed participants for 1 year.²¹² This study reported no clinically significant difference in side effects with similar complaints in both groups with regard to mask discomfort, machine noise, and nasal stuffiness.²¹² In addition, in one other available study,²¹³ there was no difference between BPAP and CPAP treatment in sleep quality as assessed by the Pittsburgh Sleep Quality Index (see supplemental material, **Table S6**).

Overall, the quality of evidence for side effects was low due to imprecision and potential publication bias from industry funding.

Overall Quality of Evidence

The outcomes of adherence to PAP therapy, sleepiness, and QOL were determined by the TF to be critical for decision-making. The overall quality of evidence was downgraded to very low due to imprecision and potential bias due to industry funding.

Benefits Versus Harms

There is no expected advantage of BPAP over CPAP in reducing OSA severity, which was confirmed in the meta-analysis of the limited studies available. Thus, in general, the benefits of BPAP are similar to CPAP. A potential benefit of BPAP over CPAP is improved comfort due to a lower pressure during exhalation, which may then improve patient adherence

and consequentially improve OSA-related outcomes. However, improved adherence to BPAP was not observed in the available studies that predominantly recruited PAP naïve patients. Only one study, which assessed participants that were CPAP intolerant, suggests that BPAP might improve adherence, although the precision in this study was very low and precluded any definitive statements.²⁰⁹ Finally, a small subset of patients with high PAP requirement that cannot be provided by CPAP devices, but can be provided by BPAP devices, would benefit from BPAP use. Potential harms of BPAP are, in general, like CPAP with a few notable additional considerations including the potential for suboptimal improvement in the residual AHI from an inappropriately low expiratory pressure setting and the substantially higher cost of BPAP devices. The potential benefit of a lower expiratory pressure may be less relevant since modified pressure profiles in current PAP devices perform a similar function.

Given the available data, the TF judged that the potential harms and burden of BPAP outweighed the potential benefit in adults with OSA. Therefore, the TF concluded that in general, clinicians should use CPAP over BPAP in the routine initiation of treatment of adults with OSA.

Patient Values and Preferences

The TF determined that the majority of patients would prefer their OSA be treated with CPAP rather than BPAP based on the similar benefits of treatment with BPAP and CPAP, and the potential for increased cost of BPAP, risk for incomplete treatment, and the availability of modest expiratory pressure reduction in most CPAP devices manufactured today. However, the TF also recognized that BPAP may be of benefit in some CPAP intolerant patients, despite the use of modified pressure profile. In addition, some patients may require BPAP when therapeutic pressure settings are higher than what can be delivered by a CPAP device. In these situations, BPAP devices may be needed for optimal treatment and can be utilized during an initial or subsequent in-laboratory PAP titration study. For specific patients who are unable to tolerate CPAP, due to high pressure requirements, a trial of BPAP may be offered either during the in-laboratory titration or following a period of demonstrated non-acceptance.

Resource Use

The TF recognized that there are significant differences in the cost of BPAP and CPAP devices between countries and medical systems, with small differences in some regions and larger differences in others. While the TF did not identify cost-effectiveness studies and did not undertake a comprehensive cost comparison of BPAP versus CPAP devices, the TF determined based on its collective clinical experience that the cost of BPAP could result in greater resource use.

Educational, Behavioral, and Troubleshooting Interventions With PAP Versus PAP Alone

This section addresses PICO question 10 (see **Table 1**) and resulted in two recommendation (see Recommendations 7 and 8 in the companion clinical practice guideline).⁸ A total of 18 RCTs were identified that evaluated the use of some combination of

an educational, behavioral, or troubleshooting intervention as an adjunct to initiation of PAP therapy compared to PAP therapy with standard of care alone on PAP adherence, sleepiness, and QOL.^{207,214–230} Data were not available to assess the effect of these interventions on sleepiness or QOL. Given the substantial heterogeneity in the interventions assessed, the TF decided to divide interventions into one of three broad categories: (1) educational interventions—interventions focused primarily on providing information at initiation of PAP about what OSA is, the downstream consequences of the disorder, what PAP therapy involves, and the potential benefits of PAP therapy; (2) behavioral interventions—interventions focused on behavior change related to use of PAP therapy using strategies such as cognitive behavioral therapy or motivational enhancement; and (3) troubleshooting interventions—interventions focused on close patient communication to identify PAP-related problems and to initiate potential solutions. Of note, both behavioral and troubleshooting interventions include some amount of patient education to motivate the behavior change or understand how to address problems; the TF considered this an integral part of the behavioral or troubleshooting intervention.

All studies included in this assessment compared at least one of these interventions to a standard of care which varied substantially across studies in terms of the level and intensity of care provided, resulting in heterogeneity across studies. Similarly, the intensity of the intervention varied substantially across studies. Overall, there were 7 RCTs^{207,214,215,220,221,229,230} identified that compared a pure educational intervention versus usual care, 6 RCTs^{214–219} that compared a behavioral intervention versus usual care, and 9 RCTs^{207,220,222–228} that compared a troubleshooting with education intervention versus usual care. Although several studies had more than one intervention arm, the TF did not compare the effectiveness of different interventions against each other. Meta-analyses were performed to assess the efficacy of educational, behavioral, and troubleshooting interventions as an ancillary treatment when combined with PAP therapy to increase PAP adherence, thereby improving symptom control in the treatment of OSA as compared with PAP therapy without such adjunctive intervention. The meta-analyses are provided in the supplemental material, **Figure S78** through **Figure S82**. Summary of Findings tables are also included in the supplemental material, **Table S7** through **Table S9**. A summary of the evidence for each outcome by intervention is provided below.

Adherence (Educational Interventions)

A total of 7 RCTs were identified assessing the impact of a pure educational intervention as an adjunct to PAP therapy to improve adherence with PAP.^{207,214,215,220,221,229,230} The delivery of education varied substantially and included being given written materials, watching a video, or face-to-face didactic sessions. All studies included participants with a mean AHI in the severe range and follow-up ranged from 1 month to 1 year. Meta-analysis of all 7 studies demonstrated a clinically significant difference in PAP usage of 0.6 h/night (95% CI: +0.0 to 1.1 h/night) (see supplemental material, **Figure S78**). One trial was excluded from the meta-analysis as the study had undue leverage (weighting) due to standard deviations reported for PAP adherence that were much lower than what the TF would

expect in typical OSA populations being treated with PAP.²³¹ The magnitude of effect observed in that study was not different from that seen in the meta-analysis of the other studies. A meta-analysis of 3 RCTs^{214,221,229} demonstrated that the mean estimate of the impact of an education intervention on obtaining PAP usage > 4 h/night was clinically significant, with an odds ratio of 1.2 (95% CI: 0.8 to 1.9) (see supplemental material, **Figure S79**).

Overall, these results demonstrate a clinically significant improvement in PAP adherence in adults with OSA with an educational intervention compared to usual care. The quality of evidence for adherence was moderate due to imprecision.

Adherence (Behavioral Interventions)

The efficacy of a behavioral intervention as an adjunct to PAP therapy to improve adherence was evaluated based on 6 RCTs.^{214–219} There was substantial heterogeneity in terms of the type of intervention (motivational enhancement, cognitive behavioral therapy, stage matched intervention), delivery of intervention (individual, group, peer), and duration of intervention. Follow-up ranged from 1 month to 1 year. A meta-analysis of all 6 RCTs demonstrated a clinically significant difference in PAP usage of 1.2 h/night (95% CI: 0.3 to 2.0 h/night) (see supplemental material, **Figure S80**). Similarly, a meta-analysis of 5 of these RCTs^{86,214,216–218} reporting on obtaining PAP usage > 4 h/night found behavioral interventions were associated with a clinically significant odds ratio of 3.1 (95% CI: 1.7 to 5.9) for being adherent (see supplemental material, **Figure S81**).

Overall, these results demonstrate a clinically significant improvement in PAP adherence in adults with OSA with behavioral interventions compared to usual care. The quality of evidence for behavioral interventions to increase PAP adherence ranged from moderate to high, depending on the measure employed, due to imprecision.

Adherence (Troubleshooting Interventions)

A total of 9 RCTs evaluated the efficacy of education combined with troubleshooting interventions as an adjunct to PAP therapy to improve adherence.^{207,220,222–228} Substantial heterogeneity was found in the delivery of the intervention including home visits, phone calls from medical or non-medical personnel, automated phone calls, and inquiries via computer. While most studies relied on participants reporting problems, at least one²²⁸ used objective data obtained from the PAP device itself. Follow-up assessments ranged from 1 month to 1 year. Meta-analysis demonstrated a clinically significant difference in PAP usage of 0.7 h/night (95% CI: 0.2 to 1.1 h/night) (see supplemental material, **Figure S82**).

Overall, the results demonstrate a clinically significant improvement in PAP adherence in adults with OSA with troubleshooting combined with education interventions compared to usual care. The quality of evidence for troubleshooting combined with education interventions to increase PAP adherence was moderate due to imprecision.

Overall Quality of Evidence

The overall quality of evidence based on the critical outcome of adherence for the use of educational, behavioral, and

troubleshooting interventions was downgraded to moderate due to imprecision.

Benefits Versus Harms

The benefits of all three types of interventions include increased adherence with PAP therapy along with the presumed downstream effects of increased adherence, such as better control of OSA symptoms.¹⁸¹ In addition, increased knowledge and mastery of CPAP therapy would lead to improvements in psychological well-being. Educational interventions, which are typically one-time sessions providing information about OSA and PAP therapy have minimal burden and are relatively easy to implement in virtually all healthcare settings. Behavioral and troubleshooting interventions do impose burdens on the patient including time required and cost to receive the intervention. In addition, the behavioral and troubleshooting interventions may cause a sense of loss of privacy or discomfort to patients. Finally, these interventions require development of infrastructure and expertise that may not be readily available in some healthcare settings. Overall, the TF judged that the benefits of an educational intervention strongly outweigh any potential harms or burdens, while the benefits of a behavioral and/or troubleshooting intervention likely outweigh the harms and burdens of such interventions in most patients.

Patient Values and Preferences

Based on their clinical expertise the TF determined that the vast majority of patients would want an educational intervention provided with PAP therapy, and the majority of patients would want a behavioral and/or troubleshooting intervention to facilitate improved adherence with PAP therapy.

Resource Use

The TF did not identify cost-effectiveness studies evaluating educational, troubleshooting, and behavioral interventions. The cost of implementing educational, troubleshooting, and behavioral interventions by health care providers will vary depending on the complexity of the intervention. For example, educational interventions can range from providing patients with literature to review regarding the diagnosis and treatment of OSA to dedicated one-on-one sessions with a respiratory therapist on how to use PAP therapy. Behavioral therapy interventions may require the most resources given the need for trained behavioral specialists to implement the intervention, the patient's time, and the length and number of sessions needed for a successful program. However, this increased resource use may be offset by the increase in PAP adherence obtained and the relative improvement in patient symptoms. The TF judged that resource use for educational, troubleshooting, and behavioral interventions is warranted to ensure adequate PAP adherence.

Telemonitoring Versus No Telemonitoring Interventions With PAP

This section addresses PICO question 11 (see **Table 1**) and resulted in one recommendation (see Recommendation 9 in the companion clinical practice guideline).⁸ A total of 5 RCTs were identified that evaluated the use of remote monitoring of PAP

variables to trigger early interventions versus no such system as an adjunct to PAP therapy for the treatment of adults with OSA.^{228,232–235} Outcomes assessed included adherence to PAP therapy, sleepiness, QOL and PAP-associated side effects. All studies evaluated outcomes at 2–3 months after PAP initiation. However, details about the triggers for intervention and the intensity of the intervention used when poor usage patterns were identified varied greatly across studies likely resulting in heterogeneity of results. Some studies only triggered interventions based on low usage while other studies also triggered interventions for high mask leak, high delivered pressures, and/or high residual AHI. The intervention triggered by concerning PAP data also varied substantially, ranging from text messages to telephone calls, in-person visits with sleep staff, and even in-person visits with a sleep physician. Nevertheless, meta-analyses were performed to assess the efficacy of telemonitoring guided interventions as an ancillary treatment when combined with PAP therapy to increase PAP adherence and thereby improve symptom control in the treatment of OSA in adults as compared with PAP therapy without such an intervention (see supplemental material, **Figure S83** and **Figure S84**). Meta-analysis demonstrated a clinically significant improvement in PAP adherence with the use of telemonitoring. A Summary of Findings table is also included in the supplemental material, **Table S10**. A summary of the evidence for each outcome is provided below.

Adherence

The efficacy of an intervention guided by remote monitoring of PAP therapy to improve PAP adherence was evaluated using a meta-analysis of 5 RCTs that reported on hours per night of PAP usage.^{228,232–235} These studies used data from the PAP machine to guide the intervention. Four of the five studies enrolled newly diagnosed participants with OSA with minimal comorbidity and follow-up was short ranging from 1 to 3 months.^{228,232–235} The meta-analysis demonstrated a clinically significant increase in PAP usage of 1.0 h/night (95% CI: 0.5 to 1.4 h/night) (see supplemental material, **Figure S83**). A potential explanation for the increase in adherence with telemonitoring is access to real-time assistance from a clinical provider to address PAP-related issues for patients rather than waiting for an appointment to see a clinician. An alternative explanation is that daily monitoring motivates patient to have an increased sense of accountability for their care or to their health care provider.²²⁸ These mechanisms have yet to be fully evaluated.

Overall, the analyses demonstrated a clinically significant improvement in adherence in adults with OSA using telemonitoring compared to usual care. The quality of evidence for PAP adherence was high.

Sleepiness

The efficacy of a telemonitoring guided intervention as part of PAP therapy in adult participants with OSA was evaluated using a meta-analysis of 3 RCTs that reported on self-reported sleepiness using the ESS.^{228,232,234} Studies used interventions that relied on data from the PAP machine. The meta-analysis did not demonstrate a clinically significant reduction in the ESS with the telemonitoring guided intervention as compared to no such intervention (see supplemental material, **Figure S84**).

Overall, the analyses did not demonstrate a clinically significant improvement in sleepiness in adults with OSA using telemonitoring compared to usual care. The quality of evidence for self-reported sleepiness was moderate due to imprecision.

Side Effects

Two RCTs were identified that assessed the impact of a telemonitoring guided PAP adherence intervention on PAP-induced side effects; however, data were not reported in a sufficiently standardized format to allow for a meta-analysis.^{228,235} Side effects assessed included CPAP discomfort, difficulty exhaling, mask leaks, aerophagia, allergic reactions to device components, headache, facial pain or bruises, mouth dryness, or nasal congestion. Both studies demonstrated no clinically significant difference in the frequency of PAP-related side effects, with the exception of one study which suggested that telemonitoring was associated with fewer complaints of a dry mouth (see supplemental material, **Table S10**).²²⁸ The quality of evidence was low due to imprecision.

Quality of Life

The efficacy of adding a telemonitoring guided PAP intervention to PAP therapy on QOL in adult participants with OSA was evaluated in 2 RCTs, one that reported on QOL using the FOSQ²³², and the other²³⁵ using the EQ5D. In the first trial²³², the intervention relied on self-reported problems from the participant to guide management rather than data from the PAP device. In this study, no clinically significant increase in QOL was observed with the telemonitoring guided intervention (see supplemental material, **Table S10**).²³² In the other trial,²³⁵ interventions were performed by a clinician based on alerts generated by the PAP monitoring system. Clinically significant improvements in QOL with CPAP were observed in both telemonitoring and control groups; however, there was no difference in the magnitude of improvement between those who received telemonitoring and those who did not. The quality of evidence for QOL was low due to imprecision.

Overall Quality of Evidence

The outcomes of adherence to PAP therapy, sleepiness, and side effects were determined by the TF to be critical for decision-making. The overall quality of evidence based on the critical outcomes was downgraded to moderate due to imprecision.

Benefits Versus Harms

The benefits of a telemonitoring guided adherence intervention are improvements in PAP adherence to improve control of OSA symptoms and reduce the need for office visits, which might reduce healthcare costs. The primary potential harm to a patient of a telemonitoring guided adherence intervention is the potential loss of privacy, as data on PAP usage are saved on servers owned by PAP manufacturers and may be subject to changes in privacy guarantees. Furthermore, for some patients, increased communication with a health care provider or healthcare medical equipment company may be perceived as intrusive or seem more impersonal which could result in reduced patient satisfaction. Overall, the TF deemed the harms

of telemonitoring were minor for most patients and outweighed by the potential benefits.

Patient Values and Preferences

Patient satisfaction with telemonitoring guided adherence interventions was assessed in two of the reviewed studies, with discrepant findings.^{232,235} In one study, participants in the telemonitoring group indicated a greater likelihood of continuing to use CPAP compared to the usual care group, while both groups were highly satisfied with their care and were not concerned about being wirelessly monitored. In the other RCT study, participants in the telemonitoring group reported low to moderate overall satisfaction compared to those in the usual care arm (26% versus 4% respectively) with additional concerns about privacy when being identified as being nonadherent or that non-hospital personnel had access to their PAP data. Despite this, 63% of those in the telemonitoring arm placed a high or very high value on the usefulness of the telemonitoring assessment.²³⁵ Based on their clinical expertise, the TF judged that the benefits of telemonitoring guided adherence interventions outweigh the harms, and that most patients would want a telemonitoring system as part of a PAP treatment program given the improved PAP adherence, though some may have concerns of privacy or feel less satisfaction with their care.

Resource Use

For some health systems and clinical practices, there may be increased costs associated with a telemonitoring adherence intervention. Some telemonitoring systems also allow patients to self-monitor if they are comfortable with using a patient portal with a computer or smartphone or tablet. The cost of resources spent to implement such programs may be offset by potential savings due to less frequent healthcare visits. One of the studies reviewed suggested that telemonitoring may be a more cost-effective approach with an ICER of €17,359 per QALY. The TF judged that resource use for telemonitoring interventions is warranted to ensure adequate PAP adherence.

ADDITIONAL CONSIDERATIONS

The TF considered whether advancements in specific PAP delivery methods result in clinically significant improvement in patient outcomes compared with standard delivery methods and modalities. The TF reviewed evidence for advancements in PAP delivery methods including the use of modified pressure profiles, different mask interfaces, and heated humidification. The findings of the evidence review for these delivery methods are presented below.

Modified Pressure Profile PAP Versus Standard CPAP

This section addresses PICO question 7 (see **Table 1**). A total of 7 RCTs investigated the use of modified pressure profile PAP to improve clinical outcomes and reduce side effects.^{188,236–241} One of these studies used a cross-over design.²⁴⁰ Participants were predominantly male, obese, with moderate to severe OSA, and self-reportedly sleepy. The intervention was administered for a period of at least 1 month (range: 1–6 months). Meta-analyses

were performed to assess the impact of modified pressure profile PAP for the treatment of OSA in adults as compared with standard PAP (see supplemental material, **Figure S85** through **Figure S90**). The outcomes analyzed were adherence to PAP therapy, sleepiness, neurocognitive function, QOL, and side effects. A Summary of Findings is also included in the supplemental material, **Table S11**. A summary of the evidence for each outcome is provided below.

Adherence

The effect of modified pressure profile PAP in adults with OSA on PAP adherence was evaluated using a meta-analysis of 6 RCTs that reported on the number of hours per night the device was used.^{188,236–240} All 6 studies were performed in participants who were naïve to CPAP, had not used CPAP in the past year, or were not clearly specified. The meta-analysis demonstrated no clinically significant difference in adherence for participants that received modified pressure profile PAP versus standard PAP (see supplemental material, **Figure S85**). One additional RCT that was reviewed but could not be included in the meta-analysis (data on standard deviation was not provided) reported no clinically significant difference in adherence for participants that received modified pressure profile PAP versus standard PAP.²⁴¹ One of the included studies allowed participants after the RCT ended to cross-over to using a modified pressure profile PAP in an open-label study for 3 months and demonstrated an increase in adherence in those participants that had had low adherence on standard PAP (< 4 h/night), suggesting that participants with poor adherence might increase their PAP use once transitioned to modified pressure profile PAP.²³⁹ The meta-analysis demonstrated no clinically significant improvement in adherence in adults with OSA with modified pressure profile PAP compared to standard PAP in adult patients with OSA, however, the possibility of benefits in patients demonstrating poor adherence remains to be demonstrated.

Sleepiness

A meta-analysis of 5 RCTs^{188,236–239} demonstrated no clinically significant difference in self-reported sleepiness between participants on modified pressure profile PAP compared to standard PAP (see supplemental material, **Figure S86**). One additional RCT that was reviewed but could not be included in the meta-analysis reported no significant difference in ESS with modified pressure profile PAP compared to standard PAP.²⁴¹ The meta-analysis demonstrated no benefit in adults with OSA of modified pressure profile PAP compared to standard PAP in reducing sleepiness in adult patients with OSA.

Quality of Life

The efficacy of modified pressure profile PAP versus standard PAP on sleep-related QOL was evaluated based on two studies^{188,236} that reported on the FOSQ, one study²³⁷ that reported on the SAQLI, and two studies^{236,237} that reported on the Pittsburgh Sleep Quality Index. Meta-analysis demonstrated no clinically significant difference in sleep-related QOL (see supplemental material, **Figure S87** and **Figure S88**). One study²³⁶ reporting global QOL using SF-36 MCS, PCS, and vitality scores found no significant difference in any of these measures.

The meta-analyses demonstrated no clinically significant improvements in sleep-related QOL, general QOL measures, and sleep quality in adults with OSA with modified pressure profile PAP compared to standard PAP in adult patients with OSA.

Neurocognitive Function

The efficacy of modified pressure profile PAP versus standard PAP for improvement in neurocognitive function was evaluated using meta-analyses of 3 RCTs that reported on attention and vigilance using the psychomotor vigilance test (PVT).^{188,236,238} Meta-analysis demonstrated a clinically significant standardized mean difference of 0.3 (95% CI: 0.0 to 0.6) in PVT reaction time in favor of standard PAP over modified pressure profile and a clinically significant standardized mean difference in PVT lapses of 0.2 (95% CI: -0.2 to 0.7) (see supplemental material, **Figure S89** and **Figure S90**). Given the absence of testing of other important neurocognitive domains and findings from the present meta-analyses, together with imprecision of the point estimate of effect, there was insufficient evidence demonstrating that neurocognitive function in adults with OSA is improved with modified pressure profile PAP compared to standard PAP in adults with OSA.

Side Effects

The efficacy of modified pressure profile PAP versus standard PAP in reducing PAP-related side effects in adults with OSA was evaluated; however, data were not reported in a sufficiently standardized format to perform meta-analyses except for the outcome of sleep quality. Only 3 RCTs reported data on side effects.^{188,239,241} One study had participants answer a questionnaire that assessed a broad range of side effects including mouth dryness, eye watering, chest pressure, cold sensation, frequent awakening, mask leak, and machine noise.²⁴¹ At 7 weeks, there were no significant differences in any of these side effects between the modified pressure profile PAP and standard PAP groups.²⁴¹ Another study assessed participant side effects and comfort, but did not specify what was assessed.²³⁹ This study reported no differences in side effects or participant comfort between the groups at 3 months.²³⁹ The third study assessed mask comfort and sleep quality using a visual analog scale.¹⁸⁸ There were no differences in mask comfort between the groups; however, there was a trend in sleep quality being worse in the modified pressure profile PAP group at 90 and 180 days after the start of therapy.¹⁸⁸ Overall, there were no clinically significant differences in side effects or in participant preference^{188,240} between modified pressure profile PAP and standard PAP. Nevertheless, analyses from at least one study²³⁹ suggest that certain patient populations, particularly poorly adherent patients, may benefit from modified pressure profile PAP, though this requires further investigation.

Nasal PAP Versus Intranasal PAP Versus Oral PAP Versus Oronasal PAP

This section addresses PICO question 8 (see **Table 1**). A total of 11 studies (3 observational studies and 8 RCTs) were identified which evaluated the effects of different PAP interfaces on reducing AHI, improving adherence to PAP therapy, sleepiness and QOL and reducing side effects.^{208,242–251} Participants

in the 8 RCTs were predominantly middle-aged males without major medical comorbidities with moderate to severe OSA who were treated with each interface for at least 1 and up to 8 weeks (median duration of 4 weeks) in either parallel or cross-over designs. Participants were previously untreated except for one study²⁴³ in which participants established on PAP treatment for > 6 months were randomized to intra-nasal versus nasal treatment. Generally, participants in these studies were not selected based on specific side effects (eg, nasal congestion, oral dryness) or mask interface intolerance, except for one study where participants with significant nasal resistance were excluded.²⁴⁸ Data on adherence for nasal versus oronasal interfaces were also analyzed from 3 non-randomized studies.^{249–251} Participants were predominantly male without major medical comorbidities, with previously untreated moderate to severe OSA, and were treated for at least 3 weeks up to 24 months. Meta-analyses were performed comparing different interfaces to standard nasal interfaces for the outcomes of OSA severity, adherence, and self-reported sleepiness (see supplemental material, **Figure S91** through **Figure S98**). A Summary of Findings is also included in the supplemental material, **Tables S12–S14**. A summary of the evidence for each outcome is provided below.

OSA Severity

The efficacy of intra-nasal compared to nasal interfaces for the treatment of OSA severity in adults was evaluated using a meta-analysis of 3 cross-over RCTs; two of 3–4 weeks duration^{208,242} involving newly treated participants with a range of PAP pressures, and one for a 1-week period²⁴³ in participants previously established on nasal PAP treatment at ≥ 12 cm H₂O for > 6 months. There was no clinically significant difference in AHI (see supplemental material, **Figure S91**).

The efficacy of oronasal compared to nasal interfaces for the treatment of OSA severity in previously untreated adults was evaluated using a meta-analysis of 2 cross-over RCTs; one of 3 weeks duration²⁴⁵ and one²⁴⁸ of 4 weeks duration. Residual AHI was higher with oronasal than nasal interfaces, although this difference was not clinically significant (see supplemental material, **Figure S95**).

There was insufficient evidence to perform a meta-analysis on OSA severity for oral versus nasal interfaces. One RCT employing a 4-week cross-over design²⁴⁶ demonstrated no clinically significant differences in AHI with oral compared with nasal interfaces.

Adherence

The efficacy of intra-nasal compared with nasal interfaces for improving adherence to PAP therapy was evaluated using meta-analyses of 2 cross-over RCTs of 3–4 weeks duration^{208,242} involving newly treated participants with a range of PAP pressures, and one RCT²⁴³ for 1 week periods in participants previously established on nasal PAP treatment at ≥ 12 cm H₂O for > 6 months. There was no clinically significant difference in mean adherence^{208,242,243} and percent nights of CPAP use^{208,242} with intra-nasal interfaces compared with nasal interfaces (see supplemental material, **Figure S92** and **Figure S93**).

The efficacy of oronasal compared with nasal interfaces for improving adherence was evaluated in meta-analyses of 3 cross-over RCTs of 3 to 4 weeks duration,^{244,245,248} which demonstrated a clinically significant improvement in adherence of 0.6 h/night (95% CI: -0.2 to 1.3 h/night) with nasal interface compared with oronasal interface (see supplemental material, **Figure S96**). A meta-analysis was performed of 3 non-randomized studies in which participants were predominantly male without major medical comorbidities, with previously untreated moderate to severe OSA, treated for at least 3 weeks up to 24 months.²⁴⁹⁻²⁵¹ This also demonstrated a clinically significant difference in adherence of 0.7 h/night (95% CI: 0.2 to 1.2 h/night) in favor of nasal interfaces (see supplemental material, **Figure S97**).

There was insufficient evidence to perform meta-analysis for the effects on adherence for oral versus nasal interfaces. The literature search identified one 8-week parallel arm RCT²⁴⁷ that demonstrated a clinically significant difference in adherence with a mean difference of 0.9 h/night (95% CI: -0.7 to 2.5 h/night) in favor of oral interfaces.

The meta-analyses demonstrated clinically significant improvements in adherence in adults with OSA with nasal interfaces compared to oronasal interfaces. The evidence review comparing adherence between oral versus nasal interfaces was limited to one study and suggested increased adherence in adults with OSA with an oral compared to a nasal interface. However, based on the clinical experience of the TF, most patients have difficulties using an oral interface over the long-term.

Sleepiness

The efficacy of intra-nasal compared with nasal interfaces for improving self-reported sleepiness was evaluated using a meta-analysis of two crossover studies, one employing a 3 week duration²⁰⁸ and one employing a 4 week duration²⁴², that demonstrated no clinically significant difference in self-reported sleepiness between intra-nasal and nasal interfaces as assessed with the ESS (see supplemental material, **Figure S94**).

The efficacy of oronasal versus nasal interfaces was evaluated using a meta-analysis of 2 RCTs.^{244,248} The meta-analysis demonstrated no clinically significant difference in self-reported sleepiness between the interfaces as assessed with the ESS (see supplemental material, **Figure S98**). There was insufficient evidence to perform meta-analysis for the effects on self-reported sleepiness for oral versus nasal interfaces. One RCT²⁴⁶ demonstrated no clinically significant difference in self-reported sleepiness with oral interfaces compared with nasal interfaces. The meta-analyses demonstrated no clinically significant differences in self-reported sleepiness between the different mask interfaces.

Quality of Life

There was insufficient evidence to perform meta-analysis for the effects of the various interface types on QOL. Only one RCT²⁰⁸ was identified that met inclusion criteria which assessed the effect of intra-nasal versus nasal interfaces on QOL over 3 weeks each in a cross-over RCT. QOL was assessed with the FOSQ and no clinically significant difference in QOL

was found comparing intra-nasal versus nasal interfaces.²⁰⁸ No RCT evidence was available to assess the effects of oronasal or oral interfaces compared to nasal interfaces on QOL. There was insufficient evidence demonstrating differences in QOL improvement on PAP with any mask interface.

Side Effects

The efficacy of the various mask interfaces in reducing PAP-related side effects in adults with OSA was evaluated. However, sufficient standardized data were not available to perform a meta-analysis for any of the interface types. A well-sealed interface is necessary for effective delivery of PAP, and mask and/or mouth leak may adversely impact treatment efficacy. Side effects have been reported with all forms of PAP interface and may adversely impact adherence. Side effects may differ between interface type and between individuals for a given interface. Improvements of air leak and other side effects through interface selection may have beneficial effects on treatment adherence and efficacy.

For intra-nasal versus nasal interfaces, side effect data were reported from 2 cross-over RCTs of 3-week and 4-week duration^{208,242} involving newly treated participants with a range of PAP pressures, or for 1 week periods²⁴³ in participants previously established on nasal PAP treatment at ≥ 12 cm H₂O for > 6 months. An overall multi-item side effect score favored intra-nasal interfaces in one study of newly treated participants,²⁰⁸ but there were no clinically significant differences in overall side effects between interfaces for the other 2 studies.^{242,243} Individual side effects including pressure sensation on the face, skin irritation, claustrophobia and obtrusiveness were in general less for intra-nasal interfaces in the 3 studies, while nasal interfaces were scored as being less obtrusive. There were no clinically significant differences between interfaces for nasal or oral congestion or dryness. In one study,²⁰⁸ overall mask satisfaction scores were significantly higher for intra-nasal interfaces while in the other 2 studies^{242,243} which determined participant preference, there was no clinically significant difference between intra-nasal versus nasal interfaces either for newly treated or previously treated participants. Overall, differences in side effects were not clinically significant between the two interfaces.

For oronasal versus nasal interfaces, two 4-week cross-over RCTs^{244,248} and two non-RCTs^{249,250} evaluating treatment periods of up to 24 months (6 months, mean of 4.5 months, respectively), reported data on side effects. In one cross-over RCT,²⁴⁴ 19 of 20 participants rated the nasal interface as more comfortable. Higher scores for nasal and throat dryness but not nasal stuffiness were clinically significant with the nasal interface while higher scores of self-reported mask leak, sore eyes, claustrophobia and difficulty exhaling were clinically significant with the oronasal interface. All participants chose the nasal interface for long-term treatment. In another cross-over RCT,²⁴⁸ mask noise and leak were greater with oronasal masks which were also reported to be harder to fit and hold in place, while other side effects did not differ. Participant preference favored nasal over oronasal masks with 21 of 33 participants selecting the nasal mask option, and only 4 choosing the oronasal mask option. In one of the non-RCTs, oronasal dryness was more

prevalent with oronasal than nasal interfaces (80% versus 46%, respectively).²⁵⁰ In a non-RCT of 2,311 participants in whom 62% were using nasal and 26% oronasal interfaces, there were greater reports in symptoms of eye irritation, dry mouth, choking sensation and psychologically perceived inconvenience with oronasal interfaces, while there were no clinically significant differences between oronasal and nasal interfaces in nasal congestion, headache, aerophagia, or family tolerance of treatment. In a multivariate analysis, PAP nonadherence in this cohort was independently associated with use of the oronasal interface.²⁴⁹ In these non-RCT cohorts, oronasal interfaces were least often chosen by participants for long-term treatment compared with nasal and intra-nasal interfaces.^{249,250} Overall, there are clinically important differences in side effects with oronasal compared with nasal interfaces. The increased side effects appear to result in a patient preference for nasal over oronasal interfaces and translate into a clinically significant reduction in adherence with oronasal compared to nasal PAP (see Adherence above). In light of this, as well as the tendency to increased residual OSA severity (see OSA Severity above) and in some studies increased pressure requirements with oronasal compared to nasal interfaces,^{248,252–257} nasal or intranasal mask interfaces may be preferred over oronasal interfaces for the routine initiation of PAP therapy in adults with OSA. However, patient factors will vary, and interface selection should be based on individual patient preference and tolerance.

For oral versus nasal interfaces, side effect data were reported in two 8-week parallel arm RCTs^{246,247} and two non-RCTs^{249,250} evaluating participants over 6 months treatment. For both RCTs, oral interfaces were associated with more oral dryness, excess salivation, lip and gum discomfort, while nasal interfaces were associated with more self-reports of air leaks, nasal dryness and strap/mask discomfort, with no differences in interface dislodgement.^{246,247} In one RCT,²⁴⁶ there was a trend for participants to prefer nasal (71%) over oral (29%) interfaces. In the non-RCTs, oral interfaces were associated with significantly more upper airway dryness and “rainout” (condensation) than nasal interfaces.^{249,250} In one study in which participants selected mask interface for initial titration and later long-term use, 27% chose oral versus 66% nasal initially, while long-term, after 6 months, 43% of those who initially selected an oral interface switched to nasal, while no one who initially selected a nasal interface switched masks.²⁵⁰ For individual patients there may be clinically important differences in side effects with oral compared with nasal interfaces, which on average lead patients to select nasal over oral interfaces, but ultimately interface selection should be based on individual patient preference and tolerance.

Humidified PAP Versus No Humidified PAP

This section addresses PICO question 9 (see **Table 1**). A total of 9 RCTs were identified that evaluated the use of PAP with humidification versus PAP without humidification to improve one or more of the following outcomes: adherence to PAP therapy, sleepiness, QOL, or PAP-related side effects including nasal discharge, nasal congestion, dry nose, epistaxis, and dry mouth/throat.^{258–266} All studies evaluated only participants with OSA who were naïve to PAP. The mean AHI in nearly

all studies was in the severe range. The duration of treatment for most studies was only 3–4 weeks, although one study did follow participants to 1 year.²⁵⁸ Most studies utilized heated humidification, except for 2 studies where one study²⁵⁹ compared both heated and cold pass-over humidification to no humidification and one study²⁶³ that did not specify the form of humidification used. Meta-analyses were performed to assess the efficacy of humidification as an ancillary treatment when combined with PAP to increase PAP adherence and QOL and reduce sleepiness and PAP-related side effects in the treatment of OSA in adults as compared with PAP therapy without humidification (see supplemental material, **Figure S99** through **Figure S106**). A Summary of Findings is also included in the supplemental material, **Table S15**. A summary of the evidence for each outcome is provided below.

Adherence

The efficacy of humidification with PAP therapy to improve PAP adherence was evaluated using a meta-analysis of 9 RCTs that reported on hours per night of PAP usage.^{258–266} The meta-analysis demonstrated no clinically significant difference in PAP usage in adults with OSA with the addition of humidification (see supplemental material, **Figure S99**).

Sleepiness

The efficacy of humidification when added to PAP for the treatment of OSA in reducing sleepiness in adults was evaluated using a meta-analysis of 8 RCTs.^{258–264,266} All of the included studies assessed self-reported sleepiness using the ESS. The meta-analysis demonstrated no clinically significant difference in self-reported sleepiness in adults with OSA with humidification as compared to no humidification (see supplemental material, **Figure S100**).

Quality of Life

A meta-analysis of 3 RCTs that reported on the effect of humidification on QOL using the SAQLI,²⁵⁸ QSQ,²⁶⁵ or FOSQ²⁶⁶ was performed to evaluate the efficacy of adding humidification to PAP for the improvement of QOL in adults with OSA. Meta-analysis demonstrated no clinically significant difference in QOL in adults with OSA with or without humidification (see supplemental material, **Figure S101**).

Side Effects

Meta-analyses were conducted for each identified PAP-related side effect whenever possible. The studies assessed only participants with newly diagnosed OSA with no prior history of treatment and only one study²⁶⁶ specifically recruited individuals with nasal symptoms. Meta-analyses of 2 RCTs^{260,262} demonstrated clinically significant reduction in the odds of nasal discharge, dry nose, epistaxis, and dry mouth/throat with the use of humidified PAP while meta-analyses of 3 RCTs^{260,262,263} demonstrated clinically significant reduction in the odds of nasal congestion and dry mouth with the use of humidified PAP (see supplemental material, **Figure S102** through **Figure S106**). In one study, while overall nasopharyngeal scores were not significantly different, complaints of dry or sore throat were significantly less with humidified than non-humidified PAP.²⁶⁶

Another study reported clinically significant reductions in the incidence of sinus pain/headache, sore throat, hoarse voice, and “smell” with odds ratios of 0.4 (95% CI: 0.1 to 1.4), 0.3 (95% CI: 0.1 to 1.6), 0.8 (95% CI: 0.2 to 3.2), and 0.7 (95% CI: 0.2 to 2.3) with humidification, respectively.²⁶⁰ However, this study reported no clinically significant differences in cough or sinus infection.²⁶⁰ Potential adverse effects of humidification including “rain out” (condensation) of water into the PAP circuit or participants’ face, nose or mouth with excessive humidity settings, or the inconvenience of purchasing distilled water and additional cleaning requirements were not reported on. Five studies^{259–262,264} reported on participant preference or satisfaction with the use of humidification, with participants on average either preferring heated humidification^{260,264} or expressing no clear preference^{261,262} for heated humidification. Overall, review of the data suggests a clinically significant reduction in the incidence of CPAP-related side effects with humidification, which together with the widespread availability of integrated humidifiers on current PAP devices, favors the routine use of humidification. However, some patients may determine that the absence of humidification results in no untoward side effects and the decision to use humidification should be based on individual patient preference and tolerance.

DISCUSSION AND FUTURE DIRECTIONS

The systematic review performed by the TF identified many areas that merit further investigation to determine effects on patient outcomes and inform clinical decision-making.

Effect of PAP on OSA-Related Outcomes

More work in both short-term and long-term studies is needed to determine the efficacy of PAP therapy to improve key outcomes currently associated with OSA including symptoms outside of excessive sleepiness (eg, nocturia, insomnia, or sexual dysfunction) impaired cognition and mood, reduced QOL, increased MVCs, as well as hypertension, cardiovascular disease, and metabolic disorders (eg, pre-diabetes and diabetes).

Neurocognitive Outcomes and Mood

Although the quality of evidence for neurocognitive outcomes was rated as moderate, the number of studies available for review was small and these studies focused on participants without baseline deficits in neurocognitive function. Therefore, RCTs targeted at addressing whether PAP improves neurocognitive outcomes in patients with OSA with baseline cognitive impairment would be highly informative. Consensus on core validated assessment tools for each neurocognitive domain should be reached on measures to be routinely included in future PAP intervention studies with sufficient power to detect meaningful changes. Similarly, trials evaluating the impact of PAP on mood in those with baseline depression or anxiety should be a priority.

Motor Vehicle Crashes

The quality of evidence regarding reductions in MVC with PAP intervention was of low to moderate quality due to issues

of study design ascertainment of the outcome. The current evidence base has been used to set public policy on driving restrictions for drivers on the state level and safety-sensitive personnel (eg, commercial motor vehicle drivers, pilots, railroad workers, etc.) at a federal level. Despite these policies, high quality data is currently not available to indicate which patients with OSA are most likely to experience a reduction in MVC risk from CPAP. Although randomized trials in this area are not feasible, larger scale, prospective studies with appropriate control groups and objective ascertainment of MVC through insurers or registries could and should be performed to further inform development of appropriate public policies. Additional studies in commercial motor vehicle drivers and other safety sensitive occupations (eg airline pilots or railroad workers) are specifically needed given that public policy decisions focus on these populations. Development of more sensitive biomarkers using driving simulators or other techniques that are highly correlated and validated against real world crash risk are needed, which can then be applied in treatment trials of patients with OSA.

Hypertension

Regarding hypertension, progress has been made in determining the beneficial effects of PAP. Relative to prior guidelines, the TF judged that PAP should be used for patients with OSA and hypertension. The BP lowering effects, though small at the patient level, may be meaningful at a population health level. However, there are still several knowledge gaps that remain to be addressed. Long-term studies are needed to determine the benefits of PAP on hypertension and hypertension-related outcomes (eg, chronic kidney disease, congestive heart failure, and stroke) for periods more than a year, particularly in patients with resistant hypertension. Furthermore, data are needed on whether patients with milder forms of OSA derive the same BP lowering benefits as patients with moderate to severe OSA. Additional investigations as to whether non-sleepy patients with OSA derive similar benefits to sleepy patients with OSA may help determine in future guidelines whether the strength of the recommendation can be increased or not. Given recent small, short-term trials showing that drug therapy lowers BP more robustly than CPAP in those with OSA and hypertension and that effects may be synergistic between anti-hypertensive medications and PAP,^{159,160} future trials should explore how OSA screening and treatment with PAP might best integrate into current guidelines on the approach to treating hypertension.

Cardiovascular Events and Metabolic Outcomes

The TF found conflicting data regarding PAP-related effects for cardiovascular events and no significant PAP-related effects on the metabolic outcomes reviewed (ie, fasting glucose, hemoglobin A1c). Non-randomized data suggest that PAP reduces cardiovascular events, while randomized control trial data have not shown any benefit. While non-randomized cohort studies are known to over-estimate therapy-related effects compared to randomized controlled designs, current RCTs are limited by several factors: the extent of PAP adherence obtained (eg, 3–4 h/night of PAP use), the severity of OSA in the patient sample, and restriction of recruitment to non-sleepy patients

(which likely contributes to sub-optimal PAP adherence). The RCT data currently available, therefore, are more informative with respect to PAP-related effectiveness, than on the efficacy of PAP in OSA on reducing cardiovascular events. Efficacy studies on the effects of PAP on metabolic disorders including diabetes, but in particular for pre-diabetes are needed. A major challenge in the implementation of such trials will be ensuring long-term adherence to PAP for time periods long enough for adequately powered studies. Studies incorporating known strategies to increase adherence (educational, behavioral, troubleshooting and telemonitoring interventions, mask optimization, etc.), development of novel methods to improve PAP adherence (see “Adherence Strategies”, below), and innovative strategies to optimize PAP adherence in the long term need to be developed as an integral component of large scale RCTs examining key outcomes. Furthermore, understanding the dose-response relationship of PAP for various cardiovascular and metabolic outcomes is needed.

Patient Groups and Comorbidities

From the review, the TF believes that additional research is needed to answer important questions regarding the foregoing outcomes in specific patient populations, through inclusion of traditionally under-represented groups including minorities, women, and older people. More work through both high-quality observational studies and RCTs are needed to determine whether treatment of OSA with PAP improves neurocognitive, cardiovascular, and metabolic outcomes in these under-represented groups. Another research priority is the development of methods to increase PAP adherence in groups that traditionally have low adherence (eg, African-Americans, adolescents, the cognitively impaired) to ensure health equity. Patient groups with comorbidities that are highly prevalent in OSA and for which OSA treatment may reduce the risk of additional events or disease progression that merit further investigation include those with a history of stroke, myocardial infarction, heart failure, and atrial fibrillation. In addition, comparative effectiveness studies are needed to assess the effects of PAP compared to other OSA treatments on OSA-related outcomes. Identifying patient subgroups that may benefit from one intervention compared to another will help to realize the goal of precision medicine.

PAP Modalities and In-Laboratory Versus APAP Strategies

While the TF recommended either APAP or CPAP should be used in the treatment of OSA, there are additional questions to be addressed. Recent data suggest that the blood pressure reduction reported with APAP may not be as robust with CPAP—whether this difference has clinical relevance is unclear.^{156,157} In addition, studies are needed in patients with comorbid conditions commonly seen in sleep clinic populations (eg, obstructive and restrictive lung disease, CHF, pulmonary hypertension, neuromuscular disease, co-existing central sleep apnea, etc.) to determine the benefits, risks, and contraindications of APAP versus in-laboratory based PAP. Existing APAP algorithms could prove to be suboptimal, for example, in patients with markedly altered respiratory mechanics, requiring the development of modified and/or enhanced algorithms.

Further research will also be required to determine whether application of existing automated BPAP algorithms may be preferable to CPAP or APAP in such patients and whether further development of automated PAP algorithms is required.

More work is also needed to establish the cost-effectiveness of CPAP compared to APAP as well as PAP compared to other therapies in the long-term treatment of OSA. The impact of mask leak on APAP effectiveness and patient adherence also needs to be determined. In addition, little remains known about patient preferences for strategies using either CPAP or APAP, which would be informative for future guidelines.

Review of data regarding BPAP for the treatment of OSA led the TF to recommend that BPAP should not be used in the routine treatment of OSA. Further research, however, should clarify patient groups that might benefit from BPAP. For example, research evaluating the benefit, risks, contraindications, and outcomes of BPAP in nonadherent patients or patients deemed to be at high risk of nonadherence are needed. Such data would inform if BPAP should be used as initial therapy or rescue therapy in certain subgroups.

Adherence Strategies

All medical therapies have challenges with patient adherence. PAP therapy for OSA has unique challenges as available data indicate that optimal benefit is derived from continued use throughout the patient’s sleeping period while clinical trials continue to demonstrate suboptimal group adherence ranging from 3–5 h/night. Post-hoc analyses of recent RCTs focusing on cardiovascular events suggest better outcomes with more consistent PAP use across the night. However, these analyses are confounded by concerns as to whether PAP-adherent patients are also more adherent to non-PAP therapies for healthy lifestyle habits (eg, smoking cessation, regular exercise) or comorbid disorders (eg, beta-blockers for coronary artery disease, statins for hyperlipidemia, or anti-hypertensives for hypertension), which may explain the positive findings. Given this, substantial work remains to be done to determine the optimal combination of strategies to maximize adherence including PAP-related technologies (eg, cloud-based monitoring systems), mask interfaces, educational, behavioral and troubleshooting interventions. Effective adherence approaches can then be deployed in future RCTs examining the potential benefits of PAP for OSA-related outcomes. Of note, virtually all research on increasing adherence has evaluated outcomes at 3 months or less, despite evidence that usage continues to wane over time long-term. Evaluation of strategies to maintain adherence long term is a critical research priority. The quality of evidence with respect to mask interfaces remains low. RCTs should be performed examining effectiveness of different mask types on OSA severity, pressure requirements, side effects, and adherence. Such studies will need to carefully consider whether patient factors such as nasal obstruction and related symptoms may affect efficacy of therapy and adherence. Furthermore, given differences in facial structure, studies of mask type need to be conducted across a broad range of racial and ethnic groups. A better understanding of the effects of humidification in promoting adherence is needed and which patient subgroups are most likely to benefit (eg, all patients, nonadherent patients,

nasal obstruction, or oro-nasal dryness). This would have implications for patient preference and the cost-effectiveness of these interventions. RCTs examining whether APAP, mask type, humidification and modified pressure profiles improve adherence and clinically relevant outcomes in poorly adherent patients or patient at high risk of nonadherence are needed.

Significant progress has been made in examining educational, behavioral, troubleshooting, and telemonitoring strategies that can improve adherence to PAP. Future research should focus on strategies for identification of patient-factors that place them at risk for nonadherence prior to PAP use, and the development and validation of specific algorithms (eg, number of hours, significant leaks, residual AHI, residual central events, or some combination) to utilize with telemonitoring in order to identify nonadherent patients early after initiation of PAP. Comparative effectiveness studies and implementation research of these strategies will be needed to develop a comprehensive adherence program that can be deployed into routine clinical care as well as for all long-term randomized clinical trials of CPAP.

ABBREVIATIONS

AASM, American Academy of Sleep Medicine
 AHI, apnea-hypopnea index
 APAP, auto-adjusting positive airway pressure
 BP, blood pressure
 BPAP, bilevel positive airway pressure
 CPAP, continuous positive airway pressure
 DBP, diastolic blood pressure
 EPAP, expiratory positive airway pressure
 ESS, Epworth Sleepiness Scale
 FOSQ, Functional Outcomes of Sleep Questionnaire
 GRADE, Grading of Recommendations Assessment, Development and Evaluation
 HADS, Hospital Anxiety and Depression Scale
 IPAP, inspiratory positive airway pressure
 LVEF, left ventricular ejection fraction
 MSLT, Multiple Sleep Latency Test
 MVC, motor vehicle crashes
 MWT, Maintenance of Wakefulness Test
 OSA, obstructive sleep apnea
 OSLER, Oxford Sleep Resistance Test
 PAP, positive airway pressure
 PICO, Patient, Population or Problem, Intervention, Comparison, and Outcomes
 QOL, quality of life
 QSQ, Quebec Sleep Questionnaire
 RCT, randomized controlled trial
 RDI, respiratory disturbance index
 REI, respiratory event index
 SAQLI, Calgary Sleep Apnea Quality of Life Index
 SBP, systolic blood pressure
 SF-36, Short Form of the Medical Outcomes Survey
 SMD, standardized mean differences
 T2DM, type 2 diabetes mellitus
 TF, task force

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DISCLOSURE STATEMENT

Dr. Indu Ayappa disclosed that she receives royalties from patents held on some PAP devices. Dr. Ayappa's potential conflict was managed by requesting that she refrain from participation on any discussions pertaining to devices for which she may hold a patent. She was also asked to refrain from voting on recommendations pertaining to those devices. Dr. Sanjay Patel disclosed that he receives compensation from Bayer Pharmaceuticals to assess the impact of OSA and its treatment on pulmonary hypertension and other cardiovascular outcomes. He was asked to refrain from participation on any discussion pertaining to the use of PAP to treat hypertension. He was also asked to refrain from voting on recommendations pertaining to the use of PAP to treat hypertension. Mr. Harrod is employed by the American Academy of Sleep Medicine. No other task force members had any relevant conflicts of interest to disclose.