Clinical Practice Guidelines for the Treatment of Adult Obstructive Sleep Apnea with Positive Airway Pressure

An American Academy of Sleep Medicine Clinical Practice Guideline

Introduction: This guideline establishes clinical practice recommendations for the treatment of obstructive sleep apnea (OSA) in adults and is intended for use in conjunction with other American Academy of Sleep Medicine (AASM) guidelines on the evaluation and treatment of sleep-disordered breathing in adults.

Methods: The AASM commissioned a task force of experts in sleep medicine. A systematic review was conducted to identify studies, and the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) process was used to assess the evidence. The task force developed recommendations and assigned strengths based on the quality of evidence, the balance of clinically significant benefits and harms, patient values and preferences, and resource use. In addition, the task force adopted foundational recommendations from prior guidelines as “good practice statements”, that establish the basis for appropriate and effective treatment of OSA. The AASM Board of Directors approved the final recommendations.

Good Practice Statements: The following good practice statements are based on expert consensus, and their implementation is necessary for appropriate and effective management of OSA patients treated with PAP:

1. Treatment of obstructive sleep apnea (OSA) with positive airway pressure (PAP) therapy should be based on a diagnosis of OSA established using objective sleep apnea testing. (CONDITIONAL)
2. Adequate follow-up, including troubleshooting and monitoring of objective efficacy and usage data to ensure adequate treatment and adherence should occur following PAP therapy initiation and during treatment of OSA. (STRONG)

Recommendations: The following recommendations are intended as a guide for clinicians treating OSA in adults. A STRONG (i.e. “We recommend...”) recommendation is one that clinicians should follow under most circumstances. A CONDITIONAL recommendation (i.e. “We suggest...”) reflects a lower degree of certainty regarding the outcome and appropriateness of the patient-care strategy for all patients. The ultimate judgment regarding any specific care must be made by the treating clinician and the patient, taking into consideration the individual circumstances of the patient, available treatment options, and resources.

1. We recommend that clinicians use positive airway pressure to treat OSA in adults with excessive daytime sleepiness, compared with no therapy. (STRONG)
2. We suggest that clinicians use positive airway pressure to treat OSA in adults with impaired sleep-related quality of life, compared with no therapy. (CONDITIONAL)
3. We suggest that clinicians use positive airway pressure in hypertensive adults with OSA compared with no therapy. (CONDITIONAL)
4. We recommend that PAP therapy be initiated using either APAP at home or in-lab CPAP titration in adults with OSA and no significant comorbidities. (STRONG)
5. We recommend that clinicians use APAP or CPAP for ongoing treatment of OSA in adults. (STRONG)
6. We suggest that clinicians use CPAP over BPAP in the routine treatment of adults with OSA. (CONDITIONAL)
7. We suggest that clinicians not use modified pressure profile PAP, over standard CPAP, in the routine initiation of PAP therapy in adults with OSA. (CONDITIONAL)
8. We suggest that either nasal or intranasal interface be used, over oronasal or oral interfaces, in the routine initiation of PAP therapy in adults with OSA. (CONDITIONAL)
9. We suggest that heated humidification be used with PAP devices for the treatment of adults with OSA. (CONDITIONAL)
10. We recommend that educational interventions be given with initiation of PAP therapy in adults with OSA. (STRONG)
11. We suggest that behavioral and/or troubleshooting interventions be given with initiation of PAP therapy in adults with OSA. (CONDITIONAL)
12. We suggest that clinicians use tele-monitoring guided interventions in the routine initiation of PAP therapy in adult OSA patients. (CONDITIONAL)

1.0 INTRODUCTION

Since the publication of the previous AASM positive airway pressure (PAP) practice parameters,1-3 the scientific literature has continued to expand regarding the effects of PAP on clinical outcomes in adults with obstructive sleep apnea (OSA). A major barrier to maximizing the effectiveness of PAP therapy has been adherence to treatment. Research on improving PAP adherence and advancements in device technology have continued to evolve. Given these advancements, updating the prior practice parameters was considered timely.
The AASM commissioned a task force (TF) of content experts to update and consolidate previous AASM PAP practice parameters and reviews relevant to the treatment of adult OSA with PAP modalities. Prior practice parameters included guideline statements regarding the efficacy of BPAP for central sleep apnea (CSA) and hypoventilation, which are addressed in other active AASM guidelines and are not considered here.

2.0 BACKGROUND

Obstructive sleep apnea is a common sleep disorder affecting 26% of adults, with 10% estimated to have moderate to severe disease. Untreated OSA is associated with multiple adverse health outcomes including daytime sleepiness and decreased quality of life as well as increased risk of motor vehicle accidents (MVA), systemic hypertension, diabetes, coronary artery disease, stroke, atrial fibrillation, congestive heart failure, and mortality. OSA is defined by repetitive upper airway collapse and arousals from sleep, traditionally quantified with testing during sleep by the apnea-hypopnea index (AH), 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. Obesity is a prominent risk factor for OSA as demonstrated by the concurrent rise in the prevalence of OSA as obesity rates have risen. 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. Furthermore, individuals of African American or Asian race are at higher risk for OSA compared with similarly-aged Caucasians.

An important and well-recognized direct consequence of OSA is excessive daytime sleepiness, which can interfere with productivity both at home and the workplace, and has been associated with an increased risk of MVA. OSA has been associated with quality of life (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 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 effects on executive function and vigilance.

OSA is also associated with a number of systemic disorders. It is strongly linked with cardiovascular (CV) 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. Although the evidence is conflicting and sometimes confounded by obesity, OSA has been shown to impair insulin sensitivity and be associated with type 2 diabetes mellitus (T2DM).

The pathogenic role of upper airway collapse was initially described in the 1960’s, 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. Since then, other modes, such as bi-level PAP (BPAP), which delivers pressure support to augment ventilation, and auto-adjusting PAP (APAP), where computer algorithms control pressure levels, have been developed.

Regardless of these technological advancements, the importance of continuous application of PAP during sleep when the airway is vulnerable to collapse is of primary concern. 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, with at least four hours of use during sleep per night often used clinically to define minimal acceptable levels of adherence.\textsuperscript{16, 17}

Adherence to CPAP is often suboptimal, so an efficacious but potentially more comfortable alternative therapy with better adherence is desirable. Further technological advances in PAP therapy have occurred over time to increase patient comfort, and thereby adherence with treatment. The 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 of care with PAP therapy in many markets. The current generation of PAP devices also integrates modified pressure profiles and is offered as standard of care. This option transiently lowers the treatment pressure during expiration 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 in the machine,\textsuperscript{18} 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 third-party payors has made objective adherence monitoring a standard of care in the U.S.

Because device improvements have only made a modest impact on adherence,\textsuperscript{19} 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 educational interventions.\textsuperscript{20} 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.\textsuperscript{21} 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 CPAP adherence. A major challenge however has been developing an intervention intensive enough to be effective, but not so expensive to reduce feasibility in clinical practice. In this milieu, the use of tele-monitoring 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. 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 in real time.\textsuperscript{22, 23} While originally developed to improve comfort, the technology has increasingly been utilized as an alternative to in-lab CPAP 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 have returned, there is the potential for incomplete treatment of OSA.\(^{23}\)

With these key issues in mind, this document provides a comprehensive update of the latest evidence and a synthesis of clinical practice recommendations that are intended to be patient-centric and broadly inform clinicians caring for adult patients with OSA. Several prior recommendations on the management of OSA with PAP were determined by the TF to be no longer pertinent and were not addressed in the present guideline. Prior guidelines also included consensus statements that were not based on an evidence review. Nevertheless, the TF adopted and modified two prior statements as good practice statements, as they were considered essential to providing high quality care to OSA patients treated with PAP.

### 3.0 METHODS

#### 3.1 Expert Task Force

The AASM commissioned a TF of both board-certified sleep medicine specialists and experts with proficiency in the use of PAP in adults with OSA to develop this guideline. 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 conflicts of interest 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 conflicts of interest are listed in the Disclosures section.

#### 3.2 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 Directors (BOD) 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. In addition to patient-oriented outcomes, several 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, left ventricular ejection fraction (LVEF), neurocognitive function, hospitalization rate, and motor vehicle accidents. Discussion of these outcomes is included in some of the recommendations; however these outcomes were not considered critical for decision-making and were not considered in making the final recommendations.

In order to determine whether the mean changes in these outcomes were clinically significant and warrant recommendations for clinical practice, the TF set clinical significance threshold (CST) for each outcome. The CST 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 CST 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 CSTs for the clinical outcome measures is presented in Table 3. The CSTs were established based on findings in the literature, and clinical judgement and experience of the TF.

**Table 1 - PICO Questions**

1. In adult patients with OSA, does CPAP versus no treatment improve AHI/RDI/REI, sleepiness, neurocognitive function, quality of life, and motor vehicle accidents? (See Recommendation 4.1ai)
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)? (See Recommendation 4.1a(ii))
3. In adult patients with OSA, does PAP versus no therapy reduce cardiovascular event rates (incident hypertension, MI, revascularization procedures, hospitalization for heart failure, stroke, arrhythmia, sudden death, and cardiovascular mortality), hospitalization rates, and all-cause mortality? (See Recommendation 4.1aiii)
4. In adult patients with OSA, does initiation of PAP based on an in-laboratory vs. ambulatory APAP-based strategy improve AHI/RDI, adherence, sleepiness, and quality of life? (See Recommendation 4.2a)
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? (See Recommendation 4.3a)
6. In adult patients with OSA, does BPAP or auto-BPAP versus CPAP improve AHI/RDI, adherence, sleepiness, neurocognitive function, and quality of life, and reduce side effects? (See Recommendation 4.4a)
7. In adult patients with OSA, does the addition of modified pressure profile PAP to PAP therapy improve adherence, sleepiness, and quality of life, and reduce side effects? (See Recommendation 4.5a)
8. In adult patients with OSA, does oral CPAP versus nasal (nasal mask vs. intranasal) CPAP versus oronasal CPAP improve AHI/RDI, adherence, sleepiness, and quality of life, and reduce side effects? (See Recommendation 4.6a)
9. In adult patients with OSA, does humidified PAP versus standard PAP improve adherence, sleepiness, quality of life, and reduce side effects? (See Recommendation 4.7a)
10. In adult patients with OSA, do educational or behavioral interventions versus no intervention prior to or during PAP treatment improve adherence, sleepiness, and quality of life? (See Recommendation 4.8a and 4.8aii)
11. In adult patients with OSA, do interventions guided by monitoring of OSA and PAP parameters during PAP treatment versus no monitoring improve adherence, sleepiness, and quality of life, and reduce side effects? (See Recommendation 4.9a)

**Table 2 - “Critical” Outcomes by PICO**

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
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<tbody>
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<td>Sleepiness</td>
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<td></td>
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</tr>
<tr>
<td>Adherence</td>
<td></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quality of Life</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Side Effects</td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<td></td>
</tr>
<tr>
<td>Blood Pressure Control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
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<tr>
<td>Cardiovascular Event Rate</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>All-Cause Mortality</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>✓</td>
</tr>
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</table>

**Table 3 – Summary of Clinical Significance Thresholds for Clinical Outcome Measures**

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Clinical Significance Threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHI/RDI/REI</td>
<td>50% reduction</td>
</tr>
<tr>
<td>Adherence</td>
<td>0.5 hours/night; 10% patient use &gt;4 hours/night</td>
</tr>
<tr>
<td>Subjective sleepiness</td>
<td>---</td>
</tr>
<tr>
<td>ESS</td>
<td>2 points</td>
</tr>
<tr>
<td>Objective sleepiness</td>
<td>---</td>
</tr>
<tr>
<td>----------------------</td>
<td>-----</td>
</tr>
<tr>
<td>MWT</td>
<td>2 minutes</td>
</tr>
<tr>
<td>Osler</td>
<td>2 minutes</td>
</tr>
<tr>
<td>MSLT</td>
<td>1 minutes</td>
</tr>
<tr>
<td>Osler, MWT combined</td>
<td>0.2 (SMD)</td>
</tr>
<tr>
<td>MWT, Osler, MSLT combined</td>
<td>0.2 (SMD)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Quality of Life</th>
<th>---</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOSQ</td>
<td>1 point</td>
</tr>
<tr>
<td>SAQLI</td>
<td>1 point</td>
</tr>
<tr>
<td>SF-36</td>
<td>---</td>
</tr>
<tr>
<td>(Physical Component Summary)</td>
<td>3 points</td>
</tr>
<tr>
<td>(Mental Component Summary)</td>
<td>3 points</td>
</tr>
<tr>
<td>(Vitality Summary)</td>
<td>12.5 points</td>
</tr>
<tr>
<td>QSQ</td>
<td>---</td>
</tr>
<tr>
<td>(Daytime Sleepiness)</td>
<td>1.8 points</td>
</tr>
<tr>
<td>(Diurnal Symptoms)</td>
<td>2.0 points</td>
</tr>
<tr>
<td>(Nocturnal Symptoms)</td>
<td>1.5 points</td>
</tr>
<tr>
<td>(Emotions)</td>
<td>1.1 points</td>
</tr>
<tr>
<td>(Social Interactions)</td>
<td>2.5 points</td>
</tr>
<tr>
<td>FOSQ, SAQLI, and/or QSQ combined</td>
<td>0.2 (SMD)</td>
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</table>

<table>
<thead>
<tr>
<th>Blood Pressure</th>
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</thead>
<tbody>
<tr>
<td>24-hour mean</td>
<td>1 mm Hg</td>
</tr>
<tr>
<td>SBP</td>
<td>---</td>
</tr>
<tr>
<td>(24-hr)</td>
<td>2 mm Hg</td>
</tr>
<tr>
<td>(Nighttime)</td>
<td>2 mm Hg</td>
</tr>
<tr>
<td>(Daytime)</td>
<td>2 mm Hg</td>
</tr>
<tr>
<td>DBP</td>
<td>---</td>
</tr>
<tr>
<td>(24-hr)</td>
<td>1 mm Hg</td>
</tr>
<tr>
<td>(Nighttime)</td>
<td>1 mm Hg</td>
</tr>
<tr>
<td>(Daytime)</td>
<td>1 mm Hg</td>
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<table>
<thead>
<tr>
<th>Mood</th>
<th>---</th>
</tr>
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<tbody>
<tr>
<td>HADS Depression</td>
<td>2 points</td>
</tr>
<tr>
<td>HADS Anxiety</td>
<td>2 points</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cardiovascular event rate</th>
<th>Risk ratio of 0.8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence rate of all-cause mortality</td>
<td>Risk ratio of 0.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>LVEF</th>
<th>4%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting Glucose</td>
<td>0.6 mmol/L</td>
</tr>
<tr>
<td>Hemoglobin A1C</td>
<td>0.3%</td>
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<table>
<thead>
<tr>
<th>Neurocognitive Function</th>
<th>0.2 (SMD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalization rate</td>
<td>Risk ratio of 0.9</td>
</tr>
<tr>
<td>Motor Vehicle Accidents</td>
<td>Risk ratio of 0.9</td>
</tr>
<tr>
<td>Side Effects</td>
<td>Odds ratio of 0.9</td>
</tr>
</tbody>
</table>

1. AHI – apnea/hypopnea index; RDI – respiratory disturbance index; REI – respiratory event index; ESS – Epworth sleepiness score; MWT – maintenance of wakefulness test; Osler – Oxford sleep resistance test; MSLT – multiple sleep latency test; FOSQ – functional outcome of sleep questionnaire; SAQLI – Calgary sleep apnea quality of life index; SF-36 - Short form - 36 item; QSQ – Quebec sleep questionnaire; SBP – systolic blood pressure; DBP – diastolic blood pressure; HADS – Hospital Anxiety and Depression Scale; LVEF – left ventricular ejection fraction; SMD – Standardized mean difference

3.3 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. RCTs and observational studies that were cited in the prior AASM PAP practice parameters\textsuperscript{1,3} were included for data analysis only if they met the current inclusion criteria.

The initial literature search in PubMed and Embase was performed in April 2015 and was limited to randomized controlled trials (RCTs). A second literature search was performed using broader search terms to identify articles in PubMed and Embase that may not have been captured from the targeted PICO question searches (see supplemental material). In addition, for PICO questions 1 (motor vehicle accidents only), 5, 6 and 8, where the evidence based on RCTs was low or not available, the TF also searched for observational studies. A third literature search was performed in September 2016 to identify studies that were published since the second literature search to update the body of evidence for the guideline. These searches identified a total of 1,388 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 51 additional articles for a total of 1,439 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 263 articles from the literatures searches were accepted and considered for meta-analysis and evidence grading. Upon review of these articles, 169 studies were determined to be suitable for meta-analysis and/or grading.
3.4 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 types: continuous PAP (CPAP); auto-adjusting PAP (APAP); bilevel PAP (BPAP); 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 (explanations of these categories are provided in Recommendation 4.8). Treatment delivery strategies were categorized as APAP-initiated (ambulatory) and in-lab initiated 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. Post-treatment data were used for meta-analysis, except where change values were determined to be more meaningful to the reader (i.e., 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 post-treatment or change values (i.e.,
combined MWT and OSLER (Oxford sleep resistance test), combined FOSQ and SAQLI, combined 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 (CST) (see Table 3).

3.5 Strength of Recommendations
The assessment of evidence quality was performed according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) process. The TF assessed 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, and author disclosures), imprecision (95% confidence interval relative to the CST), inconsistency (I² cutoff of 75%), 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 patients would see. The quality of the evidence was based on outcomes that the TF deemed critical for decision making.

2. Benefits vs. 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 body of evidence.

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 CPAP device type or approach to patient care over another for the treatment of adults with OSA.

Taking these major factors into consideration, each recommendation statement was assigned a strength (Strong or Conditional). Additional information is provided in the form of “Remarks” immediately following the recommendation statements, when deemed necessary by the TF. Remarks are based on the evidence evaluated during the systematic review and are intended to provide context for the recommendations and guide clinicians in implementing the recommendations in daily practice.

Discussions accompany each recommendation to summarize the relevant evidence and explain the rationale leading to each recommendation.

3.6 Approval and Interpretation of Recommendations
A draft of the guideline 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 was submitted to the AASM Board of Directors (BOD) who subsequently approved these recommendations.
The recommendations in this guideline define principles of practice that should meet the needs of most patients in most situations. A STRONG recommendation is one that clinicians should, under most circumstances, always follow (i.e., something that might qualify as a Quality Measure). A CONDITIONAL recommendation reflects a lower degree of certainty in the appropriateness of the patient-care strategy, requires that the clinician use their clinical knowledge and experience, and strongly considers the individual patient’s values and preferences to determine the best course of action. The ultimate judgment regarding any specific care must be made by the treating clinician and the patient, taking into consideration the individual circumstances of the patient, available treatment options, and resources.

The AASM expects this guideline to have an impact on professional behavior, patient outcomes, and, possibly, health care costs. This clinical practice guideline reflects the state of knowledge at the time of publication and will be reviewed and updated as new information becomes available.

4.0 GOOD PRACTICE STATEMENTS

The following are good practice statements, the implementation of which is deemed necessary for appropriate and effective management of OSA patients treated with PAP.

Treatment of obstructive sleep apnea (OSA) with positive airway pressure (PAP) therapy should be based on a diagnosis of OSA established using objective sleep apnea testing.25

This good practice statement applies specifically to a new diagnosis of OSA. Patients with previously established diagnoses of OSA already on PAP therapy and with good symptom control should continue PAP therapy, even when prior testing results are not readily available.

Adequate follow-up, including troubleshooting and monitoring of objective efficacy and usage data to ensure adequate treatment and adherence should occur following PAP therapy initiation and during treatment of OSA.

OSA is a chronic disease that rarely resolves except with substantial weight loss or successful corrective surgery. As with other chronic diseases, periodic follow-up by a trained health care provider is necessary to confirm adequate treatment, assess symptom resolution, and promote continued adherence to treatment. Initial treatment of OSA requires close monitoring and early assessment of difficulties with PAP use, as adherence over the first few days to weeks has been shown to predict adherence at 6 to 12 months.18, 21, 26 Education and troubleshooting interventions (see Recommendation 4.8) to address issues such as poor mask fitting, air leaks, claustrophobia, or nasal symptoms by trained sleep educators or other trained clinical personnel (e.g. sleep technologists, respiratory therapists, nurses, and advanced care practitioners) can help minimize PAP-related side effects and promote adherence. In particular, for patients prescribed APAP, an education session should be conducted by trained staff that includes education on PAP use, mask fittings, and potentially daytime nap acclimatization.

Objective monitoring of PAP therapy should be performed to complement patient reporting of difficulties with PAP use and because patients routinely overestimate their use of PAP treatment. Objective data permits trained health care providers and patients to have a frank discussion regarding barriers that negatively impact adherence and to identify potential solutions. Recent advances in PAP tele-monitoring technology (e.g. PAP-based modem, bluetooth, or wifi connectivity) allow for PAP usage and therapy data to be transmitted to cloud-based systems...
and allow home medical equipment and trained health care providers to more readily identify patients most at risk of longer term non-adherence (see Recommendation 4.9).

The timing of adequate follow-up after treatment is initiated will vary depending on the patient circumstances. While a yearly evaluation by a trained health care provider is reasonable, longer periods of follow-up may be reasonable for selected patients who are highly adherent to PAP therapy, have sustained resolution of OSA-related symptoms, and have no concerns regarding their PAP therapy. In contrast, patients with persistent or recurrent sleep-related complaints or persistent difficulties with PAP use will require more frequent follow-up to address their issues and may require continued care by either a board-certified sleep physician or trained health care provider.

5.0 CLINICAL PRACTICE RECOMMENDATIONS

The following clinical practice recommendations are based on a systematic review and evaluation of evidence and the GRADE methodology. Remarks are provided to guide clinicians in the implementation of these recommendations. All figures, including meta-analyses and Summary of Findings tables are presented in the supplemental material. Table 5 shows a summary of the recommendation statements including the strength of recommendation and quality of evidence. A flowchart for the implementation of the recommendations is presented in Figure 2.

Table 4. – Implications of Strong and Conditional Recommendations for Clinician Users of AASM Clinical Practice Guidelines

| Strong Recommendation – “We recommend…” | Almost all patients should receive the recommended course of action. Adherence to this recommendation could be used as a quality criterion or performance indicator.* |
| Conditional Recommendation – “We suggest…” | Different choices will be appropriate for different patients, and the clinician must help each patient arrive at a management decision consistent with her or his values and preferences.* |

The ultimate judgment regarding the suitability of any specific recommendation must be made by the clinician.

*For additional information, see Morgenthaler 2016.

Table 5. - Summary of Recommendation Statements

<table>
<thead>
<tr>
<th>Recommendation Statement</th>
<th>Strength of Recommendation</th>
<th>Evidence Quality</th>
<th>Benefits vs. Harms</th>
<th>Patient Values &amp; Preferences</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.1ai We recommend that clinicians use PAP to treat OSA in adults with excessive daytime sleepiness, compared with no therapy. (See PICO 1)</td>
<td>Strong</td>
<td>High</td>
<td>High certainty that benefits outweigh harms</td>
<td>Vast majority of well-informed patients would most likely choose the intervention</td>
</tr>
<tr>
<td>4.1a(ii We suggest that clinicians use PAP to treat OSA in adults with impaired sleep-related quality of life, compared with no therapy. (See PICO 2)</td>
<td>Conditional</td>
<td>Moderate</td>
<td>Moderate certainty that benefits outweigh harms</td>
<td>Majority of well-informed patients would most likely choose the intervention</td>
</tr>
<tr>
<td>4.1iii We suggest that clinicians use PAP to treat OSA in hypertensive adults, compared with no therapy. (See PICO 3)</td>
<td>Conditional</td>
<td>Moderate</td>
<td>Low certainty that benefits outweigh harms</td>
<td>Majority of well-informed patients would most likely choose the intervention</td>
</tr>
<tr>
<td>There is insufficient and inconclusive evidence to support the use of PAP to treat asymptomatic adults with OSA, on the basis of reduced cardiovascular events and mortality rates. No recommendation. (See PICO 3)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>4.2a We recommend that PAP therapy be initiated using either APAP at home or in-lab CPAP titration in adults with OSA and no significant comorbidities. (See PICO 4)</td>
<td>Strong</td>
<td>High</td>
<td>High certainty that benefits and harms of the two approaches are similar</td>
<td>Vast majority of well-informed patients would most likely choose APAP in the home or in-lab CPAP titration for PAP initiation depending on what is the more convenient and cost-effective intervention.</td>
</tr>
<tr>
<td>4.3a We recommend that clinicians use either APAP or CPAP for ongoing treatment of OSA in adults. (See PICO 5)</td>
<td>Strong</td>
<td>Moderate</td>
<td>High certainty that benefits and harms of the two approaches are similar</td>
<td>Vast majority of well-informed patients would most likely choose either intervention</td>
</tr>
<tr>
<td>4.4a We suggest that clinicians use CPAP over BPAP in the routine treatment of adults with OSA. (See PICO 6)</td>
<td>Conditional</td>
<td>Low</td>
<td>Low certainty that benefits outweigh harms</td>
<td>Majority of well-informed patients would most likely choose the intervention</td>
</tr>
<tr>
<td>4.5a We suggest that clinicians not use modified pressure profile PAP, over standard CPAP, in the routine initiation of PAP therapy in adults with OSA. (See PICO 7)</td>
<td>Conditional</td>
<td>Moderate</td>
<td>Low certainty that benefits outweigh harms</td>
<td>Majority of well-informed patients would most likely not choose the intervention</td>
</tr>
<tr>
<td>4.6a We suggest that either nasal or intranasal interface be used, over oronasal or oral interfaces, in the routine initiation of PAP therapy in adults with OSA. (See PICO 8)</td>
<td>Conditional</td>
<td>Low</td>
<td>Low certainty that benefits outweigh harms</td>
<td>Majority of well-informed patients would most likely choose the intervention</td>
</tr>
<tr>
<td>4.7a We suggest that heated humidification be used with PAP devices for the treatment of adults with OSA. (See PICO 9)</td>
<td>Conditional</td>
<td>Moderate</td>
<td>Low certainty that benefits outweigh harms</td>
<td>Majority of well-informed patients would most likely choose the intervention</td>
</tr>
<tr>
<td>4.8ai We recommend that educational interventions be given with the routine initiation of PAP therapy in adults with OSA.</td>
<td>Strong</td>
<td>Moderate</td>
<td>High certainty that benefits outweigh harms</td>
<td>Vast majority of well-informed patients would most likely choose the</td>
</tr>
<tr>
<td>Intervention Description</td>
<td>Certainty</td>
<td>Benefit</td>
<td>Harm</td>
<td>Patient Choice</td>
</tr>
<tr>
<td>--------------------------</td>
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</tr>
<tr>
<td>Behavioral and/or troubleshooting interventions be given with routine initiation of PAP therapy in adults with OSA. (See PICO 10)</td>
<td>Conditional</td>
<td>Moderate</td>
<td>Majority of well-informed patients would most likely choose the intervention</td>
<td></td>
</tr>
<tr>
<td>Clinicians use tele-monitoring guided interventions to improve adherence in the routine initiation of PAP therapy in adults with OSA. (See PICO 11)</td>
<td>Conditional</td>
<td>Low</td>
<td>Majority of well-informed patients would most likely choose the intervention</td>
<td></td>
</tr>
</tbody>
</table>
Figure 2 – Flow-chart for implementation of clinical practice guidelines

Diagnosis of OSA has been established by objective sleep testing by a physician

Does the patient have excessive daytime sleepiness, hypertension, or reduced sleep-related QOL? (see Recommendation 4.1ai,iii)

Yes

Discuss treatment options for OSA

No

Do the patient and clinician agree that PAP is the preferred treatment choice?

Yes

Pursue alternative selected therapy

No

Does the patient have significant comorbidities?

Yes

Consider initiating PAP using in-lab strategy

No

Consider initiating PAP using APAP at home or in-lab titration (see Recommendation 4.2a and 4.8a)

Treat patients with CPAP or APAP over BPAP (see Recommendations 4.1a, 4.3a, and 4.4a)

Consider using standard PAP over modified pressure profile PAP (see Recommendation 4.5a)

Conducted During PAP Initiation and Follow-Up

Consider using nasal or intranasal interface over oronasal or oral interface (see Recommendation 4.6a)

Consider using heated humidification with PAP therapy (see Recommendation 4.7a)

Use educational interventions with routine initiation of PAP therapy (see Recommendation 4.8ai)

Consider using behavioral and/or troubleshooting interventions with PAP therapy (see Recommendation 4.8aii)

Consider follow-up using telemonitoring to improve adherence (see Recommendation 4.9)

Discuss if other reasons to treat OSA. Consider therapy options or conservative management

a = Symptoms that can impair sleep-related QOL include but are not limited to snoring, sleep-related choking, difficulties maintaining sleep, disruption of bedpartner’s sleep, morning headaches, impairments in productivity or social functioning, and daytime fatigue. b = Comorbidities may include: congestive heart failure, chronic opiate use, significant lung disease such as chronic obstructive pulmonary disease, neuromuscular disease, history of uvulopalatopharyngoplasty, those with known sleep-related oxygen requirements or expected to have nocturnal arterial oxyhemoglobin desaturation due to conditions other than OSA including hypoventilation syndromes and central sleep apnea syndromes. c = Alternative therapies may include, but are not limited to, weight loss, positional therapy, oral appliance therapy or surgical interventions. d = BPAP is defined as a respiratory assist device that delivers inspiratory and expiratory positive airway pressure without a back-up respiratory rate. e = BPAP devices may need to be used for patients with therapeutic pressure requirements greater than can be provided with CPAP; the decision to use BPAP should be based on the physician’s clinical judgement and needs of the individual patient. f = Modified pressure profile PAP refers to a group of technologies using proprietary algorithms to either reduce the expiratory or end-inspiratory pressure delivered by PAP devices to improve patient comfort. g = PAP therapy should be performed in conjunction with adequate follow-up, including troubleshooting, and monitoring of objective efficacy and usage data to ensure adequate treatment and adherence. h = Recommendations included within these boxes can be considered concurrently. i = Educational interventions include those focused primarily on providing information prior to and/or at initiation of PAP about what obstructive sleep apnea (OSA) is, its downstream consequences, what PAP therapy is, how to use it, and the potential benefits of PAP therapy. j = Behavioral interventions include those focused on behavior change related to use of PAP therapy using strategies such as cognitive behavioral therapy or motivational enhancement. Troubleshooting interventions include those focused on close patient communication to identify PAP-related problems and to initiate potential solutions. k = Telemonitoring interventions include those that remotely monitor data obtained from a PAP device to identify PAP-related problems and to initiate potential solutions. l = Conservative management include interventions such as weight loss, positional maneuvers, avoidance of alcohol near bedtime.
4.1 Positive Airway Pressure (PAP) therapy vs. no therapy for the treatment of adult patients with OSA

4.1ai We recommend that clinicians use positive airway pressure to treat OSA in adults with excessive daytime sleepiness, compared with no therapy. (STRONG)

4.1aii We suggest that clinicians use positive airway pressure to treat OSA in adults with impaired sleep-related quality of life, compared with no therapy. (CONDITIONAL)

Remarks: Sleep-related quality of life (QOL) in adult patients with OSA may be adversely affected by OSA-related symptoms. This recommendation is based on symptoms identified by the literature review that can adversely affect sleep-related QOL in adult patients with OSA. Examples of symptoms include, but are not limited to: snoring, sleep-related choking, difficulties maintaining sleep, disruption of bedpartner’s sleep, morning headaches, impairments in productivity or social functioning, and daytime fatigue.

4.1aiii We suggest that clinicians use positive airway pressure in hypertensive adults with OSA compared with no therapy. (CONDITIONAL)

There is insufficient and inconclusive evidence to support the use of PAP in asymptomatic adults with OSA, on the basis of reduced cardiovascular events and mortality rates. No recommendation.

4.1b Summary

The TF assessed whether PAP should be offered to adult patients with OSA, based on improvements in the critical outcome of sleepiness, compared to no therapy. Meta-analyses demonstrated a clinically significant improvement in sleepiness with the use of PAP to treat adults with OSA as compared with no treatment. The overall quality of evidence, based on the critical outcome of sleepiness, was high.

The TF also assessed whether PAP should be offered to adult patients with OSA to improve the critical outcome of sleep-related QOL, compared to no therapy. OSA-related symptoms can reduce sleep-related quality of life, examples of which include, but are not limited to; snoring, nocturnal choking, difficulties maintaining sleep, disruption of their partner’s sleep, morning headaches, or daytime fatigue. Meta-analysis of sleep-related QOL as assessed by the Calgary Sleep Apnea QOL Index (SAQLI) and the Functional Outcomes of Sleep Questionnaire (FOSQ), demonstrated clinically significant improvement. However, meta-analyses of general QOL, as assessed by the SF-36 component scores, demonstrated no clinically significant improvement. The overall quality of evidence, based on the critical outcome of QOL, was moderate due to imprecision.

The TF assessed whether PAP should be used in hypertensive adult patients with OSA, compared to no therapy to reduce the critical outcome of BP. Meta-analyses demonstrated clinically significant BP reductions in nocturnal, daytime, and 24-hour systolic and diastolic BP when all patients in the studies were considered, with the largest effects seen for nocturnal measurements. When stratified by resistant hypertensive, hypertensive, and normotensive status, BP reduction was clinically significant in the meta-analyses for the hypertensive group and for certain BP measures in patients with resistant hypertension. The overall quality of evidence, based on the critical outcome of BP, was moderate due to imprecision. Based on the evidence, the TF judged that CPAP should be used in adult patients with OSA and hypertension to improve OSA symptoms and BP control, recognizing that
the majority of studies recruited patients with predominantly moderate to severe OSA. (Note: studies did not systematically report BP based on OSA severity, which limited the TF ability to make recommendations specific to OSA severity.)

The TF assessed whether PAP compared to no therapy should be offered to adult patients with OSA to improve the critical outcomes of CV and mortality event rates. Meta-analyses of observational studies suggested a reduction in CV events and mortality. Meta-analysis of RCTs demonstrated no clinically significant improvements in CV events and mortality. The quality of evidence for incident CV events and mortality ranged from very low to moderate due to study type and imprecision. Thus, the TF judged that the meta-analyses demonstrated insufficient and inconclusive findings regarding the difference in incident CV events and mortality with the use of PAP. Therefore, no recommendation was made regarding the use of PAP based on reduced incident CV events and mortality.

The potential harms of PAP therapy include side-effects such as nasal dryness or irritation, dry mouth, sore throat, and sinus infection as well as loss of intimacy, all of which are reversible with discontinuation of PAP (see supplemental material, Table S16). The potential burdens to the patient may include the costs of treatment and inconvenience such as maintaining the equipment and attending follow-up visits with the sleep clinician. Nevertheless, the TF determined that in adults OSA patients with excessive sleepiness, impaired sleep-related quality of life, or hypertension, the benefits of PAP therapy compared to no PAP therapy likely outweigh the potential harms and burdens, and that the majority of well-informed patients would choose the intervention over no treatment. Although no recommendation was made on the use of PAP therapy to reduce incident CV events and mortality, there may be some patients that place a high value on any intervention that potentially reduces CV risk even when they are asymptomatic (e.g. without excessive sleepiness). In this situation, the patient and clinician should have a balanced discussion about the current state of the evidence about CV risk reduction with PAP therapy for OSA and the potential harms of PAP therapy when there are no other indications to treat the patient's OSA. Conversely, the uncertainty of any CV benefit, may lead some asymptomatic OSA patients to decline treatment of their OSA. In these patients conservative management of OSA, with monitoring for development of OSA symptoms over time may be appropriate.

4.1c Discussion
A total of 76 RCTs and 15 non-randomized studies investigated the use of PAP to improve one or more of the following outcomes: OSA severity, sleepiness, quality of life (QOL), mood, neurocognitive function, rate of motor vehicle accidents, 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 subjective sleepiness. Studies were performed in multiple countries. RCTs were reviewed for all outcomes with the exception of MVA, for which non-randomized studies were reviewed. 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 apnea/hypopnea index (AHI) or the respiratory disturbance index (RDI). For this analysis, the two
measures were considered equivalent. Participants were subjectively sleepy, with the exception of 1 study that
recruited non-sleepy participants with mild to moderate OSA.48 All studies were RCTs, with 3 studies using a
randomized, cross-over design.37, 31, 50 Participants were randomized to CPAP or a control intervention. The
current interventions utilized included sham CPAP (n=5),32, 40, 50, 55, 60 conservative measures (advice on weight
loss or good sleep habit counseling), no intervention (n=3),44, 48, 59 sham surgery (n=1),57 placebo tablet (n=1),31
and nasal dilator strips (n=1).27 The duration of intervention was at least 1 month (range: 1 – 6 months).

A meta-analysis of 11 RCTs27, 31, 32, 40, 44, 48, 50, 55, 57, 59, 60 demonstrated a clinically significant mean difference in
OSA severity of -23 events/hr (95% CI: -29 to -18 events/hr) 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/hr (95% CI: -37 to -40 events/hr) or an AHI reduction of 86% with PAP (see supplemental material, Figure S2). 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 subjective sleepiness as determined by the
ESS and objective sleepiness as determined by the MSLT, MWT, and the OSLER. Participants were subjectively 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).29, 42, 51, 74, 80 Seven studies recruited patients with concomitant hypertension29, 34, 52, 61, 68, 74, 80 and one study56 recruited patients with concomitant T2DM. The control intervention employed was predominantly sham PAP or no PAP with one study51 using nasal dilator strips, one study60 using sleep hygiene and counseling, and one study61 asked patients to continue with their normal medication.

A meta-analysis of 36 RCTs27-57, 74, 80, 82-84 demonstrated a clinically significant reduction in subjective sleepiness of -2.4 points in the ESS score (95% CI:-2.9 to -1.9 points) in patients on PAP compared to controls (see supplemental material, Figure S3). A sub-analysis removing 5 studies29, 51, 52, 74, 80 that recruited non-sleepy participants still demonstrated a clinically significant reduction in subjective sleepiness of -2.8 points (95% CI:-3.4 to -2.2 points) in adults with OSA as assessed with the ESS (see supplemental material, Figure S3). A sub-analysis of the 5 studies recruiting only non-sleepy OSA patients demonstrated an ESS reduction of -1.1 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 to assess objective wakefulness demonstrated a clinically significant standardized mean difference (SMD) in objective sleepiness of 0.5 (95% CI: 0.2 to 0.8) with the use of PAP31, 37, 39, 42, 43, 47, 56 (see supplemental material, Figure S4). In contrast, a meta-analysis of 7 RCTs29, 30, 35, 36, 48, 51, 58 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 subjective sleepiness and objective 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 QOL in adults with OSA was evaluated using meta-analyses combining studies that reported on the FOSQ (n=8), 29, 31, 38, 48-50, 55, 57 and the SAQLI (n=5), 44, 47, 53, 56, 61. In addition, meta-analyses were also performed for the SF-36 component summary scores, specifically the mental component score (n=10), 29, 30, 37, 42, 44, 49, 53, 57, 61, 84 the physical component score (n=9), 29, 30, 36, 42, 44, 49, 53, 57, 84 and the vitality score (n=6) 30, 37, 44, 49, 53, 61 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 subjectively sleepy, with the exception of one study that recruited non-sleepy participants with mild to moderate OSA 29 and two studies 37, 38 that specifically recruited patients with mild OSA and symptoms of sleepiness. All studies were RCTs, with 5 studies 30, 31, 37, 38, 50 using a randomized, cross-over design. Participants were randomized to CPAP or a control intervention. Sham PAP (n=7), 29, 42, 49, 50, 53, 55, 56 conservative measures (advice on weight loss or good sleep habit counseling) or no intervention (n=4), 44, 48, 61, 84 placebo tablet (n=4), 30, 31, 37, 38 and sham surgery (n=1) 57 were utilized as control interventions. The length of the intervention was for 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 17 RCTs investigated the efficacy of CPAP to improve QOL in adults with OSA. 29-31, 37, 38, 42, 44, 47-50, 53, 55-57, 61, 84 Meta-analysis of some measures of QOL demonstrated a clinically significant difference with CPAP while others did not. A meta-analysis of 8 RCTs 29, 31, 37, 48-50, 55, 57 reporting on FOSQ and 5 RCTs 44, 47, 53, 56, 61 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, 29, 30, 37, 42, 44, 49, 53, 57, 84 the mental component summary score, 29, 30, 37, 42, 44, 49, 53, 57, 61, 84 and the vitality score 30, 37, 44, 49, 53, 61 demonstrated no clinically significant improvement in QOL using CPAP. Overall, the analyses suggest that CPAP is effective in improving sleep-related QOL, but not overall QOL. 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 PATIENTS):

A total of 27 RCTs measured BP before and after PAP therapy. 29, 32, 34, 41, 45, 48, 52, 56, 61-66, 68-73, 80, 84, 85, 88, 116 Of these, five specifically included hypertensive patients a priori, 34, 52, 68, 80, 116 and five focused on resistant hypertension (patients treated with ≥ 3 antihypertensive medications). The majority of RCTs studied mixed populations of normotensives and hypertensives, many of whom were treated with antihypertensive drugs. Two trials recruited only normotensive patients. 63, 71 Most RCTs did not specify sleepiness a priori, however, a few RCTs were limited to non-sleepy or sleepy patients, with most studies 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 patient selection or outcome assessment. Several control conditions were utilized, ranging from sham PAP to usual care to an oral placebo tablet. 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 CV risk. 117 Some studies utilized office or lab-based measurements limited to the daytime hours 31, 48 and one study utilized home daytime measurements.

Meta-analyses were performed on several measures of BP including: nighttime systolic and diastolic; daytime systolic and diastolic; 24-hour systolic and diastolic; and 24-hour mean (see supplemental material, Figure S10.
For the entire patient 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 mm Hg (95% CI: -6.0 to -2.4 mm Hg), and -2.3 mm Hg (95% CI: -3.7 to -0.9 mm Hg), respectively (see supplemental material, Figure S10 and Figure S11). Clinically significant reductions in daytime SBP and DBP of -2.8 mm Hg (95% CI: -4.2 to -1.3 mm Hg) and -1.9 mm Hg (95% CI: -2.9 to -0.9 mm Hg) 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 mean SBP and DBP of -1.5 mmHg (95% CI: -2.3 to -0.7 mm Hg) 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 mean 24-hr 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 specified severe OSA defined by an AHI >30 events/h. Two studies included patients with an AHI of 5-30 events/h and none exclusively recruited patients 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. However, whether this reflects the effect of PAP treatment, or patient adherence with therapies in general, remains to be answered. Some trials used fixed CPAP titrated during PSG in the sleep laboratory and some used APAP, while others 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.

The BP reductions associated with RCTs of PAP therapy found in these meta-analyses, if sustained, would result in substantial reductions in long-term CV risk. Importantly, the meta-analyses did not take into account clinical trials showing greater BP-lowering effects related to antihypertensive drugs compared to PAP therapy in those with OSA.

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

**Blood Pressure (Resistant Hypertensive Patients):**
A total of 5 of the 27 RCTs reported on the effects of PAP therapy on BP in patients with resistant hypertension at baseline. Patients had predominantly moderate to severe OSA. Except for daytime SBP, meta-analysis demonstrated a clinically significant reduction in nighttime SBP and DBP (-3.3 mm Hg [95% CI: -6.1 to -0.4 mm Hg] and -2.2 mm Hg [95% CI: -4.3 to -0.0 mm Hg], respectively), daytime DBP (-1.1 mm Hg [95% CI: -3.4 to +1.1 mm Hg]), and 24-h SBP and DBP, (-2.2 mm Hg [95% CI: -5.1 to +0.8 mm Hg], and -2.1 mm Hg [95% CI: -4.1 to -0.0 mm Hg], respectively) with PAP therapy, respectively (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 patients was moderate due to imprecision.
**BLOOD PRESSURE (HYPERTENSIVE PATIENTS):**

A total of 5 of the 27 RCTs reported on the effects of PAP therapy on BP in patients with hypertension at baseline. Patients had predominantly moderate to severe OSA. Meta-analyses demonstrated a clinically significant reduction of 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 a clinically significant reduction in 24-hr 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 did demonstrate a clinically significant reduction in mean 24-hr BP of -2.1 mm Hg (95% CI: -3.6 to -0.7 mm Hg; 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 patients was moderate due to imprecision.

**BLOOD PRESSURE (NORMOTENSIVE PATIENTS):**

A total of 3 of the 26 RCTs reported on the effects of PAP therapy on BP in normotensive patients at baseline. Meta-analyses demonstrated no clinically significant reduction in daytime and nighttime systolic and diastolic BP (see supplemental material, Figure S30 through Figure S33). However, one study demonstrated a clinically significant reduction in mean 24-hour DBP of -1.4 mm Hg (95% CI: -3.2 to 0.4 mm Hg) with PAP therapy. In addition, another study demonstrated a clinically significant reduction in mean 24-h BP of -10.4 mm Hg (95% CI: -18.89 to -1.9 mm Hg) with PAP therapy. 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 patients was low due to very high imprecision.

**CARDIOVASCULAR EVENTS (CV EVENTS):**

The TF reviewed both RCT and non-randomized data regarding the effects of PAP on cardiovascular event rate. Three RCTs assessed the impact of PAP therapy on CV event rate, which were variably defined by composite outcomes. The studies recruited patients with at least moderate OSA severity (AH1 >15-20/h), middle to older age, predominantly male and overweight to obese, followed for an average of 3 to 5 years. Studies of patients examining incident CV events (primary prevention studies; e.g. first ischemic stroke or younger non-sleepy patient prior CV events) and recurring CV events (secondary prevention studies; e.g. non-sleepy patients with newly re-vascularized coronary artery disease, or prior diagnosis of coronary artery disease or cerebrovascular disease) were included for analysis. The largest trial to date showed no clinically significant impact of CPAP therapy on secondary prevention in adults with established CV disease. The meta-analysis did not demonstrate a clinically significant reduction in the rate of CV events occurring with the use of PAP (see supplemental material, Figure S34).

Eleven non-randomized studies assessed the impact of PAP on CV event rate. Most studies included patients 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. The majority of studies measured composite outcomes of fatal and non-fatal CV events, while two studies were limited to incident arrhythmias. Two studies were also limited to patients with heart failure. Meta-analysis of 11 non-RCTs demonstrated a clinically significant reduction in the 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 patients who refused PAP therapy, raising questions of adherence with other medical therapies that may impact outcomes. Non-systematic ascertainment of study subject characteristics, and the outcomes typical of non-randomized studies, may be biased in the data abstraction process. 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, it is unknown what impact interim advances in CV 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 CV 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 treatment remains to be answered. Furthermore, whether interventions that lead to greater PAP use would have demonstrated a beneficial impact of PAP on CV event reduction is unknown, but suggested in secondary analyses performed in several studies. Two reasons for the lower adherence may be the inclusion of less symptomatic/sleepy patients and exclusion of patients with the most severe disease – given that symptoms and OSA severity are predictors of PAP adherence. In addition, the benefits of PAP on CV event risk may be greater in more symptomatic and more severe disease, the groups that were excluded from the RCTs.

Due to inconsistent findings regarding the effects of PAP to reduce CV event rates, the TF made no recommendation for the use of PAP to reduce CV event rate in adults with OSA. The quality of evidence for CV 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. The studies recruited patients with at least moderate OSA severity (AHI >15-20/h), middle to older age, predominantly male and overweight to obese, followed for an average of 3 to 5 years. Both primary and secondary prevention studies were included for analysis. The largest trial to date showed no clinically significant impact of CPAP therapy on mortality in adults with established CV disease. 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 identified reported on mortality associated with the use of PAP versus control conditions in patients with or without heart failure (see supplemental material, Figure S37). A meta-analysis of these studies demonstrated a clinically significant reduction in the 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 0.24 (95% CI: 0.11 to 0.53) and 0.38 (95% CI: 0.21 to 0.72) for heart failure and no heart failure patients, respectively (see supplemental material, Figure S38 and Figure S39).
Similar to evidence review for cardiovascular event rates, 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 overall quality of evidence for recommendation 4.1ai, based on the critical outcome of sleepiness, was high. The overall quality of evidence for recommendation 4.1aii, based on the critical outcome of sleep-related QOL, was moderate due to imprecision. The overall quality of evidence for recommendation 4.1aiii, based on the critical outcome of BP, was moderate due to imprecision.

**BENEFITS VS 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, MVAs, and reduction in BP. 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. 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 clinical provider. 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 elevated BP.

**PATIENT VALUES AND PREFERENCES:**
The TF judged that the majority of sleepy patients or 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 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 the majority of OSA patients with hypertension would want their OSA treated to help reduce BP as the benefits may include reduced BP medication requirements and reduction in CV risk. Patients suffering from symptoms of OSA (i.e., excessive sleepiness) may be more accepting of CPAP therapy, with the possibility of secondary benefits related to CV risk reduction. Asymptomatic patients with OSA, however, may have a more nuanced view of whether to pursue treatment of OSA, particularly given the availability of alternative antihypertensive treatments. The TF recognizes that some asymptomatic patients will place a high value on any intervention that potentially reduces long-term CV events, including CPAP therapy.

A few studies support the observation that asymptomatic or minimally symptomatic OSA patients may experience improvements in sleepiness symptoms they had not previously appreciated. For these patients, a short-term therapeutic trial of CPAP may be accepted by the patient to assess if they derive personal benefits from treatment. For other asymptomatic patients, the uncertainty of any CV benefit, may lead them to decline treatment of OSA, regardless of their OSA severity. For example, evidence from some RCT studies that selectively recruited non-sleepy subjects demonstrated no benefits in BP or CV risk reduction with CPAP. Given the absence of high quality evidence for the use of PAP to treat asymptomatic adults with OSA, conservative management of...
OSA in asymptomatic 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,127 two studies128,129 were identified demonstrating the cost effectiveness of CPAP. The first study128 demonstrated an incremental cost-effectiveness ratio (ICER) of $15,915 per quality-adjusted life year (QUALY) with CPAP therapy while another study129 performed for the National Institute of Health Research in the UK 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 quality of life. 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 US 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 a number of other outcomes to be important but not critical for decision-making for the development of the recommendations. These outcomes included neurocognitive function, mood, MVA, fasting glucose, hemoglobin A1C, LVEF, and incident hospitalization. A summary of the findings for each of these outcomes is presented below.

**NEUROCOGNITIVE FUNCTION:**

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.29,31,36,37,47,48,57,82,83 Two studies recruited elderly participants (age ≥65).47,82 One study37 recruited sleepy participants with mild OSA and one study29 recruited non-sleepy participants with mild to moderate OSA. The studies included for analysis did not enroll patients with concurrent mild cognitive impairment or dementia. However, one study demonstrated that their patients 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.82 Sham PAP (n=1),29 conservative measures (advice on weight loss or good sleep habit counseling) (n=3),47,48,82 and placebo tablet (n=3)31,36,37 were utilized as control interventions.

The intervention lasted for a period of 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 difference between PAP and control groups in the domains of neurocognitive function tested, which included executive function, processing speed, attention/vigilance, memory, and intelligence. Overall, the analyses suggest that CPAP use 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).36, 37, 47, 84, 98

Three studies were performed with participants who had moderate to severe OSA and were subjectively sleepy,36, 47, 98 one study recruited minimally sleepy participants with mild to moderate OSA,84 and one study37 recruited participants specifically with mild OSA and symptoms of sleepiness. Two studies recruited only older subjects.47, 98

All studies were RCTs, with 2 studies using a randomized, cross-over design.36, 37 Participants were randomized to CPAP or a control intervention. No intervention (n=3),47, 84, 98 or placebo tablet (n=2),38 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 patients studied did not have 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 ACCIDENTS:
The efficacy of CPAP in improving MVA in adults with OSA was evaluated using meta-analyses examining the relative risk reduction of obstacles hit during driving simulation in 4 RCTs29, 36, 37, 48 and MVA in 10 non-randomized studies86, 87, 89-91, 93-96, 100 (see supplemental material, Figure S49 through Figure S51).

In studies that used driving simulator data and had control patients with untreated OSA, all but one study29 was performed with participants that were subjectively sleepy. One study29 recruited non-sleepy participants with mild to moderate OSA and one study37 recruited patients specifically with mild OSA with symptoms of sleepiness. Sham CPAP (n=1),29 conservative measures (advice on weight loss or good sleep habit counseling) (n=2),48, 51 and placebo tablet (n=3)30, 36, 37 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 patient motivations when driving in simulated versus real world conditions.

For studies examining MVA risk reduction, the TF included 10 non-randomized studies with pre- and post-CPAP assessment of MVA by self-report or objective reports and performed a meta-analyses on these studies.86, 87, 89-91, 93-96, 100 Patients had predominantly moderate to severe OSA and were subjectively sleepy by self-report,87 ESS or another tool,86, 89, 93, 95, 96, 100 or data80, 91 was not reported. Most studies compared patients for a period pre-CPAP intervention to post-CPAP intervention. Two studies compared changes in MVA in OSA patients to a non-OSA control group followed over time to control for secular trends,86, 91 while one study90 compared changes in MVA to non-OSA patients also followed over time. Outcome assessment was through self-report,87, 89, 93, 95, 96, 100 data from transportation offices,90, 91 or data86 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 studies86, 87, 89-91, 93-96, 100 comparing OSA patients before and after treatment demonstrated a mean crash rate risk ratio of 0.3 (95% CI: 0.2 to 0.4) (see supplemental material, Figure
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 MVA data and self-report from questionnaires. However, the TF did not include any studies of the effect of PAP on accident rates in commercial drivers before and after CPAP use, thus these results should not be extrapolated to professional drivers. The quality of evidence for MVA ranged from low to moderate. The quality of evidence from RCTs for the use of PAP to reduce MVA was downgraded due to imprecision and was moderate. The quality of evidence from observational studies for the use of PAP to reduce MVA was low and was downgraded due to study design.

**Fasting Glucose and Hemoglobin A1C:**
A total of 7 RCTs conducted in several countries assessed fasting glucose before and after 6 to 12 weeks of PAP therapy in primarily obese, male subjects with at least moderate to severe OSA. Four studies included non-diabetic patients, 33, 40, 54, 60 and 3 studies 56, 97, 99 included patients with type 2 diabetes mellitus (T2DM). 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 co-morbid OSA may reduce insulin resistance. Whether this translates into a reduction in HbA1c levels or a reduction in risk of incident diabetes has not been evaluated in any studies to date.

The efficacy of PAP in reducing HbA1C in adults with OSA and T2DM was evaluated using a meta-analysis of three RCTs. 33, 40, 54, 60, 60, 60, 77, 97, 99 The studies were performed in primarily clinic-based populations. Participants had T2DM and were predominantly male, obese, with moderate to severe OSA. Two of the three studies recruited patients that as a group were not subjectively sleepy based on the ESS. 97, 99 The mean baseline HbA1C ranged from 7.3 to 8.5%. Participants were randomized to CPAP or a control intervention, which included either sham CPAP or usual care97, 99 for diabetes management. Patient follow-up at the end of the intervention ranged from 3-6 months. Of the three studies, only one showed a significant reduction in HbA1C. 97 A meta-analysis of the three studies did not demonstrate a clinically significant improvement in HbA1C with PAP (see supplemental material, Figure S53). Mean CPAP use across participants in the three studies ranged from 3.6h – 5.2 h/night. Whether interventions that lead to greater PAP use could demonstrate an improvement in glycemic control remains unknown. However, a non-randomized study of PAP acceptors with T2DM found no improvement in HbA1c with 3 months of CPAP at a mean adherence of 5.4 h/night suggesting the level of use needed for any benefit may be much higher than traditional thresholds for adherence. 133 A non-randomized study of non-diabetics found glycemic benefit only in those OSA patients achieving a very high level of CPAP use (>= 8hrs/night on ≥ 90% of nights), however, this level of use was achieved in only 6% of patients. 134

Overall, the TF judged that analyses do not support that PAP reduces fasting glucose or HbA1C in adult OSA patients with or without T2DM. The quality of evidence for the efficacy of PAP to reduce fasting glucose and hemoglobin A1C was high.

**Left Ventricle Ejection Fraction:**
Eight RCTs measuring left ventricle ejection fraction (LVEF) by echocardiography or radionuclide ventriculography compared the efficacy of PAP versus control conditions (see supplemental material, Figure S54 through Figure S56). 60, 62, 67, 70, 77, 81, 92 The studies were performed across a number of countries. Studies on heart failure patients 67, 70, 77, 78 recruited from cardiology or heart failure clinics while studies of patients without heart failure 50, 62, 81 recruited primarily from sleep clinics. Patients 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: 1–6 month follow-up). Either sham PAP60, 62, 70, 78 or no PAP67, 77, 81 was employed as the control intervention.

Meta-analysis of all patients in these studies showed no clinically significant improvement in LVEF.60, 62, 67, 70, 77, 78, 81, 92 When limited to patients with heart failure, a meta-analysis of five RCTs demonstrated no clinically significant improvement in LVEF.67, 70, 77, 81, 92 In addition, a meta-analysis of the three RCTs that were conducted in patients without heart failure demonstrated no clinically significant improvement in LVEF.60, 62, 81

Overall, the analyses suggest that PAP does not result in clinically significant improvements in LVEF in adults with OSA and heart failure. The quality of evidence for LVEF was moderate due to imprecision.

HOSPITALIZATION:

Two non-randomized studies reported on hospitalization rates associated with PAP versus control conditions.103, 108 A meta-analysis of these studies did not demonstrate a significant reduction in hospitalization rate associated with PAP therapy compared with control conditions (see supplemental material, Figure S57). Overall, the analyses did not support that CPAP reduced the hospitalization rate in adults with OSA, although very few studies were identified that met criteria for analysis. The quality of evidence for hospitalization rate was very low due to study type and imprecision.

4.2 In-lab PAP titration vs. APAP at home for initiation of PAP for the treatment of adult patients with OSA

4.2a We recommend positive airway pressure therapy be initiated using either APAP at home or in-lab PAP titration in adults with diagnosis of OSA and no significant comorbidities. (STRONG)

Remarks: When APAP is initiated in the home setting, therapy is continued over the long term by either using a fixed CPAP setting determined from PAP monitoring data or continued in the auto-adjusting mode. The choice of PAP initiation in the home or lab should be based on access, cost-effectiveness, and patient preference.

This recommendation is based on studies that excluded patients 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.

This recommendation is based on the clinical trials reviewed, in which mask fittings, education on PAP use at a sleep center and/or close follow-up by trained staff during the treatment period were provided to the APAP strategy group. In some studies daytime nap acclimatization was also offered.

4.2b Summary

The TF examined whether initiation of PAP using an in-laboratory titration vs. APAP at home (i.e. without an in-laboratory titration) improved critical outcomes of adherence, quality of life, and sleepiness. Meta-analyses demonstrated no clinically significant differences in adherence, quality of life, or sleepiness between APAP at home and in-laboratory PAP titration. The overall quality of evidence for this recommendation was high. Potential benefits of using APAP in the home setting include lower cost, reduced time away from home, faster initiation of treatment, and greater access to care. The potential benefits of an in-lab PAP titration include education provided by a trained sleep technologist and the ability to provide interventions to make PAP treatment
more comfortable for the patient. While APAP at home is more cost-effective than in-laboratory CPAP titration, in certain regions and settings out-of-pocket expenses for patients may be less with in-laboratory titration. The potential harms of PAP therapy initiation without an in-laboratory titration study are the potential for inadequate patient education, and inability to identify and immediately address problems related to mask fit or leak. In contrast, the potential harms of PAP therapy initiation with an in-laboratory titration study include the additional night of testing required with attendant costs, as well as potential delay in initiation of therapy. The TF determined that the majority of well-informed adult patients with OSA and without significant comorbidities would prefer initiation of PAP using the most rapid, convenient and cost-effective strategy. This recommendation assumes that adequate education on PAP use and mask fittings with or without daytime nap acclimatization by trained staff are available. Independent of payor restrictions, home APAP will be more rapid and convenient for most patients and has been shown to be more cost-effective. Nevertheless, for OSA patients without comorbidities, final determination of which strategy is ideal for an individual patient should be based on the sleep physician’s judgment, patient preferences and abilities, anticipated or known previous difficulty with PAP treatment, and availability of resources and cost of each strategy in a particular region.

4.2c Discussion
A total of 9 RCTs investigated initiation of PAP using APAP compared to an in-laboratory titration to improve one or more of the following outcomes: AHI/RDI, adherence, sleepiness, and QOL.\textsuperscript{135-143} Studies included only patients with high clinical suspicion of moderate to severe OSA and most excluded subjects with certain comorbidities. Patients were predominantly middle-aged males with daytime sleepiness and moderate to severe OSA. Most patients in these studies using APAP had mask fittings, and education on PAP use at a sleep center. Some studies also offered daytime nap acclimatization. Early follow-up by trained staff during the treatment period was also common. All studies used the 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 efficacy of APAP versus in-lab PAP titration for the treatment of OSA in adults as compared with no therapy. 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 efficacy of PAP in reducing OSA severity in adults who initiated PAP using APAP was evaluated using a meta-analysis of 3 RCTs that reported on the AHI.\textsuperscript{136, 140, 144} Patients were randomized to in-laboratory CPAP titration versus APAP at home 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 OSA severity (see supplemental material, Figure S58) when PAP was initiated using APAP.\textsuperscript{136, 140, 144} Overall, the analyses demonstrate that both APAP and in-laboratory PAP initiation similarly improves OSA severity. The quality of evidence for improvement of OSA severity was high.

Adherence:
Improvement in adherence to PAP in adults with OSA, after initiation of PAP using APAP versus an in-laboratory titration, was evaluated using a meta-analysis of 9 RCTs that reported on adherence.\textsuperscript{135-143} Patients were randomized to in-laboratory CPAP titration versus a home-based pathway that included APAP with outcomes assessed after at least 4 weeks of treatment (range 1 month to 6 months). The meta-analysis demonstrated no clinically significant difference in adherence when comparing APAP versus in-lab titration (see supplemental
material, **Figure S59**). Overall, the analyses demonstrate that PAP initiation using an APAP or in-laboratory titration is followed by similar levels of PAP adherence. The quality of evidence for adherence was high.

**Sleepiness:**

The efficacy of PAP initiation using APAP versus an in-laboratory titration for the treatment of subjective sleepiness in adults was evaluated using a meta-analysis of 8 RCTs that reported on the ESS.\(^{135,142}\) Patients were randomized to in-laboratory CPAP titration vs a home-based, unattended APAP titration with outcomes assessed after at least 4 weeks of treatment (range 1 month to 3 months). The meta-analysis demonstrated no clinically significant difference in subjective sleepiness when PAP therapy was initiated using APAP compared to an in-laboratory titration (see supplemental material, **Figure S60**). Overall, the analyses suggest that therapy using APAP compared to an in-laboratory titration results in similar improvements in sleepiness in patients with high clinical suspicion of OSA and without comorbid conditions. The quality of evidence for sleepiness was high.

**Quality of Life:**

Meta-analyses of RCTs that reported on the SAQLI,\(^ {140,142}\) FOSQ,\(^ {137,138,142}\) and SF-36 component summary scores\(^ {137,142}\) were performed to assess the efficacy of PAP initiation using APAP versus an in-laboratory titration for the improvement in QOL. Patients were randomized to in-laboratory CPAP titration vs a home-based pathway that included APAP with outcomes assessed after 3 months. A meta-analysis combining 3 RCTs measuring sleep-related QOL with FOSQ\(^ {137,138,142}\) and 2 RCTs measuring QOL with SAQLI\(^ {140,142}\) demonstrated no clinically significant difference in QOL when comparing an APAP versus an in-lab treatment titration (see supplemental material, **Figures S61**). Two RCTs\(^ {137,142}\) 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 APAP versus an in-lab titration (see supplemental material, Table S4). Overall, the analyses suggest that PAP initiation using an APAP or an in-laboratory titration similarly improve 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, while the quality of evidence for SF-36 vitality, FOSQ, and SAQLI was high.

**Side Effects:**

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

**Overall Quality of Evidence:**

The overall quality of evidence, based on the critical outcomes of adherence, quality of life, and sleepiness, was high.

**Benefits vs Harms:**

The potential benefits of PAP initiation using 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, out-of-pocket costs to patients may be lower with in-lab PAP titration due to payor coverage policies.\(^ {139,142,144}\) 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. 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 adherence in the APAP arm and the side effects of PAP that have been reported were deemed by the TF to be similar for both PAP initiation strategies. These include but are not limited to nasal dryness or irritation, dry mouth, sore throat, and sinus infection. The TF determined that the potential benefits of PAP initiation using either APAP at home or in-lab 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. The TF considered issues of patient access for in-lab CPAP titration and APAP at home. From a logistical standpoint, APAP setup requires one step after patient diagnosis of OSA – a visit to educate on APAP use and provision of the APAP device. In-lab PAP titration, however, requires two steps – one visit for the titration study and another for PAP education and provision of the PAP device. Regional variations in the time to get scheduled for an additional sleep study for PAP titration and navigating the healthcare system for PAP setup subsequent to titration can be substantial, which would favor APAP at home. 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-lab titration strategy followed by PAP setup. Until such barriers are removed, in-lab CPAP titration may be preferable to prevent delays in treatment.

With respect to patient preferences, only one randomized trial was identified, that assessed patient preference. In that study, 62% of patients in the in-lab CPAP titration strategy would have preferred home management, compared to 6% of patient in the APAP at home group that would have preferred in-lab based management. The TF also recognized that clinicians may need to consider patient burdens associated with in-lab CPAP titration or APAP in the home. For example, with respect to in-lab CPAP titration, some patients may find it difficult to spend a night away from home to 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-lab CPAP titration may be more favorable as a sleep technologist can provide education and other intervention during this initial introduction to PAP therapy.

The time when patients first seek OSA evaluation is a time when motivation to address OSA symptoms is high. 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 (e.g., 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. 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 nap acclimatization by trained staff are available. Determination of which strategy is ideal for an individual patient should be based on patient comorbidities and the sleep physician’s consideration of patient preference, patient access, and cost of each strategy.

**Resource Use:**
Four studies evaluated cost, of which three reported a slightly reduced cost for a home-based diagnostic and treatment pathway, and one reported a lower cost for APAP compared to in-laboratory titrations (cost reduction range of 25-84% in favor treatment arms including APAP in the home). While in-laboratory
titration cost includes 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 an APAP strategy for the diagnosis of OSA for patients without significant comorbidities at high risk of moderate to severe OSA or in patients with established diagnoses of OSA, while recognizing that in some regions due to patient access and patient preference that in-lab CPAP titration may be more effective.

4.3 APAP vs. CPAP for the treatment of adult patients with OSA

4.3a We recommend that clinicians use APAP or CPAP for ongoing treatment of OSA in adults. (STRONG)

Remarks: This recommendation is based on studies that usually excluded patients 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 of nocturnal arterial oxyhemoglobin desaturation due to conditions other than OSA, including hypoventilation syndromes and central sleep apnea syndromes.

4.3b Summary

The TF examined whether APAP versus CPAP improved clinical outcomes of adherence, sleepiness, and quality of life. Meta-analyses demonstrated no clinically significant differences between APAP versus CPAP in adherence, subjective and objective sleepiness, or quality of life. The overall quality of evidence for this recommendation was moderate due to imprecision. The TF determined that the benefits and risks of APAP and CPAP are similar and the balance of effects does not favor either intervention. The main potential benefit of APAP to patients is the expedited access to initiation of treatment and potential for reduced costs of care. However, in some regions of the world there may be a substantial increase in cost associated with APAP. Although meta-analyses demonstrated a lack of clinically significant differences in treatment adherence and outcomes, and patient preference varied between studies, the TF determined that individual patient tolerance of treatment, adherence, and symptom response may differ for one form of PAP or the other. Thus, the TF determined that either APAP or CPAP should be used for ongoing treatment of adult OSA, with the choice of therapy being tailored to patient tolerance and symptom responses.

4.3c Discussion

A total of 26 RCTs were identified that investigated the effects of APAP compared with fixed CPAP in reducing side effects and improving one or more of the following outcomes: AHI/RDI, treatment adherence, sleepiness, QOL, neurocognitive function. Subjects were predominantly male, with previously untreated moderate to severe OSA and no major medical co-morbidities. Subjects were randomized to CPAP vs APAP for at least 4 weeks up to a maximum of 24 weeks (median 8 weeks). In the studies reviewed, patients with conditions that increased the risk of central sleep apnea (e.g. congestive heart failure or opiate use), hypoventilation syndromes (e.g. significant lung disease such as chronic obstructive lung disease), neuromuscular disease, patients with sleep-related oxygen requirements or 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 often not included. Thus, results of meta-analyses should not be extrapolated to these patients. For each outcome, important differences in patient 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). Residual AHI values were obtained in a majority of studies from PSG recordings on treatment, while several studies reported AHI values from the PAP device microprocessor. Meta-analyses demonstrated no clinically significant differences in residual AHI between APAP and CPAP. Overall, the analyses support the conclusion that both CPAP and APAP similarly improve 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). 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 used. In addition, a meta-analysis of 2 RCTs demonstrated that the percent of nights APAP was used >4h was not clinically significant compared to CPAP. Overall, the analyses support the conclusion that adherence to APAP and CPAP 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 that reported on the Oxford sleep resistance test (OSLER), 4 studies that reported on the Epworth sleepiness scale (ESS), and 2 studies that reported on the maintenance of wakefulness test (MWT). Meta-analyses combining studies reporting on the OSLER and MWT demonstrated no clinically significant mean differences in subjective or objective sleepiness (see supplemental material, Figure S66 and Figure S67). Overall, the analyses support the conclusion that APAP and CPAP similarly reduce sleepiness. The overall quality of evidence for sleepiness was moderate due to imprecision.

**QUALITY OF LIFE:**
Meta-analysis of studies that reported on the SAQLI, SF-36 component summary scores, and the FOSQ was 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, and SF-36 physical component summary, mental component summary, and vitality scores (see supplemental material, Figure S68 through Figure S71). Overall, the analyses support the conclusion that APAP and CPAP similarly improve QOL. The overall quality of evidence for QOL ranged from moderate to high and was downgraded due to imprecision.
NEUROCOGNITIVE FUNCTION:

Two RCTs studied patients’ attention-span using the Psychomotor Vigilance Test (PVT). Patients were randomized to APAP vs CPAP in a parallel design for 6 months or in a cross-over study for 6 weeks per arm. Meta-analyses of these studies demonstrated no clinically significant differences in attention as measured by both mean reaction time and lapses on the PVT (see supplemental material, Figure S72 and Figure S73). Overall, the analyses support the conclusion that APAP and CPAP similarly improve 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, with 6 of the studies 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. In 4 of these studies, there was less pressure discomfort with APAP than CPAP, and in at least 2 of the studies, less nasal irritation or machine noise with APAP than CPAP. On the other hand, in 1 study more discomfort due to pressure variation with APAP was noted. Overall, differences in side effects between APAP and CPAP 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, sleepiness, and quality of life were determined by the TF to be critical for decision-making. The overall quality of evidence was moderate due to imprecision.

BENEFITS VS HARMs:

Potential benefits of APAP over CPAP include expedited initiation of OSA treatment and the ability to adjust therapeutic pressures as OSA severity changes with weight fluctuations, nighttime alcohol consumption, seasonal variations (e.g. upper respiratory tract infections), and changes in upper airway anatomy. Potential disadvantages of APAP, which may be observed for some patients, include higher cost, and sleep disruption from pressure fluctuations or the return of 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. 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 favor either intervention. Therefore, the TF 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. The proportion of subjects 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, physicians should discuss with their patient which form of PAP is best suited to the individual patient’s needs.

**RESOURCE USE:**

The main potential advantage of APAP vs CPAP is the potential cost saving related to initiation of therapy without prior in-laboratory PSG-based manual CPAP titration. However APAP-based strategies may require other resources, the cost and availability of which may vary by region as discussed in section 4.2. The TF did not perform a systematic review to identify cost-effectiveness studies of APAP vs CPAP devices. However, in some regions of the world, market and other factors may lead to substantial increased cost associated with APAP compared with fixed CPAP, which may therefore impact on the feasibility of APAP-based treatment.

**4.4 BPAP or auto-BPAP vs. CPAP for the treatment of adult patients with OSA**

**4.4a We suggest that clinicians use CPAP over BPAP in the routine treatment of adults with OSA. (CONDITIONAL)**

*Remarks: For the implementation of this recommendation, APAP is considered equivalent to CPAP.*

This recommendation is based on BPAP defined as a respiratory assist device that delivers inspiratory and expiratory positive airway pressure without a back-up respiratory rate.

BPAP devices may need to be used for patients with higher therapeutic pressure requirements than can be provided by CPAP devices during in-lab PAP titration. The decision to use BPAP should be based on the physician’s clinical judgement and needs of the individual patient. Furthermore, this recommendation is for the treatment of OSA. Treatment of other forms of sleep-related breathing disorders associated with hypercapnia, which may require the use of BPAP, are covered in other AASM guidelines. 5, 171

**4.4b Summary**

BPAP has been used as an alternative therapy for CPAP, in part related to issues of patient intolerance of high CPAP settings. 172 The TF examined whether BPAP versus CPAP improves the critical outcomes of adherence, sleepiness, and quality of life (Note: while no direct evidence was available for the comparison of APAP to BPAP, the TF considers APAP to be equivalent to CPAP for the implementation of this recommendation. See recommendation 4.3 and Figure 2.). Meta-analyses demonstrated no clinically significant differences in adherence and subjective sleepiness with BPAP compared to CPAP, nor OSA severity. However, a single study demonstrated a clinically significant improvement in adherence when BPAP was used as a rescue therapy. 173 Studies reporting on quality of life demonstrated no clinically significant differences. The overall quality of evidence for this recommendation was very low due to publication bias from industry funding and imprecision associated with small sample size. The main potential benefit of BPAP over CPAP or APAP is improved comfort by lowering the pressure during exhalation, which may then increase adherence. The potential harms of BPAP over CPAP or APAP are a sub-optimally low expiratory pressure level that fails to prevent the occurrence of obstructive breathing events. Furthermore, the historically perceived benefits of BPAP are less likely to be relevant since modified pressure profile technology, which also lowers expiratory pressures, has been integrated into PAP devices. The TF determined that although the benefits of treatment with BPAP and CPAP or APAP are similar, the low quality of evidence and potential harms or burdens, did not favor the regular use of BPAP. Potential burdens or harms that were considered included incomplete treatment from an inappropriately low expiratory pressure setting and the higher cost of BPAP. Therefore, the TF determined that the majority of well-
informed adult patients with OSA would prefer initiation of treatment with CPAP or APAP over BPAP. However, there is a small subset of patients that require PAP treatment with pressures higher than the 20 cm H2O, which most CPAP units are not typically capable of delivering. In these situations, BPAP devices may be needed for optimal treatment and can be utilized during an initial or subsequent in-lab PAP titration study. For specific patients who are unable to tolerate CPAP or APAP, a trial of BPAP may be offered either during the in-lab titration or following a period of demonstrated non-acceptance.

4.4c Discussion

A total of five RCTs compared the use of BPAP to CPAP to improve one or more of the following outcomes: AHI, adherence, sleepiness, neurocognitive function, QOL, and reduction of side effects. Subjects were predominantly male, middle aged, referred to sleep clinics without concomitant medical or psychiatric disorders with moderate to severe OSA, randomized to CPAP vs BPAP for duration of either 1 month, 3 months, or 12 months of PAP use. Only one study included subjects who had previously showed non-adherence with CPAP (<4 h/night), whereas the other 4 studies included PAP naïve subjects. The average therapeutic pressure reported in the studies was ~10 cm H2O and none of the studies specifically selected patients with high PAP requirements. Four of the studies implemented modified pressure profile technology. All 5 studies titrated CPAP and BPAP pressure levels during an attended laboratory study. Meta-analyses were performed to assess the effects of BPAP compared with CPAP in improving AHI, 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:

A meta-analysis of two RCTs did not demonstrate a clinically significant difference in residual AHI with treatment using BPAP compared to CPAP (see supplemental material, Figure S75). Subjects were randomized to BPAP vs CPAP for duration of 1 month or 3 months of PAP use. 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 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 studies in PAP naïve patients and 1 study in CPAP non-adherent patients that reported on adherence. Subjects were randomized to BPAP vs 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. The study using BPAP with a modified pressure profile as a rescue therapy in patients non-adherent to CPAP after ≥ 2 weeks demonstrated a clinically significant increase in adherence of 0.8 h/night (95% CI: -0.03 to 1.6 h/night) in the BPAP compared to the CPAP group. Overall, the analyses suggest that BPAP conferred no clinically significant advantage over CPAP in improving adherence, except potentially as rescue therapy for patients’ non-adherent 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 three RCTs that reported on the ESS.\textsuperscript{174,175,177} Subjects were randomized to BPAP vs CPAP for a duration of 4 weeks\textsuperscript{174} or 3 months\textsuperscript{175,177} of PAP use. The meta-analysis demonstrated no clinically significant difference in subjective sleepiness in adults with OSA treated with BPAP compared to CPAP (see supplemental material, Figure S7). However, the studies did demonstrate an improvement in subjective sleepiness with both BPAP and CPAP use compared to before initiation of treatment. Overall, the analyses suggest that BPAP compared to CPAP similarly reduces sleepiness in adults with OSA. The quality of evidence for subjective 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 efficacy of BPAP compared to CPAP for the improvement in QOL in adults with OSA. However, the TF reviewed available data from two RCTs that reported on the FOSQ.\textsuperscript{173,174} Subjects were randomized to BPAP vs CPAP for a duration of 1 month\textsuperscript{174} and 3 months\textsuperscript{173} of PAP use. One of the studies examined the effects of BPAP compared to CPAP on QOL in patients intolerant of CPAP, while the other study recruited patients naïve to PAP, thus they were not combined for meta-analysis. Neither study\textsuperscript{173,174} 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 results in similar effects on sleep-related QOL in adult patients with OSA. 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. Subjects in the one RCT of CPAP versus BPAP that reported side effects followed patients for 1 year.\textsuperscript{176} 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.\textsuperscript{176} In addition, in one other available study,\textsuperscript{177} there was no difference between BPAP and CPAP treatment in sleep quality as assessed by the PSQI (see supplemental material, Table S6). 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, sleepiness, and quality of life 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 vs 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 considered to be similar to CPAP. Another 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 was not reported in the available studies that predominantly recruited PAP naïve patients. Only one study, which assessed patients that were CPAP intolerant, demonstrated that BPAP improved
adherence. 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, similar to 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 ongoing treatment of adults with OSA.

**PATIENT VALUES AND PREFERENCES:**
The TF determined that the majority of patients would prefer their OSA treated with CPAP rather 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 PAP devices manufactured today. However, the TF also determined that BPAP may be of benefit in some CPAP intolerant patients, despite the use of modified pressure profile. In addition, some patients that 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-lab PAP titration study. For specific patients who are unable to tolerate CPAP, a trial of BPAP may be offered either during the in-lab titration or following a period of demonstrated non-acceptance.

**RESOURCE USE:**
The TF recognized that there are significant differences in cost of BPAP and CPAP devices between countries and medical systems, with small differences in some regions and significant 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.

### 4.5 Modified pressure profile PAP versus standard CPAP for the treatment of adult patients with OSA

**4.5a** We suggest that clinicians not use modified pressure profile PAP, over standard CPAP, in the routine initiation of PAP therapy in adults with OSA. (CONDITIONAL)

*Remarks: Modified pressure profile PAP refers to a group of technologies using proprietary algorithms to either reduce the expiratory or end-inspiratory pressure delivered by PAP devices to improve patient comfort*

**4.5b Summary**
The TF examined whether modified pressure profile PAP compared to standard PAP improved the critical outcomes of adherence, sleepiness, quality of life, and side effects. The overall quality of evidence for this recommendation was low due to imprecision and potential publication bias from industry funding. Meta-analyses demonstrated no clinically significant differences in adherence, sleepiness, and quality of life with modified pressure profile PAP versus standard PAP. Insufficient, standardized data were available to perform a meta-analysis on side effects, although the reported data demonstrated no clinically significant differences. The potential benefits of modified pressure profile PAP include an improvement in adherence and reduced side
effects, which may then improve sleepiness and other outcomes. The potential harms of modified pressure profile PAP were considered to be similar to standard PAP. The potential burdens to the patient were also considered to be minimal but could include the need for education on the use of the modified pressure profile feature, increased costs by region or reduced accessibility to devices with modified pressure profile features. The TF determined that there were no clear benefits to routine initiation of treatment with modified pressure profile PAP, compared to standard PAP for OSA, despite perceived minimal potential harms and burdens. The TF judged that the majority of well-informed adult patients with OSA would not have an initial preference for treatment with modified pressure profile PAP over standard PAP due to the lack of established benefits. The TF recognizes that modified pressure profile PAP may have value in some patients in other contexts (e.g. poorly adherent patients or difficulties tolerating CPAP during in-lab titration studies); therefore, the pressure profile which minimizes side effects and optimizes adherence should be used.

4.5c Discussion

A total of 6 RCTs investigated the use of modified pressure profile PAP to improve clinical outcomes and reduce side effects.\textsuperscript{150, 178-182} One of these studies used a cross-over design.\textsuperscript{182} The 6 studies included to assess the outcomes of interest were performed in several countries in clinic-based populations. Participants were predominantly male, obese, with moderate to severe OSA, and subjectively sleepy. The intervention was administered for a period of at least 1 month (range: 1 – 6 months). Meta-analyses were performed to assess the efficacy of modified pressure profile PAP for the treatment of OSA in adults as compared with standard PAP (see supplemental material, Figure S78 through Figure S83). The outcomes analyzed were adherence, sleepiness, neurocognitive function, QOL, and side effects. A summary of finding table is also included in the supplemental material, Table S7. A summary of the evidence for each outcome is provided below.

Adherence:

The effect of modified pressure profile PAP in adults with OSA on adherence was evaluated using a meta-analysis of 6 RCTs that reported on the number of hours per night the device was used.\textsuperscript{150, 178-182} All 6 studies were performed in participants that 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 S78). 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.\textsuperscript{183} One of the included studies allowed patients 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 patients that had had low adherence on standard PAP (<4 hours/night), suggesting that participants with poor adherence might increase their PAP use once transitioned to modified pressure profile PAP.\textsuperscript{181} The quality of evidence for adherence was low due to imprecision and potential publication bias from industry funding. Overall, the TF judged that there was no clinically significant improvement in adherence with modified pressure profile PAP compared to standard PAP in adult patients with OSA, but recognized the possibility of benefits in patients demonstrating poor adherence.

Sleepiness:

A meta-analysis of 5 RCTs\textsuperscript{150, 178-181} demonstrated no clinically significant difference in subjective sleepiness between participants on standard PAP compared to modified pressure profile PAP (see supplemental material, Figure S79). 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. The quality of evidence for sleepiness was low due to imprecision and potential publication bias from industry funding. Overall, the TF judged that there was no clinical benefit 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 that reported on the FOSQ and one study that reported on the SAQLI. Meta-analysis demonstrated no clinically significant difference in sleep-related QOL (see supplemental material, Figure S80). One study reporting global QOL using SF-36 MCS, PCS, and vitality scores found no significant difference in these measures (see supplemental material, Table S7). In addition, meta-analysis of two studies reporting on the Pittsburg Sleep Quality Index (PSQI) demonstrated no clinically significant difference in sleep quality (see supplemental material, Figure S81). The overall quality of evidence for QOL ranged from very low to low due to imprecision and potential publication bias from industry funding. Overall, the TF judged that there were no clinically significant improvements in sleep-related QOL, general QOL measures, and sleep quality 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). 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: 0.0 to 0.5) (see supplemental material, Figure S82 and Figure S83). The quality of evidence for neurocognitive outcomes was low due to imprecision and potential publication bias from industry funding. Given the absence of testing of other important neurocognitive domains and findings from the present meta-analyses, the TF judged there was insufficient evidence demonstrating that neurocognitive function is improved with modified pressure profile PAP compared to standard PAP in adult patients 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. Only 3 RCTs reported data on side effects. 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. At 7 weeks, there were no significant differences in side effects between the modified pressure profile PAP and standard PAP groups. Another study assessed patient side effects and comfort, but did not specify what was assessed. This study reported no differences in side effects or patient comfort between the groups at 3 months. The third study assessed mask comfort and sleep quality using a visual analog scale. 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. The quality of evidence for reduction in side effects was low due to potential publication bias from industry funding and the use of non-standard methodologies in assessing the outcomes. Overall, the TF concluded that there were no clinically significant differences in side effects between modified pressure profile PAP and standard PAP.
OVERALL QUALITY OF EVIDENCE:
The overall quality of evidence, based on the critical outcomes of adherence, sleepiness, and side effects, was downgraded to low due to imprecision and potential publication bias from industry funding.

BENEFITS VS HARMs:
Modified pressure profile PAP may provide potential benefits in improving adherence to PAP and thereby reduce sleepiness and improve quality of life. However, the meta-analyses performed do not support this conclusion. Nevertheless, certain patient populations, particularly poorly adherent patients, may benefit from modified pressure profile PAP, as suggested in post-hoc analyses performed in one study. Any potential benefit of modified pressure profile PAP must be weighed against potential harm from incomplete treatment, potential side effects, need for additional education on the use of the modified pressure profile feature, and increased costs (in certain regions). In all studies, both modified pressure profile PAP and standard PAP resulted in similar reductions in OSA severity. Side effects associated with modified pressure profile PAP were judged to be similar to standard PAP based on qualitative review of data. The TF judged potential harms in the use of modified pressure profile to be minimal, though there were no clear benefits to routine initiation of treatment with modified pressure profile PAP. Modified pressure profile PAP may have value in some patients in other contexts (e.g. poorly adherent patients), therefore the recommendation is limited to the initiation of PAP, where there was sufficient evidence to guide an evaluation of benefits vs. harms.

PATIENT VALUES AND PREFERENCES:
Based on their clinical expertise, the TF determined that there were no clear benefits to routine initiation of PAP therapy with modified pressure profile compared to standard PAP for the treatment of OSA despite perceived minimal potential harms and burdens. Analyses from at least one study, however, suggest that there may be a subgroup of patients poorly adherent to standard PAP, which may improve adherence with the initiation of modified pressure profile PAP, for which clinical trials are absent.

RESOURCE USE:
The TF did not identify cost-effectiveness studies and did not undertake a comprehensive cost comparison of modified pressure profile PAP versus standard PAP. However, the TF determined based on its collective clinical experience that the resource use of modified pressure profile PAP was not likely to be significantly higher than standard PAP, since the technology is typically embedded with most devices available from major manufacturers.

4.6 Nasal PAP vs. Intranasal PAP vs. Oral PAP vs. Oronasal PAP for the treatment of adult patients with OSA

4.6a We suggest that either nasal or intranasal interface be used, over oronasal or oral interfaces, in the routine initiation of PAP therapy in adults with OSA. (CONDITIONAL)

4.6b Summary
The TF examined whether oral, nasal (“nasal mask”), intranasal (“nasal pillows”), or oronasal (“full face mask”) interfaces improved the critical outcomes of adherence, sleepiness, and quality of life. Meta-analysis demonstrated a clinically significant improvement in adherence with nasal PAP versus oronasal interfaces, but there was no clinically significant difference in adherence between nasal or intra-nasal interfaces. One study
demonstrated a clinically significant improvement in adherence with oral versus nasal interfaces. Meta-analysis demonstrated no clinically significant improvement in subjective sleepiness with intranasal versus nasal interfaces, oronasal versus nasal interfaces, and oral versus nasal interfaces. Finally, studies reporting on quality of life demonstrated no clinically significant differences with intra-nasal versus nasal interfaces. Side effects varied between interface types, and between individuals for a given interface. The overall quality of evidence for this recommendation was low due to imprecision, study design and/or potential risk of bias from industry funding. The potential benefits of appropriate mask selection include reduction of side effects such as air leak and discomfort (see supplemental material, Table S16), which may then improve adherence and subsequently patient outcomes. The harms of inappropriate mask selection could include an increase in these same side effects and thereby reduced adherence. Although only limited data regarding patient preference are available, patients tend to prefer nasal or intranasal interfaces over oronasal or oral interfaces. Based on clinical experience, the TF determined that the majority of well-informed patients would choose nasal or intranasal interfaces over oronasal or oral interfaces in the initiation of PAP therapy. However, individual patient factors or preferences may vary during the initial titration, whether attended or unattended, or during the course of home treatment; therefore the mask interface which minimizes side effects and optimizes seal, efficacy, and adherence should be used.

4.6c Discussion
A total of 7 RCTs were identified which evaluated the effects of different PAP interfaces on reducing AHI, improving adherence, sleepiness and QOL and reducing side effects.\textsuperscript{170, 184-189} Subjects in all 7 RCTs were predominantly middle-aged males without major medical co-morbidities with moderate to severe OSA who were treated with each interface for at least one and up to 8 weeks (median duration of 4 weeks) in either parallel or cross-over designs. Subjects were previously untreated except for one study\textsuperscript{185} in which subjects established on PAP treatment for >6 months were randomized to intra-nasal vs nasal treatment. Subjects in these studies were not selected based on specific side effects (nasal congestion, oral dryness, etc.) or mask interface intolerance. Data on adherence for nasal vs. oronasal interfaces were also analyzed from 3 non-randomized studies.\textsuperscript{190-192} Subjects were predominantly male without major medical co-morbidities, 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 subjective sleepiness (see supplemental material, Figure S84 through Figure S89). The Summary of Findings tables are presented in the supplemental material, Table S8 through Table S10. 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 of 3 – 4 weeks duration\textsuperscript{170, 184} involving newly treated patients with a range of PAP pressures, or for 1 week periods\textsuperscript{185} in patients 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 S84).

There was insufficient evidence to perform a meta-analysis on OSA severity for oronasal and oral versus nasal interfaces. One RCT employing a 3-week cross-over design\textsuperscript{187} and one RCT employing a 4-week cross-over design\textsuperscript{188} demonstrated no clinically significant differences in AHI with oronasal or oral interfaces respectively, compared with nasal interfaces (see supplemental material, Table S9 and Table S10).
The TF judged based on the evidence review that there were no clinically significant differences in AHI reduction between the different mask interfaces. The quality of evidence for OSA severity for either intranasal or oronasal interfaces compared to nasal interfaces and for oral interfaces compared to nasal interfaces ranged from very low to low due to imprecision and potential publication bias from industry funding.

**ADHERENCE:**

The efficacy of intra-nasal compared with nasal interfaces for improving adherence was evaluated using meta-analyses of 2 cross-over RCTs of 3 – 4 weeks duration involving newly treated patients with a range of PAP pressures, or for 1 week periods in patients previously established on nasal PAP treatment at ≥ 12 cm H2O for > 6 months. There was no clinically significant difference in mean adherence in h/night and percent nights of CPAP use with intra-nasal interfaces compared with nasal interfaces (see supplemental material, Figure S85 and Figure S86).

The efficacy of oronasal compared with nasal interfaces for improving adherence was evaluated in meta-analyses of 2 cross-over RCTs of 3 and 4 weeks duration, which demonstrated a clinically significant improvement in adherence of 0.8 h/night (95% CI: -0.1 to 1.8 h/night) with nasal interface compared with oronasal interface (see supplemental material, Figure S88). A meta-analysis was performed of 3 non-randomized studies in which subjects were predominantly male without major medical co-morbidities, with previously untreated moderate to severe OSA, treated for at least 3 weeks up to 24 months. 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 S89).

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 RCT that demonstrated a clinically significant difference in adherence with a mean difference of 0.9h/night (95% CI: -0.7 to 2.5 h/night) in favor of oral interfaces (see supplemental material, Table S10).

The TF judged that there were clinically significant improvements in adherence 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 with an oral compared to a nasal interface. However, based on clinical experience, the TF determined that most patients have difficulties using an oral interface over the long-term. The quality of evidence for adherence ranged from very low to low due to imprecision, study design, and potential publication bias from industry funding.

**SLEEPINESS:**

The efficacy of intra-nasal compared with nasal interfaces for improving subjective sleepiness was evaluated using a meta-analysis of two crossover studies; one employing a 3 week duration and one employing a 4-week duration that demonstrated no clinically significant difference in subjective sleepiness between intra-nasal and nasal interfaces as assessed with the ESS (see supplemental material, Figure S87).

There was insufficient evidence to perform meta-analysis for the effects on sleepiness of oronasal versus nasal interfaces, and oral versus nasal interfaces. Two, four-week cross-over RCTs demonstrated no clinically significant difference in subjective sleepiness with oronasal or oral interfaces compared with nasal interfaces, respectively (see supplemental material, Table S9 and Table S10).
The TF judged based on the evidence review that there were no clinically significant differences in improvements of subjective sleepiness between the different mask interfaces. The quality of evidence for subjective sleepiness was low due to imprecision and potential publication bias from industry funding.

**QUALITY OF LIFE:**

There was insufficient evidence to perform meta-analysis for the effects of the various interface types on QOL. Only one RCT\(^\text{170}\) was identified that met criteria which assessed the effect of intra-nasal versus nasal interfaces on QOL over 3 weeks each in a cross-over RCT (see supplemental material, Table S8). QOL was assessed with the FOSQ and no clinically significant difference in QOL was found comparing intra-nasal versus nasal interfaces.\(^\text{170}\)

No RCT evidence was available to assess the effects of oronasal or oral interfaces on QOL. The TF judged that there was insufficient evidence to demonstrate differences in QOL improvement on PAP with any mask interface. The quality of evidence for QOL for comparisons of intra-nasal with nasal interfaces was low due to imprecision and potential publication bias from industry funding.

**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.

For intra-nasal versus nasal interfaces, side effect data were reported from 2 cross-over RCTs of 3-week and 4-week duration\(^\text{170, 184}\) involving newly treated patients with a range of PAP pressures, or for 1 week periods\(^\text{185}\) in patients previously established on nasal PAP treatment at $\geq 12$ cm H\(_2\)O for $> 6$ months. An overall multi-item side effect score favored intra-nasal interfaces in one study of newly treated patients,\(^\text{170}\) but there were no clinically significant differences in overall side effects between interfaces for the other 2 studies.\(^\text{184, 185}\) 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 unstable. There were no clinically significant differences between interfaces for nasal or oral congestion or dryness. The quality of evidence was low due to imprecision and potential publication bias from industry funding (see supplemental material, Table S8). Overall, TF members considered that side effect differences were not clinically significant between the two interfaces.

For oronasal versus nasal interfaces, one 4-week cross-over RCT\(^\text{186}\) and 2 non-RCTs\(^\text{190, 191}\) evaluating treatment periods of up to 24 months (6 months, mean of 4.5 months, respectively), reported data on side effects. In the one cross-over RCT,\(^\text{186}\) 19 of 20 subjects 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 subjective mask leak, sore eyes, claustrophobia and difficulty exhaling were clinically significant with the oronasal interface. In one of the non-RCTs, oronasal dryness was more prevalent with oronasal than nasal interfaces (80% vs 46%, respectively).\(^\text{190}\) In a cohort of 2,311 subjects in whom 62% were using nasal and 26% oronasal interfaces, there were greater reports in symptoms of eye irritation, dry mouth, choking sensation and physiological 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 multivariate analysis, PAP non-adherence in this cohort was associated with choking on PAP and use of the oronasal interface.\(^\text{191}\) The quality of evidence for side effects was very low due to study design, imprecision, and potential publication bias from industry funding (see supplemental material, Table S9). Overall, the consensus of
TF members was that for individual patients there may be clinically important differences in side effects with oronasal compared with nasal interfaces, and that 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 and two non-RCTs evaluating subjects 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 subjective air leaks, nasal dryness and strap/mask discomfort, with no differences in interface dislodgement.

In the non-RCTs, oral interfaces were associated with significantly more upper airway dryness and “rainout” (condensation) than nasal interfaces. The quality of evidence for side effects was very low due to study design, imprecision, and potential publication bias from industry funding. The consensus of TF members was that for individual patients there may be clinically important differences in side effects with oral compared with nasal interfaces, and that interface selection should be based on individual patient preference and tolerance.

**OVERALL QUALITY OF EVIDENCE:**
The quality of evidence based on the critical outcomes of adherence, sleepiness, and QOL were downgraded to low due to study design (non-RCT), imprecision, and potential risk of publication bias from industry funding.

**BENEFITS VS HARMs:**
Though the available data are limited, meta-analysis suggests a clinically significant reduction in adherence with oronasal compared to nasal PAP. 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 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. An additional potential harm includes the observation of increased residual OSA severity and increased pressure requirements with the use of oronasal compared to nasal interfaces, which could adversely affect adherence. Benefit versus harm may vary between individuals for different interfaces, therefore the interface which proves most beneficial, by reducing side effects and optimizing adherence, should be used.

**PATIENT VALUES AND PREFERENCES:**
In comparing intra-nasal vs nasal interfaces, the available data included two cross-over RCTs of 3-4 week duration, involving newly treated patients with a range of PAP pressures, or for 1 week periods in patients previously established on nasal PAP treatment at ≥ 12 cm H2O for > 6 months. In one study of PAP naïve subjects overall mask satisfaction scores were significantly higher for intra-nasal interfaces. In contrast, in the other 2 studies which specifically determined patient preference, there was no clinically significant difference between intra-nasal versus nasal interfaces either for newly treated or previously treated subjects. In comparing oronasal vs nasal interfaces, nasal interfaces were rated as significantly more comfortable and were chosen over oronasal interface by all subjects for long-term treatment in one 4 week cross-over RCT. In 2 nonrandomized studies evaluating treatment periods of up to 24 months, oronasal interfaces were least often chosen by patients for long-term treatment compared with nasal and intra-nasal interfaces. For oral compared with nasal interfaces, in one 4-week cross-over RCT there was a trend for patients to prefer nasal (71%) over oral (29%) interfaces. In one non-randomized study involving predominantly male subjects without

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major medical co-morbidities with previously untreated moderate to severe OSA, in which patients selected mask interface for initial titration and later long-term use, 27% chose oral vs 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.\(^{190}\)

Based on these data and their clinical expertise, the TF determined that the majority of well-informed patients would prefer initiating PAP therapy with a nasal or intranasal interface over oronasal interface, and that an oral interface would be only rarely preferred.

**RESOURCE USE:**

The TF did not identify cost-effectiveness studies comparing specific mask types. Identification of the optimal mask type for an individual patient with respect to comfort, seal and tolerability is an important aspect of optimizing PAP adherence and efficacy. Financial considerations may limit the number of masks which patients can try while attempting to identify the optimal interface. Furthermore replacement of worn or broken masks may also be limited by financial constraints. There was a consensus among TF members that DME and third party payors should maintain policies which support flexibility in initial mask choice and which provide for regular replacement of masks to ensure continued comfort, seal and treatment efficacy.

### 4.7 Humidified PAP vs. No Humidified PAP for the treatment of adult patients with OSA

#### 4.7a We suggest that heated humidification be used with PAP devices for the treatment of adults with OSA.

*(CONDITIONAL)*

#### 4.7b Summary

The TF examined whether humidified PAP versus standard PAP improves the critical outcomes of adherence, sleepiness, quality of life, and side effects. Meta-analyses demonstrated no clinically significant improvement in PAP adherence, sleepiness, and quality of life, with the use of humidification compared with no humidification. However, meta-analyses demonstrated a clinically significant reduction in several side-effects associated with the use of CPAP including dry mouth/throat, nasal discharge, nasal congestion, dry nose, bleeding nose, sinus pain or headache, sore throat, hoarse voice, and reduced smell, but not sinus infection or cough. The overall quality of evidence based on the critical outcomes was low due to imprecision. The potential harms of humidified PAP include over-humidification with condensation (i.e. “rain-out”) in the PAP circuit, face, and/or nose of the patient. The potential burdens to the patient include increased size of the PAP unit, cost of distilled water, and additional maintenance requirements. The TF determined that the benefits of humidification likely outweigh the potential harms and burdens in most patients; however, some patients may eventually determine that the absence of humidification results in no untoward side effects and may choose to stop the use of humidification. The TF also determined that the majority of well-informed adult patients with OSA would prefer PAP treatment with humidification over PAP therapy without humidification.

#### 4.7c Discussion

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, sleepiness, QOL, and reduce PAP-related side effects including nasal discharge, nasal congestion, dry nose, epistaxis, and dry mouth/throat.\(^{198-206}\) All studies evaluated only OSA patients 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
Most studies utilized heated humidification, except for 2 studies where one study compared both heated and cold passover humidification to no humidification and one study 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 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 S90 through Figure S97). A Summary of Findings tables is also included in the supplemental material, Table S11. 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 8 RCTs that reported on hours per night of PAP usage. The meta-analysis demonstrated no clinically significant difference in PAP usage with the addition of humidification (see supplemental material, Figure S90). The quality of evidence for PAP adherence was high.

**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. All of the included studies assessed subjective sleepiness using the ESS. The meta-analysis demonstrated no clinically significant difference in subjective sleepiness with humidification as compared to no humidification (see supplemental material, Figure S91). The quality of evidence for sleepiness was high.

**Quality of Life:**

A meta-analysis of two RCTs that reported on the effect of humidification on QOL using either the SAQLI or the QSQ 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 with or without humidification (see supplemental material, Figure S92). The overall quality of evidence for QOL was low due to imprecision.

**Side Effects:**

Meta-analyses were conducted for each identified PAP-related side effect whenever possible. Meta-analyses of 2 RCTs demonstrated clinically significant reduction in the odds of nasal discharge, dry nose, and nose bleeding, and dry mouth/throat while a meta-analyses of 3 RCTs demonstrated clinically significant reduction in the odds of nasal congestion, and dry mouth with the use of humidified PAP (see supplemental material, Figure S93 through Figure S97). One 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. However, this study reported no clinically significant differences in reduction of cough and sinus infection. All of these studies only assessed patients with newly diagnosed OSA with no prior history of treatment and none of the studies recruited specifically individuals with a history of nasal or sinus disease. Overall, these results suggest a clinically significant reduction in the incidence of CPAP-related side effects with humidification. The quality of evidence for side effects was moderate due to imprecision and was low with the exception of dry mouth.

**Overall Quality of Evidence:**
The quality of evidence for adherence and sleepiness was rated as high, while the quality of evidence for quality of life and side effects was rated as low. The overall quality of evidence was downgraded to low due to imprecision.

**Benefits vs Harms:**

The benefits of humidification include a reduction in potential side effects from PAP therapy. The primary potential harm of humidification is condensation or “rain out” (condensation) of water into the PAP circuit, face, and nose or mouth of the patient and may include sinus infections from bacterial growth within the humidification unit if not cleaned regularly. These side effects can be readily addressed by patient education on adjusting the level of humidification and education on regular cleaning of the equipment. Potential burdens of adding humidification are added costs to purchasing PAP therapy and costs of distilled water in some regions of the world, an increase in the size of the PAP unit, and increased maintenance requirements to replace the water chamber and clean the humidifier. Overall, the TF determined that the benefits of humidification outweigh the potential harms and burdens in most patients.

**Patient Values and Preferences:**

Based on their clinical expertise, the TF determined that the majority of patients would want PAP treatment with humidification to minimize side effects from PAP, despite no evidence of a clinically significant benefit in terms of PAP adherence or reduction in OSA symptoms (i.e. sleepiness). However, some patients may eventually determine that the absence of humidification results in no untoward side effects when using PAP therapy and may choose to stop the use of humidification.

**Resource Use:**

The TF did not identify cost-effectiveness studies comparing humidified PAP to standard PAP. Most manufacturers include a humidifier as a standard of care with PAP devices, which should not increase resource use for most patients. However, use of a humidifier can place financial burden on some patients that have difficulties in affording distilled water or the replacement of humidifier chambers. The TF judged that resource use for humidification is warranted to reduce side effects from PAP therapy.

4.8 Educational and behavioral interventions with CPAP vs. CPAP alone for the treatment of adult patients with OSA

4.8ai We recommend that educational interventions be given prior to initiation of PAP therapy in adults with OSA. (STRONG)

4.8aII We suggest that behavioral and/or troubleshooting interventions be given during initiation of PAP therapy in adults with OSA. (CONDITIONAL)

Remarks: This recommendation is based on interventions defined as follows:

Educational interventions: Interventions focused primarily on providing information prior to initiation of PAP about what obstructive sleep apnea (OSA) is, its downstream consequences, what PAP therapy is and the potential benefits of PAP therapy.
Behavioral interventions: Interventions focused on behavior change prior to and during initiation of PAP related to use of PAP therapy using strategies such as cognitive behavioral therapy or motivational enhancement.

Troubleshooting interventions: Interventions focused on close patient communication to identify PAP-related problems and to initiate potential solutions during initiation of PAP.

The intervention period may include interactions prior to, during and after PAP titration and follow-up.

4.8b Summary
The TF examined whether educational, behavioral, or troubleshooting interventions versus no intervention prior to or during PAP treatment improves the critical outcome of adherence. Quality of life was initially considered a critical outcome, however none of the accepted studies reported on this outcome. Meta-analyses demonstrated a clinically significant improvement in PAP adherence with all three types of interventions. The overall quality of evidence was moderate due to imprecision. The potential harms of each of these interventions are minimal. The potential burdens to the patient are negligible for educational interventions but include the time required to receive the intervention and the cost of the additional care for the more intensive behavioral and troubleshooting interventions. The TF determined that the benefits of behavioral and troubleshooting interventions likely outweigh the potential harms and burdens in most patients, while the benefits of educational interventions more certainly outweigh potential harms and burdens. Based on clinical experience, the TF determined that the improvement in adherence from all three interventions would be valued by most patients. Furthermore, the TF determined patients would value the feelings of mastery and resulting psychological well-being afforded by these interventions. As such, the TF determined that the vast majority of well-informed adult patients with OSA would prefer an educational intervention be provided with initiation of PAP therapy over initiation of PAP without education. In addition, the TF determined that the majority of well-informed adult patients with OSA would likely prefer a behavioral and/or troubleshooting intervention be given with initiation of PAP therapy over initiation of PAP therapy without any such intervention.

4.8c Discussion
A total of 16 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 to improve PAP adherence, sleepiness, and QOL.\textsuperscript{169, 207-221} Data were not available to assess the effect of these interventions on sleepiness and quality of life. 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 to a substantial degree 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 5 RCTs identified that had a comparison of a pure educational intervention versus standard of care, 6 RCTs that had a comparison of a behavioral intervention versus standard of care, and 9 RCTs that had a comparison of a troubleshooting with education intervention versus standard of 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 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 S98 through Figure S102. Summary of Findings tables are also included in the supplemental material, Table S12 through Table S14. A summary of the evidence for each outcome for each intervention is provided below.

**Adherence (Educational Interventions):**

A total of 5 RCTs were identified assessing the impact of a pure educational intervention as an adjunct to PAP therapy to improve adherence with PAP. The delivery of education varied substantially and included being given written materials, watching a video, or face-to-face didactic sessions. Studies were from several countries. All studies included subjects with a mean AHI in the severe range and follow-up ranged from 1 month to 1 year. Meta-analysis of all 5 studies demonstrated a clinically significant difference in PAP usage of 0.7 hours/night (95% CI: 0.2 to 1.3 hours/night) (see supplemental material, Figure S98). One trial was excluded from 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. 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 2 RCTs demonstrated a clinically significant difference in odds of PAP usage >4 hours per night, with an odds ratio of 1.5 (95% CI: 0.7 to 3.2) (see supplemental material, Figure S99). Overall, these results demonstrate a clinically significant improvement in PAP adherence with an educational intervention. 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. 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. Populations studied included those from several countries. A meta-analysis of all 6 RCTs demonstrated a clinically significant difference in PAP usage of 1.2 hours/night (95% CI: 0.3 to 2.0 hours/night) (see supplemental material, Figure S100). Similarly, a meta-analysis of 5 of these RCTs reporting on mean PAP usage >4 hours per night found the behavioral interventions were associated with a clinically significant increased odds ratio of 3.1 (95% CI: 1.7 to 5.9) for being adherent (see supplemental material, Figure S101). Overall, these results demonstrate a clinically important improvement in PAP adherence with behavioral interventions. 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.\(^{169, 213, 215-221}\) 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 patients reporting problems, at least one\(^{221}\) used objective data obtained from the PAP device itself. Studies included patients from several countries and follow-up assessments ranged from 1 month to 1 year. Meta-analysis demonstrated a clinically significant difference in PAP usage of 0.7 hours/night (95% CI: 0.2 to 1.1 hours/night) (see supplemental material, Figure S102). 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 vs 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.\(^{143}\) In addition, increased knowledge and mastery of CPAP therapy would lead to improvements in psychological well-being. Educational interventions, which are 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 all 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 comparing educational, troubleshooting, and behavioral interventions. The cost of implementing educational, troubleshooting, and behavioral interventions by healthcare providers will vary depending on the complexity of the intervention. For example, educational interventions can be as simple as 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 needed 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.
4.9 Monitoring vs. no monitoring during the treatment of adult patients with OSA

4.9a We suggest that clinicians use tele-monitoring guided interventions in the routine initiation of PAP therapy in adult OSA patients. (CONDITIONAL)

Remarks: This recommendation is based on interventions defined as follows: Tele-monitoring includes the remote monitoring of PAP parameters such as residual OSA severity, PAP use, unintentional mask leaks, and PAP settings.

4.9b Summary

The TF examined whether interventions guided by monitoring of OSA and PAP parameters during PAP treatment versus no monitoring improve critical outcomes of adherence, sleepiness, and side effects. Quality of life was initially considered a critical outcome, however none of the accepted studies reported on this outcome. Meta-analyses demonstrated a clinically significant improvement in adherence with use of tele-monitoring. PAP-associated side effect severity scores tended to be lower with tele-monitoring guided intervention although these differences were not clinically significant. The overall quality of evidence was low due to imprecision. The potential harms of remote monitoring guided interventions are small, primarily related to potential loss of privacy. Substantial heterogeneity in how tele-monitoring guided interventions are implemented could lead to substantial increases in costs to healthcare systems, or conversely, may reduce costs if reductions in healthcare utilization substantially offset the investment in tele-monitoring systems. No cost effectiveness studies were identified during the literature review. Nevertheless, the TF determined that the benefits of tele-monitoring guided adherence interventions likely outweigh the potential harms and burdens in most patients. Based on clinical experience, the TF determined that the improvement in adherence would be valued by most patients. The TF also determined that the majority of well-informed adult patients with OSA would prefer enrollment in such a system over treatment without such an intervention.

4.9c Discussion

A total of 2 randomized controlled trials (RCTs) were identified that evaluated the use of an intervention to improve adherence and sleepiness triggered by data collected from remote monitoring of positive airway pressure (PAP) usage versus no such system as an adjunct to PAP therapy for the treatment of adults with OSA. Outcomes assessed included adherence, sleepiness, QOL and PAP-associated side effects. In reviewing studies assessing the impact of a tele-monitoring guided PAP adherence intervention, the triggers for intervention and the intensity of the intervention used when poor usage patterns were identified across studies varied resulting in likely heterogeneity of results. For example, one study reviewed PAP information daily and contacted patients when the mask leak was greater than 40 L/m for more than 30% of the nights, for <4 hours of PAP use after two nights, a 90th percentile pressure > 16 cm H2O, or residual AHI > 10 events/h and implemented over the phone or in person solutions. The other study used a collaborative management approach and contacted patients when PAP adherence was < 4 hours, AHI > 10 events/h, and/or mask leak > 0.4L/s that were addressed over the phone or with an in-person visit. Nevertheless, meta-analyses were performed to assess the efficacy of such an intervention 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 S103 and Figure S104). Meta-analysis demonstrated a clinically significant improvement in adherence with the use of tele-monitoring. A Summary of Findings table is also
included in the supplemental material, Table S15. A summary of the evidence for each outcome is provided below.

**Adherence:**
The efficacy of an adherence intervention guided by remote monitoring of PAP therapy to improve PAP adherence was evaluated using a meta-analysis of 2 RCTs that reported on hours per night of PAP usage.\(^{221, 223}\) These studies used data from the PAP machine to guide the intervention.\(^{221, 223}\) The studies enrolled newly diagnosed OSA patients with minimal co-morbidity and follow-up was short ranging from 1 to 3 months. Both studies were from North America. The meta-analysis demonstrated a clinically significant increase in PAP usage of 1.4 hours per night (95% CI: 0.5 to 2.2 hours/night) (see supplemental material, Figure S103). A potential explanation for the increase in adherence with tele-monitoring is access to real-time assistance by 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 in their care or to their health care provider.\(^{221}\) These mechanisms have yet to be fully evaluated. Overall, the analyses demonstrated a clinically significant improvement in adherence with tele-monitoring. The quality of evidence for PAP adherence was moderate due to imprecision.

**Sleepiness:**
The efficacy of a tele-monitoring guided intervention as part of PAP therapy in adult OSA patients was evaluated using a meta-analysis of two RCTs that reported on subjective sleepiness using the ESS.\(^{221, 223}\) Both 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 tele-monitoring guided intervention as compared to no such intervention (see supplemental material, Figure S104). Overall, the analyses did not demonstrate a clinically significant improvement in sleepiness with tele-monitoring. The quality of evidence for subjective sleepiness was low due to imprecision.

**Side Effects:**
Only one RCT was identified that assessed the impact of a tele-monitoring guided PAP adherence intervention on PAP-induced side effects.\(^{221}\) As such, no meta-analysis was performed. This one study of 54 patients found no clinically significant improvement in CPAP discomfort, difficulty exhaling, mask leaks, or nasal congestion. Improvements in dry mouth were identified (see supplemental material, Table S15). The quality of evidence was low due to imprecision.

**Quality of Life:**
The efficacy of adding a tele-monitoring guided PAP intervention to PAP therapy on QOL in adult OSA patients was evaluated from a single RCT that reported on QOL using the FOSQ.\(^{223}\) The intervention relied on self-reported problems from the patient to guide management rather than data from the PAP device. The study demonstrated no clinically significant increase in FOSQ with the tele-monitoring guided intervention (see supplemental material, Table S15).\(^{223}\) The quality of evidence for QOL was low due to imprecision.

**Overall Quality of Evidence:**
The outcomes of adherence, 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 low due to imprecision.
**BENEFITS VS HARMS:**

The benefits of a tele-monitoring 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 tele-monitoring 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 communications with a health care provider or healthcare medical equipment company may be perceived as intrusive. Overall, the TF deemed the harms of tele-monitoring were minor for most patients and outweighed by the potential benefits.

**PATIENT VALUES AND PREFERENCES:**

Based on their clinical expertise, the TF judged that the benefits of tele-monitoring guided adherence interventions outweigh the harms, and that the majority of patients would want a tele-monitoring system as part of a PAP treatment program given the improved PAP adherence.

**RESOURCE USE:**

For some health systems and clinical practices, there may be increased costs associated with a tele-monitoring adherence intervention. Some tele-monitoring 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 in need for less frequent healthcare visits. The TF did not identify cost-effectiveness studies comparing tele-monitoring to no tele-monitoring intervention for PAP. The TF judged that resource use for tele-monitoring interventions is warranted to ensure adequate PAP adherence.

6.0 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 is needed to determine the efficacy of PAP therapy to improve key outcomes currently associated with OSA including impaired cognition and mood, reduced QOL, increased MVAs, as well as hypertension, CV disease, and metabolic disorders (e.g. 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 subjects without baseline deficits in neurocognitive function. Therefore, RCTs targeted at addressing whether PAP improves neurocognitive outcomes in OSA patients 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, anxiety, or impaired QOL should be a priority.

**Motor Vehicle Accidents:**

The quality of evidence regarding reductions in MVA 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 (e.g. 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 OSA patients are most likely to experience a reduction in MVA risk from CPAP. Although randomized trials in this area are not feasible, larger scale, prospective studies with appropriate control groups and objective ascertainment of MVA through insurers or registries could and should be performed to further inform development of appropriate public policies. Studies in commercial motor vehicle drivers are specifically needed given that public policy decisions focus on this population. 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 OSA patients.

Hypertension:
In the area of 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 (e.g. 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 OSA patients derive similar benefits to sleepy OSA patients 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,122, 123 future trials should explore how OSA screening and treatment with PAP might best integrate into current guidelines in the approach to treating hypertension.

Cardiovascular Events and Metabolic Outcomes:
The TF found conflicting data regarding PAP-related effects for CV events and no significant PAP-related effects for the metabolic outcomes reviewed (i.e. fasting glucose, hemoglobin A1C). Non-randomized data suggest that PAP reduces CV events, while recent 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 (e.g. 3-4 hours per night of PAP use), the severity of OSA in the patient sample, and restricting 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 CV events. Efficacy studies on the effects of PAP on metabolic disorders including diabetes, but in particular 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 for adequately powered studies. Studies incorporating known (education, behavioral therapy, tele-monitoring and troubleshooting, humidification, 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 RCTs and observational studies are needed to determine whether treatment of OSA with PAP improves neurocognitive, CV, and metabolic outcomes in these under-represented groups. Another area of research priority includes the development of methods to increase PAP adherence in groups that traditionally have low adherence (e.g. African Americans, adolescents, or the cognitively impaired) to ensure health equity. Patient groups with co-morbidities that are highly prevalent for 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 vs. 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 CPAP, may not be as robust with APAP – whether this difference has clinical relevance is unclear. In addition, studies are needed in patients with co-morbid conditions commonly seen in sleep clinic populations (e.g. 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 vs in-lab 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 bi-level PAP algorithms may be preferable to PAP 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, contraindication, and outcomes of BPAP in non-adherent patients or patients deemed to be at high risk of non-adherence 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 hours/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 more adherent to non-PAP therapies for co-morbid disorders (e.g. beta-blockers for CAD, statins for hyperlipidemia, or anti-hypertensives for hypertension) which may explain findings of the improved OSA-related
outcomes. Given this, substantial work remains to be done to determine the optimal combination of strategies to maximize adherence including PAP-related technologies (e.g. modified pressure profile, heated humidification, cloud-based monitoring systems), mask interfaces, educational and behavioral interventions, and tele-monitoring-based troubleshooting interventions. Effective adherence approaches can then be deployed in future randomized controlled trials 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 sleep apnea 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 (e.g. all patients, non-adherent 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 vs CPAP, mask type, humidification and modified pressure profiles improve adherence and clinically relevant outcomes in poorly adherent patients or patient at high risk of non-adherence are needed.

Significant progress has been made in examining educational, behavioral, and tele-monitoring strategies that can improve adherence to PAP. Future research should focus on strategies for identification of patient-factors that place them at risk for non-adherence prior to PAP use; and the development and validation of specific algorithms (e.g. number of hours, significant leaks, residual AHI, residual central events, or some combination) to utilize with tele-monitoring in order to identify non-adherent 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.

**Disclosures**

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. No other task force members had any relevant conflicts of interest to disclose.

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REFERENCES


2215 58. Engleman HM, Martin SE, Deary IJ, Douglas NJ. Effect of continuous positive airway pressure treatment on daytime function in
2217 59. Ip MS, Tse HF, Lam B, Tsang KW, Lam WK. Endothelial function in obstructive sleep apnea and response to treatment. Am J
2219 60. Nguyen PK, Katikireddy CK, McConnell MV, Kushida C, Yang PC. Nasal continuous positive airway pressure improves
2220 myocardial perfusion reserve and endothelial-dependent vasodilation in patients with obstructive sleep apnea. J Cardiovasc Magn
2222 61. Craig SE, Kohler M, Nicoll D et al. Continuous positive airway pressure improves sleepiness but not calculated vascular risk in
2223 patients with minimally symptomatic obstructive sleep apnoea: the MOSAIC randomised controlled trial. Thorax.
2224 2012;67(12):1090-1096.
2227 63. Drager LF, Bortolotto LA, Figueiredo AC, Krieger EM, Lorenzi GF. Effects of continuous positive airway pressure on early signs
2229 64. Drager LF, Pedrosa RP, Diniz PM et al. The effects of continuous positive airway pressure on prehypertension and masked
2231 65. Lozano L, Tovar JL, Sampol G et al. Continuous positive airway pressure treatment in sleep apnea patients with resistant
2233 66. Pedrosa RP, Drager LF, de PaulaLK, Amaro AC, Bortolotto LA, Lorenzi-Filho G. Effects of OSA treatment on BP in patients with
2235 67. Kaneko Y, Floras JS, Usui K et al. Cardiovascular effects of continuous positive airway pressure in patients with heart failure and
2239 69. Cross MD, Mills NL, Al-Abri M et al. Continuous positive airway pressure improves vascular function in obstructive sleep
2241 70. Egea CJ, Aizpuru F, Pinto JA et al. Cardiac function after CPAP therapy in patients with chronic heart failure and sleep apnea: a
2243 71. Jones A, Vennelle M, Connell M et al. The effect of continuous positive airway pressure therapy on arterial stiffness and
2244 endothelial function in obstructive sleep apnea: a randomized controlled trial in patients without cardiovascular disease. Sleep Med.
2245 2013;14(12):1260-1265.
2246 72. Pepperell JC, Ramdasssingh-Dow S, Crossthwaite N et al. Ambulatory blood pressure after therapeutic and subtherapeutic nasal
2248 73. Ryan CM, Usui K, Floras JS, Bradley TD. Effect of continuous positive airway pressure on ventricular ectopy in heart failure
2250 74. Barbe F, Duran-Cantolla J, Sanchez-de-la-Torre M et al. Effect of continuous positive airway pressure on the incidence of
2251 hypertension and cardiovascular disease in patients with obstructive sleep apnea: a randomized controlled trial. JAMA.
2253 75. Parra O, Sanchez-Armengol A, Capote F et al. Efficacy of continuous positive airway pressure treatment on 5-year survival in
2256 Outcomes in Coronary Artery Disease Patients with Non-Sleepy Obstructive Sleep Apnea: The RICCADS Randomized
2257 Controlled Trial. Am J Respir Crit Care Med. 2016.
2258 77. Mansfield DR, Gollogly NC, Kaye DM, Richardson M, Bergin P, Naughton MT. Controlled trial of continuous positive airway
2260 78. Smith LA, Vennelle M, Gardner RS et al. Auto-titrating continuous positive airway pressure therapy in patients with chronic heart
2262 79. Usui K, Bradley TD, Spaak J et al. Inhibition of awake sympathetic nerve activity of heart failure patients with obstructive sleep
2264 80. Barbe F, Duran-Cantolla J, Capote F et al. Long-term effect of continuous positive airway pressure in hypertensive patients with
2266 81. Craig S, Kyliintreas I, Kohler M et al. Effect of CPAP on Cardiac Function in Minimally Symptomatic Patients with OSA: Results
2270 83. Kushida CA, Nichols DA, Holmes TH et al. Effects of continuous positive airway pressure on neurocognitive function in
2273 2016.
2274 85. Muxfeldt ES, Margallo V, Costa LM et al. Effects of continuous positive airway pressure treatment on clinic and ambulatory blood
2275 pressures in patients with obstructive sleep apnea and resistant hypertension: a randomized controlled trial. Hypertension.


Marshall NS, Neill AM, Campbell AJ. Randomised trial of compliance with flexible (C-Flex) and standard continuous positive airway pressure for severe obstructive sleep apnea. Sleep Breath. 2008;12(4):393-396.


