Treatment of Central Sleep Apnea in Adults:

An American Academy of Sleep Medicine Clinical Practice Guideline

Introduction: This guideline establishes clinical practice recommendations for treatment of central sleep apnea (CSA) syndromes in adults.

Methods: The American Academy of Sleep Medicine (AASM) commissioned a task force of experts in sleep medicine to develop recommendations and assign strengths based on a systematic review of the literature and an assessment of the evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology. The task force provided a summary of the relevant literature and the certainty of evidence, the balance of benefits and harms, patient values and preferences, and resource use considerations that support the recommendations. The AASM Board of Directors approved the final recommendations.

Good Practice Statement: The following good practice statement is based on expert consensus, and its implementation is necessary for the appropriate and effective management of patients with CSA. The optimal approach to CSA treatment should incorporate clinical features, co-morbid conditions, and polysomnographic findings in an individualized manner. Specifically, clinicians must prioritize optimizing therapy for the conditions contributing to central apneas and improving patient-reported outcomes rather than solely focusing on eliminating disordered breathing events. Once therapy for CSA has been initiated, persistence of central respiratory events should prompt re-evaluation of the underlying risk factors and consideration of alternative treatment options.

Recommendations: The following recommendations are intended as a guide for clinicians in choosing a specific treatment for adults with CSA. Each recommendation statement is assigned a strength ("Strong" or "Conditional"). A "Strong" recommendation (i.e., "We recommend…") is one that clinicians should follow under most circumstances. A "Conditional" recommendation (i.e., "We suggest …") is one that clinicians should offer to most patients if clinically appropriate. Some recommendations include remarks that provide additional context to guide clinicians with implementation of this recommendation.

1. The AASM suggests using continuous positive airway pressure (CPAP) over no CPAP in adults with CSA due to the following etiologies: 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. (Conditional recommendation, low certainty evidence.)

2. The AASM suggests using bilevel positive airway pressure (BPAP) *with a backup rate* over no BPAP with a backup rate in adults with CSA due to the following etiologies: primary CSA, CSA due to medication or substance use, treatment-emergent CSA, and CSA due to a medical condition or disorder. (Conditional recommendation, very low certainty).

3. The AASM suggests **against** the use of BPAP *without a backup rate* in adults with CSA due to the following etiologies: 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. (Conditional recommendation, very low certainty).

4. The AASM suggests using adaptive servo ventilation (ASV) over no ASV in adults with CSA due to the following etiologies: 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. (Conditional recommendation, low certainty).

Remarks: Devices that deliver adaptive servo ventilation have different proprietary algorithms for sensing and responding to respiratory events. Safety data is not available for all devices on the market. Increased mortality was associated with only one device in patients with heart failure with reduced ejection fraction and this device is no longer being manufactured.

5. The AASM suggests using low-flow oxygen over no low-flow oxygen in adults with CSA due to heart failure. **(**Conditional recommendation, low certainty).

6. The AASM suggests using low-flow oxygen over no low-flow oxygen in adults with CSA due to high altitude. (Conditional recommendation, very low certainty)

Remarks: Patients with transient and mild CSA symptoms at high altitude may reasonably decline treatment with low-flow oxygen.

7. The AASM suggests using oral acetazolamide over no acetazolamide in adults with CSA due to the following etiologies: 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. (Conditional recommendation, low certainty).

8. The AASM suggests using oral acetazolamide over no acetazolamide in adults with CSA due to high altitude. (Conditional recommendation, very low certainty)

9. The AASM suggests using transvenous phrenic nerve stimulation (TPNS) over no TPNS in adults with CSA due to the following etiologies: primary CSA and CSA due to heart failure who have failed other therapies. (Conditional recommendation, very low certainty).

INTRODUCTION

This clinical practice guideline updates the previously published American Academy of Sleep Medicine (AASM) practice parameters on the treatment of central sleep apnea syndromes (CSA) and reflects current recommendations of the AASM.[1, 2] Since these publications, the AASM has modified its development of clinical practice guidelines according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) process.[3] Several notable developments have taken place since the publication of the previous guidelines, including newly published studies on ASV and the introduction of phrenic nerve stimulation as a novel therapy for CSA.

Central sleep apnea (CSA) is a form of sleep-disordered breathing (SDB) in which cessations or decreases in airflow are coupled with corresponding absence or reduction of respiratory effort.[4] CSA is not a single disorder but represents central breathing instability in various clinical conditions, including heart failure, obstructive sleep apnea (OSA), and opioid analgesic use. The sleep state (specifically non-rapid eye movement or NREM sleep) removes the wakefulness "drive to breathe," rendering respiration critically dependent on the partial pressure of carbon dioxide ($PaCO_2$) and unmasking the hypocapnic apneic threshold. Accordingly, central apnea results from transient cessation of ventilatory motor output, which occurs when inhibitory influences promoting instability predominate over excitatory influences favoring stable breathing. The pathogenesis of CSA can vary depending on the underlying clinical condition. However, in non-hypercapnic central apnea, the final common pathway involves post-hyperventilation hypocapnia, which leads to central apnea. The development and persistence of CSA through multiple mechanisms exemplify the concept of "equifinality," where central apnea can be triggered by distinct etiological pathways. Opioid-induced CSA is somewhat distinct from other types of CSA in that the breathing pattern can occur with a depressed central respiratory drive and decreased chemosensitivity unlike the increased chemosensitivity present in other types of CSA such as hypoxia or heart failure (HF) related CSA. This pathophysiological heterogeneity may account for the diverse clinical presentations of CSA and the lack of a universally effective treatment for all patients.[5] The management strategy should consider polysomnographic findings, individual patient factors, and the underlying conditions, which should be addressed as a key component of the therapeutic plan.

The International Classification of Sleep Disorders-3rd edition, text revision (ICSD-3-TR) classifies CSA in adults into six categories: primary CSA, CSA with Cheyne-Stokes respiration (CSR) (frequently due to underlying HF), CSA due to a medication or substance, CSA due to a medical disorder without Cheyne-Stokes, treatment-emergent CSA, and CSA due to high altitude.[4] Though the definition of CSA requires that >50% of respiratory events be central in nature, in some patients, the true nature of the sleep-related breathing disorder (whether central or obstructive), cannot be determined with confidence during routine polysomnography (i.e., without the use of esophageal pressure monitoring). This is especially true of patients whose respiratory events are predominantly hypopneas.[6] As such, the true classification of the underlying sleep-related breathing disorder can be challenging in the clinical setting. In addition, patients frequently present with mixed disorders, in which both obstructive and central events occur, and the choice of treatment should address both disorders if present. CSA is associated with sleep fragmentation, daytime sleepiness, insomnia, and poor quality of life, and may portend a poor clinical outcome. In addition, CSA can be associated with significant adverse clinical consequences, including increased mortality and hospitalization in patients with heart failure.[7] [8] In a recent 21-year retrospective study of the Veterans Health Administration's electronic medical records, almost one-fifth of patients with CSA died within five years of diagnosis.[9] As the accompanying systematic review (cite) demonstrates, treatment of central sleep apnea is warranted to mitigate long-term adverse consequences.

CSA remains a poorly understood and sometimes misinterpreted disorder, particularly in terms of its mechanisms, clinical manifestations, and treatment indications.[10] Significant knowledge gaps in the pathogenesis of the respiratory control instability underlying CSA hinder the development of a pathogenesis-based classification system. This lack of understanding also complicates the identification of clinical and physiological factors that contribute to the onset of CSA across different health conditions.

The aforementioned knowledge gaps present two major challenges. First, the current classification relies on clinical presentation rather than underlying pathophysiology. Polysomnographic criteria for CSA classification, particularly hypopnea scoring, are inconsistently applied in clinical practice and were seldom utilized in the studies reviewed by the task force (TF). Second, treatment options targeting specific mechanistic pathways of CSA are limited. There is a lack of treatment strategies based on precise pathophysiological traits of individual CSA syndromes. These challenges and limitations have impeded progress in the field for decades, leading to a narrow range of treatment options for CSA patients.

These guidelines are limited by the quantity, quality, and variability of available studies. CSA is less common and less well understood than OSA, and consequently, there are fewer studies and investigations on the disorder. This lack of research has been further compounded by recent clinical trials in both CSA and OSA, which failed to demonstrate clinical benefits of treatment. Considering the limited number of studies available for certain patient populations and the shared pathophysiological mechanisms across various types of CSA, the TF aimed to group studies that evaluated similar treatments across different CSA subtypes. When appropriate, the TF reviewed both individual and grouped data to provide a more comprehensive assessment of treatment effectiveness and enhance confidence in clinically relevant recommendations.

This guideline, in conjunction with the accompanying systematic review (cite), provides a comprehensive update of the available evidence and a synthesis of clinical practice recommendations for the treatment of CSA. It is intended to optimize patient-centric care by broadly informing clinicians who care for patients with CSA.

METHODS

The AASM commissioned a TF of sleep medicine clinicians with expertise in 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.

The TF conducted a systematic review of the published scientific literature, focusing on patient-oriented, clinically relevant outcomes. The key terms, search limits, and inclusion/exclusion criteria specified by the TF are detailed in the supplemental material of the accompanying systematic review (cite). The purpose of the review was to determine whether the interventions provided clinically significant improvements in relevant outcomes in relation to no treatment. 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 (cite the SR). The TF established a hierarchy of critical outcomes according to their importance to assess the effectiveness of treatment in adults with CSA. The following outcome measurement tools were considered most critical for decision-making: 1) excessive sleepiness; 2) disease severity (in order of importance - apnea-hypopnea index [AHI], central apnea index [CAI], central apnea-hypopnea index [CAHI], oxygen desaturation index [ODI]); 3) cardiovascular disease (6-minute walk distance [6MWD], New York Heart Association [NYHA] class); 4) hospitalizations; 5) patient-reported sleep quality; 6) mortality. Adverse events within the accepted literature were included in assessing the balance of beneficial and harmful effects. When the available evidence was not sufficient, other important outcomes were considered for decision-making. The clinical practice recommendations were then developed according to the GRADE process.[3, 11] The TF assessed the following four components to determine the direction and strength of a recommendation: quality of evidence, balance of beneficial and harmful effects, patient values and preferences, and resource use. Additionally, the impact on equity, feasibility, and acceptability was discussed. There was no direct evidence regarding health equity. For example, there was no direct evidence for individuals with mobility limitations or facial deformities that historically have received inequitable care and where certain treatments may not work as effectively for various reasons. Details of these assessments can be found in the accompanying systematic review. Taking these major factors into consideration, each recommendation statement was assigned a strength ("Strong" or "Conditional"). Additional information is provided in the form of "Remarks" immediately following the recommendation statements, when deemed necessary by the TF. Remarks are based on the evidence evaluated during the systematic review and are intended to provide context for the recommendations and to guide clinicians in the implementation of the recommendations in daily practice.

This clinical practice guideline reflects the evidence and state of knowledge at the time of the last literature search, July 2024. Scoping literature searches are performed annually on all published AASM clinical practice guidelines to review new evidence. Based on this review, updates may be made if there are significant changes in areas such as the available interventions, outcomes of interest (or values placed on outcomes), or evidence regarding the existing benefits and harms. The ultimate judgment regarding the suitability of any specific recommendation requires the clinician to use clinical knowledge and experience and strongly consider the individual patient's values and preferences to determine the best course of action.

RECOMMENDATIONS

The following clinical practice recommendations are based on a systematic review and evaluation of evidence using the GRADE process. The implications of the strength of recommendations for guideline users are summarized in **Table 1**. Remarks are provided to guide clinicians in the implementation of these recommendations.

Table 1 – Implications of Strong and Conditional Recommendations for Users of AASM Clinical Practice Guidelines

User	Strong Recommendations *"We recommend…"*	Conditional Recommendations *"We suggest…"*
Clinicians	Almost all patients should be offered the recommended course of action. Adherence to this recommendation could be used as a quality criterion or performance indicator.	Most patients should be offered the suggested course of action; however, different choices may be appropriate for different patients. The clinician must help each patient determine if the suggested course of action is clinically appropriate and consistent with their values and preferences.
Patients	Almost all patients should be offered the recommended course of action, although a small proportion of patients would not choose it.	Most patients should be offered the suggested course of action, though some may not choose it. Different choices may be appropriate for different patients. The patient should work with their clinician to determine if the suggested course of action is clinically appropriate and consistent with their values and preferences.
Policy Makers	The recommended course of action can be adopted as policy for most situations. Adherence to the recommended course of action could be used as a quality criterion or performance indicator.	The ultimate judgment regarding the suitability of the suggested course of action must be made by the clinician and patient together, based on what is best for the patient. This decision-making flexibility should be accounted for when establishing policies.

GOOD PRACTICE STATEMENT

The following good practice statement is based on expert consensus, and its implementation is necessary for the appropriate and effective management of patients with CSA. The optimal approach to CSA treatment should incorporate clinical features, co-morbid conditions, and polysomnographic findings in an individualized manner. Specifically, clinicians must prioritize optimizing therapy for the underlying condition and improving patient-reported outcomes rather than solely focusing on eliminating disordered breathing events. Once therapy for CSA has been initiated, persistence of central respiratory events should prompt re-evaluation of the underlying risk factors and consideration of alternative treatment options.

Table 2 – Summary of recommendations

ADULTS WITH CENTRAL SLEEP APNEA							
Intervention	**Strength of recommendation**	Critical Outcomes Meeting the Clinical Significance Threshold*					
		Excessive sleepiness	Disease severity	CVD	Hospitalizations	Sleep quality^	Mortality
CPAP[1]	Conditional for	N	Y	N	no CST[a]	-	Y
BPAP with a backup rate[2]	Conditional for	Y	Y	Y	-	-	-
BPAP without a backup rate[1]	Conditional against	-	Y	Y	-	-	-
ASV[1]	Conditional for	N	Y	N	N	N	N
Low-flow O2[3]	Conditional for	N	Y	N	no CST[a]	no CST[b]	-
Acetazolamide[1]	Conditional for	Y	Y	N	-	no CST[b]	-
TPNS[4]	Conditional for	Y	Y	Y	-	-	N

ADULTS WITH CENTRAL SLEEP APNEA DUE TO HIGH ALTITUDE**					
Intervention	**Strength of recommendation**	Critical Outcomes meeting Clinical Significance Threshold*			
		Excessive sleepiness	Disease severity	Daytime functioning	Quality of life
Low-flow O2	Conditional for	N	Y	no CST[b]	no CST[b]
Acetazolamide	Conditional for	-	Y	-	-

*Clinical significance thresholds can be found in the accompanying systematic review; CVD – cardiovascular disease; ^ – patient-reported outcome measure
– outcome not reported.
[1] – 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
[2] – primary CSA, CSA due to medication or substance use, treatment-emergent CSA, and CSA due to a medical condition or disorder
[3] – CSA due to heart failure
[4] – primary CSA and CSA due to heart failure who have failed other therapies
N – no; Y – yes; [a] –data was reported as a continuous outcome and could not be assessed for clinical significance. [b] –outcome was reported using a tool that the TF did not establish an a priori CST and could not be assessed for clinical significance.
**Recent ascent to high altitude (at least 2,500 meters [8,202 feet])

ADULTS WITH CENTRAL SLEEP APNEA

Recommendations with sufficient evidence for specific interventions for the treatment of adults with CSA are presented below and summarized in Table 2. Remarks are provided to guide clinicians in the implementation of these recommendations. For all interventions, the TF assessed effectiveness for the treatment of CSA in adults based on the following critical outcomes: excessive sleepiness, disease severity (AHI, CAI, CAHI, ODI), cardiovascular disease, hospitalizations, decrease in mortality, daytime functioning, and quality of life.

CONDITIONAL Recommendations:

Recommendation 1: The AASM suggests using CPAP over no CPAP in adults with CSA due to the following etiologies: 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. (Conditional recommendation, low certainty evidence)

The TF identified 11 RCTs ranging from one night to six months. The pooled results demonstrated clinically significant improvements in disease severity (AHI) and reduction in mortality. The pooled results for excessive sleepiness, disease severity (CAI), cardiovascular disease, and hospitalizations did not meet clinical significance. The potential benefits of CPAP had a small effect size. No serious adverse events were reported in the studies included. The undesirable effect size was deemed trivial. The TF judged the potential benefits of CPAP outweigh the potential harms.

The overall quality of evidence was low due to imprecision. The cost of CPAP was determined to be moderate. There was no direct evidence of the impact of CPAP on health equity, as cost varies depending on insurance coverage and access to sleep centers. The intervention was determined to be feasible to implement.

Recommendation 2: The AASM suggests using BPAP with a backup rate over no BPAP with a backup rate in adults with CSA due to the following etiologies: primary CSA, CSA due to medication or substance use, treatment-emergent CSA, and CSA due to a medical condition or disorder. (Conditional recommendation, very low certainty).

The TF identified 6 RCTs and 3 observational studies ranging from one night to six months of treatment. The pooled estimates demonstrated clinically significant improvements in excessive sleepiness, disease severity (AHI, CAI, CAHI), and cardiovascular disease with a small effect size. Small undesirable effects related to the mask interface were reported anecdotally in a few patients, and 1 patient (of the 128 total participants who enrolled and completed treatment in the 9 studies) was reported to have died due to cardiovascular causes. The TF judged that the potential benefits of BPAP with a backup rate outweigh the potential harms.

The overall quality of evidence was very low due to imprecision. The cost of BPAP with a backup rate was considered moderate. There was no direct evidence that the BPAP with a backup rate would impact health equity; however, due to payor coverage variability, the intervention might reduce health equity. Treatment with BPAP with a backup rate was found to be acceptable and probably feasible to implement.

Recommendation 3: The AASM suggests <u>against</u> the use of BPAP without a backup rate in adults with CSA due to the following etiologies: 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. (Conditional recommendation, very low certainty)

The TF identified one RCT of bilevel without a backup rate. However, this study utilized a very modest level of pressure support to provide comfort that can be considered more similar to present-day CPAP with modified pressure relief settings. The results demonstrated clinically significant improvements in disease severity (AHI, CAI) and cardiovascular outcomes after 3 months of treatment, with a small effect size. However, extensive literature shows that BPAP without a backup rate can induce CSA and periodic breathing if excessive pressure

support is provided.[12-14] While these studies were conducted in healthy individuals or those with OSA, they provide indirect evidence regarding the potential harms of BPAP without a backup rate in adults with CSA. Thus, the undesirable effect size was deemed to be large.

The TF judged that the potential harms of BPAP without a backup rate outweigh the potential benefits. The certainty of the evidence was rated as very low due to imprecision. The cost of the treatment was considered moderate. BPAP was determined to be feasible to implement. There was no direct evidence that the treatment would reduce health equity, but it may not be acceptable.

Recommendation 4: The AASM suggests using ASV over no ASV in adults with CSA due to the following etiologies: 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. (Conditional recommendation, low certainty).

Remarks: Devices that deliver adaptive servo-ventilation have different proprietary algorithms for sensing and responding to respiratory events. Safety data are not available for all devices on the market. Increased mortality was associated with only one device in patients with heart failure with reduced ejection fraction, and this device is no longer being manufactured.

The TF identified 12 RCTs ranging from one night to five years. The pooled estimates demonstrated clinically significant improvements in disease severity (AHI, CAI, CAHI). The pooled results for excessive sleepiness, cardiovascular disease, hospitalizations, and patient-reported sleep quality did not meet clinical significance. The TF also considered the effect of ASV on polysomnographic sleep architecture parameters and found a clinically significant effect on the arousal index. The potential benefits of ASV had a moderate effect size. The TF reviewed the pooled estimate on all-cause mortality and cardiovascular mortality in all RCTs, specifically in patients with heart failure with reduced ejection fraction (HFrEF). There was no change in mortality with ASV. The undesirable effect size was deemed small. The TF judged the potential benefits of ASV to outweigh the potential harms.

The overall quality of evidence was low and was downgraded due to imprecision and risk of bias. The cost of ASV was considered moderate. There was no direct evidence that ASV would impact health equity; however, due to payor coverage variability and the need to access a sleep lab, the intervention might reduce health equity. Treatment with ASV was found to be acceptable and probably feasible to implement.

Recommendation 5: The AASM suggests using low-flow oxygen over no low-flow oxygen in adults with CSA due to heart failure. (Conditional recommendation, low certainty)

The TF identified 7 RCTs and 3 observational studies. The study duration varied from one night to one year. The pooled estimates demonstrated clinically significant improvement in disease severity (AHI, CAI). The pooled results for excessive sleepiness and cardiovascular disease (6MWD) did not meet clinical significance. There were reduced hospitalizations and improvements in patient-reported sleep quality, as measured by outcomes without pre-specified CSTs. Though limited effects on patient-related outcomes, a small effect size was seen on sleep disordered breathing events. The TF identified 2 RCTs that reported on the presence of adverse events related to cardiac events. The undesirable effect size was deemed trivial. The TF judged that the potential benefits of low-flow oxygen outweigh the potential harms.

The overall quality of evidence was low due to imprecision. All judgments were based on the studies evaluating low-flow oxygen treatment. The recommendation was limited to CSA in heart failure given the insufficient evidence in other forms of CSA. The cost of low-flow oxygen was considered moderate. There was no direct evidence that the low flow oxygen would impact equity. However, it is not standard of care, may not be covered by all payors, and might reduce health equity. Treatment with low-flow oxygen was found to be acceptable and feasible to implement.

Recommendation 6: The AASM suggests using low-flow oxygen over no low-flow oxygen in adults with CSA due to high altitude. (Conditional recommendation, very low certainty)

Remarks: Patients with transient and mild CSA symptoms at high altitude, may reasonably decline treatment with low-flow oxygen.

The TF identified one randomized cross-over study of healthy volunteers at 3800 meters ascension and found a single night of low-flow oxygen therapy led to a clinically significant improvement in disease severity (ODI) after a single night of treatment. There were improvements in daytime functioning and quality of life for which there were no pre-specified CSTs. However, there was no clinically significant improvement in excessive sleepiness. The potential benefits of low-flow oxygen had a moderate effect size. No adverse events were reported. The undesirable effect size was deemed trivial. The TF judged that the potential benefits of low-flow oxygen outweigh the potential harms.

The overall certainty of evidence was very low due to imprecision and risk of bias. The cost of the treatment was considered moderate. There is no direct evidence that the treatment would impact equity. However, low-flow oxygen is not the standard of care, may not be covered by all payors, and might reduce health equity. There may be important uncertainty and variability about the value of outcomes depending on time spent and activities planned at altitude. The intervention was determined probably feasible to implement.

Recommendation 7: The AASM suggests using oral acetazolamide over no acetazolamide in adults with CSA due to the following etiologies: 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. (Conditional recommendation, low certainty)

The TF identified 3 RCTs where the study duration varied from three to six nights. The participants in the studies received a dosage of acetazolamide ranging from 250 milligrams (mg) to 1,000 mg. The pooled estimates showed clinically significant improvements in excessive sleepiness and disease severity (AHI) with no significant improvement in cardiovascular parameters. The potential benefits of acetazolamide had a moderate effect size. The undesirable effects were considered trivial and included paresthesia of hands and feet, impaired taste, and increased diuresis. The TF judged that the potential benefits of acetazolamide outweigh the potential harms.

The overall quality of evidence was low due to imprecision. The cost of medication was considered negligible, the intervention was determined to be feasible to implement and acceptable. There was no direct evidence that the treatment would impact equity.

Recommendation 8: The AASM suggests using oral acetazolamide over no acetazolamide in adults with CSA due to high altitude. (Conditional recommendation, very low certainty)

The TF identified 2 RCTs that demonstrated a clinically significant improvement in disease severity (AHI, desaturation index) and sleep architecture following 1-2 nights of treatment with 250 mg of acetazolamide. The potential benefits of acetazolamide had a moderate effect size. The undesirable effects were considered trivial, and included paresthesia of hands and feet, impaired taste, and increased diuresis. The TF judged that the potential benefits of acetazolamide outweigh the potential harms.

The overall quality of evidence was very low due to imprecision and indirectness. The cost of medication was considered negligible. There was no direct evidence that the treatment would affect health equity. The intervention was acceptable and feasible to implement.

Recommendation 9: The AASM suggests using TPNS over no TPNS in adults with CSA due to the following etiologies: primary CSA and CSA due to heart failure who have failed other therapies. (Conditional recommendation, very low certainty)

The TF identified one RCT, three observational studies, and five subgroup post-hoc analyses and long-term follow-ups stemming from the RCT. The follow-up period was six months in the original RCT and one night to 12 months in the observational studies. Subgroups of the RCT were followed for one, three, and five years. The results demonstrated clinically significant improvement in excessive sleepiness, disease severity (CAI), and cardiovascular outcomes (6MWD) but no effect on mortality and left ventricular ejection fraction (LVEF). The potential benefits of TPNS had a moderate effect size. Undesirable effects were considered small and included impending device pocket erosion, implant site hematoma and infection, lead dislodgment, lead displacement, and lead component failure. The TF judged that the potential benefits of TPNS outweigh the potential harms.

The overall quality of evidence was very low due to imprecision. While there was no direct evidence that the treatment would impact equity, due to its high cost, the need for a subspecialty cardiology service, and additional training of sleep technologists and physicians, the intervention might decrease overall health equity or disproportionately affect certain groups. The intervention's feasibility was thought to be low due to the resources needed to build the required infrastructure, including the availability of trained electrophysiologists capable of inserting the devices. Due to these considerations, as well as the invasive nature of this treatment, the task force suggested phrenic nerve stimulation in patients who have first tried and failed other available therapies.

No Recommendations (or Knowledge Gap)

The TF used 'no recommendation' when there was value in the findings but thought further research and innovation for this intervention is needed. There was insufficient and inconclusive evidence to make recommendations for the following: zolpidem or other hypnotics; BPAP with a backup rate in CSA due to heart failure; low flow oxygen in primary CSA, CSA due to medication or substance, and treatment-emergent CSA (TECSA); TPNS in CSA due to medication or substance and TECSA. The evidence is reported in the accompanying systematic review and supplemental materials.

DISCUSSION

Central sleep apnea (CSA) remains a challenge for clinicians in both diagnosis and management (JCSM). Most forms of CSA, with the possible exception of opioid-induced CSA, share a common mechanism involving

oscillatory ventilatory drive. This is typically caused by hyperpnea and increased chemosensitivity to carbon dioxide, which leads to recurrent central respiratory events during sleep.

The paucity of studies in every patient population and the shared pathogenesis necessitated grouping data across CSA subtypes with similar treatments. Safety data from studies on heart failure-associated CSA (HF-CSA) were used as a proxy to assess the safety of treatments in other CSA subtypes. The TF found this approach valuable for confirming the safety of interventions and the direction of their impact on specific outcomes. Nonetheless, the recommendations were still tailored to address individual CSA syndromes wherever possible.

In its comprehensive review of the literature, the TF noted that studies evaluating treatment of CSA remain dominated by short term (weeks to months) studies evaluating positive airway pressure devices, especially CPAP and ASV. The TF rarely encountered a trial that addressed long-term multi-year outcome of treatment with any modality. Furthermore, very few studies were powered to address long term outcomes of interest such as mortality as identified during the planning phase of this systematic review (cite). The TF, therefore, attempted whenever possible to consider the longest available duration of therapy of any evaluable outcome.

Following the GRADE methodology,[3] the overall quality or certainty of the evidence was low or very low across critical outcomes due to risk of bias, indirectness, and/or imprecision. The strength of the recommendations reflected the extent to which the TF was confident that the desirable effects of an intervention outweighed the undesirable effects, or vice versa, across the range of subgroup populations for whom the recommendation is intended. The smaller the net benefit or harm and the lower the certainty of evidence about the net effect, the more likely the TF was to conclude that a conditional recommendation for or against the intervention will be appropriate. The balance of effect (desirable and undesirable effect) was assessed alongside values of people affected and resource use.

Finally, an important consideration when evaluating the literature and the TF's recommendation is the heterogeneity of the definition used for the classification of CSA and the exclusion of OSA in most studies.[15] Studies used various cutoffs of central to obstructive event ratios resulting in some studies including patients who would be classified as having OSA under the current scoring criteria.[16] This practice may, to some extent, improve the 'real world' relevance of the findings.

Despite the slow progress in CSA research, the period since the last AASM guidelines on CSA was notable for two important developments featured in these guidelines. The first is the development of the TPNS, a fully implantable neurostimulator that became Food and Drug Administration (FDA) approved and commercially available (Remede®, Zoll) in 2016. The second is the publication of a trial[17] addressing the safety and efficacy of a peak flow based ASV device in patients with HFrEF. These two developments underpin the major updates to the guidelines and are further discussed below.

PAP therapies

CPAP continues to be widely used for CSA. In its review of the literature, the TF found that available studies investigating CPAP in patients with CSA have shown decreased AHI[18-23], but only one study reported the effect of CPAP on central events specifically. While CPAP has been used for CSA of varied etiologies, there is no established or widely accepted mechanism of action in any of these settings. A key question is whether CPAP effects are

mediated by the prevention of upper airway obstruction or by stabilizing the ventilatory control system. Overall, the TF found that the level of evidence was weak, and it is reflected by the recommendation. Given that CPAP is widely available, and most sleep clinicians and teams have extensive experience in its administration and management, it is a reasonable first consideration despite the weak evidence. However, given that CPAP is only effective at reducing AHI and has not been shown to consistently reduce the central events, it is critical to confirm responsiveness with sleep testing and review of PAP-generated data if this modality is used. Persistence of central apnea after an appropriate trial period of CPAP warrants consideration of an alternative treatment modality.

Bilevel positive pressure without a backup rate (BPAP) is often initiated during PAP titration studies when CPAP alone fails to control central apnea. However, this mode is likely to worsen central apnea during sleep.[13] In fact, BPAP is often used as an experimental intervention to induce central apnea and periodic breathing during sleep.[14] Therefore, the TF recommended against using BPAP without a backup rate for treatment of CSA. While BPAP inhibits ventilatory motor output, and hence may trigger central apnea, adding a backup rate renders the device as a form of controlled ventilation and prevents the development of CSA. The initiation of BPAP with a backup rate is a pragmatic decision anchored in the need to treat the underlying condition. Expiratory PAP (EPAP) eliminates upper airway obstruction, which commonly co-exists with CSA. Adding the combination of inspiratory PAP (IPAP) and a backup rate supports alveolar ventilation. BPAP without a backup rate is not recommended due to the potential for exacerbating hyperventilation, central apneas and hypocapnia.[12, 13]

Since its introduction, ASV has been highly effective in controlling central apneas in patients with various causes of CSA. However, enthusiasm for ASV decreased following the publication of the SERVE-HF trial[24], an RCT that evaluated ASV in patients with HFrEF. The trial failed to meet its primary endpoints and showed no benefit from ASV. Further analysis revealed an increased cardiovascular and all-cause mortality rate in the treatment group, raising concerns about the safety of ASV, and leading to the manufacturer issuing a field safety notice[25] recommending against using ASV in patients with HFrEF and CSA.[1]

The SERVE-HF trial and its subsequent post-hoc studies did not provide mechanistic insights into this unexpected finding, which contradicted previous observational studies and smaller trials. Given these existing concerns, the TF set out to reevaluate the use of ASV in CSA across all relevant CSA populations with a priori assumption of harm or at least serious concerns about using ASV in patients with HFrEF and CSA, particularly focusing on all-cause and cardiovascular mortality. The TF prioritized RCTs for mortality outcomes but also reviewed all available observational studies on ASV in patients with HFrEF.

The systematic review of all RCTs found no impact of ASV on mortality. The inclusion of the ADVENT-HF trial[17], a recent large trial, was critical to this comprehensive assessment and likely contributed to the finding of no effect on mortality. While exploring a mechanistic explanation for these results is appealing, it was beyond the scope of this review. Notably, there are no verified mechanisms of harm for ASV beyond previous small mechanistic studies showing that excessive pressure can depress the cardiac output,[26, 27] which interestingly, apply to all PAP modalities including CPAP and BPAP.

As a result, the TF issued a weak recommendation in favor of ASV use across all CSA settings, with several caveats. One key observation is that complex ventilatory assist devices, like ASV, have been produced by different manufacturers, each using their proprietary algorithm. These devices are rarely subjected to rigorous comparative bench or clinical evaluation. An important recent study[28] highlighted differences in the performance of various ASV

devices in response to simulated respiratory events, demonstrating significant variability in delivered therapy based on the device's algorithm. One of these ASV devices was used in the ADVENT trial with no associated harm in patients with HFrEF but is not currently available in the US market. Other available ASV modalities have not been tested in RCTs in patients with HFrEF.

Given these evidence gaps, the TF emphasizes caution in using ASV for CSA treatment in patients with HFrEF, calls for further mechanistic research, and urges funding agencies to support studies evaluating the safety and efficacy of ASV as well as other treatment modalities for CSA. The TF also strongly advises clinicians to engage in shared decision-making with patients, providing detailed discussions of the existing literature to inform treatment decisions.

A more recent hypothesis[29] suggests that oscillatory breathing may be a compensatory or less harmful form of CSA or SDB, potentially explaining the results of a trial evaluating ASV in CSA that did not show clinical benefit. However, this hypothesis needs to be tested and, if proven, can apply to all treatment modalities of CSA and not specifically ASV.

Oxygen

Using supplemental oxygen in patients with CSA has been studied since the late 1980s. As this therapeutic option is easy to apply, there is a high degree of interest in using it in clinical practice. All studies on oxygen in patients with CSA have been performed with low flow oxygen, which is consequently the only focus of this guideline. About half of the RCTs and observational studies followed the patients for eight weeks or longer, which allows evaluating patient-reported outcome measures (PROMs). However, there were no relevant effects on sleepiness, insomnia, or exercise tolerance.

The individual response regarding breathing disturbances, symptoms, and consequences of the disease should be re-evaluated before prescribing oxygen over the long term. As oxygen treatment is available in many healthcare systems, this treatment option is clinically relevant. On the other hand, as oxygen is currently not standard of care for the treatment of CSA, it is not covered by all insurance companies, which limits patients' access to this option. Based on the reviewed evidence and these considerations, the TF provided a low certainty recommendation in favor of using low flow oxygen for CSA in HF.

Acetazolamide

Evidence to support the role of acetazolamide in CSA was limited to primary CSA, CSA due to heart failure, CSA due to medication or substance use, treatment-emergent CSA, CSA due to a medical condition or disorder, and CSA due to high altitude in adults where it was found to reduce the AHI. There was an overall improvement in the Epworth Sleepiness Scale. The change in LVEF in the CSA due to heart failure group failed to meet the clinical significance threshold. These results, however, are limited to a small number of studies, with small subject numbers and over a relatively short period of time. Side effects related to acetazolamide included mild paresthesia. Overall, the TF felt these side effects were trivial. Although the TF felt the certainty of evidence for acetazolamide was low and outcomes focused mainly on central AHI, rather than objective cardiac markers or quality of sleep or life, they felt the balance of effects favored the use of acetazolamide. The TF felt the cost of acetazolamide to be negligible and the treatment to be acceptable and feasible. There were no studies of resource requirements or cost-

effectiveness. Given that CSA due to heart failure or high altitude is characterized by hyperventilation, the TF raised concerns that acetazolamide, a respiratory stimulant, may disturb acid base balance and electrolytes, which could lead to arrhythmias. Thus, if a two to four-week trial of acetazolamide was to be considered as a replacement or additional diuretic, a follow-up assessment of electrolytes is recommended in addition to AHI, sleep quality, cardiac function, and side effects. The TF recommended that future research of acetazolamide should include assessment of ventilation during sleep, quality of sleep and life, plus objective markers of cardiac function, and electrolytes.

High Altitude

CSA or periodic breathing, typically occurring during NREM sleep, develops commonly in those who ascend to high altitudes (>2500 m) including in healthy individuals.[30-38] Many will acclimate over time while at altitude with either resolution of CSA events or resolution of sleep-related symptoms.[39-42] The definitive treatment for high altitude-related CSA is descent. CSA is thought to develop as a function of alterations in acid-base status, chemo-responsiveness, and ventilatory control in response to high altitude hypobaric hypoxemia.[43-45] The clinical significance of CSA at altitude is unknown, though it does not appear to be directly related to the risk of high-altitude pulmonary or cerebral edema.[46, 47]

Low flow oxygen (very low certainty) and acetazolamide (very low certainty) have been shown to acutely reduce the severity of CSA due to high altitude, as measured by the AHI or ODI.[48-51] It is notable that reduced AHI or ODI may not necessarily translate into improvements in subjective or objective sleep quality or daytime symptoms. Given the low risk, low cost, and feasibility of these interventions, however, the task force felt it was reasonable to pursue low flow oxygen or acetazolamide as treatment options if individuals were concerned about developing CSA or were symptomatic with CSA at altitude. Because studies typically involved only a single night or two of therapy, the task force could not make recommendations about the duration of therapy, especially since some individuals may eventually acclimate over time.

It is worth noting that OSA is a highly prevalent disease which may also worsen at altitude. There are theoretical risks whereby CPAP use at altitude when used to treat OSA may either induce, worsen, or improve CSA at altitude. This is an area that requires further study since OSA is a highly prevalent disorder, and individuals will require guidance about continuing CPAP for OSA at altitude (as it pertains to CSA risk).

TPNS

The evidence supporting the use of TPNS primarily comes from an RCT that enrolled 151 participants, 64% of whom had CSA due to heart failure, and 11% had primary CSA.[52] Patients with opioid-related CSA were excluded from the study. Since TPNS targets central apneas specifically, the ideal candidate for this treatment is a patient with few or no obstructive events. The RCT evaluated TPNS over a six-month period, with extended follow-up reported for smaller cohorts lasting up to five years.[53-55] The study found improvements in central event indices, desaturation index, quality of life, and several sleep architecture measures.

However, the cost and availability of TPNS therapy may be prohibitive for many patients. Establishing a successful TPNS program requires substantial infrastructure and training for both cardiologists (electrophysiologists) and sleep specialists to manage these patients. The high cost, invasive nature of the procedure, and the resources needed—combined with the relatively small sample size of published studies and the lack of comprehensive long-term

follow-up—tempered the positive trial results in the task force's assessment. Consequently, the task force issued a conditional recommendation for TPNS, suggesting it as an option for patients who have not responded to other treatments, thereby introducing it to the sleep clinicians' armamentarium.

Conclusion

Effective treatment for central sleep apnea remains elusive and has received substantially less attention than obstructive sleep apnea. Positive airway pressure, in all its modalities, has received the lion's share of research on treatment modalities of CSA. However, whether long-term, clinically important outcomes are improved remains an open question. The introduction of TPNS provides a promising option that awaits long-term outcome data. Overall, limitations in existing studies precluded strong recommendations for any intervention and highlighted the need for mechanistic studies to identify and test optimal interventions for CSA treatment.

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ACKNOWLEDGMENTS

The task force extends its gratitude to…

SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication
Submitted in final revised form
Accepted for publication
Address correspondence to:

DISCLOSURE STATEMENT

The development of this paper was funded by the American Academy of Sleep Medicine (AASM).