Treatment of Central Sleep Apnea in Adults:

An American Academy of Sleep Medicine systematic review, meta-analysis, and GRADE assessment.

Introduction: This systematic review provides supporting evidence for the accompanying clinical practice guideline on the treatment of central sleep apnea syndrome in adults.

Methods: The American Academy of Sleep Medicine commissioned a task force of experts in sleep medicine. A systematic review was conducted to identify studies that compared the use of positive airway pressure therapies (PAP), non-PAP therapies, and pharmacological treatment to no treatment to improve patient-important outcomes. Statistical analyses were performed to determine the clinical significance of using various interventions to treat CSA in adults. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) process was used to assess the evidence for making recommendations.

Results: The literature search resulted in 6,662 articles out of which 100 articles provided data suitable for statistical analyses. The task force provided a detailed summary of the evidence along with the certainty of evidence, the balance of benefits and harms, patient values and preferences, and resource use considerations.

Keywords: central sleep apnea, central sleep-disordered breathing, therapy, systematic review

INTRODUCTION

This systematic review is intended to provide supporting evidence for a clinical practice guideline (CPG) on the treatment of central sleep apnea syndromes (CSA) in adults and update the evidence review conducted for the previously published American Academy of Sleep Medicine (AASM) guideline on the treatment of CSA in 2012[1] and updated in 2016.[2]

BACKGROUND

CSA is a significant clinical problem that contributes to adverse outcomes independently or in co-morbid disorders.[3-8] CSA is a manifestation of breathing instability, either as a primary condition, or in association with several co-morbid conditions including CSA due to heart failure, CSA due to medication or substance use, treatment-emergent CSA, and CSA due to a medical condition or disorder.[9] The occurrence of CSA in the context of an underlying disease state underscores the critical need to address associated conditions as an integral part of CSA management.

CSA results from abolished ventilatory motor output, manifesting as an absence, or near absence, of flow and effort on polysomnography (PSG). The fundamental cause of CSA is removal of wakefulness drive to breathe, rendering ventilatory motor output dependent on the metabolic ventilatory control system. Accordingly, non-rapid eye movement (NREM) sleep unmasks a highly sensitive and reproducible hypocapnic apneic threshold, resulting in central apnea when the level of partial pressure of carbon dioxide ($PaCO_2$) drops below this threshold.[10] Experimentally, central apnea in sleeping humans can be induced using nasal mechanical ventilation to reduce $PaCO_2$. The magnitude of hypocapnia required to induce central apnea is referred to as the "CO_2 reserve;" a narrow CO_2 reserve reflects high loop gain and hence increased propensity to central apnea.[3]

Hypocapnia is a potent mechanism of central apnea and must be of sufficient magnitude and duration to affect medullary rhythmogenesis. The duration of hyperventilation is a critical determinant of central apnea, given the time required for decreased PaCO2 to reach the medulla. This may explain the lack of central apnea following

induced brief arousals in sleeping humans,[11] and the dearth of studies demonstrating the efficacy of suppressing arousals for the treatment of CSA. Therefore, the contribution of arousals to the genesis of central apnea and the impact of suppressing arousals on central apnea severity await empirical proof.

Central apneas rarely occur as a single event, other than post-sigh events, but as recurrent cycles of apnea or hypopnea, alternating with hyperpnea, reflecting the high gain of the closed-loop cycle that characterizes ventilatory control. This concept is described using the engineering concept of "loop gain," in which the response of the ventilatory system to changing arterial CO_2 represents chemoreflex sensitivity (the controller), and the effectiveness of the lung/respiratory system in lowering end tidal CO_2 in response to hyperventilation represents the plant.[12] Changes in either parameter alters the magnitude of hypocapnia required to induce central apnea. Central apnea is associated with several consequences that conspire to promote further breathing instability. Due to the inertia of the ventilatory control system, once ventilatory motor output completely ceases, rhythmic breathing does not resume at eupneic $PaCO_2$.[13]

CSA may also influence the development of obstructive sleep apnea (OSA). For example, individuals with unfavorable upper airway anatomy are dependent on ventilatory motor output to preserve upper airway patency. Accordingly, pharyngeal obstruction develops when the ventilatory drive reaches a nadir during induced periodic breathing.[14] Studies using upper airway imaging have demonstrated that central apnea and hypopnea result in pharyngeal narrowing or occlusion in normal individuals and patients with central apnea.[15, 16] Pharyngeal collapse, combined with mucosal and gravitational factors, may impede pharyngeal opening and necessitate a substantial increase in respiratory drive that perpetuates breathing instability.

The pathophysiologic overlap between central and obstructive apnea provided a physiologic rationale to "repurpose" continuous positive airway pressure (CPAP) for the treatment of central apnea. CPAP therapy was found to be efficacious by Issa and Sullivan[17] in an observational study of patients with CSA. One possible mechanism of positive airway pressure (PAP) response is the relief of upper airway narrowing or obstruction during central apnea and hypopneas, decreased frequency of post-apneic arousals and ventilatory overshoot.[16] Other potential mechanisms include increased lung volumes, reduced plant gain, and reduced loop gain.[18] However, CPAP rarely eliminates CSA, and most studies have noted residual disease.[1] The development of adaptive servo-ventilation (ASV) provided a new therapeutic tool that could support ventilation while dampening ventilatory overshoot.

Arousals from sleep and episodic desaturation are immediate physiologic consequences that may perpetuate breathing instability. Thus, mitigation of arousals and dampening of hypoxia have emerged as potential therapeutic approaches. Triazolam was associated with decreased central apnea index and brief arousals in a small observational study[19]; these data provided the basis for testing hypnotics as a potential CSA treatment. In another observational study, central apneas were reduced by oxygen therapy irrespective of the presence or absence of heart failure or Cheyne-Stokes respiration. These studies launched the era of treating CSA by mitigating its immediate consequences and dampening post-apneic overshoot and subsequent hypocapnia.

The plasticity of the propensity to central apnea, as evidenced by the CO_2 reserve, provides another physiologic pathway for treating central apnea. The first agent tested for this purpose was acetazolamide, which aimed to acidify the cerebrospinal fluid (CSF), thus increasing ventilatory motor output. Multiple studies have tested the potential therapeutic effect of acetazolamide in CSA due to various etiologies.[20-23] A more recent innovation was the advent of phrenic nerve stimulation as a direct approach to restoring respiration in patients with central apnea. Controlled studies have demonstrated evidence of this intervention's continued efficacy, an encouraging observation while awaiting studies addressing long-term outcomes and real-world experience.

It is important to note that most treatments for CSA lead to improvement but rarely eliminate it entirely. This differs from OSA treatments, where success is typically defined by fully or nearly normalizing breathing. One possible explanation is that multiple pathways can lead to central apnea—a concept known as equifinality, in which different mechanisms can produce the same outcome, in this case, central apnea.

Central sleep apnea and periodic breathing are common in non-acclimatized individuals ascending to high altitudes, affecting most individuals above 2,500 – 3,000 meters. The underlying mechanism is hypobaric hypoxia leading to hyperventilation and subsequent hypocapnia. Typical symptoms include fragmented sleep, hypoxemia, and frequent arousal. CSA and periodic breathing typically resolve with acclimatization over days to weeks, but the timeline varies. Adaptation occurs among residents living at high altitude (e.g., Andean, Tibetan, Ethiopian populations). Typical physiologic adaptations include blunted chemosensitivity. However, periodic breathing may persist in individuals living at very high altitude (>3,500 meters).

Treatment strategies for CSA and periodic breathing at high altitude vary depending on the severity, duration of exposure, and individual patient factors. Most studies have focused on acetazolamide and supplemental oxygen, with limited evidence regarding positive pressure modalities. Acetazolamide, a carbonic anhydrase inhibitor, is one of the most widely used medications to prevent and manage high-altitude periodic breathing and central apnea. It works by inducing mild metabolic acidosis, stimulating ventilation, and reducing the frequency of apnea episodes. Studies have shown that acetazolamide is effective for acute exposure to high altitude and chronic cases in residents living at altitude. Supplemental oxygen can mitigate hypoxemia, the primary trigger for CSA at altitude. This approach is often recommended for climbers or those temporarily visiting high altitudes and effectively reduces central apneas and periodic breathing. Overall, the literature on CSA at high altitude remains limited. Gradual ascent and prolonged acclimatization mitigate the risk of central apnea over time.

Optimal treatment of CSA requires combining treatment of CSA with robust management of underlying or co-morbid conditions. For example, optimal treatment of heart failure, using medications, devices, or surgical interventions, may significantly alleviate CSA associated with HF.[24-26] Similarly, opioid discontinuation is likely to ameliorate CSA, although it has not been adequately studied. Finally, seeking lower altitude to treat high altitude CSA is therapeutic. In the case of persistent treatment-emergent central sleep apnea (TECSA), most of the large studies and registries include treatment with CPAP or ASV. Nevertheless, there has not been an effective treatment for persistent CSA that is widely accepted by patients or providers. Furthermore, there is limited information on the symptomatology of the problem and acceptable outcomes of therapy, further hindering investigations in this area.

The aims of the present systematic review were to (1) assess the efficacy of PAP therapies, non-PAP therapies, and pharmacological treatment for the treatment of CSA in adults, (2) to evaluate the potential for adverse effects of these interventions, and (3) to identify gaps in the treatment research literature and offer recommendations for optimizing quality and uniformity of future investigations.

METHODOLOGY

Expert Task Force

The AASM commissioned a task force (TF) of sleep medicine clinicians with expertise in the treatment of CSA. 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 these documents. In accordance with the AASM's

COI policy, TF members with a Level 1 conflict were not allowed to participate. TF members with a Level 2 conflict were required to recuse themselves from any related discussion or writing responsibilities. All relevant conflicts of interest are listed in the Disclosures section.

PICO Questions

PICO (Patient, Intervention, Comparison, and Outcomes) questions were developed by the TF based on a review of the existing AASM practice parameters on the treatment of CSA and a review of systematic reviews, meta-analyses, and guidelines published since 2012 and 2016. The AASM Board of Directors approved the final list of questions presented in **Table 1** before the literature searches were performed. Through consensus, the TF then developed a list of patient-oriented, clinically relevant outcomes to determine the efficacy of the interventions. The TF rated the relative importance of each outcome to determine which outcomes were critical versus important for decision-making. A summary of these outcomes by PICO is presented in **Table 2**.

The TF set a clinical significance threshold (CST) for each outcome to determine whether the mean differences between treatment and control or before and after treatment in the outcomes assessed were clinically significant. 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. CSTs were determined based on a TF literature review of commonly used thresholds. When no clearly established threshold values could be determined, the TF used their clinical judgment and experience to establish a CST based on consensus. A summary of the CSTs for the clinical outcome measures is presented in **Table 3**.

Table 1 – PICO Questions

1	**PATIENT OR PROBLEM:** Adults with primary central sleep apnea (CSA), adults with CSA due to heart failure, adults with CSA due to a medical condition or disorder, adults with CSA due to a medication or substance, adults with treatment emergent CSA **INTERVENTIONS:** Positive airway pressure therapies - Continuous positive airway pressure (CPAP), bilevel positive airway pressure (BPAP), BPAP with a backup rate, adaptive servo-ventilation (ASV) Non-PAP therapies - Oxygen therapy, transvenous phrenic nerve stimulation, positional therapy Pharmacological therapies - Carbonic anhydrase inhibitors (acetazolamide), hypnotics (zolpidem, temazepam, triazolam) **COMPARISON:** Placebo, standard care, or no treatment **OUTCOMES:** Critical - Excessive sleepiness, disease severity, cardiovascular disease/stroke, mortality, hospitalization, sleep quality (patient reported) Important - daytime functioning or work performance, quality of life, fatigue, vigilance/alertness, insomnia, sleep architecture (polysomnography), cognitive functioning
2	**PATIENT OR PROBLEM:** Adults with CSA due to high altitude periodic breathing (recent ascent >2,500 meters) **INTERVENTION:** Positive airway pressure therapies - CPAP, BPAP, BPAP with a backup rate, ASV

	Non-PAP therapies - Oxygen therapy, positional therapy Pharmacologic therapies - Carbonic anhydrase inhibitors (acetazolamide), theophylline, hypnotics (zolpidem, temazepam, triazolam) **COMPARISON:** No treatment **OUTCOMES:** Critical - Excessive sleepiness, disease severity, daytime functioning or work performance, quality of life Important - sleep architecture (polysomnography)

Table 2 – Outcomes by PICO Question

Outcomes	PICO Question #	
	1	2
Excessive Sleepiness	√*	√*
Disease Severity	√*	√*
Cardiovascular Disease	√*	-
Mortality	√*	-
Hospitalization	√*	-
Sleep Quality (Patient Reported)	√*	-
Daytime Functioning or Work Performance	√	√*
Quality of Life	√	√*
Fatigue	√	-
Sleep Architecture (PSG)	√	√
Adverse Effects	√*	-

*Outcomes considered critical for decision-making.
-Not an outcome for the PICO question

Table 3 – Summary of Clinical Significance Thresholds for Outcome Measures

Outcome Measure	Clinical Significance Threshold†
Excessive sleepiness	
Epworth Sleepiness Scale (ESS)	-2 points[27, 28]
Maintenance of Wakefulness Test (MWT)	+2 minutes
Stanford Sleepiness Scale (SSS)	-1 point
Disease severity	
Apnea-hypopnea index (AHI)	≥50% reduction from baseline
Central apnea index (CAI)	≥50% reduction from baseline
Central apnea-hypopnea index (CAHI)	≥50% reduction from baseline
Oxygen desaturation index (ODI)	≥50% reduction from baseline
Oxygen saturation <90%[a]	≥50% reduction from baseline
Cardiovascular disease/stroke	
Left ventricular ejection fraction (LVEF)	+5% (absolute)
6-minute walk distance (6MWD)	+32 meters
B-type natriuretic peptide	≥50% reduction from baseline
Heart rate	No CST
Systolic blood pressure	-2 mmHg

Diastolic blood pressure	-1 mmHg
New York Heart Association (NYHA) classification	No CST
Mortality	
All-cause reported deaths	Risk ratio of 0.8
Hospitalization	
Incidence rate	Risk ratio of 0.9
Sleep quality (patient reported)	
Pittsburgh Sleep Quality Index (PSQI)	-3 points[29]
Sleep Sufficiency Index	No CST
Daytime functioning or work performance	
Short form questionnaire-36 (SF-36)	+3 points
Lake Louise acute mountain sickness (AMS) Score	No CST
Trail making test	No CST
Duke activity status index	No CST
Specific activity scale	No CST
Minnesota living with heart failure (MLHF)	No CST
Four choice reaction time	No CST
Paced Auditory Serial Addition Test (PASAT) 2	No CST
PASAT 4	No CST
Quality of life	
Patient global assessment	No CST
Quality of Life	No CST
Profile of Mood State-Adolescent (POMS-A)	No CST
SF-12	+4 points
EuroQoL (EQ)-5D	No CST
Fatigue	
Chronic Heart Failure Questionnaire	+2 points (0.5 points per question)
Subjective questionnaire	No CST
Sleep architecture (PSG)	
Total sleep time (TST, minutes)	+15 minutes
Sleep efficiency (SE)	+10%
Rapid eye movement (REM, % of TST)	+5% of TST
Sleep stage N1 (% of TST)	-5% of TST
Sleep stage N2 (% of TST)	-5% of TST
Slow wave sleep (SWS, % of TST)	+5% of TST
Arousal index	≥25% reduction from baseline or reduction to ≤12 events/hr

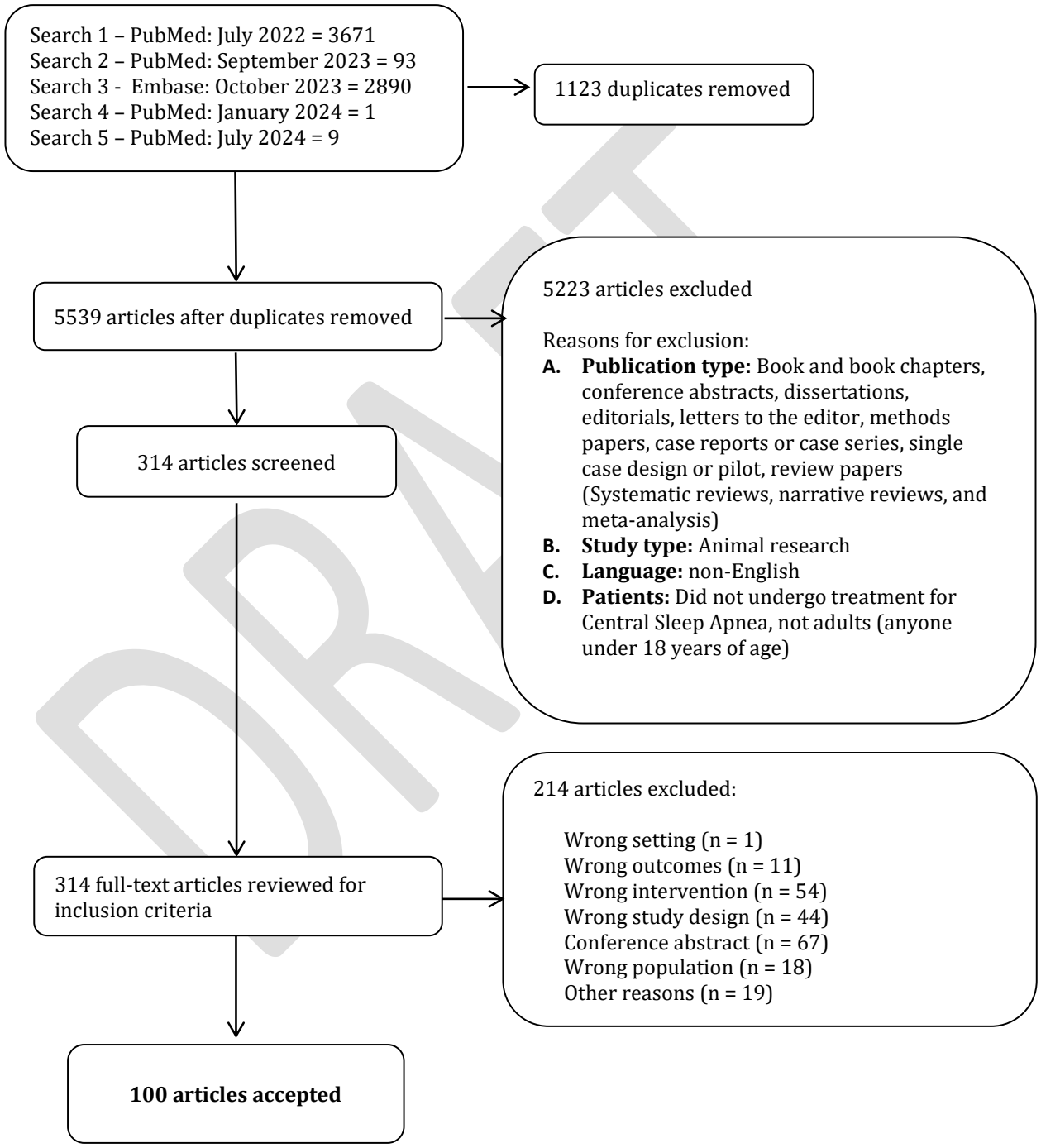
† The clinical significance thresholds are for comparison of pre- versus posttreatment effects as well as between intervention and control. [a] percent time in bed.

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. The TF performed literature searches to address each PICO question using the PubMed database (see

Figure 1). The key terms, search limits, and inclusion/exclusion criteria specified by the TF are detailed in the supplemental material.

Figure 1. Evidence flow diagram



Statistical and Meta-analysis and Interpretation of Clinical Significance

Meta-analysis was performed on outcomes of interest, when possible, for each PICO question (see **Table 1**). Comparisons of interventions to controls and/or assessment of efficacy before and after treatment of CSA were performed. Posttreatment data from each arm were used for meta-analysis of RCTs when change values were not reported and baseline values between the two study groups were statistically similar. Single-arm (within-group) pre- and posttreatment data that addressed the PICO question were extracted from RCTs that published findings on multiple treatment groups and were included in the meta-analyses with observational studies. Pre- and posttreatment data were used for meta-analyses of observational studies. The pooled results for each continuous outcome measure were usually expressed as the mean difference between the intervention and control for RCTs or pretreatment versus posttreatment for observational studies; however, for some outcomes where individual component scales were pooled, a standardized mean difference (SMD) or effect size was determined. The pooled results for dichotomous outcome measures were expressed as the risk ratio or risk difference between the intervention and comparator or pre- versus posttreatment. The relative risk data were converted to an absolute risk estimate expressed as the number of events/1000 patients treated. The analyses were performed using Review Manager 5.3 software by pooling data across studies for each outcome measure. Analyses were performed using either a fixed or 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 size, or the risk difference for dichotomous outcomes, of each treatment approach to the CST (see **Table 3**).

GRADE Assessment for Developing Recommendations

The evidence was assessed according to the GRADE process for the purposes of making clinical practice recommendations. The TF considered the following four GRADE domains: quality of evidence, balance of beneficial and harmful effects, patient values and preferences, and resource use, as described below:

1. **Quality of evidence:** Based on an assessment of the overall risk of bias (randomization, blinding, allocation concealment, selective reporting), imprecision (95% confidence interval crosses the CST and/or sample size < 200 participants), inconsistency ($I^2 \geq 50\%$), indirectness (study population vs target patient population), and risk of publication bias, the TF determined their overall confidence that the estimated effect found in the body of evidence was representative of the true treatment effect that typical patients with sleep-disordered breathing would see. The certainty of the evidence was based on outcomes that the TF deemed critical for decision making; important outcomes were not considered when determining the overall certainty of evidence.
2. **Benefits vs harms:** Based on the analysis of adverse effects reported within the accepted literature and on the clinical expertise of the TF, the TF determined whether the beneficial outcomes of using each intervention outweighed any harms.
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 most patients, and if patients would use the intervention based on the relative harms and benefits identified.
4. **Resource use:** Based on the clinical expertise of the TF members and any data published on the topic relevant to resource use, the TF determined whether the accessibility and costs associated with each intervention compared favorably to those associated with alternative interventions. Information on costs to both patients and the health care system, impact on health equity, acceptability, and feasibility to implement the interventions were considered.

A summary of each GRADE domain is provided after the detailed evidence review for each PICO question.

Public Comment and Final Approval

Drafts of the systematic review and accompanying guideline were made available for public comment for a four-week period on the AASM website. AASM members, the general public and other relevant stakeholders were invited to provide feedback on the drafts. The TF took into consideration all the comments received and made decisions about whether to revise the draft based on the scope and feasibility of comments. The public comments and revised documents were submitted to the AASM Board of Directors who subsequently approved the final documents for publication.

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

RESULTS

The aims of the current literature review and data analyses were to address two PICO questions pertaining to the treatment of CSA. Detailed summaries of the evidence identified in the literature searches and the statistical analyses performed by the TF are provided below. For the recommendation process, the TF prioritized data from RCTs. When available, observational data was used to supplement the RCT findings, and these results were included in the analyses. The results discussed below primarily focus on RCT data, except where otherwise noted; the supplemental material includes meta-analyses from all data sources considered. Each evidence summary is accompanied by a discussion of the quality of evidence, balance of benefits and harms, patient values and preferences, and resource use considerations that contributed to the development of the clinical practice recommendations, which are provided in the accompanying clinical practice guideline.

ADULTS WITH CENTRAL SLEEP APNEA

Continuous positive airway pressure (CPAP)

Sixteen RCTs[30-45] and 14 observational studies[46-58] investigated the use of CPAP to improve one or more of the following outcomes: excessive sleepiness, disease severity, cardiovascular disease, hospitalization, mortality, fatigue, or sleep architecture. Of these, the TF used 11 RCTs for decision making in the CPG. Participants in the RCTs had a mean age of 60 years (4% female). The duration of follow-up ranged from one night to one year in the RCTs. The duration of follow-up ranged from one to three months in the observational studies. Meta-analyses were performed to assess the efficacy of CPAP. Single-arm (within-group) data was extracted in eight of the 14 RCTs[38-45] and included in the meta-analyses with observational studies. The meta-analyses and summary of findings table are provided in the supplemental material (Figure S1 through Figure S39; Table S1). A summary of the evidence for each outcome is provided below.

Critical Outcomes

The TF determined the following outcomes to be critical for evaluating the efficacy of CPAP: excessive sleepiness, disease severity, cardiovascular disease, mortality, and hospitalizations. None of the studies identified in our literature review reported data for the following critical outcomes: patient-reported sleep quality.

EXCESSIVE SLEEPINESS: The pooled effect of three RCTs (single arm pre versus posttreatment data)[39-41] did not show a clinically significant reduction in excessive sleepiness measured by the Epworth Sleepiness Scale (ESS) compared to baseline (MD -1.86, 95% CI -3.71 to 0.00; n=42). The duration of patient follow-up after treatment was six weeks to three months (see supplemental material, Figure S1). One study[43] reported excessive sleepiness using the Maintenance of Wakefulness Test (MWT) which showed a clinically significant reduction in excessive sleepiness compared to baseline (MD 5.8, 95% CI 1.63 to 9.97; n=13). The duration of patient follow-up after treatment was six months.

DISEASE SEVERITY: Six RCTs[30-34, 37] reported disease severity measured by Apnea-hypopnea Index (AHI). The analysis showed a clinically significant reduction in AHI in the CPAP group (MD -17.43, 95% -21.01 to -13.86; n=363) resulting in a 57.7% reduction in AHI from baseline for the CPAP group. The duration of patient follow-up after treatment was up to three months (see supplemental material, Figure S2).

One RCT[37] reported disease severity using the Central Apnea Index (CAI). The analysis showed a non-clinically significant reduction in CAI in the CPAP group (MD -17.3, 95% CI -25.76 to -8.84; n=28). There was a 48.3% reduction of CAI from baseline for the CPAP group. The duration of patient follow-up after treatment was one night (see supplemental material, Figure S3). One RCT[37] reported disease severity measured by the Oxygen Desaturation Index (ODI). The analysis showed a non-clinically significant reduction in ODI in the CPAP group (MD -15.6, 95% CI -18.01 to -13.19; n=28). There was a 40.8% reduction of ODI from baseline for the CPAP group. The duration of patient follow-up after treatment was one night (see supplemental material, Figure S4).

CARDIOVASCULAR DISEASE: One RCT[30] reported cardiovascular disease measured by the 6-minute walk test (6MWD). The analysis showed a non-clinically significant improvement in cardiovascular disease, measured by the 6MWD, in the CPAP group compared to control (MD 20.8, 95% CI 6.14 to 35.46; n=258). The duration of patient follow-up after treatment was three months (see supplemental material, Figure S5).

Five RCTs[31-34, 36] reported cardiovascular disease measured by left ventricular ejection fraction (LVEF). The analysis showed a clinically significant improvement in cardiovascular disease, measured by LVEF, in the CPAP group compared to control (MD 5.99, 95% CI 1.85 to 10.12; n=106). The duration of patient follow-up after treatment was from one to three months (see supplemental material, Figure S6).

One RCT[32] reported cardiovascular disease measured by systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR). The analysis did not show a clinically significant improvement in SBP in the CPAP group compared to control (MD 14.6, 95% CI -6.23 to 35.43; n=18). A separate analysis for DBP did not show a clinically significant improvement in the CPAP group compared to control (MD 0.1, 95% CI -12.38 to 12.58; n=18). A third analysis showed a reduction in HR in the CPAP group compared to control (MD -6.5, 95% CI -20.7, 7.7; n=18), however, there was no a priori CST for HR. The duration of patient follow-up after treatment was one month (see supplemental material, Figure S7 to S9).

HOSPITALIZATIONS: One RCT[30] reported hospitalization data, measured by hospital admissions per patient per year. The analysis did not show an improvement in hospitalizations in the CPAP group compared to control (MD 0.05, -0.11 to 0.21; n=258). There was no a priori CST for hospitalizations measured per patient per year. The duration of patient follow-up after treatment was three months (see supplemental material, Figure S10).

MORTALITY: The pooled effect of two RCTs[30, 36] showed a clinically significant reduction in mortality in the CPAP group compared to control (RR 0.87, 95% CI 0.59 to 1.29; n=324) with an absolute risk difference of 19 fewer deaths per 1,000 participants. The duration of patient follow-up after treatment was three months (see supplemental material, Figure S11). For disease severity and cardiovascular disease outcomes, only data from RCTs are reported above. Additional data from the single-arm pre- posttreatment/observational meta-analyses are described in the supplemental material (Figures S12 to S22).

Important Outcomes

The TF determined the following outcome to be an important outcome but not critical for evaluating the efficacy of CPAP to treat adults with CSA: fatigue and sleep architecture.

FATIGUE: Two RCTs[31, 34] reported fatigue data measured by the Chronic Heart Failure Questionnaire (CHFQ) which showed a clinically significant improvement in the CPAP group compared to control (MD 5.02, 95% CI 2.59, 7.45; n=41). The duration of patient follow-up after treatment was three months (see supplemental material, Figure S23).

SLEEP ARCHITECTURE (PSG): Three RCTs[32, 34, 35] reported sleep architecture measured by sleep efficiency (SE) during polysomnography (PSG). The analysis did not show a clinically significant improvement in SE in the CPAP group compared to control (MD -3.3, 95% CI -12.73 to 6.14; n=247). The duration of patient follow-up after treatment was one to three months (see supplemental material, Figure S24).

Six RCTs[31-35, 37] reported sleep architecture measured by total sleep time (TST, minutes), rapid eye movement (REM, %), and slow wave sleep, (SWS, %) during PSG. TST did not show a clinically significant improvement in the CPAP group compared to control (MD 2.42, 95% CI -14.98 to 19.82; n=310). REM (%) did not show a clinically significant improvement in the CPAP group compared to control (SMD -0.09 (95% CI -0.33 to 0.15; n=310). The SMD re-expressed as REM%, showed a mean decrease of -0.65% (95% CI -2.4 to 1.08). SWS (%) showed a clinically significant improvement in the CPAP group compared to control (SMD 0.53, 95% CI 0.02 to 1.03; n=310). The SMD re-expressed as SWS%, showed a mean increase of 5.9% (95% CI 0.22 to 11.74). The duration of patient follow-up after treatment was one to three months (see supplemental material, Figure S25-27).

Two RCTs[33, 35] reported sleep architecture measured by sleep stage N1 (%), PSG and sleep stage N2 (%), PSG. The analysis showed a non-clinically significant improvement in sleep stage N1% in the CPAP group compared to control (SMD -0.22, 95% CI -0.49 to 0.05; n=223). Re-expressed as N1%, there was a mean decrease of -3.09% (95% CI -6.87 to 0.7). The analysis did not show a clinically significant improvement in sleep stage N2% in the CPAP group compared to control (SMD 0.04, 95% CI -0.22 to 0.31; n=223). Re-expressed as N2%, there was a mean increase of 0.6% (95% CI -3.26 to 4.59). The duration of patient follow-up after treatment was one month (see supplemental material, Figure S28 and S29).

Six RCTs[31-35, 37] reported sleep architecture measured by number of arousals/hour (PSG). The analysis showed a clinically significant reduction in the number of arousals/hour in the CPAP group compared to control (MD -12.88, 95% CI -22.4 to -3.36; n=310). There was a 35.8% reduction of arousals for the CPAP group. The duration of patient follow-up after treatment was one to three months (see supplemental material, Figure S30). For sleep architecture, only data from RCTs are reported above. Additional data from the single-arm pre-

posttreatment/observational meta-analyses, in addition to daytime outcomes, are described in the supplemental material (Figures S31 to S39).

OVERALL QUALITY OF EVIDENCE: The TF determined that the overall certainty of evidence for the use of CPAP in adults with CSA due to primary CSA, CSA due to heart failure, CSA due to medication or substance use, treatment-emergent CSA, and CSA due to a medical condition or disorder was low based on the critical outcomes and downgrading of the evidence due to imprecision in both the randomized and observational studies (see supplemental material, Table S1).

BENEFITS VS HARMS: The potential benefits of CPAP in adults with CSA due to primary CSA, CSA due to heart failure, CSA due to medication or substance use, treatment-emergent CSA, and CSA due to a medical condition or disorder include a clinically significant improvement in disease severity measured by AHI and mortality. Additional outcomes (patient-reported excessive sleepiness, 6MWD) changed in the desired direction but did not meet the CST. The potential harms were judged as trivial. Based on their combined clinical experience, the TF judged that the potential benefits of CPAP outweigh the potential harms.

RESOURCE USE: The current cost of CPAP can range from $500 to $1,000 depending on the delivery system. Additional costs of maintenance and replacement parts for tubing, mask interface, and other accessories increases the overall cost of the intervention over time. The TF judged this cost as moderate. This judgment was based on estimated costs in the United States.

PATIENTS' VALUES AND PREFERENCES: The TF judged that there is probably no important uncertainty or variability in how much patients value the main outcomes. Given the clinically significant improvement in disease severity and mortality, the TF judged that most adults with CSA would generally be accepting of treatment with CPAP.

Bilevel positive airway pressure (BPAP) with a backup rate

Six RCTs[37, 38, 59-62] and five observational studies[49, 50, 56, 63, 64] investigated the use of BPAP with a backup rate to improve one or more of the following outcomes: excessive sleepiness, disease severity, cardiovascular disease, or sleep architecture. Of these, the TF used six RCTs and three observational studies for decision making in the CPG. Participants in the RCTs had a mean age of 61 years old. The duration of follow-up ranged from one night to six weeks in the RCTs. The duration of follow-up ranged from one night to six months in the observational studies. Meta-analyses were performed to assess the efficacy of BPAP with a backup rate. Single-arm (within-group) data was extracted in all six RCTs and included in the meta-analyses with observational studies. The meta-analyses and summary of findings table are provided in the supplemental material (Figure S40 through Figure S59; Table S2). A summary of the evidence for each outcome is provided below.

Critical Outcomes

The TF determined the following outcomes to be critical for evaluating the efficacy of BPAP with a backup rate: excessive sleepiness, disease severity, and cardiovascular disease. None of the studies identified in our literature review reported data for the following critical outcomes: hospitalizations, mortality, or patient reported sleep quality.

EXCESSIVE SLEEPINESS: One study[61] reported excessive sleepiness measured by the ESS. The analysis showed a clinically significant reduction in excessive sleepiness compared to baseline (MD -2.1, 95% CI -4.53 to 0.33; n=20). The duration of patient follow-up after treatment was six weeks (see supplemental material, Figure S40).

DISEASE SEVERITY: Nine studies[37, 38, 50, 56, 59-63] reported disease severity measured by AHI. The analysis showed a clinically significant reduction in AHI compared to baseline (MD -33.65, 95% CI -41.44 to -25.86; n=128). The baseline mean AHI was 44 events/hour, resulting in a 77% reduction. The duration of patient follow-up after treatment was between one night and six months (see supplemental material, Figure S41).

Five studies[37, 59, 60, 62, 63] reported disease severity measured by CAI. The analysis showed a clinically significant reduction in CAI compared to baseline (MD -15.66, 95% CI -25.12 to -6.2; n=69). The baseline mean CAI was 22 events/hour resulting in a 71% reduction. The duration of patient follow-up after treatment was six weeks (see supplemental material, Figure S42).

One study[38] reported disease severity measured by CAHI. The analysis showed a clinically significant reduction in CAHI (MD -15.5, 95% CI -19.95 to -11.05; n=11). The baseline mean CAHI was 26 events/hour resulting in a 59% reduction. The duration of patient follow-up after treatment was one night (see supplemental, Figure S43).

Three studies[37, 60, 61] reported disease severity measured by ODI. The analysis showed a clinically significant reduction in ODI (MD -20.46, 95% CI -30.55 to -10.38; n=49). The baseline mean ODI was 35 events/hour resulting in a 59% reduction. The duration of patient follow-up after treatment was six weeks (see supplemental, Figure S44).

Three studies[38, 56, 63] reported disease severity measured by percentage of sleep time with oxygen saturation <90%. The analysis showed a clinically significant reduction in the percentage of sleep time with an oxygen saturation <90% (MD -26.19, 95% CI -42.88 to -9.49; n=33]. The baseline mean for disease severity was 31% resulting in an 84% reduction. The duration of patient follow-up after treatment was between one night to three months (see supplemental, Figure S45).

CARDIOVASCULAR DISEASE: Three studies[50, 61, 63] reported cardiovascular disease measured by LVEF. The analysis showed a clinically significant improvement in LVEF compared to baseline (MD 7.83, 95% CI 3.12 to 12.54; n=34). The duration of patient follow-up after treatment was between six weeks and six months (see supplemental, Figure S46).

In one study[50] that compared BNP to baseline, the analysis did not show a clinically significant improvement (MD -319.8, 95% CI -872.89 to 233.29; n=7) nor in another study[63] that compared BNP values to control (MD-250.6, 95% CI -549.81 to 48.61; n=14). The duration of patient follow-up after treatment was three to six months (see supplemental, Figures S47 and S48).

Two studies[61, 64] reported HR as a measure of cardiovascular disease. The analysis showed a decrease in HR favoring the BPAP with a backup rate group compared to baseline (MD -2.51, 95% CI -9.09 to 4.07; n=29). There was no a priori CST for HR. The duration of patient follow-up after treatment was six weeks (see supplemental, Figure S49).

Important Outcomes

The TF determined the following outcomes to be important outcomes but not critical for evaluating the efficacy of BPAP with a backup rate to treat adults with CSA: sleep architecture.

SLEEP ARCHITECTURE (PSQ): Several objective measures were used to report sleep architecture. Five studies[37, 38, 60, 61, 64] measured TST. The meta-analysis showed a clinically significant improvement for use of BPAP with a backup rate compared to baseline (MD 48.58, 95% CI -9.07 to 106.22; n=69). The duration of patient follow-up after treatment was six weeks (see supplemental, Figure S50). The meta-analysis of three studies[38, 60, 64] did not show a clinically significant improvement in SE for BPAP with a backup rate compared to control (MD 7.27, 95% CI -4.78 to 19.32; n=35). The duration of patient follow-up after treatment was six weeks (see supplemental, Figure S51).

A meta-analysis of two studies[56, 61] showed a non-clinically significant improvement in N1% and N2% for BPAP with a backup rate compared to baseline (N1% MD -4.06, 95% CI -11.66 to 3.54; n=39) (N2% MD -1.44, 95% CI -7.31 to 4.43). The duration of patient follow-up after treatment was six weeks (see supplemental, Figures S52 to S53). Six studies[37, 56, 60, 61, 63, 64] reported N3% and REM%. Both analyses showed a non-clinically significant improvement in N3% and REM% for the BPAP with a backup rate group compared to baseline (N3% MD 2.55, 95% CI 0.14 to 4.97; n=84) (REM% MD 2.6, 95% CI 0.73 to 4.48; n=95). The duration of patient follow-up after treatment was six weeks (see supplemental, Figures S54 to S55). The analysis of one study[37] showed an improvement in SWS% and REM % for the BPAP with a backup rate group compared to baseline (MD 11.2, 95% CI 4.53 to 17.87; n=14). There was no a priori CST (see supplemental, Figure S56).

Six studies[37, 38, 56, 60, 63, 64] reported arousal index. The meta-analysis showed a clinically significant improvement in arousals for BPAP with a backup rate compared to baseline (MD -21.94, 95% CI -33.59 to -10.29; n=75). The duration of patient follow-up after treatment was between one night to six weeks (see supplemental, Figure S57). One study[61] reported both movement arousals and respiratory-related arousals. One analysis did not show an improvement in movement arousals with use of BPAP with a backup rate (MD 5.5, 95% CI -0.35 to 11.35; n=20) while respiratory-related arousals showed a clinically significant improvement for BPAP with a backup rate (MD -12.5, 95% CI -20.04 to -4.96; n=20). The duration of patient follow-up after treatment was six weeks (see supplemental, Figures S58 to S59).

OVERALL QUALITY OF EVIDENCE: The TF determined that the overall certainty of evidence for the use of BPAP with a backup rate in adults with CSA due to primary CSA, CSA due to medication or substance use, treatment-emergent CSA, and CSA due to a medical condition or disorder was very low based on the critical outcomes and downgrading of the evidence due to imprecision in both the randomized and observational studies (see supplemental material, Table S2).

BENEFITS VS HARMS: The potential benefits of BPAP with a backup rate in adults with CSA due to primary CSA, CSA due to medication or substance use, treatment-emergent CSA, and CSA due to a medical condition or disorder include a clinically significant improvement in excessive sleepiness, disease severity measured by AHI, CAI, and CAHI, and cardiovascular disease. The potential harms were judged as small and related to side effects associated with use of the CPAP mask interface. Based on their combined clinical experience, the TF judged that the potential benefits of BPAP with a backup rate outweigh the potential harms.

RESOURCE USE: The cost of BPAP devices with a backup rate ranges from $1,700 to $3,000 depending on the delivery system. Additional costs of maintenance and replacement parts for tubing, mask interface, and other supplies increases the overall cost of the intervention over time. The TF judged this cost as moderate. This judgment was based on estimated costs in the United States.

PATIENTS' VALUES AND PREFERENCES: The TF judged that there is probably no important uncertainty or variability in how much patients value the main outcomes. Given the clinically significant improvement in excessive sleepiness, disease severity, and cardiovascular disease, the TF judged that most adults with CSA would generally be accepting of treatment with BPAP with a backup rate.

Bilevel positive airway pressure (BPAP)

One RCT[65] investigated the use of BPAP without a backup rate to improve disease severity and cardiovascular disease. Since only one study reported on these outcomes, a meta-analysis could not be performed. When outcome data was not presented for both the BPAP group and control, the TF used pre- and posttreatment data from the BPAP group for analysis. Participants had a mean age of 50 years old. The duration of follow-up for reported outcomes was 3 months. Follow up data for survival was on average 31 ± 2.3 months. The analyses and summary of findings table are provided in the supplemental material (Figures S60 to S67; Table S3). A summary of the evidence for each outcome is provided below.

Critical Outcomes

The TF determined the following outcomes to be critical for evaluating the efficacy of BPAP: disease severity and cardiovascular disease. None of the studies identified in our literature review reported data for the following critical outcomes: excessive sleepiness, hospitalizations, mortality, or patient reported sleep quality.

DISEASE SEVERITY: One study[65] reported disease severity measured by AHI and CAI. The analysis showed a clinically significant reduction in AHI compared to baseline (MD -23.1, 95% CI -31.08 to -15.12; n=10) resulting in an approximate 82% reduction in AHI. There was also a clinically significant reduction in CAI compared to baseline (MD -10.6, 95% CI -11.13 to -10.07, n=10), resulting in an approximate 95% reduction in CAI. The duration of patient follow-up after treatment was three months (see supplemental material, Figures S60 and S61).

CARDIOVASCULAR DISEASE: One study[65] reported cardiovascular disease using several measures: LVEF, BNP, SBP, DBP, NYHA functional class score, and HR. There were clinically significant improvements in LVEF (MD 13, 95% CI 3.25 to 22.75 n=21), BNP (MD -106.3, 95% CI -220.78, 8.18; n=21), SBP (MD -11.4, 95% CI -27.32 to 4.52; n=21), and DBP (MD -7.2, 95% CI -17.62, 3.22, n=21). The analysis showed a reduction in NYHA classification (MD -0.7, 95% CI -1.26 to -0.14; n=21) and HR (MD -4.5, 95% CI -18.95 to 9.95; n=21); however, there were no a priori CSTs for NYHA or HR. The duration of patient follow-up after treatment was three months (see supplemental material, Figures S62 to S67).

Important Outcomes

None.

OVERALL QUALITY OF EVIDENCE: The TF determined that the overall certainty of evidence for the use of BPAP without a backup rate in adults with CSA due to primary CSA, CSA due to heart failure, CSA due to medication or substance use, treatment-emergent CSA, and CSA due to a medical condition or disorder was very low based on the critical outcomes and downgrading of the evidence due to imprecision and indirectness in the randomized study (see supplemental material, Table S3).

BENEFITS VS HARMS: The potential benefits of BPAP without a backup rate in adults with CSA due to primary CSA, CSA due to heart failure, CSA due to medication or substance use, treatment-emergent CSA, and CSA due to a

medical condition or disorder were judged as small. The potential harms were judged as large due to indirect evidence that central apnea may be worsened by BPAP without a back-up rate.[66-68] Based on their combined clinical experience, the TF judged that the potential harms of BPAP without a backup rate in adults outweigh the potential benefits.

RESOURCE USE: The average cost of BPAP is approximately $1,500. The TF judged this cost as moderate. This judgment was based on estimated costs in the United States.

PATIENTS' VALUES AND PREFERENCES: The TF judged that there is probably no important uncertainty or variability in how much patients value the main outcomes. Given the evidence of harms related to BPAP, the TF judged that most adults with CSA would probably not accept treatment with BPAP without a backup rate.

Adaptive servo-ventilation (ASV)

Twelve RCTs[69-80] and 36 observational studies[37, 39, 40, 42-45, 49, 51, 52, 56, 59-62, 81-101] investigated the use of ASV to improve one or more of the following outcomes: excessive sleepiness, disease severity, cardiovascular disease, mortality, hospitalization, or sleep architecture. Of these, the TF used 12 RCTs for decision making in the CPG. Participants in the RCTs and the observational studies had a mean age of 64 years (12% female). The duration of follow-up ranged from one night to five years in the RCTs and one night to one year in the observational studies. Meta-analyses were performed to assess the efficacy of ASV. The meta-analyses and summary of findings table are provided in the supplemental material (Figure S68 through Figure S130; Table S4). A summary of the evidence for each outcome is provided below.

Critical Outcomes

The TF determined the following outcomes to be critical for evaluating the efficacy of ASV: excessive sleepiness, disease severity, cardiovascular disease, hospitalizations, mortality, and patient-reported sleep quality.

EXCESSIVE SLEEPINESS: Three RCTs[69, 71, 76] reported excessive sleepiness measured by the ESS. The analysis did not show a clinically significant difference in ESS in the ASV group compared to control (MD -0.57, 95% CI -0.96 to -0.18; n=1518). The duration of patient follow-up after treatment was three to 12 months (see supplemental material, Figure S68).

DISEASE SEVERITY: Multiple tools were used to measure disease severity among included studies, such as AHI, CAI, CAHI, ODI, and percentage of total sleep time with an oxygen saturation < 90%. The pooled results of ten RCTs[69, 70, 73-80] showed a clinically significant improvement in AHI in the ASV group (MD -24.07, 95% CI -30.22 to -17.92; n=770) resulting in a 74% reduction in AHI for the ASV group. The duration of patient follow-up after treatment was one night to 12 months (see supplemental material, Figure S69).

Four RCTs[69, 75, 78, 80] showed a clinically significant improvement in CAI in the ASV group (MD -11.43, 95% CI -15.42 to -7.44; n=315) resulting in an 83% reduction in CAI for the ASV group. The duration of patient follow-up after treatment was between 12 weeks and one year (see supplemental material, Figure S70). One study[73] showed a clinically significant improvement in CAHI in the ASV group (MD -15.00, 95% CI -20.56 to -9.44; n=63) resulting in a 76% reduction in CAHI for the ASV group. The duration of patient follow-up after treatment was 3 months (see supplemental material, Figure S71).

Five RCTs[70, 75-78] showed a clinically significant reduction in ODI favoring the ASV group compared to control (MD -17.53, 95% CI -25.26 to -9.79; n=534) resulting in a 76% reduction for the ASV group compared to baseline. The duration of patient follow-up after treatment was between one and 12 months (see supplemental material, Figure S72). One RCT[75] showed a clinically significant reduction in the percentage of total sleep time with an oxygen saturation < 90%, resulting in a 90% reduction for the ASV group (MD -5.3, 95% CI -8.27 to -2.33; n=22). The duration of patient follow-up after treatment was six months (see supplemental material, Figure S73).

CARDIOVASCULAR DISEASE: Multiple outcomes were used to measure cardiovascular disease among included studies such as the 6MWD, LVEF (%), HR, and NYHA class. The meta-analysis of three RCTs[71, 72, 76] did not show a clinically significant difference in 6MWD in the ASV group compared to control (MD -10.68, 95% CI -38.21 to 16.85; n=1528). The duration of patient follow-up after treatment was six to 12 months (see supplemental material, Figure S74). Six RCTs[69, 71, 72, 75, 76, 79] did not show a clinically significant improvement in LVEF (%) for the ASV group compared to control (MD 1.43, 95% CI -0.53 to 3.39; n=570). The duration of patient follow-up after treatment was six to 12 months (see supplemental material, Figure S75).

One study[77] showed a reduction in HR in favor of the ASV group compared to control (MD -2.1, 95% CI -4.83 to 0.63; n=20). Another RCT[79] showed a reduction in NYHA class in favor of the ASV group (MD -0.5, 95% CI -0.82 to -0.18; n=30). There was no a priori CST for HR or NYHA. The duration of patient follow-up after treatment was six months (see supplemental material, Figures S76 and S77).

HOSPITALIZATIONS: A meta-analysis of three RCTs[70, 71, 76] did not show a clinically significant improvement in hospitalizations in the ASV group compared to control (RR 1.11, 95% CI 0.86 to 1.43; n=1649), with an absolute risk difference of 44 more hospitalizations per 1,000 participants. The duration of patient follow-up after treatment was one to 12 months (see supplemental material, Figure S78).

MORTALITY: The pooled effect of four RCTs[69-71, 76] showed no effect on all-cause mortality in the ASV group compared to control (RR 1.00, 95% CI 0.71 to 1.41; n=1716), with an absolute risk difference of 0 fewer deaths per 1,000 participants. The data from these RCTs included patients with HFrEF and HFpEF. A subgroup analysis of HFrEF participants, showed no effect on all-cause mortality in the ASV group compared to control (RR 0.97, 95% CI 0.66 to 1.42; n=1692). The duration of patient follow-up after treatment was between 12 weeks and five years (see supplemental material, Figure S79).

SLEEP QUALITY (PATIENT-REPORTED): One study[76] did not show a clinically significant difference in sleep quality measured by the Pittsburgh Sleep Quality Index (PSQI; MD 0.6, 95% CI -1.13 to 2.33; n=126) in the ASV group compared to control. The duration of patient follow-up after treatment was six months (see supplemental material, Figure S80). Additional data from randomized trials and observational studies' meta-analyses are described in the supplemental material (Figures S81 to S107).

Important Outcomes

The TF determined the following outcomes to be important outcomes but not critical for evaluating the efficacy of ASV to treat adults with CSA: daytime functioning and sleep architecture.

DAYTIME FUNCTIONING: Multiple instruments were used to measure daytime functioning among the included studies, such as the Minnesota Living with Heart Failure Questionnaire, Specific Activity Scale, and the Duke Activity Status Index. The meta-analysis from two RCTs[69, 71] showed a reduction in the Minnesota Living with

Heart Failure Questionnaire favoring the ASV group compared to control (MD -0.19, 95% CI -2.08 to 1.7; n=1388). The duration of patient follow-up after treatment was between 12 weeks and 12 months. One RCT[79] showed an increase in the Specific Activity Scale (MD 0.8, 95% CI 0.12 to 1.48; n=30) favoring the ASV group over the control. The duration of patient follow-up after treatment was six months. One RCT[76] showed a decrease in the Duke Activity Status Index (MD -1.51, 95% CI -6.39 to 3.37; n=126) favoring the control group over the ASV group. There were no a priori CSTs for the Minnesota Living with Heart Failure Questionnaire, Specific Activity Scale, or the Duke Activity Status Index. The duration of patient follow-up after treatment was six months (see supplemental material, Figures S108 and S110).

SLEEP ARCHITECTURE (PSG): Several objective measures were used to report sleep architecture. The meta-analysis of four RCTs[70, 73, 77, 78] did not show a clinically significant improvement in TST in the ASV group compared to control (MD 10.52, 95% CI -6.12 to 27.17; n=462). A meta-analysis of five RCTs[70, 73, 75, 77, 78] did not show a clinically significant improvement in SE in the ASV group compared to control (MD 5.02, 95% CI 2.57 to 7.46; n=484); nor REM% (SMD 0.39, 95% CI 0.21 to 0.57; n=484). The SMD re-expressed as REM%, showed a mean increase of 2.5% (95% CI 1.3 to 3.6); The number of arousals showed a clinically significant reduction in the ASV group compared to control (MD -16.76, 95% CI -20.02 to -13.51; n=484). A meta-analysis of four RCTs[70, 73, 75, 77] did not show a clinically significant improvement in SWS% compared to control (SMD 0.36, 95% CI 0.10 to 0.82; n=282). The SMD re-expressed as SWS%, showed a mean increase of 1.6% (95% CI -0.48 to 3.9). The duration of patient follow-up after treatment was one to 12 months (see supplemental material, Figures S111 through S115).

Sleep stage N1% and sleep stage N2% were also measured.[70, 73, 77, 78] The analysis showed a clinically significant improvement in sleep stage N1% in the ASV group compared to control (SMD -0.76, 95% CI -1.24 to -0.28; n=462). The SMD re-expressed as N1%, showed a mean decrease of -8.7% (95% CI -14.1 to -3.2). Sleep stage N2% did not show a clinically significant difference compared to control (SMD 0.47, 95% CI 0.02 to 0.92; n=462). The SMD re-expressed as N2%, showed a mean increase of 5% (95% CI 0.21 to 9.75). The number of respiratory arousals showed a clinically significant reduction in the ASV group compared to control (MD -16.91, 95% CI -25.55 to -8.27; n=462), resulting in a 49.9% reduction from baseline. The duration of patient follow-up after treatment was one to 12 months (see supplemental material, Figures S116 through S118). Additional data from the observational studies' meta-analyses are described in the supplemental material (Figures S119 to S130.

OVERALL QUALITY OF EVIDENCE: The TF determined that the overall certainty of evidence for the use of ASV in adults with primary CSA, CSA due to heart failure, CSA due to medication or substance use, treatment-emergent CSA, and CSA due to a medical condition or disorder was low based on the critical outcomes and downgrading of the evidence due to imprecision and risk of bias (see supplemental material, Table S4).

BENEFITS VS HARMS: The potential benefits of ASV in adults with CSA due to primary CSA, CSA due to heart failure, CSA due to medication or substance use, treatment-emergent CSA, and CSA due to a medical condition or disorder include a clinically significant improvement in disease severity. The potential harms were judged as small based on hospitalization rates due to heart failure or cardiovascular disease. Based on their combined clinical experience, the TF judged that the potential benefits of ASV outweigh the potential harms.

RESOURCE USE: The current cost of ASV can range from $1,495 and $1,770 depending on the delivery system. The TF judged this cost as moderate. This judgment was based on estimated costs in the United States.

PATIENTS' VALUES AND PREFERENCES: The TF judged that there is possibly important uncertainty or variability in how much patients value the main outcomes. Given the clinically significant improvement in disease severity, the TF judged that most adults with CSA would generally be accepting of treatment with ASV.

Low-flow oxygen

A total of seven RCTs[102-108] and 14 observational studies[37, 38, 48, 82, 100, 109-117] investigated the use of low-flow oxygen to improve one or more of the following outcomes: excessive sleepiness, disease severity, cardiovascular disease, hospitalizations, and patient-reported sleep quality. Of these, the TF used seven RCTs and three observational studies for decision making in the CPG. Participants in the RCTs had a mean age of 71 years (14% female). Oxygen was administered to the participants via a nasal cannula at a rate ranging from 2 L/min to 3 L/min. The study duration ranged from a single night of oxygen therapy to one year of treatment. Three RCTs[105, 106, 108] used a crossover design, with patients serving as their own controls. The observational studies were pre- posttreatment design investigating participants receiving 2 L/min to 4 L/min of oxygen for a duration of one night to three months. Meta-analyses were performed to assess the efficacy of low-flow oxygen. The meta-analyses are provided in the supplemental material, Figure S131 through Figure S176. A summary of findings table is provided in the supplemental material, Table S5. A summary of the evidence for each outcome is provided below.

Critical Outcomes

The TF determined the following outcomes to be critical for evaluating the efficacy of low-flow oxygen: excessive sleepiness, disease severity, cardiovascular disease, hospitalizations, and patient-reported sleep quality. None of the studies identified in our literature review reported data for the following critical outcomes: mortality.

EXCESSIVE SLEEPINESS: One crossover RCT[108] reported excessive sleepiness measured by the ESS. Low-flow oxygen was delivered at a rate of 2 L/min via nasal cannula. The meta-analysis did not show a clinically significant reduction in excessive sleepiness in the oxygen group compared to control (MD -0.60, 95% CI: -6.17 to 4.97; n=22). The duration of patient follow-up after treatment was four weeks (see supplemental material, Figure S131).

DISEASE SEVERITY: A meta-analysis of seven RCTs[102-108] reported disease severity measured by the AHI. Low-flow oxygen was administered at a rate ranging from 2 L/min to 3 L/min via nasal cannula. The meta-analysis demonstrated a clinically significant reduction in disease severity in the oxygen group compared to control (MD -11.07, 95% CI: -13.71 to -8.43; n=308). The baseline mean AHI was 25 events/hour in the oxygen group resulting in a 55.3% reduction of AHI for the oxygen group at the time of follow-up. The duration of patient follow-up after treatment ranged from one night to one year (see supplemental material, Figure S132).

A meta-analysis of 5 RCTs[102-104, 107, 108] reported disease severity as measured by the CAI. Low-flow oxygen was administered at a rate ranging from 2 L/min to 3 L/min via nasal cannula. The meta-analysis demonstrated a clinically significant reduction in disease severity in the oxygen group compared to control (MD -5.91, 95% CI: -8.87 to -2.95; n=246). The baseline mean CAI was 10.1 events/hour in the oxygen group resulting in a -67.1% reduction of CAI for the oxygen group at the time of follow-up. The duration of patient follow-up after treatment ranged from three months to one year (see supplemental material, Figure S133).

A meta-analysis of 4 RCTs[102, 103, 107, 108] measured ODI. Low-flow oxygen was administered at a rate ranging from 2 L/min to 3 L/min via nasal cannula. The meta-analysis demonstrated a clinically significant reduction in disease severity for the oxygen group compared to control (MD -14.29, 95% CI: -18 to -10.59; n=226). The baseline mean ODI was 19.8 events/hour for the oxygen group, resulting in a -72.3% reduction of ODI for the oxygen group at the

time of follow-up. The duration of patient follow-up after treatment ranged from one month to one year (see supplemental material, Figure S134).

A meta-analysis of 2 RCTs[104, 105] reported disease severity measured by the oxygen saturation less than 90%. Low-flow oxygen was administered at a rate ranging from 2 L/min to 4 L/min via nasal cannula. The meta-analysis demonstrated a reduction in disease severity in the oxygen group compared to control (MD -5.73, 95% CI: -8.34 to -3.13; n=64). The baseline mean of the oxygen saturation less than 90% was not reported in the included studies; therefore, the clinical significance was not calculated. The duration of patient follow-up after treatment ranged from one week to three months (see supplemental material, Figure S135).

CARDIOVASCULAR DISEASE: A meta-analysis of two observational trials[82, 109] reported cardiovascular disease measured by the 6MWD test. Low-flow oxygen was administered at a rate of 2 L/min via nasal cannula. The meta-analysis did not show a clinically significant improvement in cardiovascular disease in the oxygen group compared to baseline (MD 13.73, 95% CI: -29.73 to 57.20; n=29). The duration of patient follow-up after treatment ranged from eight weeks to three months. (see supplemental material, Figure S136).

A meta-analysis of four RCTs[102-104, 107] reported LVEF, %. Low-flow oxygen was administered at a rate ranging from 2 L/min to 3 L/min via nasal cannula. The meta-analysis demonstrated a clinically significant improvement in cardiovascular disease measured by LVEF in the oxygen group compared to control (MD 5.23, 95% CI: 2.02 to 8.44; n=224). The duration of patient follow-up after treatment ranged from three months to one year (see supplemental material, Figure S137).

A meta-analysis of two RCTs[105, 107] reported SBP and DBP. Low-flow oxygen was administered at a rate ranging from 3 L/min to 4 L/min via nasal cannula. The meta-analysis did not show a clinically significant improvement in SBP in the oxygen group compared to control (MD 1.69, 95% CI: -5.43 to 8.80; n=100), but a clinically significant improvement was observed in DBP (MD -2.39, 95% CI: -5.88 to 1.09; n=100. The duration of patient follow-up after treatment ranged from one to 12 weeks (see supplemental material, Figure S138 and S139).

HOSPITALIZATIONS: One study[116] reported hospitalization outcomes measured by incidence (times/year), length of stay, outpatient visits (times/year), and emergency visits (times/year). Low-flow oxygen was administered at a rate of 2 L/min via nasal cannula. The analysis demonstrated a reduction in incidence (MD -1.60, 95% CI: -2.09 to -1.11; n=53), reduction in length of stay (MD -4.10, 95% CI: -22.59 to 14.39; n=53), reduction in outpatient visits (MD -5.20, 95% CI: -8.35 to -2.05; n=53), and a reduction in emergency visits (MD -1.70, 95% CI: -2.58 to -0.82; n=53) compared to baseline. There were no a priori CSTs for these measures of hospitalizations. The duration of patient follow-up after treatment was six months (see supplemental material, Figure S140 to S143).

SLEEP QUALITY (PATIENT-REPORTED): One study[109] reported sleep quality with the sleep sufficiency index (no a priori CST). Low-flow oxygen was administered at a rate of 2 L/min via nasal cannula. The analysis demonstrated an increase in sleep quality from baseline favoring the oxygen group (MD 10.30, 95% CI: -4.87 to 25.46; n=22) The duration of patient follow-up after treatment was three months (see supplemental material, Figure S144).

Additional data from randomized trials and observational studies' meta-analyses are described in the supplemental material (Figures S145 to S154).

Important Outcomes

The TF determined the following outcomes to be important outcomes but not critical for evaluating the efficacy of low-flow oxygen: daytime functioning, quality of life, and sleep architecture.

DAYTIME FUNCTIONING: Three RCTs[103, 104, 107] reported the Specific Activity Scale (Mets, no CST). Low-flow oxygen was administered at a rate of 3 L/min nasal cannula. The meta-analysis demonstrated an increase in daytime functioning in favor of the oxygen group compared to control (MD 1.07, 95% CI 0.60 to 1.55; n=107). The duration of patient follow-up after treatment was 12 weeks (see supplemental material, Figure S155)

One study[104] reported anaerobic threshold and peak VO_2 (no CST). Low-flow oxygen was administered at a rate of 3 L/min nasal cannula. The analysis demonstrated an increase in anaerobic threshold favoring the oxygen group compared to control (MD 0.60, 95% CI -1.87 to 3.07; n=20) and a peak VO_2 increase (MD 2.50, 95% CI -1.25 to 6.25; n=20). The duration of patient follow-up after treatment was 3 months (see supplemental material, Figures S156 and S157).

One RCT[108] measured daytime functioning with various psychomotor tests. Low-flow oxygen was administered at a rate of 2 L/min nasal cannula. The analysis demonstrated a decrease in Reitan trail making test favoring the oxygen group (MD -1.0, 95% CI -121.60 to 119.60; n=22), an increase four-choice reaction time test favoring control (MD 0.04, 95% CI -0.24 to 0.32; n=22), an increase in PASAT 2 favoring control (MD 2, 95% CI -14.63 to 18.63; n=22), and an increase in PASAT 4 (MD 5, 95% CI -13.06 to 23.06 sec) favoring control. There were no a priori CSTs for these measures of daytime outcomes. The duration of patient follow-up after treatment was four weeks (see supplemental material, Figures S158 through S161).

QUALITY OF LIFE: One RCT[108] reported the speed on the quality-of-life score. Low-flow oxygen was administered at a rate of 2 L/min nasal cannula. The analysis demonstrated an increase in quality of life favoring the oxygen group compared to control (MD 2, 95% CI -24.36 to 28.36; n=22). There was no a priori CST for this measure. The duration of patient follow-up after treatment was four weeks (see supplemental material, Figure S162).

SLEEP ARCHITECTURE (PSG): A meta-analysis of three RCTs[105, 106, 108] measured TST and REM%. Low-flow oxygen was administered at a range of 2-4 L/min nasal cannula. The meta-analysis did not demonstrate a clinically significant improvement in TST in the oxygen group compared to control (MD 10.40, 95% CI -25.03 to 45.82; n=84) nor a clinically significant improvement in REM% (MD 2.23, 95% CI -1.52 to 5.98; n=84). The duration of patient follow-up after treatment ranged from one night to four weeks (see supplemental material, Figure S163 and S164).

A meta-analysis of two RCTs[105, 106] reported sleep stage N1%, sleep stage N2%, and SWS%. Low-flow oxygen was administered at a range of 2-4 L/min nasal cannula. The meta-analysis demonstrated clinically significant improvement in sleep stage N1% in the oxygen group (MD -13.3, 95% CI -21.71 to -4.89; n=62) but not sleep stage N2% (MD 8.42, 95% CI: 0.91 to 15.92: n=62) nor SWS% compared to control (MD 2.71, 95% CI 0.15 to 5.27; n=62). The duration of patient follow-up after treatment ranged from one to seven nights (see supplemental material, Figure S165 through S167).

Three RCTs[105, 106, 108] reported the arousal index. Low-flow oxygen was administered at a range of 2-4 L/min nasal cannula. The meta-analysis showed a clinically significant improvement in the arousal index in the oxygen group

compared to control (MD -4.09, 95% CI -9.14 to 0.96; n=84). The duration of patient follow-up after treatment ranged from one night to four weeks (see supplemental material, Figure S168).

Additional data from the observational meta-analyses are described in the supplemental material (Figures S169 to S176).

OVERALL QUALITY OF EVIDENCE: The TF determined that the overall certainty of evidence for the use of low-flow oxygen in adults with CSA due to heart failure was low based on the critical outcomes and downgrading of the evidence due to imprecision in both the randomized and non-randomized studies. The decision was driven by the low certainty in the critical outcome of disease severity (see supplemental material, Table S5).

BENEFITS VS HARMS: The potential benefits of low-flow oxygen in adults with CSA due to heart failure include a clinically significant improvement in disease severity. Low-flow oxygen demonstrated non-clinically significant reductions in excessive sleepiness and cardiovascular disease and improvement in hospitalization and patient-reported sleep quality as measured by outcomes without pre-specified CSTs. Cardiac-related adverse events were reported in two RCTs. The potential harm includes irritation from the nasal prongs and nosebleeds. Based on their combined clinical experience, the TF judged that the potential benefits of low-flow oxygen in adults with CSA due to heart failure outweigh the potential harms.

RESOURCE USE: The current cost of low-flow oxygen can range from $1,000 to $2,000 depending on the delivery system. Additional costs of maintenance and replacement parts for tubing, nasal cannulas, and other supplies can increase the overall cost of the intervention over time. The TF judged this cost as moderate. This judgment was based on estimated costs in the United States.

PATIENTS' VALUES AND PREFERENCES: The TF judged that there is possibly important uncertainty or variability in how much patients value the main outcomes due to the lack of evidence informing patient-important outcomes and long-term outcomes. Given the clinically significant improvement in disease severity, the TF judged that most patients with CSA due would generally be accepting of treatment with low-flow oxygen.

Acetazolamide

A total of four RCTs[21-23, 118] and two observational studies[119, 120] investigated the use of acetazolamide to improve one or more of the following outcomes: excessive sleepiness, disease severity, cardiovascular disease, patient-reported sleep quality, fatigue, and PSG measured sleep architecture. Of these, the TF used three RCTs for decision making in the CPG. Participants in the RCTs had a mean age of 58 years (9% female). Participants received dosages of acetazolamide from 250 milligrams (mg) to 1,000 mg for a duration of three to six nights. The observational/non-randomized studies were pre- posttreatment designs investigating participants receiving a dosage of 250 mg of acetazolamide for a duration of one to five months. Meta-analyses were performed to assess the efficacy of acetazolamide. The meta-analyses are provided in the supplemental material, Figure S177 through Figure S196. A summary of findings table is provided in the supplemental material, Table S6. A summary of the evidence for each outcome is provided below.

Critical Outcomes

The TF determined the following outcomes to be critical for evaluating the efficacy of acetazolamide: excessive sleepiness, disease severity, and cardiovascular disease, and patient-reported sleep quality. None of the studies identified in our literature review reported data for the following critical outcomes: hospitalization or mortality.

EXCESSIVE SLEEPINESS: The analysis of one RCT[21] demonstrated a clinically significant decrease in ESS in the acetazolamide group compared to control (MD -2.7, 95% CI -5.42 to 0.02; n=20). The duration of patient follow-up after treatment with 250 mg of acetazolamide or placebo was six nights (see supplemental material, Figure S177).

DISEASE SEVERITY: Three RCTs[21-23] reported disease severity measured by AHI. The dose of acetazolamide ranged from 250 mg to 1,000 mg. The meta-analysis showed a clinically significant reduction in disease severity in the acetazolamide group compared to control (MD -16.57, 95% CI -28.43 to -4.71; n=76) resulting in a -56% reduction of AHI for the acetazolamide group at the time of follow-up. The duration of patient follow-up after treatment ranged from three to six nights (see supplemental material, Figure S178).

Two RCTs[22, 23] reported disease severity using the CAI. The dose of acetazolamide ranged from 350 mg to 1,000 mg. The meta-analysis did not demonstrate a clinically significant reduction in disease severity in the acetazolamide group compared to control (MD -7.65, 95% CI -13.8 to -1.51; n=56) resulting in a -48.5% reduction of CAI for the acetazolamide group at the time of follow-up. The duration of patient follow-up after treatment ranged from three to six nights (see supplemental material, Figure S179).

CARDIOVASCULAR DISEASE: One RCT[22] reported LVEF, %. The dose of acetazolamide ranged from 3.50 mg/kg to 4.0 mg/kg. The analysis did not show a clinically significant improvement in LVEF in the acetazolamide group compared to placebo (MD -1, 95% CI -5.81 to 7.81; n=24). The duration of patient follow-up after treatment was six nights (see supplemental material, Figure S180).

SLEEP QUALITY (PATIENT REPORTED): One RCT[22] reported sleep quality measured by a subjective questionnaire. Participants patients were asked specifically if they felt improved in comparison from the first arm versus the second arm of the study. The dose of acetazolamide ranged from 3.50 mg/kg to 4.0 mg/kg. The analysis showed an improvement in the acetazolamide group (RR 7, 95% CI 1.01 to 48.54; n=24). There was no a priori CST for this measure. The duration of patient follow-up after treatment was six nights (see supplemental material, Figure S181). Additional data from randomized trials and observational studies' meta-analyses are described in the supplemental material (Figures S182 to S188).

Important Outcomes

The TF determined the following outcomes to be important outcomes but not critical for evaluating the efficacy of acetazolamide in treating adults with CSA: fatigue and sleep architecture (PSG).

FATIGUE: One RCT[22] reported fatigue measured by a subjective questionnaire. Participants patients were asked specifically if they felt improved in comparison from the first arm versus the second arm of the study. The dose of acetazolamide ranged from 3.5 mg/kg to 4.0 mg/kg. The analysis showed an improvement in the acetazolamide group (RR 3.5, 95% CI 0.91 to 13.53; n=24). There was no a priori CST for this measure. The duration of patient follow-up after treatment was six nights (see supplemental material, Figure S189).

SLEEP ARCHITECTURE (PSG): Various objective measures were used to report sleep architecture. Two RCTs[23, 118] reported SE. The dose of acetazolamide ranged from 3.5 mg/kg to 1000 mg. The analysis did not show a clinically significant reduction in the acetazolamide group compared to control (MD -1.66, 95% CI -8.84 to 5.53; n=44). The duration of patient follow-up after treatment ranged from six to seven nights (see supplemental material, Figure S190). Additionally, one study[118] reported TST and arousals. The dose of acetazolamide used ranged from 3.50 mg/kg to 4 mg/kg. The analysis demonstrated a clinically significant improvement in TST compared to

placebo (MD 42, 95% CI -28.83 to 112.83; n=12) and in the number of arousals compared to baseline (MD -5, 95% CI -15.74 to 5.74; n=12). The duration of patient follow-up after treatment was six nights (see supplemental material, Figure S191 and S192).

Additional data on sleep architecture outcomes are described in the supplemental material (Figures S193 to S196).

OVERALL QUALITY OF EVIDENCE: The TF determined that the overall certainty of evidence for the use of acetazolamide in adults with primary CSA, CSA due to heart failure, CSA due to medication or substance use, treatment-emergent CSA, and CSA due to a medical condition or disorder was low based on the critical outcomes and downgrading of the evidence due to imprecision (see supplemental material, Table S6).

BENEFITS VS HARMS: The potential benefits of acetazolamide in adults with CSA include a clinically significant improvement in excessive sleepiness and disease severity. The potential harms include mild paresthesia and impaired taste of carbonated drinks. Based on their combined clinical experience, the TF judged that the potential benefits of acetazolamide in adults with CSA outweigh the potential harms.

RESOURCE USE: The current unit cost for acetazolamide is $0.14 for a 250 mg tablet, based on estimated costs in the United States. The TF judged this cost as negligible.

PATIENTS' VALUES AND PREFERENCES: The TF judged that there is probably no important uncertainty or variability in how much patients value the main outcomes. Given the clinically significant improvement in excessive sleepiness and disease severity, the TF judged that most individuals with CSA would generally be accepting of treatment with acetazolamide.

Transvenous phrenic nerve stimulation (TPNS)

One RCT presented in three publications[121-123] and three observational studies[124-126] investigated the use of TPNS to improve one or more of the following outcomes: excessive sleepiness, disease severity, cardiovascular disease, mortality, fatigue, quality of life, and sleep architecture. Of these, the TF used one RCT and one observational study for decision making in the CPG. The follow-up period was one night to 12 months. Subgroups of the RCT were followed for one, three, and five years.[127-129] Meta-analyses were performed to assess the efficacy of TPNS. The meta-analyses and summary of findings table are provided in the supplemental material (Figure S197 through Figure S222; Table S7). A summary of the evidence for each outcome is provided below.

Critical Outcomes

The TF determined the following outcomes to be critical for evaluating the efficacy of TPNS: excessive sleepiness, disease severity, cardiovascular disease, and mortality. None of the studies identified in our literature review reported data for the following critical outcomes: hospitalization.

EXCESSIVE SLEEPINESS: One study[121] reported excessive sleepiness measured by the ESS. The analysis showed a clinically significant difference in ESS in the TPNS group compared to control (MD -3.7, 95% CI -5.47 to -1.93; n=131). The duration of patient follow-up after treatment was six months (see supplemental material, Figure S197).

DISEASE SEVERITY: One RCT[121] measured disease severity with AHI, ODI, and CAI. The analysis did not show a clinically significant improvement in AHI with a 48% reduction in the TPNS group from baseline (MD -25, 95%

-31.26 to -18.74; n=131), nor with ODI with a 43% reduction from baseline in the TPNS group (MD -16.2, 95% CI -23.49 to -8.91); n=131). There was a clinically significant improvement in CAI from baseline resulting in an 80% reduction (MD -17.3, 95% CI -21.94 to -12.66; n=131). The duration of patient follow-up after treatment was six months (see supplemental material, Figure S198 to S200).

CARDIOVASCULAR DISEASE: One study[126] reported cardiovascular disease measured by LVEF% and 6MWD. The analysis did not show a clinically significant improvement in LVEF% in the TPNS group compared to baseline (MD -0.5, 95% CI -8.46 to 7.46; n=24) but did show a clinically significant increase in the 6MWD for the TPNS group compared to baseline (MD 40.5, 95% CI -53.78 to 134.78; n=24). The duration of patient follow-up after treatment was six months (see supplemental material, Figure S201 to S202).

MORTALITY: One RCT[121] did not show a clinically significant difference in mortality in the TPNS group compared to control (RR 1.07, 95% CI 0.15 to 7.39; n=151), with an absolute risk difference of 2 more deaths per 1,000 participants. The duration of patient follow-up after treatment was 12 months (see supplemental material, Figure S203).

Additional data from the single-arm pre- posttreatment/observational studies' meta-analyses are described in the supplemental material (Figure S204 to S210).

Important Outcomes

The TF determined the following outcomes to be important outcomes but not critical for evaluating the efficacy of TPNS to treat adults with CSA: quality of life and sleep architecture.

QUALITY OF LIFE: One RCT[122] reported quality of life as measured by the Patient Global Assessment. The TPNS group was more likely to show mild or marked/moderate improvement compared to the control group (RR 5.79, 95% CI 3.21 to 10.45; n=131). There was no a priori CST. The duration of patient follow-up after treatment was six months (see supplemental material, Figure S211).

SLEEP ARCHITECTURE (PSG): One RCT[121] reported REM% and arousal index. The TPNS group showed a non-clinically significant increase in REM% (MD 1.4, 95% CI -1.41 to 4.21; n=131) favoring TPNS over control. There was a clinically significant decrease in the arousal index in the TPNS group compared to control (MD -13.5, 95% CI -19.29. -7.71; n=131). The duration of patient follow-up after treatment was six months (see supplemental material, Figure S212 to S213).

Additional data for these outcomes from the single-arm pre- posttreatment/observational studies' meta-analyses are described in the supplemental material (Figure S214 to S222).

OVERALL QUALITY OF EVIDENCE: The TF determined that the overall certainty of evidence for the use of TPNS in adults with primary CSA and CSA due to heart failure who have failed all other therapies was very low based on the critical outcomes and downgrading of the evidence due to imprecision in both the randomized and observational studies (see supplemental material, Table S7).

BENEFITS VS HARMS: The potential benefits of TPNS in adults with primary CSA and CSA due to heart failure who have failed all other therapies include a clinically significant improvement in excessive sleepiness, disease severity and cardiovascular disease (specifically 6MWD). The potential harms were judged as small and included impending pocket erosion, implant site hematoma and infection, lead dislodgment, lead displacement and lead

component failure. Based on their combined clinical experience, the TF judged that the potential benefits of TPNS in adults with CSA due to primary CSA and CSA due to heart failure who have failed all other therapies outweigh the potential harms.

RESOURCE USE: The current cost of implanting a TPNS is estimated to be around $53,000. The TF judged this cost as large. This judgment was based on estimated costs in the United States.

PATIENTS' VALUES AND PREFERENCES: The TF judged that there is possibly important uncertainty or variability in how much patients value the main outcomes. Given the clinically significant improvement in excessive sleepiness, disease severity, and cardiovascular disease, the TF judged that most adults with CSA due to primary CSA and CSA due to heart failure who have failed all other therapies would generally be accepting of treatment with TPNS.

ADULTS WITH CENTRAL SLEEP APNEA DUE TO HIGH ALTITUDE

Low-flow oxygen

One crossover RCT presented in two separate publications[130, 131] measured various outcomes of low flow oxygen for treatment of CSA at high altitude. Since only one study reported on these outcomes, a meta-analysis could not be performed. This study included 18 healthy participants (12 men, 6 women) aged 29 ± 4 years, who ascended to altitude (3800 m) and were randomized to a different treatment group each night for three nights: 1) no treatment, 2) 2L per minute supplemental oxygen or higher to maintain oxygen saturation >95%, and 3) ASV. The analyses and summary of findings table are provided in the supplemental material (Figure S223 to S229; Table S8). A summary of the evidence for each outcome is provided below.

Critical Outcomes

The TF determined the following outcomes to be critical for evaluating the efficacy of oxygen to treat adults with CSA due to high altitude: excessive sleepiness, disease severity, daytime functioning, and quality of life.

EXCESSIVE SLEEPINESS: Measured by the Stanford Sleepiness Scale (SSS), the analysis of one RCT[130] did not show a clinically significant improvement in SSS for the oxygen group compared to control (MD -0.6, 95% CI -0.94 to -0.26; n=14) The duration of patient follow-up was one night (see supplemental material, Figure S223).

DISEASE SEVERITY: One RCT[130] showed a clinically significant improvement in ODI for the oxygen group compared to control (MD -14.7, 95% CI -23.72 to -5.68; n=14). The duration of patient follow-up was one night (see supplemental material, Figure S224).

DAYTIME FUNCTIONING: One RCT[130] reported results from the Lake Louise Acute Mountain Sickness (AMS) score. There was a decrease in AMS score that favored the oxygen group compared to control (MD -1, 95% CI -2.27 to 0.27; n=14). There was no a priori CST. The duration of patient follow-up was one night (see supplemental material, Figure S225).

QUALITY OF LIFE: One RCT[131] reported both Profile of Mood State-Adolescent (POMS-A) confusion score and fatigue score as a measure of quality of life (no a priori CST). There was a decrease in POMS-A scores that favored the oxygen group compared to control (confusion-MD -1.1, 95% CI -1.91 to -0.29; n=17; fatigue-MD -3.2, 95%

CI -6.28 to -0.12; n=17). The duration of patient follow-up was one night (see supplemental material, Figure S226 and S227.

Important Outcomes

The TF determined the following outcomes to be important outcomes but not critical for evaluating the efficacy of oxygen to treat adults with CSA due to high altitude: sleep architecture.

SLEEP ARCHITECTURE (PSG): One RCT[130] reported both arousal index and sleep stage N1% as measures of sleep architecture. One analysis showed a clinically significant reduction in arousal index from baseline (MD -3.7. 95% -6.44 to -0.96; n=14). There was not a clinically significant improvement in N1% sleep in favor of oxygen (MD -3.6, 95% CI -6.06 to -1.14; n=14). The duration of patient follow-up was one night (see supplemental material, Figure S228 to S229).

OVERALL QUALITY OF EVIDENCE: The TF determined that the overall certainty of evidence for the use of low-flow oxygen in adults with CSA due to high altitude was very low based on the critical outcomes and downgrading of the evidence due to imprecision and risk of bias (see supplemental material, Table S8).

BENEFITS VS HARMS: The potential benefits of low-flow oxygen in adults with CSA due to high altitude include a clinically significant improvement in disease severity (ODI). There were improvements in daytime functioning and quality of life, as measured by outcomes without pre-specified CSTs. There were no reported adverse effects. Based on their combined clinical experience, the TF judged that the potential benefits of low-flow oxygen in adults with CSA due to high altitude outweigh the potential harms.

RESOURCE USE: The current cost of low-flow oxygen can range from $1,000 to $2,000 depending on the delivery system. The TF judged this cost as moderate. This judgment was based on estimated costs in the United States.

PATIENTS' VALUES AND PREFERENCES: The TF judged that there is possibly important uncertainty or variability in how much patients value the main outcomes. Given the clinically significant improvement in disease severity, the TF judged that most adults with CSA due to high altitude would generally be accepting of treatment with low flow oxygen.

Acetazolamide

A total of two RCTs[132, 133] investigated the use of acetazolamide in adults with CSA due to high altitude to improve one or more of the following outcomes: disease severity and PSG measured sleep architecture. Participants in the RCTs had an age range of 26-35 years[133] (100% male)[132, 133] who ascended to altitudes between 3,454 and 4,400 meters. Participants received a dosage of 250 mg of acetazolamide at various frequencies. The duration of follow-up ranged from one to two nights. One RCT[133] used a crossover design, with patients serving as their own controls, and a washout period of five to seven days. Analyses were performed to assess the efficacy of acetazolamide as a treatment for adults with CSA due to high altitude. The analyses and summary of findings table are provided in the supplemental material (Figure S230 through Figure S240; Table S9). A summary of the evidence for each outcome is provided below.

Critical Outcomes

The TF determined the following outcomes to be critical for evaluating the efficacy of acetazolamide to treat adults with CSA due to high altitude: disease severity. None of the studies identified in our literature review reported data for the following critical outcomes: excessive sleepiness, daytime functioning, or quality of life,

DISEASE SEVERITY: An analysis of one RCT[132] showed a clinically significant reduction in AHI in the acetazolamide group compared to control (MD -21; 95% CI: -34.68 to -7.32; n=20) and a clinically significant reduction in the desaturation index (MD -30.30, 95% CI: -45.19 to -15.41; n=20). Baseline values were not reported for disease severity measures. The TF compared the intervention to control to determine clinical significance. The dose of acetazolamide was 250 mg twice daily starting three days prior to ascent. The duration of patient follow-up after treatment was two nights (see supplemental material, Figure S230 and S231).

Another RCT[133] (acetazolamide dose was 250 mg every eight hours for three doses with participants used as their own controls) showed a clinically significant reduction in percentage of time with periodic breathing in the acetazolamide group compared to baseline (MD -23.7, 95% CI: -49.55 to 2.15; n=4) and in oxygen saturation < 70% (MD -11.82, 95% CI: -17.73 to -5.91; n=4). The duration of patient follow-up after treatment was one night (see supplemental material, Figure S232 and S233).

Important Outcomes

The TF determined the following outcomes to be important outcomes but not critical for evaluating the efficacy of acetazolamide to treat adults with CSA due to high altitude: sleep architecture measured by PSG.

SLEEP ARCHITECTURE (PSG): Several objective measures were used to report sleep architecture in one RCT.[132] The dose of acetazolamide was 250 mg taken twice daily. The analysis did not show a clinically significant improvement in SE compared to control (MD -11.7, 95% CI: -14.56 to -8.84; n=20); showed a clinically significant improvement in arousal index (MD -10, 95% CI: -19.62 to -0.38; n=20); a non-clinically significant improvement in REM% (MD 3.7, 95% CI: -0.86 to 8.26; n=20); a clinically significant improvement in sleep stage N1% (MD -8.2, 95% CI: -13.0 to -3.40; n=20); no difference detected in sleep stage N2% (MD 0.2, 95% CI: -5.66 to 6.06; n=20) nor sleep stage N3% (MD 0.5, 95% CI: -2.13 to 3.13; n=20); and an increase in sleep stage N4% (no CST, MD 3.9, 95% CI: -2.24 to 10.04; n=20). The duration of patient follow-up after treatment was two nights (see supplemental material, Figure S234 to 240).

OVERALL QUALITY OF EVIDENCE: The TF determined that the overall certainty of evidence for the use of acetazolamide in adults with CSA due to high altitude was very low based on the critical outcomes and downgrading of the evidence due to imprecision and indirectness (see supplemental material, Table S9).

BENEFITS VS HARMS: The potential benefits of acetazolamide in adults with CSA due to high altitude include a clinically significant improvement in disease severity and sleep architecture (arousals and N1). The potential harms include mild paresthesia, impaired taste of carbonated drinks, and diuresis. Based on their combined clinical experience, the TF judged that the potential benefits of acetazolamide in adults with CSA due to high altitude outweigh the potential harms.

RESOURCE USE: The current unit cost for acetazolamide is $0.14 for a 250 mg tablet, based on estimated costs in the United States. The TF judged this cost as negligible.

PATIENTS' VALUES AND PREFERENCES: The TF judged that there is probably no important uncertainty or variability in how much patients value the main outcomes. Given the clinically significant improvement in disease severity and sleep architecture (arousals, N1), the TF judged that most adults with CSA due to high altitude would generally be accepting of treatment with acetazolamide.

OTHER INTERVENTIONS

ASV for CSA due to high altitude

One cross over RCT presented in two separate publications[130, 131] measured various outcomes of ASV for treatment of CSA at high altitude. Since only one study reported on these outcomes, a meta-analysis could not be performed. This study included 18 healthy participants (12 men, 6 women) aged 29 ± 4 years, who ascended to altitude (3800 m) and were randomized to a different treatment group each night for 3 nights: 1) no treatment, 2) 2L per minute supplemental oxygen or higher to maintain oxygen saturation >95%, and 3) ASV. Mean use for ASV was 7 ± 1.5 hours. The analyses and summary of findings table are provided in the supplemental material (Figures S241 to S247; Table S10). A summary of the evidence for each outcome is provided below.

Critical Outcomes

The TF determined the following outcomes to be critical for evaluating the efficacy of ASV to treat adults with CSA due to high altitude: excessive sleepiness, disease severity, daytime functioning, and quality of life.

EXCESSIVE SLEEPINESS: Measured by the SSS, the analysis of one RCT[130] did not show a clinically significant improvement in SSS for the ASV group compared to control (MD -0.2, 95% CI -1.01 to 0.61; n=14; see supplemental material, Figure S241).

DISEASE SEVERITY: One RCT[130] did not show a clinically significant reduction in ODI for the ASV group compared to control (MD -6.9, 95% CI -16.73 to 2.93; n=14; see supplemental material, Figure S242).

DAYTIME FUNCTIONING: One RCT[130] reported results from the AMS score. There was a decrease in AMS score that favored the ASV group compared to control (MD -0.3, 95% CI -1.45 to 0.85; n=14). There was no a priori CST (see supplemental material, Figure S243).

QUALITY OF LIFE: One RCT[131] reported both POMS-A confusion score and fatigue score as a measure of quality of life (no a priori CST). There was a decrease in POMS-A scores that favored the ASV group compared to control (confusion-MD -0.6, 95% CI -1.47 to 0.27; n=17; fatigue-MD -1, 95% CI -4.73 to 2.73; n=17; see supplemental material, Figure S244 and S245).

Important Outcomes

The TF determined the following outcomes to be important outcomes but not critical for evaluating the efficacy of ASV to treat adults with CSA due to high altitude: sleep architecture.

SLEEP ARCHITECTURE (PSG): One RCT[130] reported both arousal index and sleep stage N1% as measures of sleep architecture. One analysis showed almost no difference in arousals compared to control (MD 0.7, 95% -3.17 to 4.57; n=14). There was also no difference detected in sleep stage N1% for the ASV group compared to control (MD 0.4, 95% CI -3.41 to 4.21; n=14; see supplemental material, Figure S246 and S247).

OVERALL QUALITY OF EVIDENCE: The TF determined that the overall certainty of evidence for the use of ASV in adults with CSA due to high altitude was very low based on the critical outcomes and downgrading of the evidence due to imprecision and risk of bias (see supplemental material, Table S10).

BENEFITS VS HARMS: The potential benefits of ASV in adults with CSA due to high altitude were judged to be trivial. The potential harms could not be determined with the current evidence. Based on their combined clinical

experience, the TF judged that there was no difference in the potential benefits or harms of ASV in adults with CSA.

RESOURCE USE: The current cost of ASV can range from $1,495 and $1,770 depending on the delivery system. The TF judged this cost as moderate. This judgment was based on estimated costs in the United States.

PATIENTS' VALUES AND PREFERENCES: The TF judged that there is possibly important uncertainty or variability in how much patients value the main outcomes. Because of the transient nature of the disease as well as the lack of feasibility in using an ASV device at high altitude, the TF decided not to prioritize this PICO question.

DISCUSSION & FUTURE DIRECTIONS

This systematic review updates the previously published practice parameters on the treatment of CSA in adults.[1, 2] The use of the GRADE methodology offers a systematic approach that minimizes bias with recommendations based on the balance between the benefits and harms of each treatment intervention. In this systematic review, RCTs generally resulted in higher quality evidence over observational studies.

The International Classification of Sleep Disorders (ICSD) 3rd edition text revision (ICSD-3-TR)[134] conceptualizes central apnea as part of several clinical syndromes. However, clinical studies do not necessarily follow the ICSD-3-TR classification in study design (see supplemental material, Table S11). Many studies include CSA of varied etiologies, whereas other studies focus exclusively on central apneas in patients with HF. Further, the basis for classification of primary CSA in some studies was unclear, often not based on a robust process of elimination of alternative conditions, and not necessarily based on a thorough process of determination, such as assessment of cardiac function or exclusion of opioid use. The pathophysiology of CSA secondary to a medical condition is heterogenous as it includes a panoply of clinical and neurological conditions with many pathophysiological mechanisms that defy easy classification. Similarly, CSA secondary to a medication may be due to hypoventilation or post hyperventilation.

Treatment options for CSA can be broadly classified into positive pressure therapy, agents that modulate ventilatory control mechanisms, such as supplemental oxygen and acetazolamide, and implanted devices that stimulate the phrenic nerve. Given the common pathophysiological pathways of all types of CSA and the limited number of available studies in each class of CSA, the TF, when appropriate, grouped studies evaluating a certain modality but in different classes of CSA. This approach allowed extrapolation of the evidence for treatment benefits in one class of CSA to other classes unless there was a strong physiologic or mechanistic reason not to do so.

CPAP therapy for CSA is "repurposed" from OSA. This was first proposed by Issa and Sullivan, who demonstrated the reversal of CSA using nasal CPAP. Mechanisms of action include: 1) elimination of concomitant obstructive events and prevention of pharyngeal narrowing during central apnea, hence mitigating ventilatory overshoot during the recovery period, and 2) increased lung volume, which may decrease plant gain by dampening changes in $PaCO_2$ for a given change in ventilation. Overall, these factors, in aggregate, should dampen the ventilatory overshoot and mitigate the perpetuation of ventilatory instability. Available studies investigating CPAP in patients with CSA have shown decreased AHI, but only one study reported the effect of CPAP on CAI per se. Interestingly, no study has reported the resolution of CSA with CPAP therapy. Further, conclusive long-term outcomes and patient-reported outcomes are lacking. While CPAP has been used for CSA of varied etiologies, several areas of uncertainty persist. A key question is whether CPAP effects are mediated by preventing upper airway obstruction or by stabilizing the

ventilatory control system. Other opportunities for future studies include investigating physiologic determinants of response that could inform the choice of CPAP for CSA.

Supplemental oxygen also attenuates central apnea by decreasing peripheral chemoreflex sensitivity and mitigating ventilatory overshoot. Additionally, oxygen therapy may also stimulate respiration via the Haldane effect. Supplemental oxygen results in a significant improvement in disease severity (AHI) and a variable effect on daytime outcomes. Differences in study design, selection criteria, and duration of treatment may have contributed to variability in outcome.

Acetazolamide is a mild diuretic and a respiratory stimulant that has been used to treat periodic breathing at high altitude and then investigated as a potential treatment of CSA, including CSA associated with Cheyne-Stokes respiration and HF. Acetazolamide has a strong safety profile and exerts no effect on the peripheral chemoresponse or sympathetic activity. Acetazolamide decreases plant gain by increasing alveolar ventilation, with no change in CO_2 chemoreflex sensitivity. There is evidence that acetazolamide may mitigate ventilatory overshoot by increasing cerebrovascular reactivity, independent of changes in peripheral or central chemoreflex sensitivities. Overall, the effect of acetazolamide on CSA appears to be modest. This may be explained by the variable dosing and duration of response to the medication. Further, using acetazolamide requires monitoring electrolytes to ascertain appropriate metabolic response. While acetazolamide has a favorable safety profile, consideration of potential dose-dependent side effects and drug-drug interaction is required.[135] Future research is needed to ascertain optimal dosing and to determine impact on long term objective and patient-reported outcomes.

TPNS is an innovative treatment for CSA. TPNS has been studied primarily in patients with CSA due to HF and, to a lesser extent, in those with primary CSA. The device is implanted by specialized electrophysiologists or cardiothoracic surgeons. Venous access is achieved through the axillary, cephalic, or subclavian vein, and the stimulation lead is positioned in the left pericardiophrenic or brachiocephalic vein, adjacent to the corresponding phrenic nerve. The device is then programmed to stimulate the phrenic nerve during sleep, inducing smooth diaphragmatic contractions that replicate normal breathing.[136] The precise mechanism by which TPNS alleviates CSA, and its symptoms remains unclear, whether through stabilizing carbon dioxide levels and ventilatory control or preventing oxygen desaturations and associated arousals and sympathetic nervous system activation. Research demonstrated an 80% reduction in the CAI, improved daytime sleepiness as measured by the ESS, enhanced quality of life, and a clinically significant increase in the 6MWD. However, it had no impact on mortality. The number of patients included in TPNS studies thus far is small, and long-term safety data is available for only a limited subset.

Limitations

Central apnea during sleep is rarely an isolated disorder. Rather, it is a manifestation of breathing instability in a variety of clinical conditions, including OSA, HF, and opioid analgesic use. Each condition leaves its distinct imprint on this phenomenon and influences the clinical syndrome with features of the underlying condition. Although our understanding of the specific mechanism(s) of central apnea has grown appreciably in the past decade, significant gaps persist. Likewise, the pathophysiologic overlap between central and obstructive sleep apnea defies separation into two distinct “silos.”

The review included studies that investigated participants with predominantly central events, whereas other studies included participants with co-morbid OSA. This would be ecologically valid as the majority of patients with central apnea seen in clinical sleep laboratories have co-morbid OSA.[137, 138] Furthermore, the majority of patients with

CSA also have co-morbid OSA because of a compromised upper airway. The burgeoning obesity epidemic may also have changed the epidemiology of CSA by increasing the prevalence of concomitant upper airway obstruction. Specifically, obese individuals with unfavorable upper airway anatomy may experience co-morbid OSA, and hence not be diagnosed with CSA. Conversely, extant studies and clinical experience are likely to underestimate the prevalence of CSA owing to the failure to identify central hypopnea in most studies and in clinical sleep laboratories.

Accurate identification of central hypopnea may have significant implications regarding the prevalence and outcome of CSA. Misclassification of central hypopneas in clinical laboratories may be exacerbated among women, especially pre-menopausal women, who are less susceptible to central apnea, relatively resistant to experimentally induced central apnea, and may instead develop central hypopnea. This could lead to being lumped under the umbrella of obstructive hypopnea. Thus, the identification of central hypopnea may mitigate gender disparity in the diagnosis of CSA.

The variability in the definition of CSA posed a unique challenge when reviewing existing literature. Many studies simply used CSA ≥5 events/hour as a criterion, whereas others required that CAI > 50% of total AHI. This criterion may have excluded some CSA patients because events scored as hypopneas were categorized as obstructive rather than central in many studies. Thus, excluding studies that do not meet the 50% threshold may diminish ecological validity and generalizability by excluding patients whose bona fide CSA is falling short on a priori restrictive definition.[139]

In addition to the limited number of RCTs and small size of most studies, the TF found that most studies had a relatively short follow up period, used various diagnostic criteria for CSA, or did not evaluate patient-related outcomes. Furthermore, there were very few studies with adequate sample sizes to address long term outcomes of interest identified during the planning phase of this systematic review, such as mortality. The TF, therefore, attempted whenever possible to consider the longest term of any evaluated outcome. Finally, many studies, especially those focusing on devices, were industry-sponsored, and may have incorporated proprietary features that prevent generalizability to similar devices. The availability of these interventions, including ASV and TPNS, varies in different areas and is subject to payors' restrictions. Thus, there is a concern regarding inequity in access to novel and expensive therapies.

Impact on research and addressing research gaps

The review identified several research gaps that require future research. First, physiology-based treatment for CSA remains elusive. The multitude of clinical syndromes that include CSA required that findings of this review be extrapolated to cover several conditions that were not specifically examined. Therefore, there is an urgent need to investigate and test CSA treatments based on the unique pathophysiology of these conditions rather than the clinical syndrome per se. In addition, there is an unmet need to include patient-reported outcomes and long-term objective outcomes in future studies investigating the treatment of CSA. Most existing therapies ameliorate but do not resolve CSA, thus perpetuating recurrent respiratory events.

Second, available studies address a single intervention. Given that the development of CSA may represent a convergence of multiple precipitating and perpetuating factors (i.e., equifinality), there is a critical need for mechanistic studies to investigate multimodality regimens targeting normalization of respiration rather than amelioration of CSA. Multimodality therapy combining positive pressure, as well as low-flow oxygen or a pharmacologic agent, may be meritorious.

Third, the breadth of the diagnostic categories poses another challenge for clinical trials. For example, CSA secondary to a medical condition, is a broad category that includes diverse clinical conditions that are unrelated etiologically. Similarly, CSA secondary to a medication includes multiple medications operating via multiple pathways. The diagnosis of primary CSA also requires a thorough process of elimination to exclude cardiac disease or medications.

Fourth, there is a critical need to develop and investigate novel treatments for CSA, incorporating the heterogeneity of the condition.[25] Finally, identification of optimal therapy requires patient-reported outcome data as well as comparative effectiveness research with head-to-head comparison of different therapeutic interventions.

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