# VA/DOD CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF CHRONIC INSOMNIA DISORDER AND OBSTRUCTIVE SLEEP APNEA

**Department of Veterans Affairs**

**Department of Defense**

## QUALIFYING STATEMENTS

The Department of Veterans Affairs (VA) and the Department of Defense (DOD) guidelines are based on the best information available at the time of publication. The guidelines are designed to provide information and assist decision making. They are not intended to define a standard of care and should not be construed as one. Neither should they be interpreted as prescribing an exclusive course of management.

This clinical practice guideline (CPG) is based on a systematic review of both clinical and epidemiological evidence. Developed by a panel of multidisciplinary experts, it provides a clear explanation of the logical relationships between various care options and health outcomes while rating both the quality of the evidence and the strength of the recommendation.

Variations in practice will inevitably and appropriately occur when providers consider the needs of individual patients, available resources, and limitations unique to an institution or type of practice. Therefore, every health care professional using these guidelines is responsible for evaluating the appropriateness of applying them in the setting of any particular clinical situation with a patient-centered approach.

These guidelines are not intended to represent VA or DOD policies. Further, inclusion of recommendations for specific testing, therapeutic interventions, or both within these guidelines does not guarantee coverage of civilian sector care.

**Version 3.0 – 2025**

***Prepared by:***

## The Management of Chronic Insomnia Disorder and Obstructive Sleep Apnea Work Group

***With support from:***

## Office of Quality and Patient Safety, Veterans Health Administration

## and

## Clinical Quality Improvement Program, Defense Health Agency

**Version 3.0 – 2025[a]**

***Based on evidence reviewed through March 31, 2024***

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# I. Introduction

The Department of Veterans Affairs (VA) and Department of Defense (DOD) Evidence-Based Practice Work Group (EBPWG) was established and first chartered in 2004, with a mission to advise the Health Executive Committee (HEC) "…on the use of clinical and epidemiological evidence to improve the health of the population…" across the Veterans Health Administration (VHA) and Military Health System (MHS), by facilitating the development of clinical practice guidelines (CPGs) for the VA and DOD populations.(1) This CPG is intended to provide healthcare providers with a framework by which to evaluate, treat, and manage the individual needs and preferences of patients with sleep disorders, specifically chronic insomnia disorder and obstructive sleep apnea (OSA), thereby leading to improved clinical outcomes.

An effort to create the Chronic Insomnia Disorder and OSA CPG was initiated in 2018. The Chronic Insomnia Disorder and OSA CPG includes objective, evidence-based information on the management of selected sleep disorders (chronic insomnia disorder and OSA). It is intended to assist healthcare providers in all aspects of patient care, including, but not limited to, screening, assessment, treatment, and follow-up. The system-wide goal of evidence-based guidelines is to improve patient health and well-being by guiding health providers taking care of patients with chronic insomnia disorder and/or OSA along management pathways supported by evidence. The expected outcome of the successful implementation of this guideline is to:

- Assess patient condition and determine, in collaboration with the patient, the best treatment method(s)
- Optimize patient health outcomes and improve quality of life (QoL)
- Minimize preventable complications and morbidity
- Emphasize the use of patient-centered care (PCC)

# II. Background

## A. Definitions and Scope

### *a. Chronic Insomnia Disorder*

An insomnia disorder is generally characterized by a persistent difficulty with sleep initiation or maintenance, associated with a perceived daytime impairment or concern/dissatisfaction with sleep.(2) The International Classification of Sleep Disorders, 3rd Edition, Text Revision (ICSD-3-TR) specifies that insomnia disorder can be either short-term, or chronic. Criteria for both include patient or caregiver report of difficulties with initiating sleep, maintaining sleep, waking up earlier than desired, resistance to going to bed on an appropriate schedule or difficulty sleeping without caregiver intervention (e.g. adults with dementia), and the difficulty is accompanied by a

daytime consequence such as fatigue/malaise, impaired attention, concentration, or memory, impaired social, occupational, or academic performance, mood disturbance, daytime sleepiness, behavior problems, reduced motivation/energy/initiative, proneness for error/accidents or a concern/dissatisfaction with sleep. These symptoms occur despite adequate opportunity and circumstances for sleep and are not better explained by an alternative diagnosis or medication. An insomnia disorder occurring at least three times per week and lasting more than three months in duration is considered "chronic." In this CPG, we use the term "chronic insomnia disorder" to align with current diagnostic criteria.(2) The Diagnostic and Statistical Manual for Mental Disorders, 5th Edition, Text Revision (DSM-5-TR) uses similar criteria for Chronic Insomnia Disorder.(3)

The diagnosis of chronic insomnia disorder requires a clinical evaluation including a sleep, medical, and psychiatric history. As discussed in this CPG, insomnia questionnaires may be useful screening tools but are not diagnostic for chronic insomnia disorder. Individuals with chronic insomnia disorder may report more difficulty going to sleep and staying asleep than is determined using objective measures, such as actigraphy or polysomnography (PSG). This discrepancy between subjective and objective measures is widely recognized by sleep experts and clinicians. Where possible in this CPG, we specify whether the systematic reviews (SRs) and randomized controlled trials (RCTs) included in our evidence review reported subjective or objective outcome measures. In routine clinical practice, objective measures are not indicated for the evaluation of insomnia unless there is a clinical suspicion of OSA or another sleep disorder. Chronic insomnia disorder is a diagnosis based on a thorough sleep history and clinical evaluation; objective testing is not required.

While the Work Group for this CPG recognized the challenges of short-term insomnia disorder (i.e., insomnia disorder symptoms present for <3 months), the focus of this guideline is patients experiencing chronic insomnia disorder. In some instances, studies did not determine or report whether study participants met diagnostic criteria for insomnia disorder but instead included a broad range of patients with insomnia symptoms. When this was the case, the term "insomnia symptoms" was used to make this distinction.

### *b. Obstructive Sleep Apnea*

Obstructive sleep apnea (OSA) is the most common type of sleep disordered breathing (SDB). This common sleep disorder is highly prevalent and an independent risk factor for cardiovascular disease (CVD) as well as motor vehicle crashes (MVCs).(4) OSA is characterized by upper airway collapse during sleep resulting in partial or complete interruption of airflow (i.e., respiratory events including apneas and/or hypopneas that may be associated with oxygen desaturation, hypercapnia, and/or arousals and sleep fragmentation).(5) An apnea is a complete or near complete (i.e., 90%) decrease in

airflow that lasts at least 10 seconds. Apneas do not require desaturation or arousal to be scored. Hypopnea is a 30% or greater decrease in airflow that is at least 10 seconds in duration and is associated with either a ≥3% oxygen desaturation or arousal.(6) Common symptoms of OSA include daytime sleepiness, snoring, sensations of gasping or choking upon awakening from sleep, and witnessed breathing interruptions during sleep.(7) Traditionally, the diagnosis of OSA was made by an attended overnight in-lab polysomnogram (PSG); however, home sleep apnea testing (HSAT) that focuses solely on diagnosing SDB is increasingly used. Current guidelines are that HSAT is appropriate to diagnose uncomplicated patients that have an increased risk of moderate to severe OSA.(8) Importantly, a non-diagnostic and/or negative HSAT for OSA is unable to rule out OSA and further testing is recommended, preferably a PSG, though HSAT can be repeated if clinically appropriate.(4,8) According to the ICSD-3 TR, OSA can be diagnosed when a patient has at least a minimum number of respiratory events per hour during sleep (or, in the case of HSAT, per hour of recording). These event indices are used to categorize OSA by severity. Mild OSA is defined as ≥5 to <15 events per hour with the presence of symptoms; moderate OSA is defined as ≥15 to <30 events per hour; and severe OSA is defined as ≥30 events per hour. In crafting recommendations, the Work Group specified when a recommendation applies only to a subset of OSA patients at a given severity level. However, the apnea-hypopnea index (AHI) or respiratory event index (REI) are not the sole indicators of OSA severity in a given patient, as this parameter does not account for oxygen desaturation frequency or oxygen saturation nadir, the duration of the respiratory event, sleep fragmentation, or comorbid illnesses.(9-11)

## B. Epidemiology and Impact in the General Population

Sleep disturbances affect 50% of the general adult population worldwide.(12) In the United States (U.S.), the National Institutes of Health (NIH) estimate that roughly 30-40% of the general population complain of sleep disruption.(13,14) Insomnia is the most common sleep complaint among adults; approximately 5%-50% of adults in the U.S. have experienced insomnia symptoms.(12,14) The prevalence of chronic insomnia disorder is estimated to be between 6%-23%.(12,14) Risk for insomnia is more prevalent among women, older adults, shift workers, family history of insomnia, and patients with co-existing medical and psychiatric disorders.(14) Additional factors associated with an increased risk include being African American, serving in the military, and those experiencing lower socioeconomic status or adverse social determinants of health. Other risk factors include race African American, military personnel, and social determinant of health. (15-18)

OSA is one of the most common sleep disorders, with a prevalence that ranges from 9% to 38%.(19) The prevalence of OSA increases with age, body mass index (BMI), and males (2:1), but after menopause the risk in women increases.(20) Other risk

factors of OSA include obesity, retrognathia, laxity of the soft palate, smoking, family history of OSA, pregnancy, and alcohol consumption.(21) OSA is associated with higher rates of motor vehicle accidents, depression, diabetes, metabolic syndrome, cardiovascular disease, and strokes.(22)

The personal impacts of sleep disturbances include daytime sleepiness and impaired daytime functioning.(14) Societal burdens of insomnia include decreased life satisfaction; decreased physical and mental health QoL; workplace absenteeism and decreased productivity; and increase in workplace errors and accidents.(12) Sleep disturbances significantly contribute to increased disease, accidents, and lost productivity creating a growing economic burden accounting for approximately $411 billion a year or 2.3% of the gross domestic product.(13)

## C. Sleep Disorders in the Department of Veterans Affairs and the Department of Defense

Sleep disorders are highly prevalent in the DOD and VA populations. In the RAND report, Sleep in the Military, 48.6% of military personnel surveyed had poor sleep quality (Pittsburgh Sleep Quality Index [PSQI] score >5).(23) In a more recent meta-analysis, the prevalence of poor sleep quality among global military personnel and Veterans was 69%.(24) In a cohort of US military service members and Veterans, 16% endorsed symptoms consistent with insomnia disorder, and the prevalence of sleep medication use was 23%.(25) The prevalence of insomnia symptoms has been reported to be as high as 41% in service members deployed to combat and 25% in noncombatants.(18) In a large cohort of soldiers preparing for deployment, insomnia symptoms were present in 19.9% of individuals.(18) Although OSA is the most frequently diagnosed sleep disorder in service members, (26) recent findings suggest an increasing incidence of both insomnia and sleep apnea across all branches of military service.(27) Similarly, a review of VA medical records revealed an increase in documented diagnoses of both OSA and insomnia, with 22% of outpatients diagnosed with sleep-related breathing disorders and 11.8% diagnosed with insomnia in 2018.(28) Of note, medical records are unlikely to reflect the true prevalence of insomnia disorder since documentation of insomnia in the medical record is inconsistent and assessment for diagnostic criteria is rare.(29) Patient screening confirms the divergence of documented insomnia, and the prevalence obtained from screening. Among Veterans seeking treatment at the VA San Diego Healthcare System (N=843) more than half had screened positive for clinically significant insomnia symptoms, as measured by the Insomnia Severity Index (ISI). (30) Of these, 23.6% reported moderate insomnia (ISI scores 15 – 21) and 9.6% reported severe insomnia (ISI scores 22 – 28). (31) The largest prospective observational study of active-duty service members referred to a sleep center diagnosed insomnia in 32.7% of patients, OSA in 30.4%, and comorbid insomnia and obstructive sleep apnea (COMISA) in 36.9%.(32) Notably, patients with insomnia only and COMISA reported

worsened symptoms of sleep disorders, fatigue, sleep-related impairment, and psychiatric disorders compared to those with OSA only. Further, in sharp contrast to civilian cohorts, there were minimal differences between men and women in terms of sleep-related symptoms, impairment, or apnea-hypopnea index (AHI), suggesting military service itself may lead to distinct sleep disorder phenotypes that differ negligibly by sex.(33) Additionally, both military personnel and Veterans with sleep disorders often also have posttraumatic stress disorder (PTSD), symptoms of anxiety and depression, and traumatic brain injury (TBI).(34)

### a. Agenda for Increased Access to Behavioral Interventions for Insomnia Disorder

As described above, insomnia disorder is a highly prevalent condition among both military personnel and Veterans, (23,31) with about 16% of military personnel,(25) 11% of community-residing Veterans,(35) and up to half of Veterans enrolling in VA healthcare.(31) Further, despite OSA being the current clinical and operational focus of the military, it appears that insomnia creates a higher burden of morbidity in military personnel and Veterans.(32) For example, two meta-analyses have demonstrated a higher relative risk of suicide in Veterans with sleep disturbances.(36,37) Sleep disturbance has also been shown to precede suicide in Veterans (38) and suicide attempts in service members.(39) Unfortunately, access to behavioral interventions for insomnia disorder are limited,(40) and some research suggests minimal implementation of guideline-concordant insomnia treatment among VA providers.(41)
Considering the mental and physical health risks of poor sleep (e.g., anxiety, depression, suicide, CVD), and Veterans' desire for assistance with sleep (42,43) increased access to treatment for insomnia disorder is essential. A report sponsored by the DOD on sleep in military service members states:

> "Policy changes are needed within the military health system and VHA to address this inconsistency between healthcare practice and the empirical evidence. Continued dissemination efforts, greater education about (CBT-I) for primary care providers, and more training for mental healthcare providers are needed in both the military health system and VHA to make CBT a front-line treatment for insomnia."(23)

To increase patient access to behaviorally-based insomnia disorder treatment, the following steps could be implemented(23,40,44,45):

- Increased training and dissemination of evidence-based insomnia disorder treatments (e.g., BBT-I and brief CBT-I trainings are available to all VA providers).

- Healthcare provider education on insomnia disorder, including the adverse impact of chronic insomnia disorder on health outcomes, how to diagnose insomnia disorder, the process by which insomnia develops from an acute to chronic condition, how to describe behavioral treatments to patients, and identifying appropriate candidates for behavioral treatment
- Documentation of insomnia disorder in the medical record
- Insomnia screening for primary prevention
- Leverage all empirically supported treatment delivery formats (46) (e. g. digital approaches) and protocol adaptations (47) to ensure access for remote and underserved communities in particular, and for increasing overall patient access to behaviorally based insomnia treatments
- Increased use of care models, such as stratified (48) and stepped care, to ensure that "scarce expertise is appropriately targeted" (49) and as consistent with recommendations by other sleep research societies (50)

### *b. Agenda for Increased Access to Mandibular Advancement Device Therapy for Indicated active-duty service members and Veterans*

As described above, OSA is highly prevalent in military and Veteran populations.(51) Because sleep disorders increase in prevalence with age, it affects a greater proportion of military leaders and can negatively impact military readiness. Military Operations are often conducted in austere environments, which can make using positive airway pressure (PAP) therapy difficult (due to limited access to electricity, distilled water, inherent burden of the PAP unit).(52) From a clinical perspective, Zhang et al. (2017) found more than 75% of Veterans with PTSD suffered from OSA, and those with OSA and PTSD were significantly less adherent to PAP therapy than Veterans with only OSA.(51,53) Lettieri et al. (2016) reported similar findings in an active-duty population where 56.6% of patients with PTSD received an OSA diagnosis and those with OSA and PTSD had significantly lower PAP adherence.(54) In a randomized crossover trial, El Sohl et al. (2017) found that Veterans with OSA and PTSD were significantly more adherent to and preferred mandibular advancement device (MAD) therapy over PAP therapy, and both therapies achieved equivalent health outcomes.(55) Providing MAD therapy is essential for managing OSA in military and Veteran populations due to the health-related risks of untreated OSA to include impaired cognitive function, increased accident and cardiovascular risk and the presence of comorbid disorders, all while considering the unique military requirements not typical of the civilian population. The Army Dental Sleep Medicine Initiative increased delivery of MADs to Army personnel over the last several years. However, this therapy is offered to only a small percentage of the DOD/VA population; further improvements in access to this treatment modality are required. Based on lessons learned in expanding this service within the DOD since

2017, recommended steps to improve patient access to and treatment with MAD are as follows:

- Increase education of primary care providers on the evidence regarding the appropriate patient criteria for MAD treatment of OSA
- Ensure MAD therapy is provided by qualified dental sleep medicine professionals
- Utilize U.S. Food and Drug Administration (FDA) approved, digitally engineered, custom fabricated, and titratable MADs
- Utilize FDA approved devices that predict MAD treatment response and verify the therapeutic mandibular position

# III. Scope of This Guideline

This CPG is based on published clinical evidence and related information available through March 31, 2024. It is intended to provide general guidance on best evidence-based practices (see Appendix A for additional information on the evidence review methodology). Although the CPG is intended to improve the quality of care and clinical outcomes (see Introduction), it is not intended to define a standard of care (i.e., mandated or strictly required care).

## A. Guideline Audience

This CPG is intended for use by VA, DOD, community providers, and others involved in the health care team evaluating and managing adults with chronic insomnia disorder and/or obstructive sleep apnea.

## B. Guideline Population

The patient population of interest for this CPG is adult patients with chronic insomnia disorder and/or obstructive sleep apnea who may receive care in the VA or DOD health care delivery systems, or VA and DOD adult beneficiaries who receive care from community-based providers. Recommendations in this CPG are applicable for any adult patients of VA or DOD, inclusive of all care locations (VA, DOD, or community-based care).

# IV. Highlighted Features of This Guideline

## A. Highlights in This Guideline Update

This document is an update to the 2019 VA/DOD Management of Chronic Insomnia Disorder and Obstructive Sleep Apnea CPG,[a] and contains the following significant revisions:

- Updated Algorithm;
- Reviewed studies focused on specific outcomes to include critical outcomes of adoption of therapy, insomnia severity, and sleep efficiency;
- Added nine new recommendations; seven reviewed and replaced, eleven amended, and two no change;
- Used more rigorous application of GRADE methodology;
- Updated Provider Guide to Sleep Education for Chronic Insomnia Disorder and Obstructive Sleep Apnea sections; and
- Updated Research Priorities section.

The body of research on the management of chronic insomnia disorder and obstructive sleep apnea continues to grow. This CPG includes updated recommendations on the following key topics.

1. Pharmacotherapy for treatment of OSA: The 2019 VA/DOD Insomnia/OSA Work Group offered no specific recommendation regarding treatment for patients with obstructive sleep apnea-related excessive daytime sleepiness. The 2025 VA/DOD Insomnia/OSA Work Group suggests that patients who fit this criterion and are optimally treated with sufficient therapy use, add armodafinil, modafinil, and solriamfetol (see Recommendation 29).
2. Herbal supplementation: The 2025 VA/DOD Insomnia/OSA CPG highlights recommendations from recent evidence focusing on cannabis and its derivatives, and magnesium (see Recommendations 13 and 15).
3. Treatment options: The 2025 VA/DOD Insomnia/OSA CPG Work Group recommended (categorized as *Strong for*) evidence-based effective therapy options for patients with obstructive sleep apnea and suggested (categorized as *Weak for*) positional therapy for patients with obstructive sleep apnea (see Recommendations 17 and 21).
4. Weight management: The 2019 VA/DOD Insomnia/OSA CPG offered no specific recommendation regarding evidence-based weight management. The 2025

[a] See the 2019 VA/DOD Clinical Practice Guideline for the Management of Chronic Insomnia Disorder and Obstructive Sleep Apnea. Available at: https://www.healthquality.va.gov/

VA/DOD Insomnia/OSA CPG suggests evidence-based weight management in combination with other treatments for obstructive sleep apnea. (see Recommendation 20).

As noted above, the methodology used in developing this CPG has been updated since the prior versions and reflects a more precise application of the methodology than used in previous iterations, which are detailed in Appendix A. It is important to note that the recommendation strength downgrades from *Weak for* to *Neither for nor against* recommendations do not imply that providers should avoid these options, rather that the data from the current systematic evidence review is insufficient to make a recommendation when using the more rigorous methodology.

The 2025 VA/DOD Insomnia/OSA CPG provides practice recommendations for the care of patients with OSA or chronic insomnia disorder as well as guidance for specialty referral. A particular strength of this CPG is the multidisciplinary stakeholder involvement in the development of the CPG from its inception, ensuring representation from the broad spectrum of clinicians engaged in the treatment and management of patients with chronic insomnia disorder and/or OSA with and without co-occurring conditions.

The 2025 VA/DOD Insomnia/OSA CPG Work Group focused largely on developing new and updated recommendations based on the systematic evidence review conducted for the priority areas addressed by the Key Questions (KQ) (see Summary of Guideline Development Methodology). In addition to the new and updated recommendations, the Work Group considered, without a complete review of the relevant evidence, the current applicability of these other recommendations included in the previous 2019 VA/DOD Insomnia/OSA CPG, subject to evolving practice in today's environment.

The 2025 VA/DOD Insomnia/OSA CPG Work Group considered the strength of the evidence cited for each recommendation in the 2019 VA/DOD Insomnia/OSA CPG, as well as the intervention's harms and benefits, patients' values and preferences, and other implications, where possible. The Work Group referred to the available evidence as summarized in the body of the 2019 VA/DOD Insomnia/OSA CPG but did not systematically reassess all the evidence. In some limited instances, relevant peer-reviewed literature published since the 2019 VA/DOD Insomnia/OSA CPG was considered, along with the original evidence base for the specific recommendation. The CPG Work Group recognizes that although there are sometimes practical reasons for synthesizing findings from a previous systematic evidence review, previous recommendations, or recent peer-reviewed publications into an updated CPG, doing so does not involve an original, comprehensive systematic evidence review and might introduce bias.

## B. Components of the Guideline

This CPG provides clinical practice recommendations for the care of patients with OSA and/or chronic insomnia disorder (see Recommendations). In addition, the Algorithm incorporates the recommendations in the context of the flow of patient care. This CPG also includes Research Priorities, which list areas the Work Group identified as needing additional research. To accompany this CPG, the Work Group also developed toolkit materials for providers and patients, including a provider summary, patient summary, and pocket card, which can be found at https://www.healthquality.va.gov/index.asp.

# V. Guideline Development Team

The VA Evidence Based Practice, Office of Quality and Patient Safety, in collaboration with the Clinical Quality Improvement Program, DHA, identified the following four providers to serve as Champions (i.e., leaders) of this CPG's Work Group: Amir Sharafkhaneh, MD, and Christi Ulmer, PhD, CBSM, DBSM, from VA; and Matthew Brock, MD, FAASM, and Vincent Capaldi, ScM, MD, DFAPA, FACP, FAASM, from DOD.

The Work Group comprised individuals with the following areas of expertise: internal medicine, sleep medicine, neurology, psychiatry, pulmonology, dental, psychology, mental/behavioral health counseling, and otolaryngology. Table 1 lists the Work Group and Guideline Development Team members. This CPG Work Group, led by the Champions, was tasked with:

- Determining the scope of the CPG;
- Crafting clinically relevant KQs to guide the systematic evidence review;
- Identifying discussion topics for the Patient Focus Group and considering the patient perspective;
- Providing direction on inclusion and exclusion criteria for the systematic evidence review and the assessment of the level and quality of evidence; and
- Developing evidence-based clinical practice recommendations, including determining the strength and category of each recommendation.

The Sigma Team, including Sigma Health Consulting and Duty First Consulting, was contracted by VA to help develop this CPG.

**Table 1. Guideline Work Group and Guideline Development Team**

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# VI. Summary of Guideline Development Methodology

The methodology used in developing this CPG follows the *Guideline for Guidelines*, an internal document of the VA/DOD EBPWG updated in July 2019 that outlines procedures for developing and submitting VA/DOD CPGs.(56) The *Guideline for Guidelines* is available at http://www.healthquality.va.gov/policy/index.asp. This CPG also aligns with the National Academy of Medicine's (NAM) principles of trustworthy CPGs (e.g., explanation of evidence quality and strength, the management of potential conflicts of interest (COI) (57), interdisciplinary stakeholder involvement, use of SR and external review).(58) This CPG also aligns with the National Academy of Medicine's (NAM) principles of trustworthy CPGs (e.g., explanation of evidence quality and strength, the management of potential conflicts of interest (57), interdisciplinary stakeholder involvement, use of SR and external review).(58) Appendix A provides a detailed description of the CPG development methodology.

## A. Evidence Quality and Recommendation Strength

The Work Group used the GRADE approach to craft each recommendation and determine its strength. Per the GRADE approach, recommendations must be evidence based and cannot be made based on expert opinion alone. The GRADE approach uses

the following four domains to inform the strength of each recommendation (see Determining Recommendation Strength and Direction).(59)

1. Confidence in the quality of the evidence
2. Balance of desirable and undesirable outcomes
3. Patient values and preferences
4. Other considerations, as appropriate (e.g., resource use, equity, acceptability, feasibility, subgroup considerations)

Using these four domains, the Work Group determined the relative strength of each recommendation (*Strong* or *Weak*). The strength of a recommendation is defined as the extent to which one can be confident that the desirable effects of an intervention outweigh its undesirable effects and is based on the framework above, which incorporates the four domains.(60) A *Strong* recommendation generally indicates *High* or *Moderate* confidence in the quality of the available evidence, a clear difference in magnitude between the benefits and harms of an intervention, similar patient values and preferences, and understood influence of other implications (e.g., resource use, feasibility).

In some instances, insufficient evidence exists on which to base a recommendation for or against a particular therapy, preventive measure, or other intervention. For example, the systematic evidence review might have found little or no relevant evidence, inconclusive evidence, or conflicting evidence for the intervention. The way this finding is expressed in the CPG might vary. In such instances, the Work Group might include among its set of recommendations a statement of insufficient evidence for an intervention that might be in common practice although it is unsupported by clinical evidence and particularly if other risks of continuing its use might exist (e.g., high opportunity cost, misallocation of resources). In other cases, the Work Group might decide to exclude this type of statement about intervention. For example, the Work Group might remain silent where an absence of evidence occurs for a rarely used intervention. In other cases, an intervention might have a favorable balance of benefits and harms but might be a standard of care for which no recent evidence has been generated.

Using these elements, the Work Group determines the strength and direction of each recommendation and formulates the recommendation with the general corresponding text, as shown in Table 2.

**Table 2. Strength and Direction of Recommendations and General Corresponding Text**

| Recommendation Strength and Direction | General Corresponding Text |
|---|---|
| Strong for | We recommend . . . |
| Weak for | We suggest . . . |
| Neither for nor against | There is insufficient evidence to recommend for or against . . . |
| Weak against | We suggest against . . . |
| Strong against | We recommend against . . . |

That a recommendation's strength (i.e., *Strong* versus *Weak*) is distinct from its clinical importance (e.g., a *Weak* recommendation is evidence based and still important to clinical care) is important to note. The strength of each recommendation is shown in Recommendations.

This CPG's use of GRADE reflects a more rigorous application of the methodology than previous iterations; the determination of the strength of the recommendation is more directly linked to the confidence in the quality of the evidence on outcomes that are critical to clinical decision making. The confidence in the quality of the evidence is assessed using an objective, systematic approach independent of the clinical topic of interest. Therefore, recommendations on topics for which designing and conducting rigorous studies might be inherently more difficult (e.g., RCTs) are typically supported by lower quality evidence and, in turn, *Weak* recommendations. Recommendations on topics for which rigorous studies can be designed and conducted might more often be *Strong* recommendations. Per GRADE, if the quality of evidence differs across the relevant critical outcomes, the lowest quality of evidence for any of the critical outcomes determines the overall quality of the evidence for a recommendation.(61,62) This stricter standard provides a consistent approach to determining recommendation strengths. For additional information on GRADE or CPG methodology, including relevant critical outcomes, see Appendix A.

## B. Categorization of 2025 Clinical Practice Guideline Recommendations

Evidence-based CPGs should be current. Except for an original version of a new CPG, staying current typically requires revision of a CPG's previous versions based on new evidence or as scheduled subject to time-based expirations.(63) For example, the USPSTF has a process for monitoring the emergence of new evidence that could

prompt an update of its recommendations, and it aims to review each topic at least every 5 years for either an update or reaffirmation.(64)

Recommendation categories were used to track how the previous CPG's recommendations could be reconciled. These categories and their corresponding definitions are similar to those used by the National Institute for Health and Care Excellence (NICE, England).(65,66) Table 3 lists these categories, which are based on whether the evidence supporting a recommendation was systematically reviewed, the degree to which the previous CPG's recommendation was modified, and whether a previous CPG's recommendation is relevant in the updated CPG.

Additional information regarding these categories and their definitions can be found in Recommendation Categorization. The 2025 CPG recommendation categories can be found in Recommendations. Appendix H outlines the 2025 VA/DOD Insomnia/OSA CPG's recommendation categories.

**Table 3. Recommendation Categories and Definitions[a]**

| Evidence Reviewed | Recommendation Category | Definition |
|---|---|---|
| **Reviewed[b]** | New-added | New recommendation |
| | New-replaced | Recommendation from previous CPG was carried forward and revised |
| | Not changed | Recommendation from previous CPG was carried forward but unchanged |
| | Amended | Recommendation from previous CPG was carried forward with a nominal change |
| | Deleted | Recommendation from previous CPG was deleted |
| **Not Reviewed[c]** | Not changed | Recommendation from previous CPG was carried forward but unchanged |
| | Amended | Recommendation from previous CPG was carried forward with a nominal change |
| | Deleted | Recommendation from previous CPG was deleted |

[a] Adapted from the NICE guideline manual (2012)(65) and Garcia et al. (2014).(66)

[b] The topic of this recommendation was covered in the evidence review carried out as part of the development of the current CPG.

[c] The topic of this recommendation was not covered in the evidence review carried out as part of the development of the current CPG.

Abbreviation: CPG: clinical practice guideline

## C. Racial and Ethnic Demographic Terminology in This Guideline

Demographic terms referring to an individual's race or ethnicity (e.g., Hispanic, Latino or Latina, Asian, Native American, Black, African American, White) can be ambiguously

defined and understood, reflecting diverse geographies, histories, cultures, and experiences. Aligned with the recent Executive Order on Further Advancing Racial Equity and Support for Underserved Communities through the Federal Government,[b] the Work Group used terms such as Black rather than African American and White rather than Caucasian to avoid presumptions about ancestry and to promote inclusivity, clarity, and consistency. However, to represent accurately the evidence on which this CPG is based, the Work Group generally deferred to racial and ethnic terminology as reported in the published SR, clinical trials, and other studies comprising that evidence when summarizing or otherwise referring to those studies. Consequently, usage of demographic terms in this CPG might appear inconsistent.

## C. Management of Potential or Actual Conflicts of Interest

Management of COIs for the CPGs is conducted as described in the *Guideline for Guidelines*.(56) Further, the *Guideline for Guidelines* refers to details in the VHA Handbook 1004.07 Financial Relationships between VHA Health Care Professionals and Industry (November 2014, issued by the VHA National Center for Ethics in Health Care),(67) as well as to disclosure statements (i.e., the standard disclosure form that is completed at least twice by CPG Work Group members and the guideline development team).(56) The disclosure form inquiries regarding relevant financial and intellectual interests or other relationships with, for example, manufacturers of commercial products, providers of commercial services, or other commercial interests. The disclosure form also inquiries regarding any other relationships or activities that could be perceived to have influenced, or that give the appearance of potentially influencing, a respondent's contributions to the CPG. In addition, instances of potential or actual COIs among the CPG Work Group and the guideline development team were subject to random web-based identification via standard electronic means (e.g., Centers for Medicare and Medicaid Services Open Payments, ProPublica).

## D. Patient Perspective

When developing a CPG, consideration should be given to patient perspectives and experiences, which often vary from those of providers.(61,68) Focus groups can be used to help collect qualitative data on patient perspectives and experiences. VA and DOD Leadership arranged a virtual Patient Focus Group on February 6th, 2024. The focus group aimed to gain insights into patients with Insomnia and/or OSA and incorporate these into the CPG, as appropriate. Topics discussed included the participants' priorities, challenges they have experienced, information they have received regarding their care and the impacts of their care on their lives.

[b] Executive Order on Further Advancing Racial Equity and Support for Underserved Communities Through the Federal Government | The White House

The Patient Focus Group comprised a convenience sample of 16 participants. Of the 16 participants, 11 identified as patients or patient/providers, one identified as a caregiver, and four identified as researchers or advocates. Of the 11 patients or patients/providers, there were 10 males and one female. Fifteen participants were Veterans who received care from the VA Health Care System, and none of the participants were service members who received care from the DOD health system. The Work Group acknowledges this convenience sample is not representative of all patients who are within the VA and DOD health care systems and, thus, findings are ungeneralizable and do not comprise evidence. For more information on the Patient Focus Group methods and findings, see Appendix H. The Patient Focus Group participants were provided the opportunity to review the final draft and provide additional feedback.

### E. External Peer Review

The Work Group drafted, reviewed, and edited this CPG using an iterative process. For more information, see Drafting and Finalizing the Guideline. Once the Work Group members completed a near-final draft, they identified experts from VA and DOD health care systems and outside organizations generally viewed as experts in their respective fields to review it. The draft was sent to those experts for a 14-business-day review and comment period. The Work Group considered all feedback from the peer reviewers and modified the CPG where justified, in accordance with the evidence. Detailed information on the external peer review can be provided by the VA Office of Quality and Patient Safety.

### F. Implementation

This CPG and algorithm are designed for adaptation by individual health care providers with respect to unique patient considerations and preferences, local needs, and resources. The algorithm serves as a tool to prompt providers to consider key decision points in the care of a patient with Insomnia/OSA. The Work Group submits suggested performance metrics for VA and DOD to use when assessing the implementation of this CPG. Robust implementation is identified in VA and DOD internal implementation plans and policies. Additionally, implementation would entail wide dissemination through publication in medical literature, online access, educational programs, and, ideally, electronic medical record programming in the form of clinical decision support tools at the point of care.

## VII. Approach to Care in the Department of Veterans Affairs and Department of Defense

### A. Patient-Centered Care

Intended to consider patient needs and preferences, guideline recommendations represent a whole/holistic health approach to care that is patient-centered, culturally

appropriate, and available to people with limited literacy skills and physical, sensory, or learning disabilities. VA/DOD CPGs encourage providers to use a patient-centered, whole/holistic health approach (i.e., individualized treatment based on patient needs, characteristics, and preferences). This approach aims to treat the condition while also optimizing the individual's overall health and wellbeing.

Regardless of the care setting, all patients should have access to individualized evidence-based care. Patient-centered care can decrease patient anxiety, increase trust in providers, and improve treatment adherence.(69,70) A whole/holistic health approach (https://www.va.gov/wholehealth/) empowers and equips individuals to meet their personal health and wellbeing goals. Good communication is essential and should be supported by evidence-based information tailored to each patient's needs. An empathetic and non-judgmental approach facilitates discussions sensitive to gender, culture, ethnicity, and other differences.

## B. Shared Decision Making

This CPG encourages providers to practice shared decision making, a process in which providers, patients, and patient care partners (e.g., family, friends, caregivers) consider clinical evidence of benefits and risks as well as patient values and preferences to make decisions regarding the patient's treatment.(71) Shared decision making is emphasized in *Crossing the Quality Chasm,* an Institute of Medicine (IOM), now NAM, report in 2001 (72) and is inherent within the whole/holistic health approach. Providers must be adept at presenting information to their patients regarding individual treatments, expected risks, expected outcomes, and levels or settings of care or both, especially where patient heterogeneity in weighing risks and benefits might exist. The VHA and DHA have embraced shared decision making. Providers are encouraged to use shared decision making to individualize treatment goals and plans based on patient capabilities, needs, and preferences.

## C. Patients with Co-occurring Conditions

Co-occurring conditions can modify the degree of risk, impact diagnosis, influence patient and provider treatment priorities and clinical decisions, and affect the overall approach to the management of Insomnia/OSA. Because Insomnia/OSA are often accompanied by co-occurring conditions, managing Insomnia/OSA collaboratively with other care providers may improve overall outcomes. Some co-occurring conditions may require early specialist consultation to determine how care will be coordinated. This approach might entail reference to other VA/DOD CPGs (e.g., Management of Substance Use Disorder [SUD], Use of Opioids in the Management of Chronic Pain; Management of Bipolar Disorder; Management of First-Episode Psychosis and

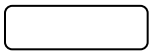
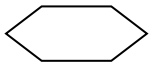
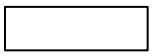
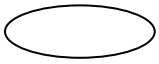
Schizophrenia; Management of Posttraumatic Stress Disorder [PTSD] and Acute Stress Disorder; Management of Major Depressive Disorder [MDD]).[c]

## VIII. Algorithm

This algorithm is designed to inform providers of the recommended interventions and appropriate timing of each of the interventions for patients with chronic insomnia disorder and/or OSA. The interventions included in the algorithm are paired with the corresponding recommendation in the VA/DOD CPG for the Management of Chronic Insomnia Disorder and OSA. The use of the algorithm format to represent patient management was chosen based on the understanding that such a format may promote more efficient diagnostic and therapeutic decision-making and has the potential to change patterns of resource use. Although the Work Group recognizes that not all clinical practices are linear, the simplified linear approach depicted through the algorithm and its format allows the provider to assess the critical information needed at the major decision points in the clinical process. It includes:

- An ordered sequence of steps of care
- Recommended observations and examinations
- Decisions to be considered
- Actions to be taken

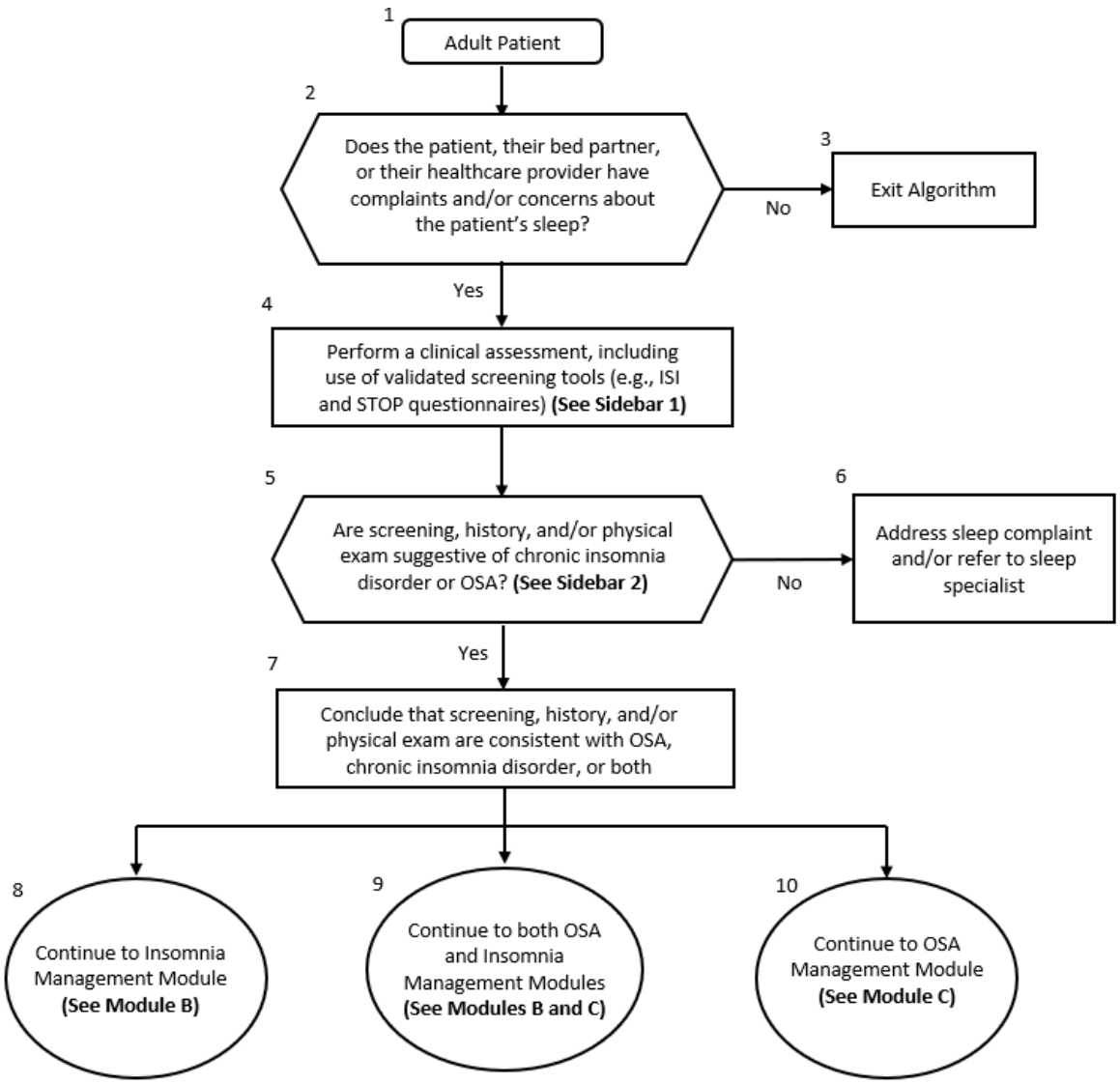
The algorithm is a step-by-step decision tree. Standardized symbols display each step, and arrows connect the numbered boxes indicating the order in which the steps should be followed.(73) Sidebars 1-9 provide more detailed information to assist in defining and interpreting elements in the boxes.

| Shape | Description |
|---|---|
|  | Rounded rectangles represent a clinical state or condition. |
|  | Hexagons represent a decision point in the process of care, formulated as a question that can be answered “Yes” or “No.” |
|  | Rectangles represent an action in the process of care. |
|  | Ovals represent a link to another section within the algorithm. |

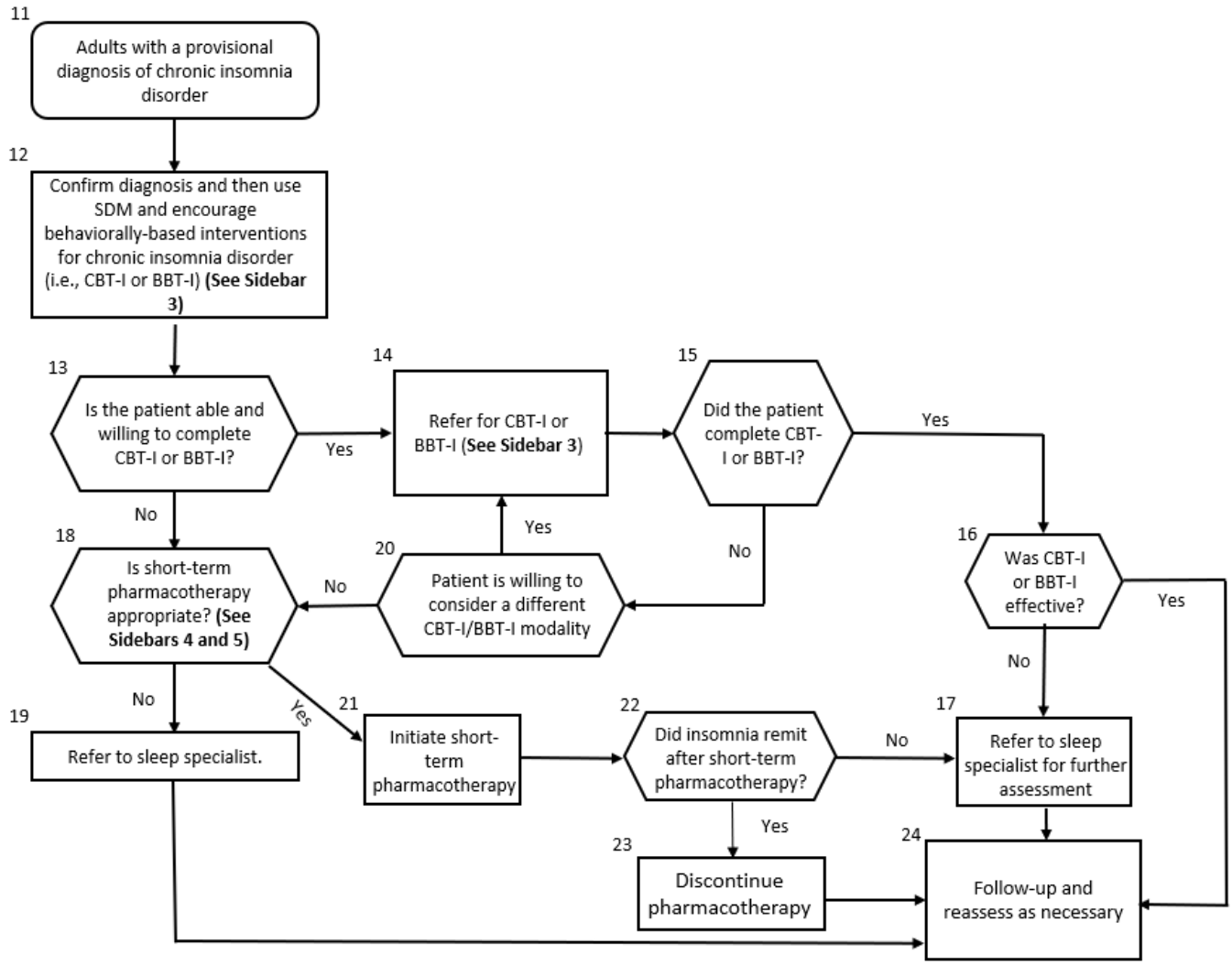
Appendix L contains alternative text descriptions of the algorithms.

[c] The VA/DOD Clinical Practice Guidelines are available at: https://www.healthquality.va.gov/

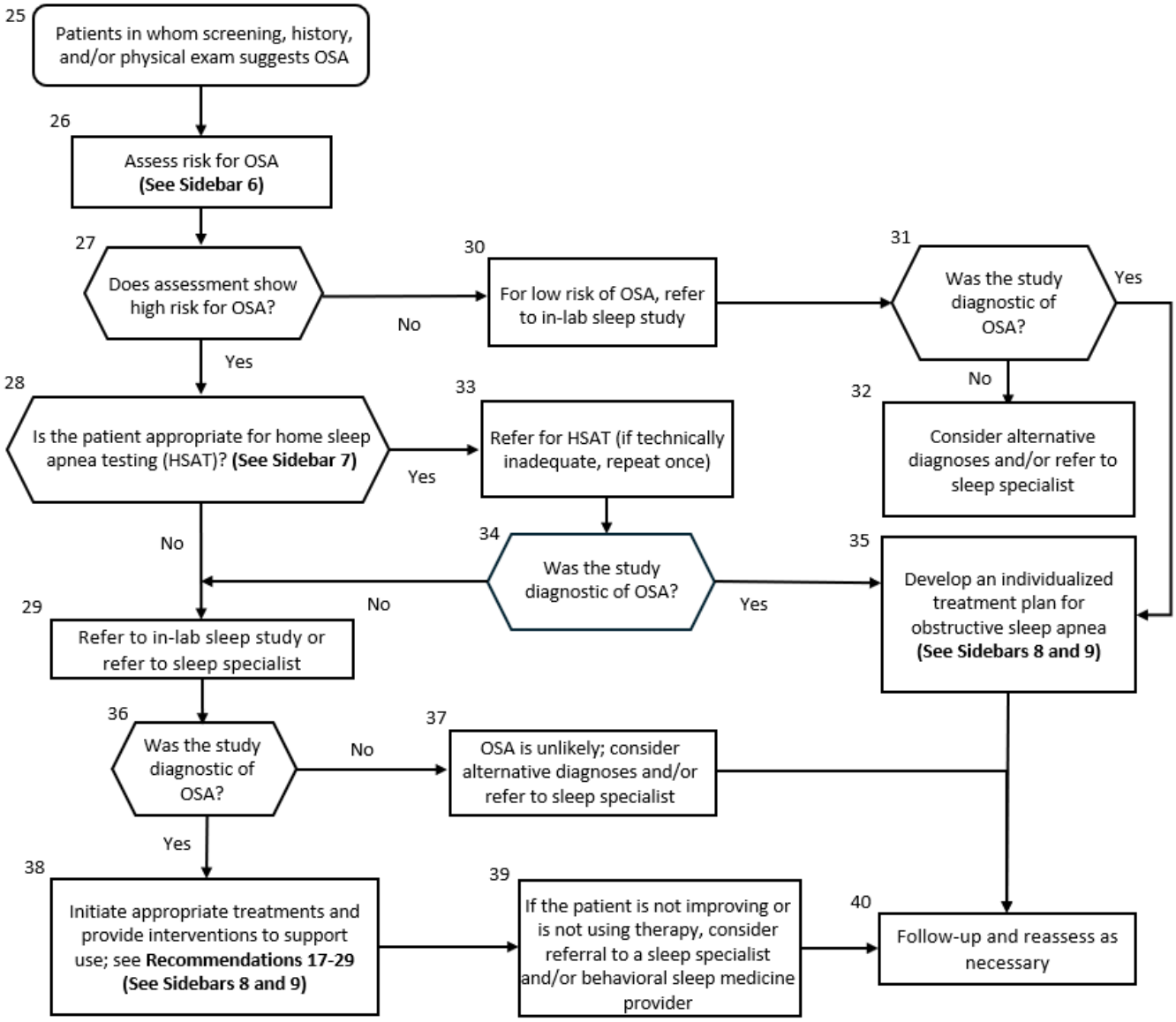
# A. Module A: Screening for Sleep Disorders



## B. Module B: Management of Chronic Insomnia Disorder



## C. Module C: Management of Obstructive Sleep Apnea



## Sidebar 1. Clinical Features of OSA and Chronic Insomnia Disorder

OSA (See Appendix F in the full CPG for detailed ICSD-3-TR Diagnostic Criteria):

- Sleepiness
- Loud, bothersome snoring
- Witnessed apneas
- Nightly gasping/choking
- Obesity (BMI > 30 kg/m²)
- Treatment resistant hypertension

Chronic Insomnia Disorder (See Appendix F in the full CPG for detailed ICSD-3 TR Diagnostic Criteria):

- Difficulty initiating sleep, difficulty maintaining sleep, or early-morning awakenings
- The sleep disturbance causes clinically significant distress or impairment in important areas of functioning
- The sleep difficulty occurs at least 3 nights per week
- The sleep difficulty has been present for at least 3 months

## Sidebar 2. Other Sleep Disorders

- Insufficient Sleep Syndrome
- Restless Legs Syndrome/ (Also known as Willis-Ekbom Disease)
- Narcolepsy/Idiopathic CNS-Hypersomnia
- Nightmare Disorder
- REM Sleep Behavior Disorder
- Circadian Rhythm Sleep-Wake Disorders
- NREM Parasomnias-Sleepwalking/Sleep Eating
- Central Sleep Apnea
- Other forms of sleep disordered breathing

## Sidebar 3. Components of Sleep Education, Overview of Behavioral Interventions, and Contraindications

Patient education and Shared Decision Making (SDM):

- General information on chronic insomnia disorder
- Education about available behavioral and psychological treatment options and available modalities
- Discussion of risks, benefits, preferences and alternatives to treatment options

Components of behavioral and psychological treatment (CBT-I and BBT-I):

- Sleep Restriction Therapy: Limits time in bed to actual sleep duration to increase sleep drive; time in bed extended across treatment
- Stimulus Control: Strengthens bed as a cue for sleep rather than wakefulness
- Arousal reduction techniques: introduction of calming bedtime routine, relaxation techniques to reduce physiological arousal such as diaphragmatic breathing, body scan, or grounding exercises

## Sidebar 3. Components of Sleep Education, Overview of Behavioral Interventions, and Contraindications

- Sleep Hygiene Education (optional): Planned changes in target behaviors and environmental factors that negatively impact sleep including light/noise exposure, eating/drinking near bedtime and at night, caffeine/nicotine/alcohol use **(See Recommendation 7)**
- Cognitive Restructuring (CBT-I only): Addresses cognitive arousal (busy or racing mind) and inaccurate sleep-related thoughts by challenging unhelpful thoughts and beliefs about sleep

Conditions requiring adaptations or delay of CBT-I/BBT-I:

- Medically unstable (delay)
- Active alcohol or drug use disorder (delay)
- Excessive daytime sleepiness (adapt/delay)
- Nighttime fall risk or inability to transfer in/out of bed (adapt)
- Engaged in exposure-based PTSD treatment (delay)
- Uncontrolled seizure disorder (delay)
- Bipolar disorder (adapt)
- Current acute mental health symptoms (delay)
- Pregnancy and postpartum insomnia

## Sidebar 4. Pharmacotherapy Considerations for Chronic Insomnia Disorder

Before starting short-term pharmacotherapy, review sleep history, reproductive status, and evaluate contraindications for pharmacotherapy:

- Evaluate for other sleep disorders (e.g., apnea, NREM parasomnias), daytime sleepiness, respiratory impairment, cognitive impairment, substance abuse history, and medication interactions

Encourage non-pharmacologic approaches (e.g., CBT-I or BBT-I) When short-term pharmacotherapy is appropriate, consider the following agents and discuss deprescribing plan:

- Low-dose doxepin; or
- Dual orexin receptor antagonists; or
- Non-benzodiazepine benzodiazepine receptor agonists (all patients offered treatment with a non - benzodiazepine benzodiazepine receptor agonist should be specifically counseled regarding the risk of complex sleep-related behaviors) **(See Recommendation 9)**

**The use of antipsychotic agents, benzodiazepines, diphenhydramine, and trazodone are NOT suggested for treatment of chronic insomnia disorder (See Recommendation 10).**

**Consider sleep specialist referral in patients who do not respond to pharmacotherapy.**

## Sidebar 5. Interventions Not Advised for Use in Chronic Insomnia Disorder

Treatments **NOT** suggested for chronic insomnia disorder:

- Alpha - stim
- Cannabis or its derivatives
- Chamomile
- Cranial electrical stimulation
- Melatonin
- Passionflower
- Saffron
- Valerian **(See Recommendations 13 and 14)**

Treatments **NOT** recommended for chronic insomnia disorder:

- Kava **(See Recommendation 12)**

## Sidebar 6. Risk of Obstructive Sleep Apnea (OSA)

Consider using STOP questionnaire for risk stratification:

1. Snoring loudly
2. Tired, fatigue, sleepy in daytime
3. Observed to stop breathing
4. Hypertension

High risk of OSA: greater than ≥2 items are answered "yes"

Low risk of OSA: less than <2 items are answered "yes"

STOP questionnaire should not replace clinical judgment; clinical assessment should include BMI >30 kg/m2, age >50, menopausal status, neck circumference, family history, and crowded oropharynx

## Sidebar 7. Appropriateness for HSAT

In-laboratory polysomnography is preferred over HSAT in the following groups:

1. Significant comorbid conditions
    - Advanced heart failure
        - Established or suspected hypoventilation/hypoxic conditions
        - Neuromuscular dysfunction
        - Advanced primary neurological conditions
        - Medication related (opioid, sedative and hypnotics)
        - Advanced respiratory comorbidities.
    - Stroke
2. Patients with significant sleep disruption (e.g. due to chronic insomnia disorder)
3. Physical, sensory and cognitive impairment
4. Chain of custody concerns
5. Low pretest probability for obstructive sleep apnea

**Sidebar 8. AHI 5 to <15 on HSAT**

1. Treatment for OSA is recommended for symptomatic patients with an AHI or REI of 5 to <15 events per hour
2. For patients who will have limitations to their work and/or lifestyle, definitive testing with an in-lab PSG is recommended
3. For the general population without such restrictions, an AHI of 5 to <15 events per hour on HSAT should be treated as OSA

**Sidebar 9. Treatment of Obstructive Sleep Apnea (OSA)**

1. Prescribe PAP as first line therapy for patient with severe OSA (i.e., AHI >30 events per hour)
2. Prescribe PAP or MAD for other OSA severity (i.e., AHI 5 to <30 events per hour), based on clinical evaluation, comorbidities, and patient preference.
3. Offer educational, behavioral therapy, and supportive interventions to improve PAP adoption and use
    - Consider a two-week course of eszopiclone to improve PAP adoption
    - Consider referral to behavioral sleep medicine provider to enhance PAP adoption and use
4. Encourage weight loss and a comprehensive lifestyle intervention program in patients with OSA who are overweight or obese.
5. Refer patients for follow up to a sleep medicine specialist:
    - Who do not adopt/use PAP and/or MAD therapy
    - With persistent symptoms despite adequate therapy

# IX. Recommendations

The evidence-based clinical practice recommendations listed in Table 4 were developed using a systematic approach considering four domains as per the GRADE approach (see Summary of Guideline Development Methodology). These domains include confidence in the quality of the evidence, balance of desirable and undesirable outcomes (i.e., benefits and harms), patient values and preferences, and other implications (e.g., resource use, equity, acceptability).

**Table 4. Evidence-Based Clinical Practice Recommendations with Strength and Category**

| Topic | Sub-topic | # | Recommendation | Strength[a] | Category[b] |
|---|---|---|---|---|---|
| *Screening* | | 1. | For screening of patients with sleep complaints, we suggest using validated screening instruments for both insomnia (e.g., Insomnia Severity Index or Athens Insomnia Scale) and obstructive sleep apnea (e.g., STOP) to identify patients who need further evaluation. | Weak for | Not reviewed, Amended |
| *Obstructive Sleep Apnea Diagnosis* | | 2. | For diagnosis of clinically suspected obstructive sleep apnea, we recommend diagnosis with polysomnography or home sleep apnea testing. | Strong for | Reviewed, New-added |
| | | 3. | For diagnosis of obstructive sleep apnea in appropriate patients*, we suggest home sleep apnea testing as an alternative to in-laboratory polysomnography. | Weak for | Reviewed, New-replaced |
| | | 4. | For diagnosis of patients with a non-diagnostic home sleep apnea test, we recommend further sleep testing for obstructive sleep apnea with in-lab polysomnography or HSAT. | Strong for | Reviewed, New-replaced |
| *Treatment of Chronic Insomnia Disorder* | *Behavioral and Psychological Treatments* | 5. | For treatment of chronic insomnia disorder, we recommend treatment with CBT-I. | Strong for | Not reviewed, Amended |
| | | 6. | For treatment of chronic insomnia disorder, we suggest treatment with BBT-I. | Weak for | Not reviewed, Amended |
| | | 7. | For treatment of chronic insomnia disorder, we suggest against sleep hygiene education as a stand-alone treatment. | Weak against | Not reviewed, Not changed |
| | *Pharmacotherapy -Insomnia* | 8. | For treatment of chronic insomnia disorder, we suggest CBT-I over pharmacotherapy as first-line treatment. | Weak for | Reviewed, Amended |
| | | 9. | For treatment of chronic insomnia disorder in patients who are offered a course of pharmacotherapy, we suggest the use of one of the following agents:<br>• Daridorexant | Weak for | Reviewed, New-replaced |

| Topic | Sub-topic | # | Recommendation | Strength[a] | Category[b] |
|---|---|---|---|---|---|
| | | | • Doxepin<br>• Eszopiclone<br>• Lemborexant<br>• Suvorexant<br>• Zaleplon<br>• Zolpidem | | |
| | *Pharmacotherapy-Insomnia (cont.)* | 10. | For treatment of chronic insomnia disorder in patients who are offered a course of pharmacotherapy, we suggest against the use of:<br>• Antipsychotic drugs<br>• Benzodiazepines<br>• Diphenhydramine<br>• Trazodone | Weak against | Reviewed, New-replaced |
| | | 11. | For treatment of chronic insomnia disorder in patients who are offered a course of pharmacotherapy, there is insufficient evidence to recommend for or against the use of ramelteon. | Neither for nor against | Reviewed, Amended |
| | *Complementary and Integrative* | 12. | For treatment of chronic insomnia disorder, we recommend against the use of kava. | Strong against | Not reviewed, Amended |
| | | 13. | For treatment of chronic insomnia disorder, we suggest against the use of cannabis and/or its derivatives. | Weak against | Reviewed, New-added |
| | | 14. | For treatment of chronic insomnia disorder, we suggest against the use of:<br>• Chamomile<br>• Melatonin<br>• Passionflower<br>• Saffron<br>• Valerian | Weak against | Reviewed, Amended |
| | | 15. | For treatment of chronic insomnia disorder, there is insufficient evidence to recommend for or against the use of magnesium. | Neither for nor against | Reviewed, New-added |
| | | 16. | For treatment of chronic insomnia disorder, there is insufficient evidence to recommend for or against:<br>• Aerobic exercise<br>• Mindfulness meditation<br>• Qigong<br>• Resistive exercise<br>• Tai chi<br>• Yoga | Neither for nor against | Not reviewed, Amended |

| Topic | Sub-topic | # | Recommendation | Strength[a] | Category[b] |
|---|---|---|---|---|---|
| ***Treatment of Obstructive Sleep Apnea*** | | 17. | For treatment of obstructive sleep apnea, we recommend one or more of the following evidence-based therapies, depending on patient values and characteristics:<br>• Mandibular advancement devices<br>• Positive airway pressure (PAP)<br>• Referral for surgical evaluation | Strong for | Reviewed, New-added |
| | | 18. | For treatment of mild to moderate obstructive sleep apnea (Event Index <30 per hour), we suggest either mandibular advancement devices or positive airway pressure as first line therapy options. | Weak for | Reviewed, Amended |
| | | 19. | For treatment of newly diagnosed obstructive sleep apnea, we suggest initiating auto-titrating over fixed continuous positive airway pressure to facilitate usage. | Weak for | Reviewed, New-replaced |
| | | 20. | For treatment of obstructive sleep apnea in patients with overweight or obesity, we suggest evidence-based weight management in combination with other treatments for obstructive sleep apnea. (See VA/DOD CPG on Management of Overweight and Obesity) | Weak for | Reviewed, New-added |
| | | 21. | For treatment of positional obstructive sleep apnea, we suggest positional therapy. | Weak for | Reviewed, New-added |
| | | 22. | For treatment of obstructive sleep apnea in appropriate* patients (including with an apnea hypopnea index of 15 or greater per hour) who have not been successful with positive airway pressure therapy, we suggest referral for evaluation for hypoglossal nerve stimulation therapy.<br><br>*Note FDA criteria for appropriate patients in the narrative. | Weak for | Reviewed, Amended |
| | | 23. | For treatment of obstructive sleep apnea in patients who cannot tolerate other recommended therapies, we suggest against oxygen therapy as a standalone treatment. | Weak against | Not reviewed, Amended |
| | | 24. | For treatment of obstructive sleep apnea, we suggest against atomoxetine or a combination of atomoxetine and oxybutynin. | Weak against | Reviewed, New-added |
| | | 25. | For treatment of obstructive sleep apnea there is insufficient evidence to suggest for or against these interventions:<br>• Expiratory positive airway pressure (EPAP)<br>• Inspiratory muscle therapy<br>• Intra-oral negative airway pressure<br>• Myofunctional exercise<br>• Neuromuscular electrical stimulation | Neither for nor against | Reviewed, New-replaced |

| Topic | Sub-topic | # | Recommendation | Strength[a] | Category[b] |
|---|---|---|---|---|---|
| | | | • Transcutaneous electrical nerve stimulation (TENS) | | |
| | | 26. | For treatment of obstructive sleep apnea in patients who are prescribed positive airway pressure therapy, we suggest the use of in-person or telehealth educational, behavioral, and supportive interventions to improve PAP usage. | Weak for | Reviewed, New-replaced |
| | | 27. | For treatment of obstructive sleep apnea in appropriate patients, we suggest up to a two-week course of eszopiclone to improve positive airway pressure usage. | Weak for | Reviewed, New-added |
| | | 28. | For treatment of obstructive sleep apnea in patients with anatomical nasal obstruction as a barrier to positive airway pressure use, we suggest evaluation for nasal surgery. | Weak for | Reviewed, Not changed |
| | | 29. | For treatment of obstructive sleep apnea-related residual excessive daytime sleepiness in patients who are optimally treated with sufficient therapy use, we suggest adding:<br>• Armodafinil<br>• Modafinil<br>• Solriamfetol | Weak for | Reviewed, New-added |

[a] For additional information, see Determining Recommendation Strength and Direction.
[b] For additional information, see Recommendation Categorization.
*For information on individuals who may not be appropriate for HSAT, see Recommendation 3

# A. Screening

## *Recommendation*

1. For screening of patients with sleep complaints, we suggest using validated screening instruments for both insomnia (e.g., Insomnia Severity Index or Athens Insomnia Scale) and obstructive sleep apnea (e.g., STOP) to identify patients who need further evaluation.
   **(Weak for | Not reviewed, Amended)**

## *Discussion*

For the purpose of screening for symptoms of chronic insomnia disorder, the Insomnia Severity Index (ISI), the Athens Insomnia Scale (AIS), and the Pittsburgh Sleep Quality Index (PSQI) (74) have high diagnostic accuracy. In a SR conducted by Chiu et al. (2016), all three measures were found to be both sensitive and specific for accurately classifying individuals with insomnia. They found no statistically significant differences between different screening tools.(75) Computed sensitivity (Se) and specificity(Sp) for the three measures were as follows: AIS Se: 91%; 95% confidence interval [CI] 0.87 – 0.93; Sp: 87%; 95% CI 0.68 – 0.95; ISI Se: 88%; 95% CI 0.79 – 0.93; Sp: 85%; 95% CI 0.68 – 0.94 and PSQI Se: 94%; 95% CI 0.86 – 0.98; Sp: 76%; 95% CI 0.64 – 0.85. In clinical samples, a cutoff score of 11 on the ISI was shown to have the greatest sensitivity and specificity for correctly identifying study participants meeting insomnia diagnostic criteria,(76) whereas a cutoff score of 6 correctly discriminated insomnia patients from controls on the AIS in 90% of cases.(77) These clinical samples were not included in our systematic evidence review and, thus, are independent from the strength of this recommendation.

For the screening of OSA, using an apnea-hypopnea index (AHI)- defined as the number of apneas and hypopneas per hour of sleep as ≥5 events per hour on PSG as the gold standard test to define OSA, our evidence review yielded data on diagnostic accuracy for only the Berlin Questionnaire (BQ), STOP-BANG questionnaire (Snoring, Tiredness, Observed apnea, high blood Pressure, Body mass index, Age, Neck circumference, male), STOP questionnaire (Snoring, Tiredness, Observed Apnea and high blood Pressure), and Epworth Sleepiness Scale (ESS).(78) In a meta-analysis of 100 studies encompassing 47,989 patients, Chiu et al. (2017) reported the sensitivity (Se), specificity (Sp), and diagnostic odds ratio (DOR) among the BQ, STOP-BANG, STOP, and ESS, according to the severity of OSA.(78) For the specified AHI ≥5 and using the reported standard thresholds of each questionnaire for high OSA risk, the pooled estimates for BQ, STOP-BANG, STOP, and ESS, respectively were: Se 76%, 88%, 87%, and 54%; Sp 59%, 42%, 42%, and 65%; and DOR 4.30, 5.13, 4.85, and 2.18.

As confirmatory objective testing is a requirement after screening for OSA, the Work Group agreed that focusing on sensitivity as the metric of choice will increase the likelihood of detecting cases while minimizing the false negative cases (patients who screen negative but could ultimately have the disease on objective testing). With that in mind, among these four screening tools, the sensitivities for STOP and STOP-BANG were the highest and like each other. Given their performance similarities and its simpler administration, STOP was included in our recommendation.

The Work Group's confidence in the quality of the evidence is moderate.(78) Several factors were considered in the Work Group's decision to recommend the ISI and AIS for insomnia disorder screening and the STOP questionnaire for the screening of OSA. Screening for both chronic insomnia disorder and OSA is an important first step in identifying patients at risk for either or both sleep disorders and can assist in the development of appropriate referrals for patients who may benefit from further assessment and intervention. The Work Group also considered the high prevalence of COMISA in patients presenting with signs and symptoms of sleep disorders, and the importance of screening for both chronic insomnia and OSA concurrently in at-risk patients.

The Work Group considered resource use. Questionnaire length and scoring processes for the screeners were reviewed. For insomnia screening, the ISI and AIS measures are comprised of only seven and eight items, respectively; scoring these measures involves a simple calculation of a sum across items. The intended purpose of each measure was also considered. The ISI and AIS were designed to assess insomnia, whereas the PSQI was designed to assess sleep quality and includes subscales focused on other sleep disorders. Based on these factors, the Work Group determined that the ISI and AIS have greater clinical utility and chose to recommend them over the PSQI for insomnia disorder screening. For OSA screening, the STOP questionnaire is a screening tool for OSA consisting of four dichotomous (yes/no) questions on 1) Snoring; 2) Tiredness, fatigue, or sleepiness during the daytime; 3) Observed apneas, and 4) history of high blood Pressure. A positive response leads to a score of 1 for any of the questions, with a total possible score of 4. A score of 2 or higher discriminates high from low risk for OSA.(79)

Future research priorities to assist with screening for chronic insomnia disorder and OSA were identified by the Work Group (See Research Priorities section for list). As many of the studies included in the SR conducted by Chiu et al. (2016) (75) related to screeners for insomnia, and the meta-analysis conducted by Chiu et al. (2017) (78) related to screening for OSA were conducted in specialty care clinics, the Work Group identified the need for further studies on screening in the primary care setting. A second priority identified was research on the development of a simple, streamlined screener for both insomnia and OSA due to the prevalence of COMISA in patients presenting

with sleep complaints. Evaluating the impact of a streamlined screener on outcomes for insomnia, OSA, or COMISA would be an important aspect of such research and well aligned with patient preferences as identified in our Patient Focus Group. Lastly, the Work Group identified evaluation of the use of machine learning/Artificial Intelligence (AI) to aid in the screening and identification of patients with insomnia, OSA, or COMISA as a future research priority.

The 2019 Work Group systemically reviewed evidence related to this recommendation; however, no new data was reviewed for the 2025 update (74-79). Therefore, it is categorized as Not Reviewed, Amended. The Work Group's confidence in the quality of the evidence was moderate. The body of evidence had some limitations, including the need for additional resources to implement screening, and the availability of resources to some providers. The benefits of the recommended screeners' use outweigh potential harms/burden. Patient values and preferences were similar because some patients advocate for timely screening and prefer early rather than delayed detection of insomnia and OSA. Other implications the Work Group considered are acceptability and feasibility, as some patients are both able and amenable to completing the ISI, AIS, and STOP Questionnaire, while others may not be. Thus, the Work Group decided on a *Weak for* recommendation.

## B. Obstructive Sleep Apnea Diagnosis

### *Recommendation*

2. For diagnosis of clinically suspected obstructive sleep apnea, we recommend diagnosis with polysomnography or home sleep apnea testing.
   **(Strong for | Reviewed, New-added)**

### *Discussion*

Obstructive sleep apnea presents itself with a multitude of symptoms. Although a constellation of symptoms makes up the OSA syndrome, the basis for the diagnosis and decision about therapy relies on defining pathophysiology. This is in sharp contrast with insomnia as its diagnosis solely relies on symptomatology. In OSA, repetitive narrowing or complete closure of the upper airways during sleep results in reduction or complete cessation of airflow, hypoxia, and sleep fragmentation. OSA therapy aims at normalization of airflow during sleep and thus, prevention of hypoxia and sleep fragmentation. The reduction or complete cessation of airflow is measured objectively through monitoring of airflow using various validated technology. In addition, consequences of this repetitive impaired flow are measured and quantified by measuring oxygenation and sleep stages. With objective sleep testing different indices of respiratory compromise are generated that will rate the severity of OSA and help with

the therapy recommendations. The work group strongly recommended an objective tool for diagnosis of OSA rather than relying on clinical symptoms and signs. The following paragraph in detail reviews the elements that helped us to determine the strength of recommendation.

The gold standard test for evaluation of sleep disordered breathing (SDB) including OSA is the attended in-lab PSG. The PSG conducted in sleep laboratory environment at night and thus, the care with trauma informed principles should be implemented to avoid further traumatization of vulnerable patients. Over the past several decades, evaluation with portable monitoring (PM) devices known as home sleep apnea tests (HSATs) have provided an alternative, home-based method of evaluating SDB. Current recommendation for PM only includes FDA approved level III or IV devices. HSAT is considered a tool to rule in rather than rule out OSA. In the prior and current CPG, the Work Group reviewed data on the validity of PM devices with a focus on the critical outcomes of sensitivity and specificity of PMs compared to in-lab PSG. An SR evaluating type IV PMs in over 2,000 pooled patients in 18 studies demonstrated unacceptable sensitivity and specificity for single or double channel type IV devices.(80) A study of clinical sample of 500 subjects, comparing concurrent peripheral arterial tonometry (WatchPat) to PSG, reported a diagnostic concordance that varied with severity of sleep apnea (42%, 41%, and 83% for mild, moderate and severe OSA, respectively).(81) One single center RCT evaluated the validity of the ApneaLink type III PM compared to in-lab PSG.(82) The evidence reviewed for the current CPG identified studies comparing Belung Ring to PSG. This device is not considered a level III device (83,84) (85,86) largely due to concerns regarding specificity of type III or IV devices in this study at the 5 events per hour cutoff. The Work Group recommends applying a cutoff of 15 events per hour for a definitive diagnosis of OSA on HSATs. For patients who undergo home testing and have a reported event index (AHI, respiratory disturbance index, or REI) of 5 to 15 events per hour, a clinical decision integrating the patient's event index, symptoms, occupation, and comorbid disorders should be used to render an appropriate diagnosis. If there is diagnostic uncertainty, either repeat testing or a referral to a sleep specialist, a sleep medicine physician or a care extender (PA and NP) under supervision of a sleep medicine physician, should be considered. If the initial HSAT is non-diagnostic of OSA (event index of <5 per hour), either a repeat HSAT or in-lab PSG should be performed.

The Work Group determined it was important to emphasize that appropriate patient selection for home testing with unattended PM is critical to utilizing this diagnostic tool. HSAT is not recommended, nor should it be performed, in patients with significant comorbid pulmonary, cardiovascular, or neuromuscular disease (see Module C: Management of Obstructive Sleep Apnea) as these conditions may be associated with other sleep disordered breathing including hypoventilation and central sleep apnea with

or without presence of comorbid OSA. Unattended PM is not recommended, nor should it be performed, in patients without a high pretest probability of sleep apnea. All patients appropriately selected for evaluation with PM should have a high pretest probability for OSA; therefore, negative, non-diagnostic, and technically inadequate studies should prompt further evaluation to ensure the absence of SDB. Depending on the results of the initial HSAT, this repeat evaluation can be either a repeat HSAT or an in-lab PSG.

Because of the risk of significant harm related to undiagnosed (and therefore untreated) OSA in this pre-selected population at high risk for the disease, the Work Group determined it was important for this guideline to explicitly state the need for repeat testing in patients for whom an HSAT does not confirm a diagnosis of OSA.

A non-diagnostic HSAT does not rule out OSA, and the clinician may consider an in-lab PSG as appropriate. This is also consistent with recommendations regarding evaluation with HSAT in other CPGs.(8,87) These CPGs from other organizations were not included in our evidence review and, thus, are independent from the strength of this recommendation.

The Work Group systemically reviewed evidence related to this recommendation (80-86).Therefore, it is categorized as Reviewed, New-added. The Work Group's confidence in the quality of the evidence was low. The benefits outweigh harms/burden as that the undiagnosed, untreated OSA may results in significant harms to patients as well as others and may result in death. There is some variation in patient values and preferences as a lack of objectively established diagnosis can have unintended consequences including affecting the individual's ability to obtain or maintain a driving license or affecting the ability to obtain disability insurance. We also considered the burden of testing comparing HSAT versus PSG. With the experience of the COVID-19 pandemic, the issue of exposure of both individuals being tested and those who will conduct the test is a major consideration. Other implications the Work Group considered are resource use, as proper diagnosis and prognostication will significantly affect the start of therapy. In addition to resource use, the Work Group considered equity as another implication, as for example patients with prior traumatic exposures may not feel comfortable sleeping in a strange or unfamiliar environment. Subgroup considerations stemming from physical and cognitive challenges may play an important role in how an objective test (PSG or HSAT) is recommended and performed. Subgroups of patients may not do well in a sleep laboratory environment particularly those with comorbid insomnia and sleep apnea. Thus, the Work Group decided on a *Strong for* recommendation.

### Recommendation

3. For diagnosis of obstructive sleep apnea in appropriate patients*, we suggest home sleep apnea testing as an alternative to in-laboratory polysomnography.

   *For information on individuals who may not be appropriate for HSAT, see narrative below.
   **(Weak for | Reviewed, New-replaced)**

### Discussion

There is some variation in patient preferences regarding this testing. Some patients may prefer to conduct testing at home, while others may prefer to conduct testing in a laboratory setting. Further, the Work Group identified effects on resource use, equity, and subgroup considerations. When discussing resources use, HSAT requires no lab time or staff to conduct the test, but it does require some patient education on test set up. Some patients may prefer to not sleep in a lab (prior trauma), HSAT provides equity to these patients. The Work Group identified the following patient subgroups who may not be appropriate for HSAT such as, patients with moderate-severe physical, sensory, or cognitive/behavioral ability, patients who will not pursue therapy (e.g., end of life, etc.), and central sleep apnea patients. Generally, HSAT is not recommended, nor should it be performed, in patients with significant comorbid pulmonary, cardiovascular, or neuromuscular disease (see Module C: Management of Obstructive Sleep Apnea) and instead in-lab PSG should be pursued.

The Work Group systematically reviewed evidence related to this recommendation, which is discussed in recommendation 2.(81,83-86) Therefore, it is categorized as Reviewed, New-replaced. The Work Group's confidence in the quality of the evidence was very low. The body of evidence had some limitations including small sample sizes in many studies and large confidence intervals in all studies.(81,83-86) The benefits of HSAT including earlier diagnosis, testing reflective of home sleep experience, less burden for caregivers, patient comfort, less routine disruption, sleeping on own schedule, and less exposure of healthcare professionals to infectious disease, slightly outweighed the potential harm which was small (possibility of the patient needing a second test and possible difficulties setting up the equipment). Patient values and preferences were similar with some patients preferring to conduct testing at home based on the Patient Focus Group (2019). Thus, the Work Group decided on a *Weak for* recommendation.

### Recommendation

4. For diagnosis of patients with a non-diagnostic home sleep apnea test, we recommend further sleep testing for obstructive sleep apnea with in-lab polysomnography or HSAT.
   **(Strong for | Reviewed, New-replaced)**

### Discussion

A non-diagnostic HSAT does not rule out OSA, and the clinician may consider an in-lab PSG as appropriate and available. Due to the risk of significant harm related to undiagnosed (and therefore untreated) OSA in this pre-selected population at high risk for the disease, the Work Group determined it was important for this guideline to explicitly state the need for repeat testing in patients for whom an HSAT does not confirm a diagnosis of OSA. Although not included in our systematic evidence review and, thus, independent from the strength of this recommendation, there is significant evidence suggesting harm in patients with undiagnosed or untreated OSA. Patients with untreated OSA have a threefold increased risk of motor vehicle crashes (MVCs) compared to the general population (88) and have a higher risk of personal injury related to those MVCs.(89,90) An SR of nine studies of patients with moderate to severe OSA by Treager et al. (2010) noted that treatment with PAP reduces crash risk and relieves excessive daytime sleepiness among these patients.(91) Elevated AHI is associated with an increased likelihood of hypertension, stroke, coronary artery disease, and heart failure, even after adjustment for other cardiovascular risk factors.(92,93) An AHI >20 events per hour confers a higher risk of stroke (94) and an AHI >30 events per hour confers a higher risk of dysrhythmias and all-cause mortality.(95,96) Because of the risk of significant harm related to undiagnosed OSA in this pre-selected population at high risk for the disease, the Work Group determined it was important for this guideline to explicitly state the need for further testing (either in lab PSG or repeat HSAT) in patients for whom an initial HSAT does not confirm a diagnosis of OSA. This is also consistent with recommendations regarding evaluation with HSAT in other CPGs.(8,87) These CPGs from other organizations were not included in our evidence review and, thus, are independent from the strength of this recommendation.

The Work Group systematically reviewed evidence related to this recommendation (81,83-86). The Work Group's confidence in the quality of the evidence for this recommendation is very low. Several factors were considered in the work group's decision to recommend repeat testing, including resource use and patient preferences. The Work Group concluded that the benefits of repeat testing in patients with a high pretest probability for OSA and a non-diagnostic HSAT outweigh concerns about the negligible harm or minor patient inconvenience of repeat testing. OSA is a serious medical disorder and undiagnosed OSA is associated with accidents (e.g., motor vehicle, industrial, work-related), adverse cardiovascular outcomes, and, in severe disease, worsened all-cause mortality. Due to this risk of significant harm related to undiagnosed OSA in a high-risk population, repeat testing is recommended to ensure the absence of OSA. Thus, the Work Group decided on a *Strong for* recommendation.

## C. Treatment of Chronic Insomnia Disorder

### *a. Behavioral and Psychological Treatments*

### *Recommendation*

5. For treatment of chronic insomnia disorder, we recommend treatment with CBT-I.

   **(Strong for | Not reviewed, Amended)**

6. For treatment of chronic insomnia disorder, we suggest treatment with BBT-I.

   **(Weak for | Not reviewed, Amended)**

### *Discussion*

Cognitive behavioral therapy for insomnia (CBT-I) is a multi-session, multi-component treatment focused on sleep-specific thoughts and behaviors. Behavioral components of CBT-I include sleep restriction therapy (i.e., limiting time in bed to sleep time followed by a gradual increase in time in bed as sleep efficiency improves), stimulus control (i.e., strengthening the association between sleep environment and sleep, and establishing consistent sleep patterns), relaxation therapy/counter-arousal strategies, and sleep hygiene education.(97,98) Cognitive therapy components target maladaptive thoughts and beliefs about sleep. Brief behavioral treatment for insomnia (BBT-I) focuses on the behavioral components of sleep restriction, stimulus control, and some sleep hygiene.(97,98)

Two SRs examined the efficacy of CBT-I.(97,99) The trials looked at outcomes in the general adult population and in subpopulations of older adults (i.e., trials that exclusively enrolled adults age 55 and older) and patients with comorbid pain.(99) The SR by Brasure et al. (2015) included 59 total trials comparing psychological interventions such as CBT-I and BBT-I with passive controls.(97) Brasure et al. (2015) reported outcomes favoring CBT- I, including statistically significant improvements in ISI, sleep efficiency, and sleep quality in the general adult, older adult, and adult with comorbid pain populations, as well as wake after sleep onset (WASO) in the general adult and older adult populations. No significant between-group differences were found in wake time after sleep onset (in adults with chronic pain).(97) Brasure et al. (2015) also reported on three RCTs comparing multicomponent behavioral therapies or BBT-I versus passive controls in older adults and found significant changes favoring BBT-I in areas of sleep efficiency, sleep quality, sleep onset latency, and WASO.(97) There was insufficient evidence to indicate the optimal frequency of appointments. Johnson et al. (2016) reviewed eight trials comparing CBT-I to waitlist control in individuals with a comorbid cancer diagnosis and found significant effects favoring CBT-I over passive treatments for improvements in ISI, sleep efficiency, sleep onset latency, and WASO.(99)

CBT-I has also been found to reduce insomnia severity, sleep onset latency, and WASO and to increase sleep efficiency and sleep quality in patients with chronic

insomnia disorder that is comorbid with another mental health disorder.(100) Based on the SR conducted by Okajima et al. (2018), treatment with CBT-I was associated with improvements in ISI, sleep efficiency, sleep onset latency, WASO, and sleep quality in patients with chronic insomnia disorder comorbid with mental health disorders including bipolar disorder, depression, PTSD, alcohol dependence, and mixed psychiatric disorders.(101) An RCT in individuals with insomnia disorder comorbid with a schizophrenia spectrum diagnosis found improvements in insomnia severity, sleep onset latency, and sleep quality.(102) There is evidence for improvement in a range of sleep measures, but some studies included individuals receiving other sleep treatments in addition to CBT-I. Also, Okajima et al. (2018) provided no information on the age and sex of study participants and limited information on mental health diagnoses.(101) There was insufficient evidence to include any recommendation regarding the treatment of chronic insomnia disorder in individuals with comorbid TBI.

Several treatment modalities are effective for delivering CBT-I including individual therapy, group therapy, telephone, assisted and unassisted digital, and guided and unguided self-help. Two SRs and 2 RCTs examined the effectiveness of CBT-I as delivered across several treatment modalities. Although there was overlap between the two SRs, both were included due to a difference in focus; digital CBT-I versus a larger range of delivery modalities. Gao et al. (2022) was a SR including 61 RCTs and compared treatment delivery modalities to passive control conditions.(103) Treatment modalities examined included individual therapy, group therapy, guided self-help, digital CBT-I, telephone CBT-I, and unguided self-help. Gao et al. (2022) reported critical outcomes favoring CBT-I (insomnia severity and sleep efficiency) at post-intervention across all treatment modalities, and improvements in important outcomes favoring CBT-I including sleep onset latency (SOL) and WASO when treatment was delivered via individual, group and guided self-help modalities. No significant differences were found at follow-up between treatment modality and passive controls on SOL and WASO when treatment was delivered via digital assisted, telephone and unguided self-help.(103) A SR by Hasan and colleagues (2022) included 54 RCTs comparing the effectiveness of digital CBT-I to both active and passive controls.(104) Hasan et al. (2022) reported outcomes favoring digital CBT-I for all modalities, with the exception of mobile apps where no significant between-group differences were found for SOL. Chao et al. (2021) was a RCT examining telephone-delivered CBT-I to waitlist in Veterans with Gulf War Illness(105) and Taylor et al. (2018) was a RCT examining in-person CBT-I to attention control among active-duty military personnel.(106) Both studies reported outcomes favoring CBT-I delivered in person or by telephone on insomnia severity, sleep efficiency, WASO, SOL, sleep quality, and mental health. Chao et al. (2021) also reported outcomes favoring telephone delivered CBT-I on fatigue severity.(105) No evidence was found for alternative treatment delivery formats for BBT-I.

Based on the strength of the evidence reviewed, Gao et al. (2022) suggested that individual therapy may be the most effective for reducing insomnia severity(103) and

Hasan et al. (2022) reported that web based CBT-I with a therapist ranked highest compared to other digital CBT-I approaches for insomnia severity, sleep efficiency and WASO.(107) Although not considered in this review, Simon et al (2023) conducted a SR of comparative effectiveness studies and, consistent with the SRs considered herein, suggested that treatment delivered synchronously with a therapist should be considered over other modalities without therapist assistance when available.(108)

For Recommendations 5 and 6, the Work Group's confidence in the quality of the evidence for CBT-I and BBT-I is moderate (i.e., the critical outcomes of insomnia severity and sleep efficiency for CBT-I and the critical outcome of sleep efficiency for BBT-I).(97,99) The quality rating for the SR of CBT-I by Johnson et al. (2016) was good overall.(99) The quality rating for the SR of CBT-I and BBT-I by Brasure et al. (2015) was fair overall, with limitations such as lack of clarity about allocation concealment and blinding of participants and study personnel.(97) In addition, an ITT analysis was performed in some, but not all, studies and several studies had high attrition.(97) Other considerations regarding the Work Group's recommendations included the benefits of the intervention seen across multiple sleep outcomes areas and no significant harms except for transient sleepiness that may result from sleep restriction caused by CBT-I or BBT-I.(99) The quality rating for the SR of CBT-I and BBT-I by Brasure et al. (2015) was fair overall, with limitations such as lack of clarity about allocation concealment and blinding of participants and study personnel.(97) CBT-I and BBT-I must be delivered by professionals trained specifically in the delivery of these treatments to not only ensure treatment fidelity but to avert potential risks posed by the sleep restriction component of these interventions. The Work Group also considered access inequality due to lack of provider availability. Given these considerations, the Work Group decided upon a "Strong for" recommendation for CBT-I. Because there is a much smaller literature base on BBT-I and the evidence on BBT-I evaluates its effect on older adults only, the Work Group decided upon a *Weak for* recommendation for BBT-I.

There is potential variation in patient values and preferences regarding behaviorally based interventions. Some patients find behavioral interventions to be burdensome and both BBT-I and CBT-I require considerable behavior change on the part of patients. Although not included in our systematic evidence review and, thus, independent from the strength of this recommendation, Morin et al. (1992) demonstrated that CBT-I was rated as more acceptable than pharmacotherapy by patients.(109) Although there is no evidence of harm from CBT-I or BBT-I in patients with comorbid mental disorders, Smith and Perlis (2006) found certain medical and mental health conditions require either delaying CBT-I or a tailored treatment approach.(110) Adherence to mood stabilizing pharmacotherapy in patients with bipolar disorder would need to be closely monitored in order to avoid precipitating hypomania or mania with sleep restriction, a component of both BBT-I and CBT-I. Similarly, some evidence suggests that sleep restriction may precipitate seizures in those with seizure disorders.(110) Delayed treatment is appropriate among those endorsing current suicidal ideation and those currently

engaged in exposure-based PTSD treatments. Patients also may have different preferences regarding CBT-I versus other treatments for chronic insomnia disorder. Smith and Perlis (2006) were not included in our systematic evidence review and, thus, did not influence the strength of this recommendation.

Despite consistency in the evidence that supports CBT-I and BBT-I as treatments for chronic insomnia disorder, there may be limited access to these interventions as they require providers with adequate specialized training in both CBT and sleep medicine. This may be particularly challenging for providers and patients located in rural/remote locations. Additionally, the relatively frequent (e.g., weekly) visits may be burdensome to patients, who may prefer a different treatment approach. As such, other treatment modalities may be considered to increase patient access to these treatments. In terms of treatment delivery modalities, Gao et al. (2022) reported that individual and group CBT-I treatment delivery formats were more acceptable than both guided and unguided self-help formats.(103) However, the workgroup acknowledged that access to provider-delivered CBT-I is limited due to incongruence between the high prevalence of insomnia disorder among military personnel and Veterans and the relatively low number of trained providers. Certain patients may have barriers to CBT-I delivery modalities involving technology (e.g., limited access to the internet, technology literacy barriers) while others may prefer alternative approaches (e.g., not interested in working with a healthcare provider).

The Work Group did not systematically review evidence related to Recommendation 5 (79,81) but integrated outcomes from newly reviewed Key Questions. Therefore, it is categorized as Not Reviewed, Amended. The Work Group's confidence in the quality of the evidence was moderate. The body of evidence had some limitations including lack of clarity about allocation concealment and blinding of participants and study personnel.(97) In addition, an ITT analysis was performed in some, but not all, studies, and several studies had high attrition.(97) The benefits of CBT-I, including reducing insomnia severity and improved sleep efficiency significantly outweighed the potential harms. Patient values and preferences varied somewhat because access to provider-assisted CBT-I is limited, alternative treatment modalities may not be equally available or appealing to all patients, and changes required for behavioral interventions can be difficult. Other considerations regarding the Work Group's recommendation included the benefits of the intervention seen across multiple sleep outcome areas and no significant harms except for transient sleepiness that may result from the sleep restriction component of CBT-I. Given these considerations, the Work Group decided upon a "Strong for" recommendation for CBT-I. Thus, the Work Group decided on a *Strong for* recommendation.

The Work Group did not systematically review evidence related to Recommendation 6 (79,81) but integrated outcomes from newly reviewed Key Questions. Therefore, it is categorized as Not Reviewed, Amended. The Work Group's confidence in the quality of

the evidence was moderate. The body of evidence had some limitations including lack of clarity about allocation concealment and blinding of participants and study personnel.(97) In addition, an ITT analysis was performed in some, but not all, studies and several studies had high attrition.(97) The benefits of BBT-I, including reducing insomnia severity and improved sleep efficiency significantly outweighed the potential harms. Patient values and preferences varied somewhat because access to BBT-I is limited, and changes required for behavioral interventions can be difficult. Like CBT-I, the Work Group considered the benefits of the intervention seen across multiple sleep outcomes areas and no significant harms except for transient sleepiness that may result from sleep restriction caused by BBT-I. Because there is a much smaller literature base on BBT-I and the evidence on BBT-I evaluates its effect on older adults only, the Work Group decided upon a "Weak for" recommendation for BBT-I. Thus, the Work Group decided on a *Weak for* recommendation.

### *Recommendation*

7. For treatment of chronic insomnia disorder, we suggest against sleep hygiene education as a stand-alone treatment.

   **(Weak against | Not reviewed, Not changed)**

### *Discussion*

Although there is variability in how sleep hygiene education is defined across studies sleep hygiene education commonly includes information about caffeine, alcohol, and nicotine use; exercise; the sleep environment; instructions on sleep-wake regularity and nap avoidance; and stress management (see Appendix D).(111) Sleep hygiene education is appropriately used in the treatment of insomnia as a component of CBT-I. This "Weak against" recommendation focuses only on sleep hygiene education as a stand-alone approach. An SR by Chung et al. (2018) included 12 studies that compared sleep hygiene education as monotherapy to CBT-I for the treatment of poor sleep or insomnia.(111) Criteria for insomnia varied between studies. None of the studies included in the review compared sleep hygiene education to no treatment. The number of sessions of sleep hygiene education ranged from one to six (median three sessions). Multiple studies described the sleep hygiene education arm as including a standardized manual, therapist training, therapist supervision, and/or treatment fidelity monitoring. Analyses by Chung et al. favored CBT-I over sleep hygiene education in areas of sleep onset latency, WASO, sleep efficiency, and PSQI and ISI scores.(111) In addition, a RCT by Morgan et al. (2012) compared self-help CBT-I (e.g., six weekly booklets that provided information on components of CBT-I) to advice on sleep hygiene. The self-help CBT-I group demonstrated significant improvements in areas of insomnia severity, sleep efficiency, and sleep quality.(112)

Although the evidence supports CBT-I over sleep hygiene education, the Work Group acknowledges that CBT-I and BBT-I require trained professionals who may not always

be readily available. In addition, patient interest in referral for CBT-I or BBT-I may be variable, and multiple appointments may be burdensome to patients. In those circumstances, providers may feel that they are left with the option of sleep hygiene education or no treatment at all. The Work Group suggests providers seek out CBT-I resources or alternative strategies such as BBT-I or self-help or internet-based CBT-I programs (see Recommendation 5 and Recommendation 6). Additionally, the Work Group recommends that providers use a patient-centered, motivational interviewing approach to encourage reluctant patients to engage in CBT-I or BBT-I. Providers can do this by providing an accurate description of the treatments, relating the treatments to the patient's own history and experience with insomnia, and relating the treatments to the patient's values and circumstances. While the Work Group does acknowledge a role for sleep hygiene education as a way to promote healthful sleep practices in general and prevent the development of poor sleep habits, the Work Group cautions that sleep hygiene education alone may not only be ineffectual but may be potentially harmful Based on clinical experience and qualitative data,(113) patients who have received sleep hygiene education alone for chronic insomnia disorder may be less likely to accept a referral for additional behavioral treatments such as CBT-I or BBT-I, believing these treatments will also be ineffectual.

The Work Group systemically reviewed evidence related to this recommendation.(111,112) The Work Group's confidence in the quality of the evidence is low. The quality rating for the SR by Chung et al. (2018) was fair because of potential bias in the included studies.(111) This stemmed from a lack of clarity about allocation concealment and blinding of participants and study personnel, including outcome assessors. The quality rating for Morgan et al. (2012) was poor because of lack of clarity on allocation concealment, lack of ITT analysis, and high attrition in both study arms.(112) Given low confidence in the quality of the evidence for the benefits of CBT-I over sleep hygiene education, the Work Group decided on a *Weak against* recommendation.

### *b. Pharmacotherapy - Insomnia*

### *Recommendation*

8. For treatment of chronic insomnia disorder, we suggest CBT-I over pharmacotherapy as first-line treatment.

   **(Weak for | Reviewed, Amended)**

### *Discussion*

Our systematic evidence review did not include any new evidence to support this recommendation so the same recommendation from the 2019 Clinical Practice Guideline was carried forward.

A SR by Mitchell et al. 2012 (114) that was not included in this systematic evidence review, and therefore did not influence the strength of the recommendation, favored CBT-I over several pharmacotherapies in both subjective and objective sleep-related outcome measures. Subjective measures included sleep diaries and questionnaires whereas objective measures included PSG and actigraphy. When compared to pharmacotherapy for chronic insomnia disorder, CBT-I may appear equivalent in short-term results (i.e., two to four weeks); however, CBT-I was superior to pharmacotherapy in long-term outcomes. Reports of adverse events from medications, which could include both subjective and objective measures, were noted to be limited in the studies included in this SR.

Hypnotic medications may cause complex behaviors such as “sleep-driving” and, in primarily depressed patients, worsening of depression, including suicidal thoughts and actions. Notably, there is a lack of clear safety data for most pharmacologic sleep treatment options beyond brief treatment periods (i.e., two to four weeks), which raises concerns about the potential for increased risks associated with longer periods of pharmacotherapy. Though a temporary increase in sleepiness may occur during sleep restriction therapy (115), a specific component of CBT-I, there are overall lesser concerns for harms associated with CBT-I as treatment-related symptoms resolve quickly as treatment continues. Although not included in our systematic evidence review, there are studies that found CBT-I may not be appropriate or may need to be delayed in some select patient groups including those with a history of mania, seizure disorder, or current suicidal ideation.(110) Sleep restriction may exacerbate these conditions.

The Work Group determined there is some variation in patient values and preferences as some patients may prefer the side effect profile of behavioral therapy over medications. However, other patients may prefer the quick, sometimes immediate effect of taking a hypnotic over the time commitment and multiple sessions required to achieve improvements with CBT-I. Further, there is a potential delay in therapy involved with finding a provider who can administer CBT-I, noting online or application-based CBT-I is now widely available and remote, asynchronous digital CBTI hubs can also serve as a force multiplier for providers.(116) Other implications considered by the work group were resource use and feasibility as CBT-I is labor intense for both patient and provider and there is a shortage of providers delivering CBT-I, including in the DOD.(117)

The Work Group reviewed the evidence related to this recommendation, but there was no new evidence. Therefore, it is categorized as Reviewed, Amended. The benefits of CBT-I for chronic insomnia disorder slightly outweighed the benefit-to-harm ratio associated with pharmacotherapy. Patient values and preferences were somewhat

varied, as were accessibility and feasibility based upon setting. Thus, the Work Group decided on a *Weak for* recommendation.

### *Recommendation*

9. For treatment of chronic insomnia disorder in patients who are offered a course of pharmacotherapy, we suggest the use of one of the following agents:
    - Daridorexant
    - Doxepin
    - Eszopiclone
    - Lemborexant
    - Suvorexant
    - Zaleplon
    - Zolpidem

    **(Weak for | Reviewed, New-replaced)**

### *Discussion*

Evidence suggests treatment with a dual orexin receptor antagonists (DORAs; daridorexant, lemborexant, suvorexant) improve sleep outcomes measures in patients with chronic insomnia.(118-120)

Xue et al. (2022)(118) focused on efficacy, included 13 RCTs exploring 5 different DORAs in 7,861 patients. In 7 RCTs, lemborexant, and suvorexant were associated with significant improvement in Insomnia Severity Index (ISI) scores compared to placebo. However, daridorexant did not lead to meaningful improvement in insomnia severity compared to placebo. Four RCTs assessed sleep efficiency (SE), with lemborexant and suvorexant associated with increased sleep efficiency in relation to placebo. Ten RCTs assessing wake time after sleep onset (WASO) were included in meta-analysis. Lemborexant (1 RCT) and suvorexant (3 RCTs) were associated with improved WASO while daridorexant was not (2 RCTs). The Xue et al. SR included trials evaluating low dose daridorexant (5mg, 10mg) which are not effective. Mignot et al. (2022)(120) evaluated two RCTs with daridorexant. One study (n=930) evaluated daridorexant 50mg, 25mg, or placebo and the other (n=924) 25mg, 10mg, or placebo. The primary efficacy endpoints were WASO and latency to persistent sleep (LPS), measured by PSG, at months 1 and 3. WASO and LPS were significantly reduced among participants in the daridorexant 50mg, and the 25mg groups compared with participants in the placebo group at month 1 and month 3. In the second study WASO and LPS was significantly reduced among participants in the daridorexant 25mg group compared with participants in the placebo group at month 1 and month 3, whereas no

significant differences in WASO or LPS were observed for the 10mg group. The recommended dosage for daridorexant is 25mg to 50mg.

The SR by Na et al. (2024)(119) focused on safety and included 11 RCTs with 7,703 patients reported in 9 publications comparing the safety of DORAs with placebo. There were no differences between any groups of DORAs and placebo in likelihood of serious treatment-emergency adverse events in comparison to placebo. Additionally, there were no differences between any of the DORAs and placebo in the incidence of treatment-emergent adverse events leading to discontinuation. Excessive daytime sleepiness occurred more frequently among those using suvorexant than placebo, but there was no difference between lemborexant or daridorexant and placebo. However, the variability in the number of RCTs associated with each active treatment and the low number of events reported in some trials might limit the robustness of certain outcomes.

Since the previous CPG in 2019, one SR was added to the evidence base which evaluated the effect of eszopiclone. This SR by Rosner et al. (2018)(121) included 14 RCTs, 6 of which met the Work Group's criteria focusing on primary chronic insomnia and requiring a placebo or active control. Study subjects (n=1980) were followed from 2 weeks to 6 months. The Work Group also reviewed the data from the 2019 CPG which incorporated a SR by Winkler et al. (2014) that included 31 RCTs published between 1992 and 2012, comparing various medications to placebo in PSG-based trials for the treatment of insomnia disorder in adults. The SR specifically included 17 RCTs studying the efficacy of different formulations, doses, and frequency of administration of four non-benzodiazepine benzodiazepine receptor agonists (non-BZD BzRAs): zolpidem, zaleplon, eszopiclone, and zopiclone (not available in the U.S.).(122) The randomized participants (n=851) included mostly women (65%) with an average age of 48 years (range 35 – 72 years) and a diagnosis of primary insomnia. Efficacy results were compiled and not reported to individual agents. For the critical outcome of sleep onset latency, a statistically significant difference favoring non-BZD BzRAs over placebo was seen in both SRs (121,122) (moderate strength evidence). For the critical outcome of WASO, non-BZD BzRAs all showed a significant effect (low strength evidence). For the important outcome of total sleep time, non-BZD BzRAs showed a significant increase (moderate strength evidence).

For eszopiclone versus placebo, the critical outcome of serious adverse events (e.g. cardiovascular events, falls) was studied in six RCTs (n=2,812)(121) (low strength evidence). No significant difference in the overall incidence was seen between eszopiclone (0-2.86%) and placebo (0-1.56%). Other adverse effects including unpleasant taste, somnolence, and myalgia were statistically higher with eszopiclone than placebo. In three RCTs of low quality, the number of withdrawals related to adverse events was not significantly different between eszopiclone and placebo.(123) Two RCTs (n=973) of low quality conducted in the general population reported no

significant difference between zaleplon and placebo in a number of individuals experiencing one or more adverse events.(123) No individual adverse event occurred more often with zaleplon than placebo. Withdrawals due to adverse events and total withdrawals were not significantly different between the zaleplon and placebo groups. The outcome of harm was evaluated in 11 zolpidem RCTs (n=2,779) by Wilt et al. (2016). The authors reported no statistically significant difference between zolpidem and placebo in the number of patients experiencing one or more adverse events; however, the quality of the evidence was low. The critical outcome of harms was reported in one moderate quality RCT (n=1,018) comparing zolpidem 12.5 mg extended release taken at least three nights per week over 24 weeks versus placebo in the general population. The incidences of adverse events including somnolence, anxiety, and disturbance in attention were statistically higher with zolpidem 12.5 mg extended release than placebo. More participants in the zolpidem 12.5 mg extended-release group experienced one or more adverse events and more total withdrawals compared to the placebo group.(123)

The evidence supporting the use of the tricyclic antidepressant (TCA) doxepin is derived from one SR by Everitt et al. (2018)(124), comprising four RCTs of very low quality strength of evidence that compared outcomes for doxepin (1mg, 3mg, 6mg, and 25-50mg) to placebo in individuals with primary insomnia disorder, with treatment durations ranging from four to 12 weeks. In analysis of three RCTs, doxepin was associated with significant improvement in the critical outcomes of SE and WASO at all doses (1mg, 3mg, 6mg, and 25-50mg) compared to placebo. However, there was no significant improvement in the critical outcome of sleep onset latency at any of the doses compared to placebo. Pooled analysis from four RCTs assessing subjective sleep quality using the ISI and PSQI indicated better sleep quality in the TCA groups. This pooled data included two RCTs using low dose doxepin (451 total patients using 1mg, 3mg, and 6mg) but also a smaller RCT using trimipramine (46 participants at 25-200mg) rather than doxepin, and another small RCT using doxepin 10mg (18 patients) in idiopathic Parkinson's disease patients with insomnia. A separate pool of data from four RCTs indicated a longer TST with various doses of doxepin (1mg, 3mg, 6mg, and 25-50mg) compared to placebo. This pooled data also included the RCT that utilized trimipramine as the TCA. There was no difference in adverse events from pooled data of six RCT TCA studies compared to placebo.

Patient values and preferences varied largely as some patients prefer non-pharmacologic intervention to treat insomnia and others prefer medications, noting that doxepin differs from many other prescription hypnotics in that it is not a controlled substance. Other implications considered by the Work Group include resource use as the costs of these medications can vary widely and some of them require prior authorization. There are important subgroup considerations in the active-duty population for which duty limitations may apply with the use of hypnotic medication. Similarly, Veterans and active-duty personnel may have a commercial driving license or operate

heavy machinery. Additionally, providers may be hesitant to use tricyclic antidepressant medication in patients with cardiac disease or those who might be susceptible to anticholinergic side effects. The lack of substantial harm using low-dose doxepin is supported by other studies not included in the data analysis that did not find adverse cardiovascular consequences associated with low-dose doxepin(125,126); this in contrast to the adverse effects of higher doses of doxepin when used in the treatment of depression.(127) All antidepressants carry a warning of an increased risk of suicide; therefore, all patients with a history of suicidal ideation or behaviors if prescribed doxepin would be considered at higher risk for suicidal ideation or attempts. Moreover, the anticholinergic effects of doxepin may be additive with other anticholinergic medications. Though two of the included RCTs in the pooled data that found no difference in adverse events between doxepin and placebo were restricted to older adults (≥ 65 years of age), geriatric patients are sensitive to the anticholinergic side effects of tricyclic antidepressants. According to the 2023 Beers Criteria, doxepin is a potentially inappropriate medication in geriatric patients and should be avoided when used in doses greater than 6 mg/day due to the potential for orthostatic hypotension, anticholinergic effects, or sedation, though it notes the safety profile of low-dose doxepin is comparable to placebo.(128)

Despite general consistency in the evidence supporting the benefits of the medications for many insomnia treatment outcomes, there is some inconsistency in patient preferences regarding treatment. As stated in Recommendation 8, non-pharmacologic treatments should be considered first before beginning pharmacotherapy. There are important subgroup considerations in the active-duty population for which duty limitations may apply with the use of hypnotic medication. Similarly, Veterans and active-duty personnel may have a commercial driving license or operate heavy machinery. Other implications considered by the Work Group include resource use as the costs of these medications can vary widely and some of them require prior authorization. Additionally, providers may be hesitant to use TCAs in patients with cardiac disease or those who might be susceptible to anticholinergic side effects. Other published literature not included in the reviewed studies of non-benzodiazepine benzodiazepine receptor agonists and, thus, independent from the strength of this recommendation, discusses the potential risk of abuse, dependence, motor vehicle accidents, and diversion.(129,130) For service members on active-duty, or for those with a commercial driver's license, limitation in duties and temporary medical profiles may need to be implemented if a non-benzodiazepine benzodiazepine receptor agonist is prescribed.

In April 2019, the FDA released a safety announcement advising healthcare professionals of the risk of serious injuries caused by sleep behaviors including sleepwalking, sleep driving, and engaging in other activities while not fully awake associated with the non-BZD BzRAs.(131) These complex sleep behaviors have at times resulted in deaths. Although these injuries are rare, they have occurred in patients

with and without a history of such behaviors, even at the lowest recommended doses, and even after taking one dose.(131) To minimize the incidence of adverse events, a non-BZD BzRA, if prescribed, should be at the lowest effective dose and for the shortest duration possible. Non-BZD BzRAs are also potentially inappropriate for geriatric patients according to the 2023 Beers Criteria.(128) Other published literature not included in the reviewed studies of non-BZD BzRAs and, thus, independent from the strength of this recommendation, discusses the potential risk of abuse, dependence, motor vehicle accidents, and diversion.(129,130) All patients should be counseled on the potential risks.

The Work Group systematically reviewed evidence related to this recommendation(118-131), therefore it is categorized as New-replaced. The Work Group's confidence in the quality of the evidence was low. The body of evidence had some limitations including risk of bias, poor study quality, inconsistency, and serious imprecision. The benefits of improved sleep outcome measures slightly outweighed the potential harm of adverse events, which was small. The benefits of pharmacotherapy for chronic insomnia [e.g., sleep efficiency, wake after sleep onset, and daytime functioning] slightly outweighed the potential harm of adverse events. Patient values and preferences varied largely because some patients prefer non-pharmacological approaches while others prefer medication intervention. Thus, the Work Group decided on a *Weak for* recommendation.

**Table. Drugs for Chronic Insomnia**

| Class | Agent | Initial Dose | Onset | Half-life | Initial Dose or Guidance: Special Populations | | |
|---|---|---|---|---|---|---|---|
| | | | | | Elderly | Renal | Hepatic |
| **Orexin Receptor Antagonists+** | Daridorexant | 25-50mg | <30 min | 8hr | No change | No change | Moderate impairment, 25mg; severe, use not recommended |
| | Lemborexant | 5mg | <30 min | 17-19hr | 5mg | No change | Moderate impairment, 5mg; severe, use not recommended |
| | Suvorexant | 10mg | 30 min | 12hr | No change | No change | Mild-moderate impairment, no change; severe impairment, use not recommended |

| Class | Agent | Initial Dose | Onset | Half-life | Initial Dose or Guidance: Special Populations | | |
|---|---|---|---|---|---|---|---|
| | | | | | Elderly | Renal | Hepatic |
| **Non-benzodiazepine benzodiazepine receptor agonists** | Eszopiclone# | 1mg | 15-30 min | 6hr (adult) 9hr (elderly) | 1mg | No change | Severe impairment, 2mg maximum dose |
| | Zaleplon# | 10mg | <30 min | 1hr | 5mg | No change | Mild-moderate impairment, 5mg; severe impairment, use not recommended |
| | Zolpidem^ | 5-10mg (males); 5mg (females) | 30 min | 2.5hr | 5mg | No change | Mild-moderate impairment, 5mg (IR), 6.25mg (ER); severe impairment, avoid |
| | Zolpidem extended release | 6.25-12.5mg (males); 6.25mg (females) | 30 min | 2.8 hr | 6.25mg | | |
| **Histamine Receptor Antagonist** | Doxepin* | 6mg (<65yo); 3mg (≥65yo) | 30 min | 15hr | 3mg | No change | 3mg |

+ Time to onset of sleep may be delayed if taken with food; # Do not take with high-fat meal; ^ Do not take with food; *Do not take within 3 hours of a meal

Non-BZD BzRAs are also potentially inappropriate for geriatric patients according to the 2023 Beers Criteria.(128)

Abbreviations: yo: years old; min: minutes; hr: hours; IR: immediate release; ER: extended release

## *Recommendation*

10. For treatment of chronic insomnia disorder in patients who are offered a course of pharmacotherapy, we suggest against the use of:
    - Antipsychotic drugs
    - Benzodiazepines
    - Diphenhydramine
    - Trazodone

    **(Weak against | Reviewed, New-replaced)**

## *Discussion*

The systematic evidence review conducted for this CPG did not identify any evidence that met inclusion criteria regarding the use of antidepressants (i.e. amitriptyline, mirtazapine), antihistamines (e.g., diphenhydramine) or antipsychotics in treating chronic insomnia disorder. The Work Group acknowledged, however, that antidepressants and first-generation antihistamines, many of which are included in cold and headache combination products, are often considered for treating insomnia due to their sedating/drowsiness properties. The antihistamines, diphenhydramine and doxylamine succinate, are indicated to help reduce the difficulty in falling asleep and, are often "prescribed" by providers as a nighttime sleep aid. However, the evidence for using these agents and other antihistamines is not supported by rigorous data for treating chronic insomnia disorder.

The Work Group also acknowledged that antipsychotics are used off-label, of which quetiapine is the most common, and have been used to treat insomnia due to their sedating and drowsiness properties. This often occurs in patients with concomitant psychiatric disorders.

### Antipsychotics

Evidence on using low-dose quetiapine for the treatment of chronic insomnia disorder is limited to a few studies and case series with short duration, small sample sizes, and vague and incomplete details, thus making any determination regarding efficacy inconclusive. Although doses of quetiapine typically used for insomnia are lower than the FDA-recommended dosage of 150 – 800 mg/day for either the immediate-release or extended-release products, all antipsychotics, including low-dose quetiapine, are known for causing harms.(132) Like all antipsychotics, quetiapine has a black box warning indicating a 1.6 to 1.7 fold increase in mortality in elderly populations with dementia-related psychosis.(133) In addition, all antipsychotics carry a strong recommendation in the 2023 Beers Criteria to avoid their use in the elderly except in schizophrenia or bipolar disorders due to an increased risk of cerebrovascular accident and a greater rate of cognitive decline and mortality in persons with dementia.(128) Anticholinergic effects, including sedating and hypotensive effects, occur with all antipsychotics in varying frequency and severity.(132) Despite significant differences in risk between the agents, it is advised that routine monitoring of metabolic parameters be conducted with all antipsychotics due to the risk of hyperglycemia, dyslipidemia, and weight gain. These adverse events worsen when the agent is combined with other agents that cause sedation, anticholinergic effects, hypotension, or weight gain. In addition, active-duty service member use of an antipsychotic may affect deploy ability (see MDD, Schizophrenia, Suicide Risk CPGs).

### Benzodiazepines

The Work Group examined an evidence base of four SRs that compared various pharmacologic interventions to placebo in treating insomnia disorder.(122,134-136) The

studies showed significantly improved sleep efficiency, sleep onset latency, sleep quality, total sleep time (TST), and WASO relative to placebo. The longest duration of follow-up was approximately seven months, but many trials in the SRs had a duration of ≤12 weeks. The authors of one of the SRs commented that, although they had significant findings, it was not clear whether these findings were clinically relevant.(122) The methodological quality of the studies included in the SRs was generally rated as fair by the authors of the reviews.(136) The main concerns were lack of clarity around randomization, allocation concealment, blinding of patients, investigators, and outcome assessors; and incomplete outcome reporting. The studies did not examine harms, doses of benzodiazepines, and the time course of changes in treatment outcomes and adverse events (ranging from 2 – 224 days; majority were <35 days of use).

Benzodiazepines may have an adverse effect on sleep architecture (slow wave sleep suppression), are difficult to taper and discontinue, and have significant interactions with alcohol and other drugs, notably other CNS depressants. They may also have a negative impact on daytime functions (e.g., driving). There are also concerns about the risk of dependency and diversion as well as harms to older patients; patients with respiratory conditions (including sleep apnea and obesity hypoventilation), neuromuscular diseases, and cognitive disorders; and those at risk for falls. Furthermore, active-duty service member use of benzodiazepines may affect deploy ability (see MDD, Schizophrenia, Suicide Risk CPGs).

**Diphenhydramine**

While no studies that met this guideline's inclusion criteria examined antihistamines for treating chronic insomnia disorder, other studies have researched the use of antihistamines in patients with primary insomnia or experiencing "sleep problems." These studies are discussed below.

One SR, comprised of four randomized trials, evaluated diphenhydramine 50 mg compared to placebo.(137) All the studies were short in duration (5 – 28 days) and included adult patients with primary insomnia per DSM-IV or predominately having trouble falling asleep. All trials used some form of subjective sleep assessment for analysis (e.g., sleep diary or questionnaire). Of the analyzable outcomes, including sleep latency, TST, number of awakenings, and sleep efficiency, all four studies using diphenhydramine resulted in mixed outcomes, with the majority not being statistically different compared to placebo. Of note, diphenhydramine had benefit on self-perceived sleep latency in many of the nursing home residents (mean age 78 years). However, several instances of daytime hypersomnolence were noted by the nursing home staff after patients had taken diphenhydramine 50 mg for five consecutive days.

Another meta-analysis evaluated two RCTs.(138) One trial compared diphenhydramine (50 mg), temazepam (15 mg), and placebo for a duration of two weeks in 25 elderly volunteers (mean age 73.9 years) with primary insomnia per DSM-IV.(139) The other

study, an industry-sponsored, multicenter trial, compared diphenhydramine (50 mg) to valerian-hops preparation for 28 nights in 184 adults (average age 44.3 years).(140) The results from the combined trials for subjective sleep latency and subjective total sleep time (sTST), resulted in a mean difference of 2.47 minutes (95% CI -8.17 – 3.23 minutes), and a 17.86 minutes increase (95% CI -3.79 – 39.51) with diphenhydramine versus placebo, respectively. Only one trial evaluated sleep efficiency. The subjective mean sleep efficiency increased 4.6% (1.44% to 7.88% higher) from baseline to week two in the diphenhydramine group relative to placebo.

Safety data using first-generation antihistamines long-term for chronic insomnia disorder was not available. Because antihistamines have antagonistic properties at the muscarinic receptor, one can expect dry eyes, dry mouth, constipation, urinary retention, and confusion to be the reason why the 2023 Beers Criteria carries a strong recommendation to avoid using these agents in older adults.(128) Tolerance to the sedative effects of these agents has been noted after three to four days of continuous use, limiting its benefit even for short-term treatment of insomnia.(128) No differences between the morning-after psychomotor impairment and morning-after memory impairment was seen with diphenhydramine compared to baseline in the trial conducted by Glass et al. (2008).(139) However, in another study using a driving simulator, diphenhydramine (50 mg) for one week impaired the driving performance, including lane keeping (steering instability and crossing the center lane), in a group of drivers with seasonal allergic rhinitis (25 to 44 years of age) to a greater extent than alcohol (approximately 0.1% blood alcohol concentration).(141) Moreover, the authors indicated that self-reported drowsiness was not a good predictor of impairment.

**Trazodone**

One SR comprising seven trials published between 1994 and 2014 reported no statistically significant differences for sleep efficiency or the rate of discontinuation due to adverse events when comparing trazodone (dose range 50 – 150 mg/prior to bedtime) to placebo in treating patients diagnosed with chronic insomnia (primary or secondary insomnia) (n=429; mean age 46 years).(136) There was no differences in sleep onset latency, TST, or WASO.(136) The SR was limited in that the mean treatment length was 1.7 weeks with a follow-up of one to four weeks, which is shorter than the typical duration of sedative hypnotic use. Further, in several of the trials, patients were also taking another antidepressant or methadone, which may have altered the results.

Everitt et al. (2018)(124) conducted an SR that included an RCT (n=278) evaluating trazodone for chronic insomnia. They found subjective sleep quality improved significantly with trazodone but there were no differences between trazodone and placebo in morning ratings of sleepiness or disruption at work or in social or family life, sleep efficiency, sleep onset latency, and WASO.

Trazodone has an FDA black box warning for the possibility of increasing suicidal thoughts and behaviors in pediatric and young adult patients (up to age 24).(142) Further, trazodone is associated with numerous other adverse events and drug-drug interactions, which outweigh any benefits for its use in treating chronic insomnia disorder.(142) Two studies found more adverse effects with trazodone than placebo (i.e., morning grogginess, increased dry mouth and thirst).(117)

The Work Group systematically reviewed evidence related to this recommendation.(138) Therefore, it is categorized as Reviewed, New-added. The Work Group's confidence in the quality of the evidence was very low. The body of evidence had some limitations including lack of clarity around randomization; allocation concealment; blinding of patients, investigators, and outcome assessors; and incomplete outcome reporting, as well as limited evidence on benefits versus harms, use in geriatric populations, and limited duration of trials.(122,134,136) The benefits of antipsychotic drugs, diphenhydramine, benzodiazepines, and trazodone were lacking. The potential harm (e.g., of adverse events) outweighed the benefits. Patient values and preferences varied largely because some patients prefer pharmacological treatment while others prefer nonpharmacological approaches or are unable to tolerate medication related adverse effects. Thus, the Work Group decided on a *Weak against* recommendation.

### *Recommendation*

11. For treatment of chronic insomnia disorder in patients who are offered a course of pharmacotherapy, there is insufficient evidence to recommend for or against the use of ramelteon.

    **(Neither for nor against | Reviewed, Amended)**

### *Discussion*

Sys et al. (2020) conducted a systematic review (SR) that assessed the efficacy of ramelteon versus placebo in older adults (≥ 65 years of age) with insomnia. Three randomized controlled trials (RCTs) were included comprising 1,256 patients who received ramelteon at 4mg (n=381), 8mg (n=531), or placebo (n=544). One RCT reported on objective sleep efficiency and found, compared to placebo, ramelteon improved objective sleep efficiency at both 4mg and 8mg. All 3 RCTs found reduction in subjective and objective sleep onset latency (SOL) for the 4mg group and reduction in objective SOL in the 8mg group compared to placebo. Subjective SOL was reduced at the 8mg dose compared to placebo in 2 RCTs with no difference found in the other RCT. One RCT measured insomnia severity using the Clinical Global Impressions instrument and found no significant difference from placebo at either 4mg or 8mg. No difference was identified in one RCT between either dose of ramelteon and placebo for daytime functioning based on visual analog scale of feelings and mood, the post-sleep questionnaire, or residual effects. There was also no difference in sleep quality between placebo and ramelteon at either dose in one RCT, based on the subjective number of

awakenings, ease of falling back to sleep, or sleep quality. A single RCT reported on objective total sleep time (TST) and found an increase in TST for ramelteon compared to placebo at both the 4mg and 8mg doses. One RCT reported on subjective changes in TST, finding an increase for the 4 mg ramelteon dose compared to placebo at week 1 and week 3, but not week 5. No differences from placebo in subjective TST were reported at the 8 mg dose. All 3 RCTs reported serious adverse events (SAEs). One RCT reported 8 SAEs but only one (a transient ischemic attack at 8mg dose) was attributed to a study medication. A sinus headache was reported in the placebo group in another RCT. The third RCT reported no SAEs in either dose of ramelteon (4mg, 8mg) or placebo.

The Work Group determined that there was large variation in patient values and preferences as some patients prefer non-pharmacologic intervention to treat insomnia and others prefer medications, noting that ramelteon differs from many other prescription hypnotics in that it is not a controlled substance. Further, the drug might negatively impact daily functions including driving, and patients may experience stigma associated with taking a sleep medication. Other implications considered by the Work Group include resource use as the cost of ramelteon is relatively high, feasibility as ramelteon requires special approval for use, and subgroup considerations in the active-duty population for which duty limitations may apply with use of a hypnotic medication. Similarly, Veterans may have a commercial driving license or operate heavy machinery. Although the reviewed data for this guideline only included evidence in older adults, a 2014 SR (135) not included in our systematic evidence review included younger patients (18-93 years old) and found that relative to placebo, ramelteon (4-32 mg) improved sleep efficiency, sleep onset latency, TST, and wake after sleep onset. Results were mixed for sleep efficiency and the only SAE with ramelteon was somnolence.

The Work Group systematically reviewed evidence related to this recommendation. (143) Therefore, it is categorized as Reviewed, New-added. The Work Group's confidence in the quality of evidence was very low due to lack of intention-to-treat analysis, lack of sample size calculations, and very serious imprecision as the SR's authors did not provide confidence intervals to gauge precision of estimates or variations in outcomes. The benefits of ramelteon were inconsistent but slightly outweighed the potential harm, which was small. Patient values and preferences varied largely because some patients do not wish to take medications for insomnia. Thus, the Work Group decided on a *Neither for nor against* recommendation.

### *c. Complementary and Integrative*

### *Recommendation*

12. For treatment of chronic insomnia disorder, we recommend against the use of kava.

**(Strong against | Not reviewed, Amended)**

### *Discussion*

Kava, or kava kava (Piper methysticum), is an herb with purported medicinal uses. Its proposed mechanisms of action include decreased levels of glutamate, activation of dopaminergic neurons, interaction with GABA receptors and elevation of dopamine and serotonin levels. It is available over the counter for a variety of reasons but carries an FDA advisory that it is not safe for human consumption.

This recommendation is carried over from the 2019 CPG despite there being no new evidence due to the WG perceiving continued clinical pertinence with patients frequently inquiring about various nutraceutical options for the treatment of chronic insomnia disorder.

The 2019 CPG WG reviewed very-low-quality evidence from one SR by Leach and Page (2015)(144) that evaluated the efficacy and safety of three herbal medicines (valerian, kava, and chamomile) for the management of insomnia. One RCT with 391 patients with insomnia evaluated the effects of kava (containing 100 mg total kavalactones) compared to valerian and placebo for four weeks. There were no differences between kava and placebo for insomnia severity, sleep onset latency, and nocturnal awakenings. No other outcomes (e.g., sleep efficiency, sleep onset latency, total sleep time (TST), wake after sleep onset (WASO), sleep quality) were reported in this study. Adverse events occurred with similar frequency between active and placebo groups.

Moreover, the FDA has issued an advisory about the risk of liver damage associated with kava.(145) The Work Group also noted that patient preferences may be variable for use of herbal supplements for insomnia. While some patients may view supplements as natural therapy, others may acknowledge stigma associated with supplement use or may be concerned about safety or effectiveness, which may impact their preferences over the long-term. Furthermore, patients may not be aware of the potentially serious adverse effects of kava.

The Work Group carried forward this recommendation from the 2019 CPG despite there being no new evidence for review. The Work Group discussed minor revisions to the recommendation text. Therefore, it is categorized as Not Reviewed, Amended. The 2019 Work Group's confidence in the quality of the evidence was very low. The body of evidence had several limitations. There was some variation in patient values and preferences regarding this intervention. Most importantly, the FDA published a memorandum that kava is not safe for human consumption. Thus, the Work Group decided on a *Strong against* recommendation.

### Recommendation

13. For treatment of chronic insomnia disorder, we suggest against the use of cannabis and/or its derivatives.

    **(Weak against | Reviewed, New-added)**

### Discussion

Cannabis is from the cannabis plant. It contains several compounds that are centrally acting, and are used both recreationally, and medically for FDA-approved indications. Cannabidiol (CBD), 9-tetrahydrocannabinol (THC) and cannabinol (CBN) are all compounds that can be isolated from the cannabis plant. Their use to treat chronic insomnia is not FDA-approved but purportedly has sleep-enhancing effects.

Very-low evidence from Narayan et al. (2024)(146) conducted a one-week, single-blind placebo run-in, followed by a two-week randomized, double-blind placebo-controlled, parallel trial to investigate the effects of CBD on sleep, anxiety and well-being. They recruited patients aged 18 to 45 with ongoing insomnia symptoms (ISI ≥ 15) and excluded patients with prior or ongoing use of medicinal or recreational drugs, history of medical conditions, took medication likely to affect sleep, were engaged in shift work, consumed excessive amount of caffeine, and screened positive for severe depressive, anxiety or OSA symptoms. Their run-in week tracked patients with actigraphy watches and sleep log while taking a placebo and further excluded patients with normal wake after sleep onset (WASO), sleep efficiency (SE), sleep onset latency (SOL) and placebo responders. Ultimately, participants took 150mg of CBD as an oil, or corn oil placebo, nightly, 60 minutes before bed. They collected ISI, sleep diary-derived sleep quality, actigraphy data, Leeds Sleep Evaluation Questionnaire (LSEQ) and Glasgow Sleep Effort Scale (GSES). Only 30 patients completed the trial. The primary outcomes of ISI scores, sleep diary-derived SOL, SE and WASO did not differ. For their secondary outcomes after the two weeks, there was no effect on subjective daily sleep quality, number of awakenings, total sleep time (TST), objective WASO, SE, SOL or TST. The LSEQ or GSES did not differ at the conclusion of the study. They reported that all adverse events were mild and transient but did not specifically list the symptoms or rates.

Wang et al. 2024 conducted a double-blind, placebo-controlled, randomized, crossover study over four weeks to study the effect of CBD-terpene on sleep. This was graded as a very low quality of evidence.(147) Of note, this manuscript had not been peer reviewed at time of the CPG review. Their primary endpoint was change in slow wave sleep (SWS) and REM sleep, as measured by a commercial sleep-tracking device. They recruited patients via social media advertising and included those endorsing difficulty initiating and/or maintaining sleep three or more nights per week for at least three months and had “severe insomnia after taking a clinically validated insomnia

severity index." They did not list their exclusion criteria. Participants took a study medication composed of hemp-derived CBD (300 mg) and one mg each of the terpenes: linalool, myrcene, phytol, limonene, α-terpinene, α-terpineol, α-pinene, and β-caryophyllene, dissolved in organic coconut oil. Placebo only contained organic coconut oil. Participants were instructed to take the capsule with a glass of water one hour before going to sleep a minimum of four nights/week. They collected their sleep data using the commercially available Whoop wrist-worn device.(148) Objective data was only analyzed on nights the participants self-reported taking the capsule. They modified Patient's Global Impression (PGI) to evaluate subjective perceptions of sleep. Ultimately, 56 participants completed the study, which did not meet their pre-determined power analysis size and resulted in a modified intent-to-treat/per-protocol approach. They did not report the patient demographics. The authors reported the treatment significantly increased the mean nightly time spent in SWS + REM (%TST) (MD = 1.3%; 95% CI 0.1 to 2.5; $p < 0.05$) and absolute mean time spent in SWS +REM and decreased the mean nightly light sleep time (%TST). It did not change the relative or absolute time in REM, mean absolute time in light sleep, or effect TST. No subjective measures were significantly different than placebo. They reported no adverse events.

Very-low quality evidence from Walsh et al. (2021)(149) conducted a double-blind, randomized, placebo-controlled, crossover design to evaluate the safety and efficacy of a cannabinoid formulation for treating chronic insomnia disorder. They included patients aged 25-70 years old with chronic insomnia and ISI > 10. Participant exclusion criteria included, but not limited to, being unwilling to cease using psychotropic, CNS-depressant, or cytochrome P450 inhibitor medications, had untreated cardiovascular, metabolic, or significant psychopathologic disorders, had other significant sleep disorders or were participating in a behavioral therapy program to improve sleep. They conducted a baseline 2-week period where patients wore a wrist activity monitor, completed a sleep diary and completed in-lab PSG. These were repeated during the test period. Participants took 0.5 mL of a cannabinoid formulation with included 20 mg/mL of THC, 1mg/mL of CBD, 2 mg/mL of CBN and naturally occurring terpenes (ZTL-101) in sunflower oil, or placebo (contained same terpenes), one hour prior to their desired sleep time. They were allowed to double their doses from the fourth night of each 2-week study period. Ultimately, 23 participants completed the protocol, of which 12 (52%) were taking a double dose of ZTL-101 by trial conclusion. Based on subjective report, participants reported improved SOL (8.4 min; 95% CI -16.3 to -0.6; $p = 0.0369$), increased TST (64.6 min; 95% CI 41.7 to 87.5, $p < 0.0001$), and improved sleep quality (0.7; 95% CI 0.5 to 1.0, $p < 0.0001$), and felt more rested/refreshed on waking (0.5; 95% CI 0.2 to 0.8; $p = 0.0007$). Based on actigraphy, ZTL-101 decreased WASO (-10.2 min; 95% CI -16.2 to -4.2; $p = 0.0021$), increased TST (33.4 min; 95% CI 23.1 to 43.8; $p < 0.001$) and sleep efficiency (2.9%; 95% CI 2.0 to 3.8; $p < 0.001$). Actigraphy measurements of SOL and arousal index were not significantly changed. On PSG measures, ZTL-101 had no significant effect on SOL, WASO, TST, SE, number of

awakenings, proportion of sleep stages, severity of OSA or PLMs. They reported no serious adverse events, however 36 nonserious adverse events possibly or likely related to ZTL-101 were noted, the three most common being xerostomia (33.3%), dizziness (25.0%), and headache / feeling abnormal (both 16.7%).

There is a large variation in patient preferences. There may be stigma involved with using cannabis derivatives. It may have significant federal versus state implications, as well as not being appropriate for active-duty service members, federal government employees or anyone subject to drug screens. Contrarily, some patients may be interested in this non-prescription alternative.

The Work Group systematically reviewed evidence for this recommendation.(146) Therefore, it is categorized as Reviewed, New-Added. The Work Group's confidence in the quality of the evidence was very low. The body of evidence had many limitations, including very small populations (not meeting power analysis), dosage and formulation heterogeneity, mixed outcomes within and across studies, and one study not yet peer reviewed.(147) Adverse events, when reported by the authors, were noted to not be severe, mild side effects appeared common. There was a large variation in patient values and preferences regarding this intervention, particularly legality issues in general, and among active-duty and federal employees. Thus, the Work Group decided on a *Weak against* recommendation.

### *Recommendation*

14. For treatment of chronic insomnia disorder, we suggest against the use of:
    - Chamomile
    - Melatonin
    - Passionflower
    - Saffron
    - Valerian

    **(Weak against | Reviewed, Amended)**

### *Discussion*

No new evidence was retrieved regarding chamomile for the update of this CPG. Consequently, the recommendation from the 2019 CPG regarding chamomile was carried forward in this recommendation. The 2019 CPG recommendation was based on one SR by Leach and Page (2015)(144) that included one randomized control trial (RCT) on chamomile (n=34). The RCT showed no difference in daytime functioning, Insomnia Severity Index (ISI), sleep efficiency (SE), sleep onset latency (SOL), total sleep time (TST), wake after sleep onset (WASO), or sleep quality compared to placebo

and no adverse effects. The quality of evidence was rated as very low due to bias, small sample size, and serious imprecision.

One new SR on melatonin for chronic insomnia by Choi et al. (2022)(150) was reviewed. The study evaluated 16 RCTs using melatonin 2 to 10 mg over 4 days to 6 months in children, adolescents, and adults (n=1,710). Melatonin formulations in the RCTs included transbuccal, fast release, immediate release, and controlled release compared to placebo. In adult patients, there was no statistically significant improvement in SOL (reduced by 2.25 minutes, n=1,349), TST (increased by 1.23 minutes, n=1,029), SE (improved by 1.22%, n=269) or sleep quality (based on Leeds Sleep Evaluation Questionnaire (LSEQ) or Pittsburg Sleep Quality Index (PSQI)). A subgroup analysis based on melatonin formulation was not performed. Safety outcomes and adverse events were not reviewed in this study. The quality of evidence was rated as low due to high risk of bias from non-random approaches, inadequate allocation concealment, attrition bias, reporting bias, unclear endpoints, and lack of wash-out periods.

One RCT by Lee et al. (2020)(151) studying the effect of passionflower extract (Passiflora incarnata Linnaeus, 60 mg) compared to placebo on sleep over 2 weeks was reviewed (n=110). Due to dropouts and exclusions, the study analyzed data from 85 participants, which fell below their pre-determined sample size for appropriate power of 98 participants. There was improvement in TST based on PSG (+23.05 minutes +/- 54.26 compared to placebo -0.16 minutes +/- 53.12). There was no difference in SE, WASO, SOL, total arousals, ISI, or PSQI. No significant adverse effects were reported. The quality of evidence was rated as very low due to being underpowered, of small sample size, and data from only one RCT.

One RCT by Pachikian et al. (2021)(152) evaluated the effect of saffron extract (15.5 mg) on sleep quality over 6 weeks in patients with mild to moderate insomnia (ISI 7 to 21) (n=66). Based on actigraphy, there was no difference to placebo in TST, SOL, WASO, or SE. Similarly, there was no difference in subjective sleep outcomes as measured by LSEQ and PSQI. Regarding side effects, one patient had palpitations that resolved after discontinuation of saffron. The quality of evidence was rated as very low due to the small sample size and data from only one RCT.

One SR by Shinjyo et al. (2020)(153) reviewed 60 RCTs evaluating valerian supplements effect on sleep, of which 5 RCTs evaluated valerian (V. officinalis) as a single herb for the treatment of insomnia over 2 to 4 weeks (n=966). The studies reviewed did not evaluate objective sleep measures such as TST, SOL, WASO, or SE. There were mixed results regarding the subjective sleep benefits from valerian compared to placebo based on PSQI, with some studies showing benefit and others showing no difference. Side effects reported include agitation, restlessness, dyspepsia, dizziness, vivid dreams, headaches, and diarrhea. The quality of evidence was rated as very low due to inconsistency in the data with variable size and direction effects,

indirectness (PSQI was the only outcome considered in the meta-analysis), and imprecision.

There is some variation in patient preference regarding this treatment. Patients can have varied opinions on taking herbal supplements to treat their medical conditions. Herbal supplements are not FDA regulated. There are concerns about the purity and composition of these herbal supplements. Herbal supplements can vary in cost from cheap to expensive, which can place an additional financial burden on patients.

Side effects for each supplement should be taken into consideration. The reviewed studies mentioned some of the side effects experienced by study participants. While not included in our systematic evidence review and, thus, independent from the strength of this recommendation, melatonin has been associated with excessive daytime sleepiness, vivid dreams, and nightmares. These side effects may not be desired in our Veteran and military populations. Valerian has also been associated with liver toxicity.(154)

Additionally, given these supplements were not shown to improve insomnia, the Work Group determined that choosing one of these supplements over proven treatments for insomnia could be detrimental to the patient.

The Work Group systematically reviewed evidence related to this recommendation for melatonin (150), passionflower (151), saffron (152), and valerian.(153) There was no new evidence regarding chamomile. Therefore, it is categorized as Reviewed, Amended. The Work Group's confidence in the quality of the evidence was very low. The body of evidence had some limitations including small sample size(151,152), risk of bias(152), imprecision of data (153), and indirectness of data.(153) The harms of chamomile, melatonin, passionflower, saffron, and valerian slightly outweighed the benefits. These supplements did not show improvement in insomnia outcomes, are associated with side effects, and can delay appropriate insomnia treatment. Patient values and preferences varied somewhat because of patient preferences to supplements, concern for quality and purity of over-the-counter supplements, and potential costs of supplements. Thus, the Work Group decided on a *Weak against* recommendation.

### *Recommendation*

15. For treatment of chronic insomnia disorder, there is insufficient evidence to recommend for or against the use of magnesium.

    **(Neither for nor against | Reviewed, New-added)**

### *Discussion*

There is currently insufficient evidence to suggest for or against the use of magnesium in the treatment of chronic insomnia. The SR by Mah et al. (2021)(155) reviewed 3

randomized control trials (RCT) that studied the effects of magnesium oxide or magnesium citrate on insomnia (n=158). The RCTs used magnesium oxide 414 mg BID, magnesium oxide 403mg TID, or magnesium citrate 640mg q AM and 320 mg q HS for a duration of 20 days to 8 weeks. Two of the three RCTs included objective measures of sleep via sleep EEG or sleep diary and were included in the meta-analysis (n=55). Sleep onset latency was reduced by 17.36 minutes compared to placebo and was statistically significant. Total sleep time was increased by 16.06 minutes compared to placebo but was not statistically significant. The RCTs reviewed showed mixed results on sleep questionnaires, where one RCT showed improvement in the Insomnia Severity Index (ISI) and another showed no difference in the Pittsburg Sleep Quality Index (PSQI). The RCTs did not systematically collect data on adverse effects from magnesium. However, one RCT commented on soft stool in all its participants taking magnesium. Overall, Mah et al. determined the quality of evidence to be low to very low due to moderate to high risk of bias in each of the RCTs. There may be some benefit to magnesium for sleep onset latency, but the evidence reviewed was not sufficient to definitively support this.

There is some variation in patient preference regarding this treatment. Patients can have varied opinions on taking herbal supplements to treat their medical conditions. Herbal supplements are not FDA regulated. There are concerns about the purity and composition of these herbal supplements. Additionally, there are numerous magnesium formulations available over the counter. Mah et al. (2021)(155) reviewed only two formulations: magnesium oxide and magnesium citrate. The absorption and effects of magnesium can differ based on what it is bound to. For example, the Sleep Foundation suggests the use of magnesium glycinate due to its improved absorption profile.(156) The different magnesium formulations can vary in cost from cheap to expensive, which can place an additional financial burden on patients.

The Work Group systematically reviewed evidence related to this recommendation (Mah et al. 2021).(155) Magnesium was not reviewed in the 2019 CPG. Therefore, this recommendation is categorized as Reviewed, New-added. The Work Group's confidence in the quality of the evidence was very low. The body of evidence had some limitations including small sample size and risk of bias. The possible benefit to sleep onset latency is balanced by the adverse effect of soft stools. Patient values and preferences varied somewhat because of their preferences regarding herbal supplements, concern for quality and purity of over-the-counter supplements, and the cost of supplements. Thus, the Work Group decided on a *Neither for nor against* recommendation.

### *Recommendation*

16. For treatment of chronic insomnia disorder, there is insufficient evidence to recommend for or against:
    - Aerobic exercise

- Mindfulness meditation
- Qigong
- Resistive exercise
- Tai chi
- Yoga

**(Neither for nor against | Not reviewed, Amended)**

### *Discussion*

Exercise and mindfulness meditation are very important for general health, and although there is a small risk of injury, it is generally not associated with harm. As such, exercise and mindfulness meditation should be considered an important aspect of overall health maintenance; however, the available evidence is insufficient to make a recommendation regarding exercise and mindfulness meditation as a primary treatment for insomnia disorder.

Aerobic exercise, resistive exercise, mindfulness meditation, tai chi, yoga, and qigong have all been studied in patients with insomnia symptoms.(157-159) A systematic review (SR) by Yang et al. (2012) focusing on the effects of exercise training programs on sleep quality did not show a significant improvement in sleep duration, sleep efficiency, or daytime functioning in middle-aged or older adults, although subjective sleep latency was decreased.(157) Three of the studies included in this review measured the impact of exercise on the likelihood of patients obtaining pharmacotherapy for insomnia symptoms and found that those subjects involved in an exercise program were less likely to use medication to assist with sleep. One of the studies included in this meta-analysis used depression as the primary condition, which lowered the quality of the evidence.(158) Most of the studies were small and of fairly low quality, which also degraded the confidence of any recommendation. The type of exercise also varied widely from high-intensity aerobic activity to slow move stretching.

Despite some evidence showing modest improvement in sleep outcomes, there is variability in provider and patient preference regarding this treatment. Some patients may be resistant to the idea of exercise as a treatment for sleep conditions or may already be engaged in an exercise regimen. It is important for providers to assess the overall readiness of patients to engage in exercise of any form and consider medical limitations to some types of physical activity.

A SR of the literature on mindfulness meditation for insomnia was conducted by Gong et al. (2016).(160) The review included six RCTs comprising a total of 330 participants. In this meta-analytic review, mindfulness meditation was not found to be superior to comparison interventions for improving insomnia severity, sleep efficiency, or sleep

quality assessed with the PSQI. However, mindfulness meditation resulted in significant improvements in both self-reported sleep quality (subjective sleep quality assessed using a single item) and subjective total wake time.

The Work Group did not systematically review evidence related to this recommendation.(157-160) Therefore, it is categorized as Not Reviewed, Amended. The Work Group's confidence in the quality of the evidence for this recommendation is very low.(157,159) The body of evidence had numerous limitations, including inconsistent definitions of sleep disorders and highly variable exercise programs. The populations studied were not necessarily generalizable to Veteran and active-duty patients, as Yang et al. (2012) focused on female middle-aged and older adults.(157) Not all of the studies, as in Gong et al. (2016), met the diagnostic criteria for chronic insomnia disorder. Mindfulness meditation requires a considerable time commitment on the part of patients, including both home practice and at least six to eight weeks of face-to-face sessions. Thus, the Work Group decided on a *Neither for nor against* recommendation.

## D. Treatment of Obstructive Sleep Apnea

### *Recommendation*

17. For treatment of obstructive sleep apnea, we recommend one or more of the following evidence-based therapies, depending on patient values and characteristics:
    - Mandibular advancement devices
    - Positive airway pressure (PAP)
    - Referral for surgical evaluation

    **(Strong for | Reviewed, New-added)**

### *Discussion*

Obstructive sleep apnea (OSA) is the collapse of the upper airway resulting in complete or partial cessation of airflow causing oxygen desaturations and sleep fragmentations. Treatments aim at preventing the upper airway airflow compromise. Positive airway pressure (PAP) therapy in the form of auto-PAP (APAP), continuous PAP (CPAP) and bilevel PAP (BPAP) is considered the first line of therapy. Mandibular advancement, using dental appliances, moves the jaw forward, increases the upper airway cross-sectional area and may reduce the upper airway obstruction. Mandibular advancement devices (MAD) can be used as a first line therapy of sleep apnea. The details of the evidence on MAD are discussed in Recommendation 18. The updated guideline strongly recommends treatment for OSA but does not limit the therapy to PAP. Rather, the providers are asked to consider patient's choices and preferences in considering

various therapies. In addition, referral for a surgical evaluation can be considered as an option (e.g. hypoglossal nerve stimulation therapy and treatment of nasal obstruction).

Many patients struggle with incorporating OSA therapy into their daily routine and may experience discomfort and sleep disturbance caused by the therapy. Adoption and maintenance use of therapy for treatment of a chronic condition like OSA are major issues that need to be addressed. Some of these are addressed in Recommendation 26 and 27 to improve adoption and maintenance use. Measures of effectiveness (rather than efficacy) such as mean disease alleviation, which integrate efficacy of therapy and adherence, may offer more practical information when comparing treatment options, according to two sources (that were not identified in the literature review and are not in our evidence synthesis).(161,162) A shared decision-making approach that ensures patients understand the pros and cons of their OSA treatment options (in the context of the patient's OSA metrics [e.g., event index], comorbidities, living arrangement, social support, occupational demands, and other factors) should be used to align OSA therapy with a patient's goals and treatment preferences.

Evidence supports an association between increasing positive airway pressure use and improved outcomes.(163-166) The relationship between PAP usage and health outcomes (specifically daytime sleepiness, quality of life (QoL), blood pressure, and cardiovascular events) among patients with mild to severe OSA has been the subject of several randomized controlled trials (RCTs).(167) A relevant systematic review (SR) and meta-analysis of 36 trials with 1,718 patients was outside of the scope of the systematic evidence review and, therefore, independent from the strength of this recommendation.(167) It found that PAP therapy compared to control conditions improved sleepiness, quality of life (QoL), and measures of daytime and nocturnal blood pressure among normotensive and, especially, hypertensive patients. Moreover, a subgroup analysis within a meta-analysis of 235 studies similarly provides evidence that PAP therapy compared with no PAP therapy improved the risk of major adverse cardiovascular events.(164) These data establish that PAP therapy, when compared with no active therapy, improves patient outcomes. The updated literature search identified an additional RCT and SR comparing CPAP vs no CPAP. As a measure of mean disease alleviation, the studies showed that CPAP use significantly reduced OSA symptoms including snoring, witnessed apnea, choking during sleep, excessive daytime sleepiness as measured by ESS, anxiety, depression, insomnia, and functionality.(168-170) The recent evidence did not show improvement in cardiovascular outcomes (CV mortality, stroke, MI, incident atrial fibrillation, and composite CV outcomes), and neurocognitive tests.(168,171)

The safety of PAP therapy has been established across multiple cohort and interventional studies. As far as side effects, PAP has been associated with nasal congestion, oronasal dryness, mask discomfort, and nocturnal awakenings.(166) The

potential concern for weight gain with PAP therapy was evaluated in a meta-analysis of three RCTs, which included 128 patients and confirmed a dose-dependent association between increasing PAP use and weight gain over two to three months of follow-up: 0.30 kg per hour of use per night (95% CI 0.03 – 0.56).(172) For example, using PAP for >4 hours per night was associated with a 1.2 kg (95% CI 0.08 – 2.25) greater weight gain than for PAP use of ≤4 hours per night. The weight gain associated with PAP use appears to be modest and was not associated with adverse metabolic effects.(172) The mechanisms underlying the relationship between PAP use and weight gain remain unclear.

OSA is an important chronic medical condition with significant symptoms and consequences. We strongly recommend treatment of OSA with options of PAP, MAD and referral for surgical evaluation. Like any chronic medical condition and its management, patient's choices and preferences and shared decision-making play an important role in adoption and maintenance of any evidence-based treatment.

The Work Group's systemically reviewed the evidence related to this recommendation.(163-166) The Work Group's confidence in the quality of the evidence is low. The Work Group also considered that the benefits of treatment of sleep apnea outweighed the minor potential harms as a failure to treat has the potential for catastrophic harms such as loss of employment, accidents, excessive daytime sleepiness, apnea and hypoxia, and serious injury due occupational hazards. The Work Group judged that there is some variation in patient preferences regarding the nightly use of therapy, and resource use issues related to reimbursement for long-term therapy are relevant. Thus, based on the recognized risk of catastrophic harms from not providing effective treatment for OSA, the Work Group decided upon a *Strong for* recommendation.

### *Recommendation*

18. For treatment of mild to moderate obstructive sleep apnea (Event Index <30 per hour), we suggest either mandibular advancement devices or positive airway pressure as first line therapy options.

    **(Weak for | Reviewed, Amended)**

### *Discussion*

Our systematic evidence review included evidence that significantly supported the 2019 Clinical Practice Guideline, and the Work Group agreed to amend the recommendation to improve clarity.

The mandibular advancement device (MAD) is the second most studied therapy for OSA, after PAP therapy. MAD is also commonly referred to as mandibular

advancement splint, mandibular advancement appliance, or mandibular repositioning appliance. Oral appliance therapy is also used to describe MAD therapy and includes oral appliances such as tongue retaining devices, which are not addressed in this guideline. MAD therapy increases the size of the upper airway, primarily in the velopharynx, by advancing or stabilizing the mandible during sleep, reducing collapsibility of the airway, and severity of OSA and snoring. (52) The Work Group specifically reviewed studies comparing PAP and MAD therapy. Some studies concluded that PAP therapy was superior in AHI reduction. (173-175) however, Xu et al 2021 found no significant difference in AHI reduction with PAP versus MAD use. While some studies found that adoption of therapy had no difference between PAP and MAD use, MAD therapy was superior in adherence (174,176) Additionally, there were no significant differences found between PAP and MAD therapies for improvement of neuro-cognitive or physical function, daytime sleepiness, quality of life (QoL), hypertension, or any other therapeutic outcomes. (173-176) The remaining evidence base reviewed in 2019 and 2025 supported that while MAD therapy may not be as efficacious in reducing the AHI as PAP therapy, the increased usage of MAD, due in part to patient preference and acceptance, can result in more effective treatment.

Other factors that influenced this recommendation include therapy feasibility and cost, patient preferences, and impact of comorbidities. When a patient's profession or lifestyle requires frequent or unpredictable travel to locations where electricity and distilled water are unavailable or unreliable, PAP may not be feasible, and MAD therapy may be preferred. While the Patient Focus Group confirmed individual preferences varied, most patients exposed to both options preferred MAD over PAP. Since considering patient preference as part of shared decision is foundational to this guideline the Work Group agreed to improve the clarity of the recommendation stating MAD is a reasonable choice as first line therapy when providing patient centered care. Importantly, consideration of patient comorbidities is critical in first line care selection. MAD therapy can simultaneously manage nocturnal bruxism, orthodontic retention, habitual mouth breathing, or severe snoring, and has shown greater therapy compliance in the presence of PTSD, claustrophobia or insomnia. Conversely, patients with significant cardiovascular or pulmonary disorders, an unstable dentition, or those who are morbidly obese may have relative contraindications to MAD and better suited for PAP therapy. Another indication for MAD is combination with PAP therapy if mask leakage or excessive PAP pressures are given as reasons for poor PAP adherence.

While not included in this CPG's systematic evidence review and, thus, independent from the strength of this recommendation, the Work Group acknowledged two studies reporting the side effects of MAD. (52,177) Sheats et al. (2017) found the primary side effects of MAD include: increased salivation, tooth or jaw pain, a period of malocclusion upon waking, tooth movement, or bite change.(177) The majority of these side effects are self-limited and easily managed by a qualified dentist and the risk of tooth

movement can be mitigated by material selection and avoidance of soft liners. Digitally engineered, custom milled appliances made of semi-rigid materials prevent or produce the least amount of tooth movement and function similarly to orthodontic retention devices (retainers). MAD therapy has the potential to trigger temporomandibular joint pain in a small percentage of patients but can also resolve pain associated with bruxism or clenching sometimes associated with sleep disordered breathing. Management and prevention of MAD therapy side effects requires a sleep physician and a dentist trained in treatment of temporomandibular joint pain using patient-specific strategies and treatment should not be discontinued until alternative therapies are identified by the sleep provider.(177)

Only custom fabricated, titratable MAD therapy delivered by a qualified dentist showed equivalent health outcomes to PAP and were recommended as first line standalone therapy option for mild and moderate OSA. Prefabricated “boil and bite” non-titratable MADs, while cheaper and more available, are less effective at managing OSA, have greater side effects, and not recommended as a first line OSA therapy(178-180). An acceptable therapeutic outcome typically requires mandibular protrusion approximating the maximum comfortable protrusion minus 3 millimeters but may require maximum comfortable protrusion. Most patients with mild to moderate OSA will respond to MAD therapy, but not all. All moderate and severe OSA patients and symptomatic mild OSA patients are indicated for an oral appliance efficacy study, preferably with in-lab titration (181). When MAD therapy resolves mild OSA symptoms, due to access to care or patient factors, providers may choose to forgo MAD efficacy studies when there are no occupational mandates such as aviation or deployment eligibility.

The Work Group’s confidence in the quality of the evidence for this recommendation is low due to the relative lack of RCTs with an adequate sample size, proper controls and blinding, objective measurements, and mitigated risk of bias.(55,174,182-184) However the 35-plus year body of evidence was acceptable to render a recommendation. The Work Group considered the importance of ensuring qualified dentists are involved in MAD selection, design, delivery, and follow-up care to include life cycle replacement. The RCT design weaknesses, variance in patient values and preferences, and variance in access to qualified sleep dentists led the Work Group to agree on a *Weak for* recommendation.

### *Recommendation*

19. For treatment of newly diagnosed obstructive sleep apnea, we suggest initiating auto-titrating over fixed continuous positive airway pressure to facilitate usage.

    **(Weak for | Reviewed, New-replaced)**

### Discussion

There are two primary PAP modalities that are most often used to treat OSA: auto-titrating positive airway pressure (APAP) and continuous or fixed PAP. Evidence from 31 RCTs reported in 1 SR by Kennedy et al. (2019) suggests auto-titrating positive airway pressure (APAP) improves PAP usage when compared to fixed CPAP, with the strength of the evidence rated as low.(185) Although usage (hours/night) was increased with APAP, there was no significant difference observed in the number of patients adhering ≥4 hours/night between APAP and fixed CPAP. Six RCTs demonstrated adding heated humidification to fixed CPAP significantly increased the average hours of CPAP use per night, although the strength of this evidence was very low. There was no evidence that other CPAP or bilevel positive airway pressure (BiPAP) modalities improved PAP usage. Overall, the evidence from Kennedy et al. (2019)(185) indicates that APAP and heated humidification are effective in improving CPAP usage, while other interventions, such as BiPAP, show no significant difference compared to fixed CPAP.

In determining whether APAP or CPAP should be used to treat a patient with OSA, other factors should guide which PAP modality is used. These could include patient preference, as patients may prefer APAP because of its adjustable pressure which can feel more comfortable; the ability to start therapy sooner; the cost of the machine; and availability of resources, including access to a sleep laboratory for PAP titration, which may also influence which modality is chosen. Auto-CPAP reduces the need for frequent manual adjustments and follow-up visits, potentially decreasing healthcare resource utilization and patient burden.

The Work Group systematically reviewed evidence related to this recommendation. (185) Therefore, it is categorized as Reviewed, New-replaced. The Work Group's confidence in the quality of the evidence for this recommendation is low. This low recommendation is based on bias and imprecision in the studies. The Work Group considered the totality of the evidence review and concluded that APAP significantly improve PAP usage, when compared to other PAP modalities, with benefits of APAP use outweighing the potential harm of not using PAP therapy due to adverse events of untreated sleep disordered breathing. Thus, the Work Group decided on a *Weak for* recommendation.

### Recommendation

20. For treatment of obstructive sleep apnea in patients with overweight or obesity, we suggest evidence-based weight management in combination with other treatments for obstructive sleep apnea. (See VA/DOD CPG on Management of Overweight and Obesity)

    **(Weak for | Reviewed, New-added)**

### Discussion

Two RCTs of evidence-based weight loss interventions versus control treatments among patients with OSA using positive airway pressure (PAP) therapy were identified.(186,187) Evidence from one study suggests weight management programs in combination with PAP therapy improves sleepiness, quality of life (QoL), and apnea-hypopnea index (AHI) at 6 and 12 months follow up.(186) Evidence from a second study (187) found a non-significant reduction in AHI compared to control. No evidence of significant harm was reported in either trial.

An additional publication was identified that was not included in our literature review because it was published after the cutoff date for this guideline evidence synthesis. The study compared tirzepatide versus placebo among patients with moderate-to-severe OSA and obesity to reduce OSA severity.(188) Results from two Phase III trials (one of patients using PAP therapy and one on untreated patients) showed that patients taking tirzepatide had a statistically significant reduction in AHI, body weight, improved sleep-related patient-reported outcomes, and other benefits after one year of therapy. While this study did not impact the strength or direction of the recommendation, additional research on pharmacotherapy for weight loss may further inform this recommendation in the future. The Work Group is aware that on December 20, 2024, the FDA approved tirzepatide for the treatment of moderate to severe OSA in patients with obesity, to be used in combination with a reduced calorie diet and increased physical activity.

In addition, two systematic reviews (SRs) were identified during the literature search conducted for the 2019 guidelines but excluded because the key question for that guideline only considered weight loss when compared to PAP therapy. In the SR by Mitchell et al. (2014)(189) the mean reduction in AHI was 16 events per hour. In a network meta-analysis Iftikhar et al. 2017(190) evaluated continuous positive airway pressure (CPAP), mandibular advancement devices (MADs), exercise-training, and dietary weight loss for sleep apnea and found that dietary weight loss reduced AHI by 12 events per hour compared to no treatment, but this was less of a reduction than what was achieved with other therapies.

Since weight loss in overweight or obese patients is beneficial in terms of their overall clinical management, these treatments (e.g., dietary intervention, bariatric surgery) should be pursued in patients with obesity and OSA. Weight loss interventions are resource-intensive and new weight loss medications can be costly and difficult to access.

The Work Group systematically reviewed evidence related to this recommendation (186,187) identified through the systematic evidence review. Therefore, it is categorized as Weak for, Reviewed, New-added. The Work Group's confidence in the quality of the evidence was low. The body of evidence had some limitations including lack of studies

of weight loss as a stand-alone intervention. Both studies evaluated weight loss in combination with PAP therapy. The benefits of weight loss improved AHI, sleepiness and sleep quality and the benefits of improved health and reduced disease severity outweigh the potential harms of the time it takes to achieve weight reduction, adherence challenges, and the need for ongoing follow-up and support to sustain weight loss. Patient values and preferences varied somewhat because some patients may prefer weight loss over other therapies, but others may find weight loss difficult to achieve. Thus, the Work Group decided on a *Weak for* recommendation. Providers should refer to the VA/DOD CPG Management of Overweight and Obesity for guidance on evidence-based weight management.

### *Recommendation*

21. For treatment of positional obstructive sleep apnea, we suggest positional therapy.

    **(Weak for | Reviewed, New-added)**

### *Discussion*

Evidence suggests treatment positional therapy shows improved outcomes in patients with positional sleep apnea.(191) In a systematic review (SR) of 5 randomized controlled trials (RCTs) Srijithesh et al. 2019 found treatment with positional sleep apnea therapy was associated with improvements in sleepiness, daytime functioning, fatigue, neurocognitive function, and mean disease alleviation. Positional therapy improved Epworth Sleepiness Scale (ESS) scores.(191) Positional therapy also showed a positive effect on cognitive outcomes as measured by motor reaction time.(191) Finally, it was associated with an improvement in AHI compared with control (Mean Difference (MD) −7.38 events per hour).(191) Positional therapy was not associated with improved functional outcomes, overall quality of life (QoL) or sleep-related QoL. No difference was found between study groups in QoL as measured by Functional Outcomes of Sleep Questionnaire (FOSQ).(191)

Some patients may prefer this treatment over other options, while some may find it uncomfortable, Further, the workgroup identified subgroup considerations of physical or cognitive limitations that may affect the patient's ability to utilize this therapy. When assessing resource use, positional therapy is a low cost, accessible treatment option.

The Work Group systematically reviewed evidence related to this recommendation (191) Therefore, it is categorized as Reviewed, New-added. The Work Group's confidence in the quality of the evidence was very low. The body of evidence had some limitations including there was only 1 SR with 5 RCTs. The strength of evidence was very low across all outcomes due to very serious limitations and serious imprecision.(191) The benefits of reducing AHI in patients with severe supine OSA include the use of a non-invasive treatment that does not require electricity, and has low risk of infection slightly outweighed the potential harm (e.g., of sleep disruption and

possible low back or extremity pain) which was small. Patient values and preferences varied somewhat, because some patients may prefer this over other treatments, while some patients may find it uncomfortable. Thus, the Work Group made the following recommendation: For patients with positional obstructive sleep apnea, we suggest positional therapy as a *Weak for* recommendation.

### Recommendation

22. For treatment of obstructive sleep apnea in appropriate* patients (including with an apnea hypopnea index of 15 or greater per hour) who have not been successful with positive airway pressure therapy, we suggest referral for evaluation for hypoglossal nerve stimulation therapy.

    *Note FDA criteria for appropriate patients in the narrative.

    **(Weak for | Reviewed, Amended)**

### Discussion

Obstructive sleep apnea (OSA) is characterized by airway collapse during sleep, leading to complete or partial episodes of breathing cessation. As many as half of patients prescribed positive airway pressure (PAP) therapy for the treatment of OSA have been unable to adopt PAP therapy long-term. Other treatment options are needed for patients who have failed or are intolerant of PAP therapy despite behavioral interventions aimed at improving use of PAP. Hypoglossal nerve stimulation therapy (HGNS) uses a different approach to dilating the upper airway and treating OSA. HGNS uses an implanted neurostimulator that dilates the upper airway by selectively stimulating branches of the hypoglossal nerve, predominantly innervating the genioglossus muscle, while the device is active during sleep (note that more than one HGNS device has been studied and that the different HGNS devices vary in the branches of the nerve targeted and number of leads, with one causing tongue protrusion and another “stiffening” [maintaining motor tone] of the tongue).

Evidence suggests that HGNS improves the apnea-hypopnea index (AHI), oxygen desaturation index (ODI), excessive daytime sleepiness, and health-related quality of life (QoL) in patients with OSA who have not been successfully treated with PAP. A SR by Kompelli et al. (2019)(192), which primarily included observational studies, found that treatment with HGNS was associated with statistically and clinically significant improvements in both objective (AHI, ODI), and subjective measures (ESS, FOSQ) in most patients. Recent crossover RCTs comparing HGNS to sham therapy found statistically significant improvements in AHI(193), excessive daytime sleepiness (194), and ODI.(194) A recent RCT that compared active HGNS to device-off HGNS (195) found statistically significant improvements in AHI and excessive daytime sleepiness. Overall, the Work Group’s confidence in the quality of evidence was moderate for AHI

and ODI and low for excessive daytime sleepiness. Adherence was assessed in the RCT by Dedhia et al. (2024)(193) and found to be higher in the sham than active group. No studies identified for this update measured “mean disease alleviation” as an outcome. Studies should incorporate mean disease alleviation, a metric that incorporates both treatment efficacy and hours of therapy use as outcomes. Studies that compare mean disease alleviation across therapies (HGNS, PAP, mandibular advancement device) and identify predictors of more favorable mean disease alleviation are needed. Although our evidence review did not include studies of MAD, clinicians may consider a trial of PAP as well as MAD prior to surgical referral. The published rates of serious adverse events from surgical implantation and device use are low (196), although one RCT (n=138 patients) reported that 72.5% of patients experienced a total of 164 procedure or study-related adverse events.(195) In this RCT, serious adverse events that were study-related included painful neck extension (1 event) and electrode cuff dislodgement (1 event).(195) The most common non-serious procedure-related adverse events were wound healing (e.g., erythema, seroma; 15.2% patients), temporary incisional numbness (13.8% patients), and post-op discomfort related to incisions (12.3% patients), and the most common non-serious study-related adverse event was discomfort due to stimulation (33% of patients).(195) Cardiovascular morbidity and mortality are considered important outcomes, but no studies directly assessed these outcomes. Indirect evidence (193) of very low strength found no difference in 24-hour systolic blood pressure between active and sham therapy. The impact of HGNS on QoL is another important outcome. Schwartz et al. (2023)(195) and Heiser et al. (2021)(194) found that active HGNS compared to sham treatment/therapy-off improves health-related QoL measures.

At the time this guideline was updated, the United States Food and Drug Administration (FDA)’s criteria indicated that this device is cleared for use in adults 18 years of age or older with a body mass index <= 40 kg/m2 (although the device was originally tested in individuals with BMI <32 kg/m2) and a diagnosis of moderate to severe OSA with AHI 15-100 events per hour who have failed or are intolerant to PAP therapy. The FDA criteria indicate that this device should NOT be used in patients with central or mixed apnea that account for more than 25% of their total AHI, “a physical condition that would keep [the] upper airway stimulation from working well” (e.g. markedly enlarged tonsils), or conditions/treatments that would compromise or prevent neurological control the upper airway, as well as an individual who cannot operate the device remote or does not have the necessary assistance to operate it, are pregnant or plan to become pregnant, requires “magnetic resonance imaging other than what is specified in the magnetic resonance conditional labeling for the HGNS system,” or have another implantable device that could have an unintended interaction with the HGNS device.(197) At the time the guideline was updated, the FDA also indicated that drug-induced sleep endoscopy should document the absence of complete concentric

collapse at the level of the velopharynx of soft palate. (See FDA Site here for complete list)

The evaluation and management of patients for HGNS therapy requires multiple disciplinary teamwork, including healthcare professionals with expertise in assessing whether the patient meets FDA criteria (e.g., healthcare professionals who can assess the airway) as well as those with surgical training and skills to implant the device and follow-up the patient post-operatively, and those trained and skilled in activating the device and titrating the stimulation settings. Patients who use HGNS therapy require periodic evaluation to assess their nightly use of the device, the effectiveness of the therapy for improving their OSA symptoms, and adverse effects of therapy. Additional team members may include staff skilled in delivering behavioral interventions (e.g. behavioral sleep medicine specialists) to improve PAP adoption of the therapy (since intolerance of PAP is a criteria) and in evaluating adequacy of social support for attending the healthcare visits required for evaluation and management of HGNS therapy. A shared decision-making approach is recommended given the surgical requirements, care coordination, and need for patients to engage in therapy daily and long-term management.

The Work Group considered the benefits and harms related to 1) referral of patients for surgical evaluation and 2) the procedure itself, acknowledging that this therapy does involve surgical intervention and the use of an implanted medical device. The Work Group considered potential harms of referring the patient for HGNS therapy to include the patient foregoing other types of OSA therapy while undergoing evaluation for the HGNS therapy. Benefits of referring patients for evaluation include the increased discussion of both surgical and non-surgical treatment options for OSA therapy that may occur while the patient is being evaluated for HGNS therapy. Benefits of receiving the HGNS therapy include a reduction in AHI.

While the available evidence supporting the treatment of OSA with HGNS therapy is consistent, there is known variability in provider and patient preferences regarding surgery and implantable devices. This variability can be based on a patient's or a provider's prior experiences with surgery. Another important consideration is the resource utilization for this treatment—specifically, the cost of surgery and the device, the need for a specially trained surgeon, and staff for follow-up management. The lack of these specialized resources across all sites could limit opportunities for individuals in some geographic areas to access this treatment, and sites may not find it feasible to provide access to the HGNS program. Furthermore, this therapy has mostly been tested in patients with a BMI less than 40 kg/m2 (most rigorously tested for BMI <32 kg/m2) and specific pattern of pharyngeal collapse during sleep endoscopy. In addition, not every patient is a good surgical candidate based on comorbid conditions, general health status, adequate psychosocial support for attending procedure-related visits and follow-

up visits long-term. An additional consideration is whether the patient had an adequate trial of PAP therapy with behavioral interventions to support PAP therapy and whether the patient is likely to adopt and use HGNS therapy long-term. Like PAP therapy, HGNS therapy requires the patient to turn the device on and off daily. The combination of these many factors can limit the utility of this treatment. The Work Group systematically reviewed evidence related to this recommendation.(192-196,198) Therefore, it is categorized as Reviewed, Amended. The Work Group's confidence in the quality of the evidence was very low. The body of evidence had some limitations, including a relatively small (fewer than 300 patients in 3 RCTs) number of studies comparing HGNS to sham or no active treatment (193) For the two studies using sham stimulation, all patients enrolled in the trial had already been successfully using the devices for at least one month prior to enrollment. For the body of evidence reviewed for this update describing procedure or study-related adverse events in patients with an HGNS device, the data were not presented in a manner allowing comparison between active treatment and device-off treatment.(195) The body of evidence for cardiovascular morbidity and mortality did not include any studies, with only one indirectly related study with a primary outcome of systolic blood pressure.(193) The benefits of referring patients for HGNS therapy for improving disease severity (AHI, daytime sleepiness, health-related QoL) were balanced with the potential harm of foregoing other OSA therapy while being evaluated for HGNS as well as the potential harm of the procedure itself, which is associated with a small risk of surgical complications, infection, unknown risks of implanted devices and chronic stimulation of the hypoglossal nerve, and requirements for another procedure to replace the battery. Patient values and preferences vary somewhat for referral for HGNS therapy and vary largely for the HGNS procedure itself; some patients prefer non-invasive treatments, while others may see HGNS as a desirable alternative to PAP therapy. Thus, the Work Group decided on a *Weak for* recommendation.

### Recommendation

23. For treatment of obstructive sleep apnea in patients who cannot tolerate other recommended therapies, we suggest against oxygen therapy as a standalone treatment.

    **(Weak against | Not reviewed, Amended)**

### Discussion

Oxygen, which may be used as a supplemental therapy in patients on positive airway pressure (PAP) with residual hypoxia, lacks sufficient evidence as a stand-alone treatment for OSA. Mehta et al. (2013) conducted an SR of 14 trials that evaluated the use of oxygen therapy as an alternative treatment in patients with OSA who do not adhere to CPAP.(199) Mehta et al. (2013) found that while oxygen therapy improved

oxygen saturation in patients with OSA, it may also increase the duration of apnea-hypopnea events.(199)

The Work Group noted that oxygen therapy may be used in the treatment of other respiratory conditions (for additional guidance see VA Directive 1173.13), and this recommendation should not be interpreted as recommending against oxygen therapy in those situations if the patient also has OSA or if oxygen is added to PAP therapy to alleviate residual hypoxia with PAP use.

While not included in our systematic evidence review and, thus, independent from the strength of this recommendation, the largest study on oxygen therapy versus CPAP, which was conducted in patients with OSA and CVD or cardiovascular risk factors, revealed that CPAP but not nocturnal oxygen resulted in a significant reduction in blood pressure.(200) Smaller studies that neither met inclusion criteria for this CPG, nor influenced the recommendation strength, demonstrated benefit in nocturnal hypoxemia with oxygen therapy in patients with OSA but no reduction in AHI or improvement in daytime functioning.(201,202)

The Work Group also considered patient values and preferences, and resource use in developing this recommendation. Some patients like nasal cannula or find this a logical therapy given that OSA is associated with hypoxia at night; however, others may be concerned with perceptions regarding use of oxygen as an indication of poor health status and risk of combustion/fire at home. The feasibility of oxygen therapy was also a consideration, for it may be difficult to obtain this treatment without evidence of nocturnal hypoxemia.

The Work Group systematically reviewed evidence related to this recommendation that was identified in the prior guidelines.(199-202) Therefore, it is categorized as Weak Against, Not reviewed, Amended. The Work Group's confidence in the quality of the evidence was low. The body of evidence had some limitations including small sample size and confounders in the analysis. The potential harms of oxygen therapy as treatment for OSA slightly outweighed the benefits. The use of home oxygen carries the small risk of adverse events, including combustion/explosion and fire, and there is some evidence it may prolong respiratory events during sleep. Patient values and preferences varied largely because Some patients like nasal cannula or find this a logical therapy given that OSA is associated with hypoxia at night; however, others may be concerned with perceptions regarding use of oxygen as an indication of poor health status and risk of combustion/fire at home. Thus, the Work Group decided on a *Weak against* recommendation.

### *Recommendation*

24. For treatment of obstructive sleep apnea, we suggest against atomoxetine or a combination of atomoxetine and oxybutynin.

    **(Weak against | Reviewed, New-added)**

### *Discussion*

Evidence from 2 RCTs (203,204) provided mixed results on whether atomoxetine or the combination of atomoxetine and oxybutynin improve critical outcomes of obstructive sleep apnea (OSA) such as reductions in apnea hypopnea index (AHI), improvements in daytime functioning, or sleep-related quality of life (QoL). The Schweitzer et al. (204) study investigated atomoxetine and the combination of atomoxetine and aroxybutynin compared to placebo. Atomoxetine showed a reduction in AHI and wakefulness after sleep onset. The combination of atomoxetine and aroxybutynin showed a reduction in AHI, daytime fatigue, and respiratory arousal. Aroxybutynin, the R-enantiomer of oxybutynin, is not approved by the FDA and not commercially available. In contrast to Aishah et al.(203) Schweitzer et al. 2023 (204), investigated atomoxetine and the combination of atomoxetine and oxybutynin compared to placebo and reported no clinically significant results improving outcomes. Although a statistically significant reduction in AHI with the atomoxetine and oxybutynin combination group was reported on day 1, these results were deemed clinically insignificant due to the lack of a sustained response in week 4. Confidence in the quality of overall evidence was rated as low due to small sample sizes and the risk for imprecision. A weak against recommendation for atomoxetine and the combination of atomoxetine and oxybutynin was made because of known harms from these medications, inconclusive evidence that they are effective in OSA, and the low quality of evidence.

It was recognized that there are large variations in patient values and preferences regarding treatment interventions for OSA. It was also acknowledged that this was in congruence with the Patient Focus Group's report desiring that healthcare providers share various treatment options earlier during their care. It was also considered that there was an increased relative risk for medication-related harm from atomoxetine and oxybutynin in the treatment population because cardiovascular disease is a common comorbidity, and the elderly are more vulnerable to anticholinergic side effects. Specifically, atomoxetine may increase blood pressure and exacerbate cardiovascular disorders and oxybutynin's anticholinergic effects can increase risk for falls and cause cognitive impairment.

The Work Group systematically reviewed evidence regarding the efficacy of atomoxetine and the combination of atomoxetine and oxybutynin in treatment of OSA.(203,204) This was categorized as a reviewed and new-added recommendation. The Work Group's confidence in the quality of evidence was low and the body of evidence was limited to 2 studies with small sample sizes and risk imprecisions. The evidence suggesting benefits of treatment were judged to be outweighed by known

harms from atomoxetine and the combination atomoxetine and oxybutynin. Thus, the Work Group decided on a *Weak against* recommendation.

### *Recommendation*

25. For treatment of obstructive sleep apnea there is insufficient evidence to suggest for or against these interventions:
    - Expiratory positive airway pressure (EPAP)
    - Inspiratory muscle therapy
    - Intra-oral negative airway pressure
    - Myofunctional exercise
    - Neuromuscular electrical stimulation
    - Transcutaneous electrical nerve stimulation (TENS)

    **(Neither for nor against | Reviewed, New- replaced)**

### *Discussion*

Transcutaneous electrical stimulation is a method of delivering a mild electrical current to the skin. Evidence suggests no benefits for this treatment compared to usual care (CPAP for OSA). Results from one randomized controlled trial (RCT) (205) showed no difference between 3 months of nocturnal bilateral transcutaneous submental electrical stimulation and usual care in apnea hypopnea index (AHI), oxygen desaturation index, or daytime sleepiness.

Myofunctional therapies involve exercise training of muscles that support the upper airway. Evidence suggests limited benefits of therapy versus sham/placebo in the treatment of obstructive sleep apnea (OSA). There were two identified studies (206,207) which showed no evidence of benefits in terms of adoption of therapy in the intervention versus sham comparison groups. One identified study of upper airway muscle training (208)showed no difference between intervention and a sham comparator group in terms of functional outcomes, quality of life (QoL), or sleep-related QoL. Four studies examined the impact of myofunctional therapy on OSA severity. One study (209) found evidence of reduction in AHI and snoring frequency in the intervention compared to a sham control; however, three other studies (206-208) found no evidence of benefit in terms of respiratory events. One systematic review (SR) (209) found evidence for reduction in daytime sleepiness and AHI with upper airway muscle training compared to no treatment or sham; however, there was no evidence that this treatment was more effective compared to or combined with other treatments, and no evidence of sustained benefit beyond 3 months. Rueda et al. 2020 (209) noted significant limitations in study design that also reduced confidence in the quality of the evidence.

Inspiratory muscle training involves breathing exercise that strengthens the muscles used for inhalation. Evidence suggests some benefits in terms of improved sleep quality and daytime sleepiness with intervention compared to control groups. One SR (210) of four RCTs showed improved patient-reported sleep quality at 6 and 12 weeks, reduction in daytime sleepiness and no difference in AHI between intervention and control. Studies included in the review were small (n=15-29 participants), which limits confidence in the evidence.

Myofunctional therapy involves a program of exercises that are designed to strengthen the muscles of the upper airway. In determining the recommendation, the workgroup considered evidence from included SRs,(209) that evaluated myofunctional therapies in combination with CPAP and found no evidence of added benefit above and beyond CPAP. The workgroup also considered evidence from the 2019 guidelines showing myofunctional therapy reduced AHI, sleepiness and snoring in some studies.(211,212) Taken together, the workgroup felt this constituted insufficient evidence to recommend for or against this treatment.

Expiratory positive airway pressure (EPAP) applies positive pressure only during the exhalation phase of breathing. One nasal EPAP device uses a mechanical valve applied to each nostril that provides very low resistance during inspiration but partially closes during exhalation, creating expiratory resistance/positive pressure that splints open the upper airway. Although no new studies were identified in the current literature search, studies in the 2019 guidelines included an RCT by Berry et al. (2011) that reported significant benefits of nasal EPAP compared to sham EPAP for all outcomes (AHI, ESS and ODI) at 3 months in individuals with mild-to-moderate OSA.(213) This study excluded patients who were previously on PAP or failed to tolerate PAP, and there is evidence that OSA may recur in patients switching from CPAP to EPAP.(214) Given this limitation, EPAP was considered to have insufficient evidence to recommend for or against its use.

Neuromuscular electrical stimulation (marketed as eXciteOSA in the US) involves the use of a device that delivers electrical stimulation to the tongue muscle using a hand-held device during the day. No SRs or RCTs were identified in the literature search for neuromuscular electrical stimulation and therefore was considered to have insufficient evidence to recommend for or against its use.

Oral negative pressure devices (e.g., iNAP) involve the use of a mouthpiece with tubing that creates negative pressure in the oral cavity with a battery-powered vacuum device. No SRs or RCTs were identified in the literature search for oral negative pressure devices and therefore were considered to have insufficient evidence to recommend for or against its use.

Based on the Patient Focus Group, the Work Group felt patients want the most effective therapies first and would not opt for these interventions, particularly given that daily training (in some studies, multiple sessions per day) is required, and there is no evidence of long-term benefit if the patient discontinues the exercises. The Work Group also noted the potential harms of delaying effective treatments that could result from use of these minimally beneficial interventions. The Work Group acknowledged that these interventions may be appropriate as "salvage therapies" when recommended treatments are not tolerated by patients; however, there was not sufficient evidence to support use of these treatments in routinely treating OSA.

The Work Group systematically reviewed evidence related to this recommendation. (205-210) Therefore, it is categorized as Reviewed, New Replaced. The Work Group's confidence in the quality of the evidence was very low. The body of evidence had limitations including very small sample size in many of the studies. The benefits of slightly reducing AHI, improving sleep quality and sleepiness over the short-term were balanced with the potential harm of patient burden of these interventions and delaying effective therapies. Patient values and preferences were similar because patients prefer to initiate the most effective therapies to reduce disease severity and other outcomes. Thus, the Work Group decided on a *Neither for nor against* recommendation.

### *Recommendation*

26. For treatment of obstructive sleep apnea in patients who are prescribed positive airway pressure therapy, we suggest the use of in-person or telehealth educational, behavioral, and supportive interventions to improve PAP usage.

    **(Weak for | Reviewed, New-replaced)**

### *Discussion*

Adoption and adherence to PAP can be a challenge in patients who suffer from OSA. Predictors of non-adherence are multifactorial. Some key challenges include poor self-efficacy, decreased understanding of treatment importance, social isolation, and lack of education.(215) Addressing these factors through targeted education, support, and strategies either in-person or by telemedicine could improve adherence rates and satisfaction among patients. The recommendation to use in-person or telehealth educational, behavioral, and supportive interventions to improve CPAP adherence in patients with OSA is based on a comprehensive review of the evidence as well as focus group data.

Based on the results of a Cochrane Review, educational, supportive, and behavioral interventions increased PAP usage.(216) Behavioral interventions showed the most significance in hourly usage with an increase in average PAP usage per night by 1.31 hours per night (95% CI: 0.95 to 1.66) when compared to usual care. Supportive interventions were found to be moderately certain to increase the average hours of PAP

usage per night by a mean of 0.70 hours/night (95% CI: 0.36 to 1.05). Educational interventions showed an increase in the mean average of PAP usage of 0.85 hours/night (95% CI: 0.32 to 1.39). Interventions combining educational, supportive, and behavioral components demonstrated improvements as well. Eleven RCTs showed an increase in average PAP use per night (MD: 0.82 hours; 95% CI: 0.20 to 1.43), and 9 RCTs reported higher adherence rates (OR: 1.71; 95% CI: 1.08 to 2.72).

Other modalities of support for patients include telemedicine and mobile applications. In a meta-analysis from Niu et al. (2023)(217) telemedicine-based follow-up significantly improved PAP use greater than 4 hours a night by 10.67% (95% CI: 4.97 to 16.37; p<0.001) and PAP usage by 0.61 hours (95% CI: 0.39)  Telehealth was also shown to be more cost-effective. In terms of mobile applications, evidence from a SR by Baptista et al. (2022)(218) highlighted the benefits of mobile applications in improving PAP adherence. The review included studies on various apps that demonstrated increased PAP usage, though the strength of evidence was very low due to poor data reporting and lack of blinding. Lastly, an RCT by Syed et al. (2021)(219) reported greater adherence in the intervention group who received personalized interface/mask fitting sessions supervised by a certified sleep technician to patients receiving their PAP machine by a durable medical supplier. The percentage of days with home auto-titrating positive airway pressure therapy (APAP) use ≥4 hours/day in the intervention group increased, highlighting the importance of education. However, the overall SoE was very low due to serious limitations in study quality and imprecision.

The evidence was largely consistent with our focus group participant values. Participants valued effective patient-provider communication, self-advocacy, and coordination of care. Adherence to PAP therapy is a challenge for many patients and low adherence limits clinical benefit. Therefore, providers are likely to value individualized patient-focused interventions. There are likely to be variations across clinical sites regarding available resources and trained clinicians to provide educational, behavioral, and supportive interventions for increased PAP adherence. In addition, in low-resource areas, telehealth, and mobile applications may also be limited. Because multiple types of interventions may be beneficial, effective approaches can be delivered by a variety of providers, including clinical psychologists, nurses, respiratory therapists, behavioral sleep medicine specialists, health educators, physicians, or sleep technicians.

The Work Group's confidence in the quality of the evidence is low to very low due to methodological limitations and variability in study outcomes. The benefits of the recommended multifaceted approach, which include increased adherence and usage of PAP, slightly outweigh the potential harms, which are minimal. Patient values and preferences varied, with many favoring non-invasive and supportive interventions. Thus, the Work Group decided upon a *Weak for* recommendation considering the strength of the evidence factors favoring these approaches.

### Recommendation

27. For treatment of obstructive sleep apnea in appropriate patients, we suggest up to a two-week course of eszopiclone to improve positive airway pressure usage.

    **(Weak for | Reviewed, New-added)**

### Discussion

Evidence suggests that a time-limited use of eszopiclone can improve positive airway pressure (PAP) adherence and usage in patients with insufficient PAP usage. The systematic review (SR) by Wang et al. (2021)(220) included six randomized controlled trials (RCTs) and two retrospective cohort studies, finding that eszopiclone significantly improved PAP usage compared to placebo or no treatment (Mean Difference: 0.83 hours/night; 95% CI: 0.70 to 0.96; P<0.00001). However, some studies found no significant differences in PAP adherence with other pharmacologic interventions such as zolpidem and zaleplon. The overall strength of evidence is very low due to serious limitations in study quality, including high risk of bias, imprecision, and inconsistency in results.

As discussed in Recommendation 9, there is general consistency in the evidence supporting the benefits in improving adherence to PAP, however, there is inconsistency in patient preferences regarding pharmacotherapy treatment. Some patients may prefer pharmacologic assistance to enhance their adherence to PAP therapy, these patient preferences should be considered in light of potential risks such as dependency and other adverse effects, especially in older adults. Other published literature not included in the reviewed studies of non-benzodiazepine benzodiazepine receptor agonists and, thus, independent from the strength of this recommendation, discusses the potential risk of abuse, dependence, motor vehicle accidents, falls in older adults, and diversion. For service members on active-duty, or for those with a commercial driver's license, limitations in duties and temporary medical profiles may need to be implemented if a sedative hypnotic medication is prescribed.

In April 2019, the FDA released a safety announcement advising healthcare professionals of the risk of serious injuries or deaths caused by sleep behaviors including sleepwalking, sleep driving, and engaging in other activities while not fully awake associated with the non-benzodiazepine benzodiazepine receptor agonists, including eszopiclone. Although these injuries are rare, they have occurred in patients with and without a history of such behaviors, even at the lowest recommended doses, and even after taking one dose. To minimize the incidence of adverse events, a non-benzodiazepine benzodiazepine receptor agonist, if prescribed, should be at the lowest effective dose and for the shortest duration possible. All patients offered non-benzodiazepine benzodiazepine receptor agonists should be counseled on these potential risks.

The Work Group systematically reviewed evidence related to this recommendation, focusing on studies that assessed the efficacy of eszopiclone in improving PAP adherence.(220) Therefore, it is categorized as Reviewed New-added. The Work Group's confidence in the quality of the evidence was very low, mainly due to the high risk of bias, imprecision, and inconsistency across studies. The benefits of eszopiclone in enhancing PAP usage slightly outweighed the potential harms, which were small but included risks such as falls and dependency. Patient values and preferences varied somewhat, with some patients valuing the pharmacologic support despite its potential risks. Thus, the Work Group decided on a *Weak for* recommendation.

### Recommendation

28. For treatment of obstructive sleep apnea in patients with anatomical nasal obstruction as a barrier to positive airway pressure use, we suggest evaluation for nasal surgery.

    **(Weak for | Reviewed, Not changed)**

### Discussion

Evidence indicates that upper airway surgery (sinonasal surgery, soft tissue pharyngeal surgery such as palatoplasty or pharyngoplasty) improves PAP adherence in patients with obstructive sleep apnea (OSA) who are struggling to tolerate this therapy. Addressing nasal obstruction is particularly pertinent for patients with OSA who report this factor is limiting their ability to tolerate positive airway pressure (PAP). Procedures such as septoplasty, inferior turbinate reduction, nasal valve repair, and functional rhinoplasty restructure the nasal airway to alleviate anatomical sources of obstruction by decreasing airflow resistance. A systematic review (SR) conducted by Camacho et al. (2015) demonstrated that after sinonasal surgery to improve nasal breathing, the proportion of patients regularly using PAP increased from 39% to 90%(221). In another SR, Ayers et al. (2016) found a mean increase in nightly PAP use of 0.62 hours after upper airway surgery.(222) The 2019 review included studies not only of nasal surgeries but also pharyngeal surgery such as tonsillectomy and uvulopalatopharyngoplasty (UPPP). Given the known risks of surgical intervention of the upper airway, there is a non-negligible level of harm associated with these treatments. However, the demonstrated benefit in improving PAP adherence leads to an estimate that the benefits slightly outweigh the harms.

Evidence supporting upper airway surgery to improve PAP tolerance is consistent. Surgical treatment has other implications that need to be considered. Operative procedures represent a cost to both the patient and the healthcare system. Furthermore, access to a qualified surgeon could be a limiting factor for some patients, especially in rural or remote areas. In addition, some patients may not be good surgical

candidates based on overall health and other risk factors. These points highlight the importance of context and patient specifics when considering surgical treatment.

The Work Group systemically reviewed evidence related to this recommendation. (221,222) Consistent with the 2019 Work Group, this Work Group's confidence in the quality of the evidence for this recommendation is very low. This is largely since nearly all the studies included in the 2019 review were observational studies or case series of small numbers of patients, with only one RCT identified. However, as the evidence remains consistent in showing benefit and the risk of adverse events is small, the benefits were deemed to outweigh the risks of surgical treatment. Patient values and preferences regarding this treatment were somewhat varied. Thus, the Work Group decided on a *Weak for* recommendation.

### *Recommendation*

29. For treatment of obstructive sleep apnea-related residual excessive daytime sleepiness in patients who are optimally treated with sufficient therapy use, we suggest adding:
    - Armodafinil
    - Modafinil
    - Solriamfetol

    **(Weak for | Reviewed, New-added)**

### *Discussion*

The evidence supporting the above recommendation derives from four systematic reviews (SRs).(223) Moderate quality evidence suggests that both modafinil and armodafinil improve the critical outcomes of sleepiness and quality of life (QoL).(224) Low-quality evidence found no significant difference in the critical outcome of serious adverse events between either modafinil or armodafinil and placebo.(225) Moderate quality evidence suggests that solriamfetol improves sleepiness.(224) High-quality evidence suggests that solriamfetol improves QoL.(226) Moderate quality evidence found no significant difference in serious adverse events between solriamfetol and placebo.(224) Although there was available data for pitolisant showing improvements in sleepiness and QoL, it was not included in the recommendation as it is not FDA-approved for the treatment of residual daytime sleepiness in patients with OSA.

There is some variation in patient preference regarding this treatment. Given that the available wake-promoting agents are controlled substances, some patients may be hesitant to take them or may be concerned about side effects. Further, some of these medications are expensive and may not be available for all patients. For active-duty service members, use of any of these medications may lead to occupational restrictions, deployment limitations or referral to a Medical Evaluation Board. Additional subgroup

considerations include caution against prescribing armodafinil, modafinil, or pitolisant in patients with cardiovascular disease.

Excessive daytime somnolence (EDS) can affect up to 18% of patients with adequately treated OSA (227) yet the definition of "optimal" is vaguely defined. The generally accepted metric for adequate device adherence for treatment of OSA is use at least 4 hours per night for at least 70% of nights. Though this is essentially a standard adopted by insurance companies to determine whether a third party should continue to pay for treatment, it does not necessarily reflect physiology. Some occupations such as pilots have enhanced adherence standards given that functional outcomes appear to show improvement up to 7 hours per night.(228) Specifically, the Federal Aviation Administration requires pilots to sleep with an OSA treatment for at least 6 hours per night, at least 75% of nights. US military services require use at least 5 hours per night, at least 90% of nights for aviators. Therefore, treating providers should confirm that patients are using their treatment for OSA during the entire sleep period before considering addition of a wake-promoting agent.

In addition to therapy adherence, it is also important to confirm that the underlying treatment is efficacious. For PAP therapy, this includes an automated interrogation of the device to ensure that the residual AHI is less than 5 events/hr. For MAD therapy, this includes confirmation of successful treatment preferably with an oral appliance titration polysomnogram. It is worth noting that the pre-treatment baseline influences the lowest AHI that is possible. For patients with very severe OSA, it may not be feasible to reduce the AHI to less than 5 and in these cases, consultation with a sleep specialist is recommended.

It is important to fully evaluate a patient's complaint of EDS to ensure that there are no medications or other sleep disorders and medical problems which might be contributing. Insufficient sleep is very common in the general population and must be ruled out as a cause of EDS prior to prescribing wake-promoting agents. Sleep diaries or actigraphy can assist in this determination. Other causes of EDS should be considered such as insufficient sleep, circadian rhythm sleep-wake disorders, medical/mental health conditions, and medications. If there is evidence of other co-occurring sleep disorders, referral to a specialty sleep medicine clinic is recommended.

The Work Group systematically reviewed evidence related to this recommendation.(223-226) Therefore, it is characterized as Reviewed, New-Added. The work group's confidence in the quality of the evidence was low. The body of evidence had some limitations including inconsistency of reported adherence. The benefits of improved sleepiness and QoL slightly outweighed the potential harm of adverse events. Patient values and preferences varied somewhat because some

patients wanted to avoid medication, and some felt that medication was highly desirable. Thus, the Work Group decided on a *Weak for* recommendation.

# X. Research Priorities

During the development of the 2025 VA/DOD Insomnia/OSA CPG, the Work Group identified topics for additional research, including areas requiring stronger evidence to support future recommendations and efforts aimed at exploring new areas to guide forthcoming CPGs.

In general, the Work Group recommends research to advance our understanding of the following:

## A. Screening

- Further studies on screening for insomnia, OSA, and/or COMISA in the primary care setting, including studies to evaluate models of care that can be implemented and sustained.
- Research to develop simple, streamlined screening tools for both insomnia and OSA is needed due to the prevalence of COMISA in patients presenting with sleep complaints.
- Evaluating the impact of screening on outcomes for insomnia, OSA, and/or COMISA on patients and healthcare systems.
- Evaluating the use of machine learning/artificial intelligence (AI) to aid in the screening and identification of patients with insomnia, OSA, and/or COMISA.

## B. Chronic Insomnia Disorder

- Studies are needed to understand how social determinants of health may impact access and use of treatments for chronic insomnia disorder.
- Studies assessing CBT-I and BBT-I in women (particularly women during and after menopause), racially/ethnically and socioeconomically diverse populations, and across age groups to make sure those populations receive effective therapeutic interventions and identify any needed adaptations for these populations who may experience disparities in access and outcomes.
- Studies that assess sequencing of CBT-I with other treatments, including sequencing of CBT-I with treatments for co-occurring psychiatric or other conditions.
- Pragmatic trials assess the outcomes of CBT-I/BBT-I in the clinical setting, especially looking at factors such as facilitators and barriers to implementation and sustainability.

- Research supporting implementation and dissemination of evidence-based behavioral insomnia treatments and evaluating effectiveness when treatments are adapted for the primary care setting, when treatments are abbreviated, and when treatments are delivered by different provider types in different clinical contexts.
- Dismantling studies to better understand the efficacy of individual components of CBT-I.
- Research assessing combinations of CBT-I plus adjunctive interventions (e.g., medication, acupuncture, mindfulness), including their relative efficacy in the presence of comorbid conditions.
- Focus on long-term outcomes of CBT-I and pharmacotherapy for insomnia as well as comparative effectiveness studies comparing CBT-I to recently FDA-approved hypnotic medications with novel mechanisms of action (e.g., dual orexin antagonists).
- RCTs in younger adults as well as in the active-duty military population that may have lower risks of side effects or adverse events when using hypnotics for short periods of time. Research is especially needed for agents that are not controlled substances.
- Comparative effectiveness trials evaluating DORAs versus non-benzodiazepine benzodiazepine receptor agonists to determine if there is a difference in functional impairment during the sleep period between these two drug classes. This is critical for patients who have a job that necessitates immediate alertness when waking from sleep and for older adults who are at risk for nighttime falls.
- Future research on cannabis and cannabinoid products to determine dosing strength and formulations with patients assessed for and meeting diagnostic criteria for chronic insomnia disorder per the ICSD-3-TR or DSM-V. Long term studies are needed to evaluate the risks of long-term use of these agents, and to assess the durability of any observed treatment benefits. Studies are also needed to evaluate potential withdrawal symptoms and risks with discontinuation.
- Well-designed placebo-controlled trials are needed to clarify the potential benefit of controlled release melatonin, passionflower, and magnesium formulations for treatment of chronic insomnia disorder

## C. Obstructive Sleep Apnea

- Studies are needed to understand how social determinants of health may impact access and use of diagnostic testing and treatments for OSA.

- Studies are needed to identify and evaluate optimal clinical care pathways for patients with OSA that incorporate patient preferences and priorities for treatment.
- Studies should incorporate mean disease alleviation, a metric that incorporates both treatment efficacy and hours of therapy use as outcomes. Studies that compare mean disease alleviation across therapies (HGNS, PAP, mandibular advancement device) and identify predictors of more favorable mean disease alleviation are needed.
- Technologies to measure and monitor treatment efficacy and adherence for oral appliance therapies are needed.
- Studies assessing the impact of HGNS therapy on cardiovascular morbidity and overall mortality are needed.
- Studies to develop and evaluate clinical care pathways for HGNS therapy are needed to optimize patient outcomes.
- Studies are needed to evaluate the potential benefits of MAD among patients who are unable to use PAP prior to HGNS therapy.
- High-quality RCTs with robust methodology, including intention-to-treat analysis and outcome assessor blinding, are needed to confirm the effectiveness of interventions to improve PAP adherence. Studies are needed to explore the long-term sustainability of these interventions and their impact on QoL and functional outcomes. Research should also investigate the potential of integrating advanced technologies, such as AI-driven applications, to provide personalized and adaptive support for PAP users.
- Dissemination and implementation of behavioral interventions for PAP treatment adoption and adherence are needed. This research should also examine the comparative effectiveness of behavioral interventions when delivered by those having expertise in BSM versus non-BSM providers.
- Well-designed RCTs with large sample sizes are needed to assess the long-term efficacy of pressure modification and humidification interventions for improving PAP adherence.
- Studies are needed to evaluate the optimal approach to treating comorbid insomnia and OSA (COMISA).
- Studies are needed to evaluate the long-term effects of eszopiclone on PAP adherence, particularly in patient populations at risk for non-adherence, including those with comorbid conditions. Comparative effectiveness studies comparing pharmacologic and non-pharmacologic interventions are also warranted. Further

research should also explore the optimal duration of eszopiclone therapy to balance efficacy and safety.

- The degree to which PAP usage is required for optimal benefit in terms of sleepiness, cognitive performance, and cardiovascular outcomes are needed as evidence that the commonly used definition of adherence as 4 hours of use per night is lacking and this level of use may not be necessary or sufficient to achieve clinical benefit.
- Research to identify a standardized approach to patients who are unable to use PAP and/or MAD and determine appropriate surgical options for treating OSA (e.g., nasal surgery to improve PAP adherence, primary surgical treatment with bi-maxillary advancement or hypoglossal nerve stimulation) or alternative/salvage therapy is needed.
- Studies are needed to understand OSA pheno/endotypes in military personnel and Veterans, especially studies that explore differences in patient outcomes, differences in optimal treatment selection, and differences in approaches to therapy adherence (e.g., pharmacological therapy versus behavioral interventions).
- Studies addressing concurrent use of PAP and mandibular advancement devices are needed.
- For patients with OSA and PTSD who are intolerant of PAP therapy, studies are needed to determine whether more advanced, non-invasive airway pressure modalities are associated with improved acceptance, adherence, and clinical outcomes.
- RCTs of atomoxetine and combination of atomoxetine and oxybutynin as a salvage or adjunctive therapy for OSA are needed.
- For residual sleepiness after treatment of OSA, RCTs and comparative effectiveness trials are needed, including amphetamine-based stimulants, modafinil/armodafinil, solriamfetol, and pitolisant given significant differences in mechanism of action and cost. Studies are also needed to assess causes of residual sleepiness in OSA, including insufficient sleep time and comorbid conditions.

# Appendix A: Guideline Development Methodology

## A. Developing Key Questions to Guide the Systematic Evidence Review

To guide this CPG's systematic evidence review, the Work Group drafted 12 KQs on clinical topics of the highest priority for the VA and DOD populations. The KQs followed

the population, intervention, comparison, outcome, timing, and setting (PICOTS) framework, as established by the Agency for Healthcare Research and Quality (AHRQ). Table A-1 lists and describes the PICOTS elements.

**Table A-1. PICOTS (229)**

| PICOTS Element | Description |
|---|---|
| **Population or Patients** | Patients of interest. It includes the condition or conditions, populations or sub-populations, disease severity or stage, co-occurring conditions and other patient characteristics or demographics. |
| **Intervention or Exposure** | Treatment (e.g., drug, surgery, lifestyle changes), approach (e.g., doses, frequency, methods of administering treatments), or diagnostic or screening test or both used with the patient or population. |
| **Comparator** | Treatment or treatments (e.g., placebo, different drugs) or approach or approaches (e.g., different dose, different frequency, standard of care) being compared with the intervention or exposure of interest described above. |
| **Outcomes** | Results of interest (e.g., mortality, morbidity, QoL, complications). Outcomes can include short, intermediate, and long-term outcomes. |
| **Timing, if Applicable** | Duration or follow-up of interest for the particular patient intervention and outcome to occur (or not occur). |
| **Setting, if Applicable** | Setting or context of interest. Setting can be a location (e.g., primary, specialty, inpatient care) or a type of practice. |

Abbreviation: PICOTS: population, intervention, comparison, outcome, timing and setting; QoL: quality of life

Because of resource constraints, all KQs of interest to the Work Group could not be included in the systematic evidence review. Thus, the Work Group selected the 12 highest priority KQs for inclusion (see Table A-2).

Using the GRADE approach, the Work Group rated each outcome on a 1-9 scale (7-9, critical for decision making; 4-6, important, but not critical, for decision making; and 1-3, of limited importance for decision making). Critical and important outcomes were included in the evidence review (see Outcomes); however, only critical outcomes were used to determine the overall quality of evidence (see Determining Recommendation Strength and Direction).

### *a. Populations*

The KQs are specific to adults 18 years or older who may be at risk of Insomnia and/or OSA.

## *b. Interventions and Comparators*

| KQs | Interventions | Comparators |
|---|---|---|
| 1 | **Pharmacotherapy**<br>**Orexin receptor antagonists**<br>Daridorexant<br>Lemborexant<br>Suvorexant<br>**Benzodiazepine receptor agonists/ Z-drugs**<br>Eszopiclone<br>Zaleplon<br>Zolpidem<br>**Benzodiazepines**<br>Alprazolam<br>Clonazepam<br>Diazepam<br>Estazolam<br>Flurazepam<br>Lorazepam<br>Oxazepam<br>Quazepam<br>Temazepam<br>Triazolam<br>**Melatonin agonists**<br>Ramelteon<br>**Antidepressants**<br>Amitriptyline<br>Doxepin<br>Mirtazapine<br>Paroxetine<br>Trazodone<br>**Over-the-counter preparations**<br>Diphenhydramine<br>Doxylamine<br>L-tryptophan<br>Melatonin<br>Valerian<br>**Other medications**<br>Gabapentin<br>Hydroxyzine<br>Quetiapine | CBT-I |

| KQs | Interventions | Comparators |
|---|---|---|
| **2** | EPAP Provent, BongoRx, and UltePAP<br>Excite OSA<br>Exercise therapy<br>iNAP<br>MAD-Mandibular devices<br>Mouth Taping<br>• Alone (e.g., porous tape over mouth to reduce mouth-breathing/encourage nose breathing)<br>• As an adjunct to treatment (e.g., in lieu of a chin strap on CPAP face mask)<br>Myofunctional treatments<br>Oral appliance therapy<br>Oxygen<br>PAP<br>Positional therapies<br>TRD-Tongue retaining devices<br>Weight loss<br>Winx<br>**Pharmacotherapy**<br>**NRIs (may ^ insomnia symptoms)**<br>Atomoxetine<br>Desipramine<br>Reboxetine<br>**Antimuscarinic + noradrenergic combination therapy**<br>Atomoxetine plus fesoterodine (ato-fes)<br>Atomoxetine plus oxybutynin (ato-oxy)<br>Atomoxetine plus r-oxybutynin (ato-roxy)<br>Duloxetine plus oxybutynin (dul-oxy)<br>Milnacipran plus oxybutynin (mil-oxy)<br>Reboxetine plus hyoscine butylbromide (reb-hyo)<br>Reboxetine plus oxybutynin (reb-oxy) | Treatment as usual (TAU)<br>Sham<br>Minimal or no intervention (waitlist control) |
| **3** | CPAP (Any type) | Dental/oral appliances<br>Mandibular advancement devices |

| KQs | Interventions | Comparators |
|---|---|---|
| 4 | **Pharmacotherapy**<br>**Orexin receptor antagonists**<br>Daridorexant<br>Lemborexant<br>Suvorexant<br>**Benzodiazepine receptor agonists/ Z-drugs**<br>Eszopiclone<br>Zaleplon<br>Zolpidem<br>**Benzodiazepines**<br>Alprazolam<br>Clonazepam<br>Diazepam<br>Estazolam<br>Flurazepam<br>Lorazepam<br>Oxazepam<br>Quazepam<br>Temazepam<br>Triazolam<br>**Melatonin agonists**<br>Ramelteon<br>**Antidepressants**<br>Amitriptyline<br>Doxepin<br>Mirtazapine<br>Paroxetine<br>Trazodone<br>**Over-the-counter preparations**<br>Diphenhydramine<br>Doxylamine<br>**Other medications**<br>Gabapentin<br>Hydroxyzine<br>Quetiapine | Placebo |

| KQs | Interventions | Comparators |
|---|---|---|
| 5 | **Pharmacotherapy**<br>**Benzodiazepine receptor agonists/ Z-drugs**<br>Eszopiclone<br>Zaleplon<br>Zolpidem<br><br>**Dual orexin receptor antagonists**<br>Daridorexant<br>Lemborexant<br>Suvorexant<br>**Antidepressants**<br>Doxepin<br>Trazodone<br><br>**Melatonin receptor agonists**<br>Ramelteon<br><br>**Other**<br>Gabapentin<br>Hydroxyzine | Placebo |
| 6 | **Pharmacotherapy**<br>**CNS Stimulants**<br>Amphetamines<br>Armodafinil<br>Methylphenidate<br>Modafinil<br>**Dopamine/Norepinephrine Reuptake Inhibitors**<br>Solriamfetol<br><br>**Other**<br>Pitolisant<br>Sodium Oxybate | Placebo |

| KQs | Interventions | Comparators |
|---|---|---|
| 7 | **Methods intended to improve adherence with CPAP**<br>CBT/ psychotherapy<br>Dental devices/Oral appliances (e.g., TAP PAP; MyTAP)<br>Education (any education program)<br>Expiratory pressure relief (EPR™)<br>Individual vs. group interventions<br>Mask type (e.g., nasal pillow, half face mask)<br>Motivational therapy<br>Nasal surgery/sinus surgery/septoplasty/turbinate reduction surgery<br>Other behavioral therapies (e.g., multicomponent, incentive-based, support groups, desensitization programs)<br>Pharmacotherapy (Refer to full list of insomnia medications from KQ 5)<br>Remote CPAP monitoring (e.g., REVAMP program)<br>Remote support (e.g., web-based support, mobile apps, SMS Messaging)<br>Titrated CPAP pressure vs. APAP | No intervention/ no therapy |
| 8 | **Herbals/ supplements**<br>5-hydroxytryptophan (5-HTP)<br>Ashwagandha<br>Cannabis/Cannabinoids<br>• Cannabidiol (CBD) oil<br>• Hemp oil<br>• Tetrahydrocannabinol (THC; including delta-8 and delta-9)<br>Chamomile<br>Gamma-aminobutyric acid (GABA)<br>Ginger<br>Glycine<br>Lavender (oral)<br>L-Theanine<br>L-Tryptophan<br>Magnesium<br>Melatonin<br>Passion flower<br>Reishi mushroom (Ganoderma lucidum)<br>Sage (oral supplement)<br>Spearmint<br>Tart Cherry Juice<br>Valerian | Placebo |

| KQs | Interventions | Comparators |
|---|---|---|
| 9 | **Technology categories**<br>Peripheral arterial technology<br>**Type 2 home testing:**<br>Onera<br>Nox T3<br>Cerebra Sleep System,<br>Zmachine Synergy,<br>Embletta mpr-pg,<br>Somnotouch resp<br>Tests that combine apnea and PO2 and Heart rate variability<br>Tests that combine photoplethysmogram sensors for blood volume changes, heart rate, and oxygen saturation for cardiopulmonary coupling (e.g., Sleep Image Ring)<br><br>**Other:**<br>Sounds generated by respiratory and cardiac functions.<br>AcuPebble SA100<br>Mandibular jaw movements<br>Sunrise technology<br>Novel patch test (Wesper)<br>Spectrophotometric methodology (Belun Ring; Sleepimage Ring)<br>**Wearable Technology:**<br>Samsung Galaxy Watch + Samsung Health Monitor app<br><br>**Note:**<br>In studies with comparison of the intervention of interest to PSG, if comparisons exist for auto scored and provider scored (physician overread) will be captured | Sleep Lab/Polysomnography |

| KQs | Interventions | Comparators |
|---|---|---|
| 10 | **CBT-I Provider* Delivered**<br>Face-to-face individual<br>Face-to-face group<br>Telehealth individual<br><br>**CBT-I Self-directed**<br>Phone apps<br>Internet<br>Workbooks<br><br>**CBT-I Partially supported**<br>Example definitions of Partial Support: Support for self-directed use of an online course or app-support by non-sleep specialist.<br><br>**BBT-I Provider* Delivered**<br>Face-to-face individual<br>Face-to-face group<br>Telehealth individual<br><br>**BBT-I Self-directed**<br>Phone apps<br>Internet<br>Workbooks<br><br>**BBT-I Partially supported**<br>Example definitions of Partial Support: Support for self-directed use of an online course or app-support by non-sleep specialist.<br><br>* Providers to include coaches and other healthcare providers | Attention control<br>Treatment as usual<br>Wait-list control |

| KQs | Interventions | Comparators |
|---|---|---|
| 11 | **Screening questionnaires:**<br>2-item Insomnia Severity Index (ISI-2)<br>3-item ISI (ISI-3)<br>Athens Insomnia Scale for non-clinical application (AIS-NCA)<br>Bergen insomnia scale (BIS)<br>Daily Cognitive-Communication and Sleep Profile (DCCASP)<br>Insomnia Daytime Symptoms and Impacts Questionnaire (IDSIQ)<br>Insomnia Screening Scale (ISS)<br>Minimal Insomnia Symptom Scale (MISS)<br>Restorative sleep questionnaire (RSQ)<br>Sleep Quality Questionnaire (SQQ)<br><br>Note: The previous evidence review covered the Athens Insomnia Scale, the ISI, and the Pittsburgh Sleep Quality Index (PSQI) | Clinical interview |
| 12 | Hypoglossal nerve stimulation | Sham (stimulator implanted but not activated) |

### *c. Outcomes*

| KQ(s) | Critical Outcomes | Important Outcomes |
|---|---|---|
| 1 | Insomnia Severity<br>SAEs<br>Sleepiness/Daytime Functioning/Fatigue<br>Suicidality/Mental Health | Sleep Efficiency/Sleep Onset Latency/Wake After Sleep Onset<br>Sleep Quality<br>Total Sleep Time |
| 2 | Adoption of Therapy (includes adherence)<br>Functional Outcomes/QoL/Sleep-Related QoL<br>Mean Disease Alleviation (MDA) which includes Hypoxic Burden Index and AHI<br>Neurocognitive<br>Sleepiness/Daytime Functioning/Fatigue | Cardiovascular Morbidity and Mortality<br>Cost, Healthcare Utilization |

| KQ(s) | Critical Outcomes | Important Outcomes |
|---|---|---|
| **3** | Adoption of Therapy (includes adherence)<br>Functional Outcomes/QoL/Sleep-Related QoL<br>Mean Disease Alleviation which includes Hypoxic Burden Index and AHI<br>Neurocognitive<br>Sleepiness/Daytime Functioning/Fatigue | Cardiovascular Morbidity and Mortality<br>Snoring |
| **4** | Insomnia Severity<br>SAEs<br>Sleep Efficiency/Sleep Onset Latency/Wake After Sleep Onset<br>Sleepiness/Daytime Functioning/Fatigue | Sleep Quality<br>Suicidality/Mental Health<br>Total Sleep Time |
| **5** | SAEs<br>Sleep Efficiency/Sleep Onset Latency/Wake After Sleep Onset<br>Sleepiness/Daytime Functioning/Fatigue | Insomnia Severity<br>Sleep Quality<br>Suicidality/Mental Health<br>Total Sleep Time |
| **6** | Functional Outcomes/QoL/Sleep-Related QoL<br>SAEs<br>Sleepiness/Daytime Functioning/Fatigue | Cardiovascular Morbidity and Mortality<br>Mean Disease Alleviation which includes Hypoxic Burden Index and AHI<br>Neurocognitive<br>Suicidality/Mental Health |
| **7** | Adoption and Adherence with CPAP: Defined by any number of hours/ night and percentage of time.<br>Duration of use | Cardiovascular Morbidity and Mortality<br>Functional Outcomes/Quality of Life<br>Mean Disease Alleviation (MDA) to include AHI and Hypoxic Burden Index<br>Mortality/Suicide Deaths<br>Neurocognitive |
| **8** | Insomnia Severity<br>Quality of Life/Functional Outcomes<br>SAEs<br>Sleep Efficiency/Sleep Onset Latency/Wake After Sleep Onset | Sleep Quality<br>Suicidality/Mental Health |
| **9** | Sensitivity<br>Specificity | Area under the ROC curve (AUC)<br>Positive and negative predicative values (PPV, NPV) |

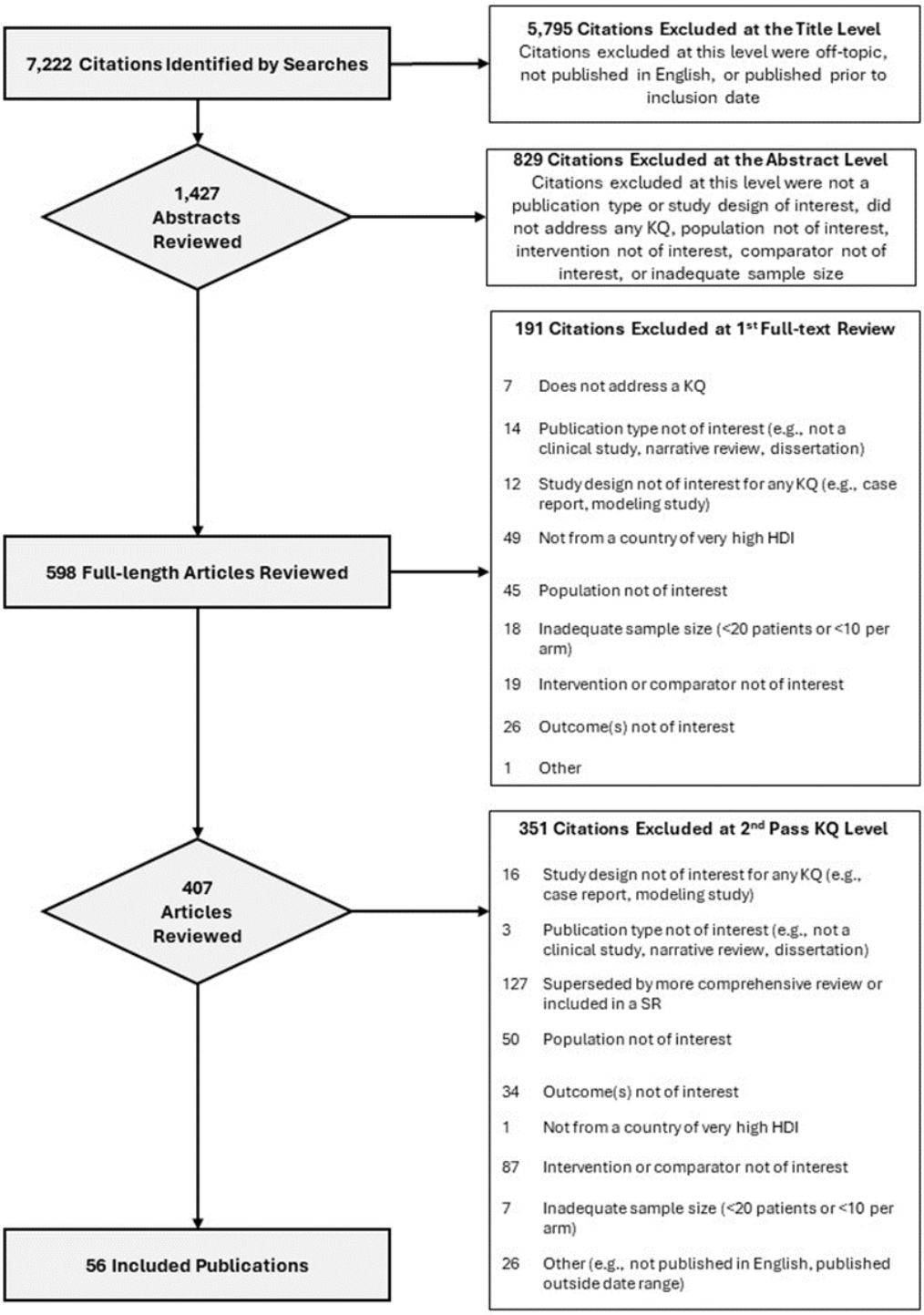
| KQ(s) | Critical Outcomes | Important Outcomes |
|---|---|---|
| **10** | Insomnia Severity<br>Sleep Efficiency | Quality of Life/Functional Outcomes<br>Sleep Onset Latency<br>Sleep Quality<br>Suicidality/Mental Health<br>Wake After Sleep Onset |
| **11** | Sensitivity<br>Specificity | Area under the ROC curve (AUC)<br>Positive and negative predicative values (PPV, NPV) |
| **12** | Mean disease alleviation (MDA) to include AHI and Hypoxic Burden Index<br>Sleepiness/ Daytime Functioning/Fatigue<br>SAEs | Cardiovascular Morbidity and Mortality<br>Mortality/Suicide Deaths<br>Neurocognitive<br>QoL/Sleep-related QoL/Functional Outcomes |

## B. Conducting the Systematic Review

Extensive literature searches identified 7,222 citations potentially addressing the key questions of interest to this evidence review. Of those, 5,795 were excluded upon title review for clearly not meeting inclusion criteria (e.g., not pertinent to the topic, not published in English, published prior to study inclusion publication date, or not a full-length article). Overall, 1,427 abstracts were reviewed, with 829 of those being excluded for the following reasons: a publication type or study design of interest, did not address any KQ, population not of interest, intervention not of interest, comparator not of interest, or inadequate sample size. A total of 598 full-length articles were reviewed. Of those, 191 were excluded at a first-pass review. Reasons for their exclusion are presented in Figure 1 below. A total of 407 full-length articles were thought to address one or more Key Questions and were further reviewed. Of these, 351 were ultimately excluded. Reasons for their exclusion are presented in Figure A-1 below.

Overall, 56 publications addressed one or more of the Key Questions and were considered as evidence in this review (see also the General Criteria for Inclusion in Systematic Review).Table A-2 indicates the number of studies that addressed each of the questions, and some papers were used for more than one Key Question.

**Figure A-1. Study Flow Diagram**




Abbreviations: KQ: key question; HDI: human development index; SR: systematic review

**Alternative Text Description of Study Flow Diagram**

Figure A-1. Study Flow Diagram is a flow chart with nine labeled boxes linked by arrows that describe the literature review inclusion-exclusion process. Arrows point down to boxes that describe the next literature review step and arrows point right to boxes that describe the excluded citations at each step (including the reasons for exclusion and the numbers of excluded citations).

1. Box 1: 7,222 citations identified by searches.
    a. Right to Box 2: 5,795 excluded at the title level. Excluded citations were off topic, not published in English, or published prior to inclusion date.
    b. Down to Box 3.
2. Box 3: 1,427 abstracts reviewed.
    a. Right to Box 4: 829 citations excluded at the abstract level. Citations excluded were unlikely to meet study design criteria, had less than 10 patients/arm, were not a full-length SR or study, were completely off topic.
    b. Down to Box 5.
3. Box 5: 598 full-length articles reviewed.
    a. Right to Box 6: 191 citations excluded at 1st pass full-article level.
        i. 7 do not address a KQ.
        ii. 14 publication type not of interest.
        iii. 12 study design not of interest.
        iv. 49 not from a country of very high HDI.
        v. 45 not from a population of interest.
        vi. 18 inadequate sample size.
        vii. 19 intervention or comparator not of interest.
        viii. 26 outcome(s) not of interest.
        ix. 1 other.
    b. Down to Box 7.
4. Box 7: 407 articles reviewed.
    a. Right to Box 8: 351 citations excluded at 2nd pass full-article level.
        i. 16 study design not of interest for any KQ.
        ii. 3 publication type not if interest.
        iii. 127 superseded by more comprehensive review or included in a SR.
        iv. 50 population not of interest.

v. 34 outcome(s) not of interest.
vi. 1 not from a country of very high HDI
vii. 87 intervention or comparator not of interest.
viii. 7 sample size too small.
ix. 26 other.

b. Down to Box 9.

5. Box 9: 56 included studies.

**Table A-2. Evidence Base for KQs**

| KQ Number | KQ | Number and Study Type |
|---|---|---|
| **KQ1** | What is the long-term efficacy on sleep outcomes, comparative effectiveness, and harms of pharmacotherapy versus CBT-I? | No studies identified |
| **KQ2** | In adults with OSA, what interventions are effective in reducing symptoms, morbidity, and mortality? | SRs: 8<br>RCTs: 13 |
| **KQ3** | What is the comparative effectiveness of CPAP versus dental/oral appliances in improving sleep outcomes? | SRs: 2<br>RCTs: 2 |
| **KQ4** | For adult patients with chronic insomnia disorder, what is the effectiveness of pharmacotherapy (FDA approved for insomnia and off label) on sleep outcomes? | SRs: 5 |
| **KQ5** | For adult patients with co-occurring OSA and chronic insomnia disorder, what is the effectiveness of pharmacotherapy (FDA approved for insomnia and off label) on sleep outcomes? | No studies identified |
| **KQ6** | For adult patients with OSA, what is the effectiveness of pharmacotherapy for managing residual sleepiness or hypersomnia? | SRs: 4 |
| **KQ7** | What methods improve adherence with CPAP? | SR: 6<br>RCTs: 1 |
| **KQ8** | What is the effectiveness of herbal remedies or dietary supplements to improve sleep outcomes? | SRs: 3<br>RCTs: 6 |
| **KQ9** | What is the accuracy of home sleep apnea testing methods and tools? | Diagnostic studies: 4<br>RCTs: 1 |
| **KQ10** | In adults with chronic insomnia, what modalities of delivery are effective for behavioral treatments for insomnia (CBT-I and BBT-I)? | SRs: 1<br>RCTs: 2 |
| **KQ11** | In adults with sleep complaints, what screening questionnaires are accurate for assessment of insomnia? | No studies identified |
| **KQ12** | In patients with OSA, what is the effectiveness of hypoglossal nerve stimulation in improving sleep outcomes? | RCTs: 3 |

| KQ Number | KQ | Number and Study Type |
|---|---|---|
| | **Total Evidence Base** | **61 papers*** |

*Some papers address more than one KQ, and some studies are reported in more than one paper, therefore the total number for the evidence base is greater than the total number of includes in the study flow diagram and description.

BBT-I: brief behavioral treatment for insomnia; CBT-I: cognitive behavioral therapy for insomnia; CPAP: continuous positive airway pressure; OSA: obstructive sleep apnea; RCT: randomized controlled trial; SR: systematic review

### *a. General Criteria for Inclusion in Systematic Evidence Review*

- Randomized control trials (RCTs) or SRs of RCTs published on or after May 15, 2018, to March 31, 2024. If multiple SRs addressed a key question, we selected the most recent and/or comprehensive review.
- Studies had to be published in English.
- Publication had to be a full clinical study or SR; abstracts alone were not included. Similarly, letters, editorials, research protocols, and other publications that were not full-length clinical studies were not accepted as evidence.
- SRs had to have searched MEDLINE or EMBASE for eligible publications, performed a risk of bias assessment of included studies, and assessed the quality of evidence using a recognizable rating system, such as GRADE or something compatible (e.g., the one used by the Evidence-based Practice Centers of the Agency for Healthcare Research and Quality). If an existing review did not assess the overall quality of the evidence, evidence from the review must have been reported in a manner that allowed us to judge the overall risk of bias, consistency, directness, and precision of evidence. We did not use an existing review as evidence if we were not able to assess the overall quality of the evidence in the review.
- RCTs are needed to assess a pharmacological or non-pharmacological treatment, care management approach or care setting, as specified in the intervention sections above, and have an independent control group. Randomized crossover trials were only included if data from the first period (prior to treatment crossover) were reported separately or an adequate washout period was used.
- If no RCTs were available to address a KQ, prospective, non-randomized comparative studies were included. Similarly, if no SRs of RCTs were available, SRs of eligible non-RCT designs were used.
- Study had to have enrolled at least 20 patients (10 per study group for RCTs and 20 for prospective non-randomized studies) unless otherwise noted.
    - Study had to have enrolled at least 85% of patients who meet the study population criteria: adults aged 18 years or older with chronic insomnia disorder

and/or OSA. If the patient population falls below this threshold but the relevant population of patients with chronic insomnia disorder and/or OSA are reported separately, then that study was included.

- To ensure applicability to the VA/DOD healthcare systems, and ensure consistency across the CPG program, inclusion of individual studies was limited to very high Human Development Index (HDI), countries with an index ≥0.8 where standards of healthcare are comparable (e.g., United States, Canada, United Kingdom, Western Europe, Israel, Japan, Hong Kong, Australia, and New Zealand). Inclusion of SRs were limited to those including more than half of the studies from eligible regions.
- These regions of interest are listed in Table 1 of the Statistical Annex of the 2023/24 Human Development Report produced by the United Nations Development Programme.
    - The study had to have reported on at least one outcome of interest.

### b. Key Question Specific Criteria for Inclusion in Systematic Evidence Review

- KQs 1 through 8, 10, and 12 included only SRs of RCTs and RCTs
- KQs 9 and 11 included SRs of diagnostic cohort studies that compared a diagnostic screening instrument to a valid reference standard report on the diagnostic characteristics of the screening instrument (e.g., sensitivity, specificity), or individual diagnostic cohort studies.

### c. Literature Search Strategy

Information regarding the bibliographic databases, date limits, and platform, provider, or both can be found in Table A-3. See Appendix K for additional information on the search strategies, including topic-specific search terms and search strategies.

**Table A-3. Bibliographic Database Information**

| Name | | Date Limits | Platform/Provider |
|---|---|---|---|
| **Bibliographic Databases** | Embase | May 17, 2018, through May 2, 2024 | Elsevier |
| | MEDLINE/Premedline | May 17, 2018, through May 2, 2024 | Pubmed |
| | PsycInfo | May 17, 2018, through May 2, 2024 | EBSCO |

### d. Rating the Quality of Individual Studies and the Body of Evidence

Sigma Health Consulting assessed the methodological risk of bias of individual diagnostic, observational, and interventional studies using the U.S. Preventive Services Task Force (USPSTF) method. Each study is assigned a rating of *Good*, *Fair*, or *Poor* based on a set of criteria that vary depending on study design. Detailed lists of criteria and definitions appear in Appendix VI of the USPSTF procedure manual.(230)

Next, the Sigma Team assessed the overall quality of the body of evidence for each critical and important outcome using the GRADE approach. This approach considers the following factors: overall study quality (or overall risk of bias or study limitations), consistency of evidence, directness of evidence, and precision of evidence. The overall quality of the body of evidence is rated as *High*, *Moderate*, *Low*, and *Very Low*.

## C. Developing Evidence-Based Recommendations

In consultation with the VA Office of Quality and Patient Safety and the Clinical Quality Improvement Program, DHA, the Sigma Team convened a three-and-a-half-day in-person recommendation development meeting from July 16–19, 2024, to develop this CPG's evidence-based recommendations. Two weeks before the meeting, the Sigma team finalized the systematic evidence review and distributed the report to the Work Group; findings were also presented during the recommendation development meeting.

Led by the Champions, the Work Group interpreted the systematic evidence review's findings and developed these CPG's recommendations. The strength and direction of each recommendation were determined by assessing the quality of the overall evidence base, the associated benefits and harms, patient values and preferences, and other implications (see Determining Recommendation Strength and Direction).

### *a. Determining Recommendation Strength and Direction*

Per GRADE, each recommendation's strength and direction is determined by the following four domains.(59) Information on each domain, questions to consider, and the resulting judgment can be found in Table A-4.

#### *1. Confidence in the Quality of the Evidence*

Confidence in the quality of the evidence reflects the quality of the body of evidence supporting a recommendation (see Rating the Quality of Individual Studies and the Body of Evidence). The options for this domain include *High*, *Moderate*, *Low*, or *Very Low*. These four ratings are a direct reflection of the GRADE ratings for each relevant critical outcome in the evidence review (see Outcomes). Per GRADE, if the quality of evidence differs across the relevant critical outcomes, the lowest quality of evidence for any of the critical outcomes determines the overall quality of the evidence for a recommendation.(61,62)

The recommendation strength generally aligns with the confidence in the quality of evidence. For example, *Strong* recommendations are typically supported by *High* or *Moderate* quality evidence. However, GRADE permits *Low* or *Very Low* quality evidence to support a *Strong* recommendation in certain instances (e.g., life-threatening situation).(59)

### 2. Balance of Desirable and Undesirable Outcomes

The balance of desirable and undesirable outcomes (i.e., benefits and harms) refers to the relative magnitudes or tradeoffs of anticipated benefits (e.g., increased longevity, reduced morbidity, improved QoL, decreased resource use) and harms (e.g., decreased longevity, increased complications, impaired QoL). The options for this domain include *benefits outweigh harms/burdens*, *benefits slightly outweigh harms/burdens*, *benefits and harms/burdens are balanced*, *harms/burdens slightly outweigh benefits*, and *harms/burdens outweigh benefits*. This domain assumes most providers will offer patients an intervention if its advantages exceed the harms. The Work Group's understanding of the benefits and harms associated with the recommendation influenced the recommendation's strength and direction.

### 3. Patient Values and Preferences

Patient values and preferences are an overarching term that includes patients' perspectives, beliefs, expectations, and goals for health and life as they might apply to the intervention's potential benefits, harms, costs, limitations, and inconvenience. The options for this domain include *similar values*, *some variation*, and *large variation*. When patient values seem homogeneous, this domain might increase the recommendation's strength. Alternatively, when patient values seem heterogeneous, this domain might decrease a recommendation's strength. As part of this domain, the Work Group considered the findings from the Patient Focus Group carried out as part of this CPG update (see Appendix H).

### 4. Other Implications

Other implications encompass the potential consequences or other impacts that might affect the strength or direction of the recommendation. The options for this domain, for example, include resource use, equity, acceptability, feasibility, and subgroup considerations. The following are example implications related to equity and subgroup considerations, respectively: some of the indicated population might be geographically remote from an intervention (e.g., complex radiological equipment); a drug might be contraindicated in a subgroup of patients.

**Table A-4. GRADE Evidence to Recommendation Framework**

| Decision Domain | Questions to Consider | Judgment |
|---|---|---|
| **Confidence in the quality of the evidence** | • Among the designated critical outcomes, what is the lowest quality of relevant evidence?<br>• How likely is further research to change the confidence in the estimate of effect? | • High<br>• Moderate<br>• Low<br>• Very Low |

| Decision Domain | Questions to Consider | Judgment |
|---|---|---|
| **Balance of desirable and undesirable outcomes** | • What is the magnitude of the anticipated desirable outcomes?<br>• What is the magnitude of the anticipated undesirable outcomes?<br>• Given the best estimate of typical values and preferences, are you confident that benefits outweigh harms/burdens or vice versa? | • Benefits outweigh harms/ burdens<br>• Benefits slightly outweigh harms/burdens<br>• Benefits and harms/ burdens are balanced<br>• Harms/burdens slightly outweigh benefits<br>• Harms/burdens outweigh benefits |
| **Patient values and preferences** | • What are the patients' values and preferences?<br>• Are values and preferences similar across the target population?<br>• Are you confident about typical values and preferences? | • Similar values<br>• Some variation<br>• Large variation |
| **Other implications (e.g., resource use, equity, acceptability, feasibility, subgroup considerations)** | • What are the costs per resource unit?<br>• Is this intervention generally available?<br>• What is the variability in resource requirements across the target population and settings?<br>• Are the resources worth the expected net benefit from the recommendation?<br>• Is this intervention and its effects worth withdrawing or not allocating resources from other interventions? | Various considerations |

### *b. Recommendation Categorization*

A summary of the recommendation categories and definitions is available in Table 3.

#### *1. Categorizing Recommendations with an Updated Review of the Evidence*

*Reviewed* refers to recommendations on topics included in this CPG's systematic evidence review. *Reviewed*, *New-added* recommendations are original, new recommendations (i.e., not included in the previous CPG). These recommendations are based entirely on evidence included in the current CPG's systematic evidence review.

*Reviewed*, *New-replaced* recommendations were in the previous CPG but revised based on the updated evidence review. These recommendations may have clinically relevant edits. *Reviewed*, *Not changed* recommendations were carried forward from the previous CPG unchanged. *Reviewed*, *Amended* recommendations were carried forward from the previous CPG with a nominal change. This allowed for the recommendation language to reflect GRADE approach, and any other not clinically meaningful edits deemed necessary. These recommendations can be based on a combination of

evidence included in the current CPG's systematic evidence review and the evidence base that supported the recommendation in the previous CPG.

*Reviewed*, *Deleted* refers to recommendations from the previous CPG that were deleted after a review of the evidence. This may occur if the evidence supporting the recommendation is outdated (e.g., there is no longer a basis to recommend use of an intervention and/or new evidence suggests a shift in care), rendering the recommendation obsolete.

### *2. Categorizing Recommendations without an Updated Review of the Evidence*

There were also cases in which it was necessary to carry forward recommendations from the previous CPG without an updated review of the evidence. Given time and resource constraints, the systematic evidence review carried out for this CPG update could not cover all available evidence; therefore, its KQs focused on new or updated research, or areas not covered in the previous CPG.

For areas in which the relevant evidence was not changed and for which recommendations made in the previous CPG were still relevant, recommendations could have been carried forward to the updated CPG without an updated review of the evidence. The evidence supporting these recommendations was thus also carried forward from the previous CPG. These recommendations were categorized as *Not reviewed*. If evidence had not been reviewed, recommendations could have been categorized as *Not changed*, *Amended*, or *Deleted*. *Not reviewed*, *Not changed* recommendations were carried forward from the previous CPG unchanged. *Not reviewed*, *Amended* recommendations were carried forward from the previous CPG with a nominal change. *Not reviewed*, *Deleted* recommendations were determined by the Work Group to not be relevant. A recommendation may not be relevant if it, for example, pertained to a topic (e.g., population, care setting, treatment) outside of the updated CPG's scope or if it was determined to be common practice.

The recommendation categories for the current CPG are noted in the Recommendations. The recommendation categories from the 2019 VA/DOD Insomnia/OSA Risk CPG are noted in Appendix C.

## D. Drafting and Finalizing the Guideline

The Work Group wrote, reviewed, and edited three drafts of the CPG using an iterative review process to solicit feedback on and make revisions to the CPG. The first and second drafts were posted online for 20 and 14 business days, respectively, for the Work Group to provide feedback. Draft 3 was made available for a 14-day peer review and comment (see External Peer Review). The Work Group reviewed all feedback submitted during each review period and made appropriate revisions to the CPG. Following the Draft 3 review and comment period, the Work Group reviewed external feedback and created a final draft of the CPG. The Champions then presented the CPG

to the VA/DOD EBPWG for approval. The Work Group considered the VA/DOD EBPWG's feedback and revised the CPG, as appropriate, to create the final version. To accompany the CPG, the Work Group produced toolkit products, including a provider summary, pocket card, and patient summary. The VA/DOD EBPWG approved the final CPG and toolkit products in January 2025.

# Appendix B: Evidence Table

**Table B-1. 2025 Insomnia/OSA Evidence Table[a,b,c,d,e,f]**

| # | Recommendation | 2019 Strength of Recommendation | Evidence | 2025 Strength of Recommendation | 2025 Recommendation Category |
|---|---|---|---|---|---|
| 1. | For screening of patients with sleep complaints, we suggest using validated screening instruments for both insomnia (e.g., Insomnia Severity Index or Athens Insomnia Scale) and obstructive sleep apnea (e.g., STOP) to identify patients who need further evaluation. | Weak for | **Additional References** (74-79) | Weak for | Not reviewed, Amended |
| 2. | For diagnosis of clinically suspected obstructive sleep apnea, we recommend diagnosis with polysomnography or home sleep apnea testing. | NA | (83-86) **Additional References** **(80-82)** | Strong for | Reviewed, New-added |
| 3. | For diagnosis of obstructive sleep apnea in appropriate patients*, we suggest home sleep apnea testing as an alternative to in-laboratory polysomnography.<br><br>*For information on individuals who may not be appropriate for HSAT, see the narrative. | Weak for | (77-81) | Weak for | Reviewed, New-replaced |

[a] 2019 CPG Recommendation # column: This indicates the recommendation number of the recommendation in the 2019 VA/DOD Insomnia/OSA Risk CPG.
[b] 2019 CPG Recommendation Text column: This contains the wording of each recommendation from the 2019 VA/DOD Insomnia/OSA CPG.
[c] 2019 CPG Strength of Recommendation column: The 2019 VA/DOD Insomnia/OSA CPG used the GRADE approach to determine the strength of each recommendation.
[d] 2019 CPG Recommendation Category column: This is the recommendation category assigned during the development of the 2019 VA/DOD Insomnia/OSA CPG. Refer to the Recommendation Categorization section for more information on the description of the categorization process and the definition of each category.
[e] 2019 CPG Recommendation Category column: This is the recommendation category assigned during the development of the 2025 VA/DOD Insomnia/OSA CPG. Refer to the Recommendation Categorization section for more information on the description of the categorization process and the definition of each category.
[f] 2019 CPG Recommendation # column: For recommendations that were carried forward to the 2019 VA/DOD Insomnia/OSA CPG, this column indicates the new recommendation(s) to which they correspond.

| # | Recommendation | 2019 Strength of Recommendation | Evidence | 2025 Strength of Recommendation | 2025 Recommendation Category |
|---|---|---|---|---|---|
| 4. | For diagnosis of patients with a non-diagnostic home sleep apnea test, we recommend further sleep testing for obstructive sleep apnea with in-lab polysomnography or HSAT. | Strong for | (81,83-86) **Additional References** (8,87-96) | Strong for | Reviewed, New-replaced |
| 5. | For treatment of chronic insomnia disorder, we recommend treatment with CBT-I. | Strong for | **(**103-106**)** **Additional References** (97-102,109,110) | Strong for | Not reviewed, Amended |
| 6. | For treatment of chronic insomnia disorder, we suggest treatment with BBT-I. | Weak for | **(**103-106**)** **Additional References** (97-102,109,110) | Weak for | Not reviewed, Amended |
| 7. | For treatment of chronic insomnia disorder, we suggest against sleep hygiene education as a stand-alone treatment. | Weak against | (111,112) | Weak against | Not reviewed, Not changed |
| 8. | For treatment of chronic insomnia disorder, we suggest CBT-I over pharmacotherapy as first-line treatment. | Weak for | (110), (114-117) | Weak for | Reviewed, Amended |

| # | Recommendation | 2019 Strength of Recommendation | Evidence | 2025 Strength of Recommendation | 2025 Recommendation Category |
|---|---|---|---|---|---|
| 9. | For treatment of chronic insomnia disorder in patients who are offered a course of pharmacotherapy, we suggest the use of one of the following agents:<br>• Daridorexant<br>• Doxepin<br>• Eszopiclone<br>• Lemborexant<br>• Suvorexant<br>• Zaleplon<br>• Zolpidem | Weak for (doxepin and non-benzodiazepine benzodiazepine receptor agonists)<br><br>Neither for nor against (suvorexant) | (118-121,124)<br>**Additional References**<br>(122,123,125-131) | Weak for | Reviewed, New-replaced |
| 10. | For treatment of chronic insomnia disorder in patients who are offered a course of pharmacotherapy, we suggest against the use of:<br>• Antipsychotic drugs<br>• Benzodiazepines<br>• Diphenhydramine<br>• Trazodone | Weak against | (124)<br>**Additional References**<br>(122,132-134,136-139,141,142) | Weak against | Reviewed, New-replaced |
| 11. | For treatment of chronic insomnia disorder in patients who are offered a course of pharmacotherapy, there is insufficient evidence to recommend for or against the use of ramelteon. | Neither for nor against | (135), (143) | Neither for nor against | Reviewed, Amended |
| 12. | For treatment of chronic insomnia disorder, we recommend against the use of kava. | Strong against | **Additional References**<br>(144,231) | Strong against | Not reviewed, Amended |
| 13. | For treatment of chronic insomnia disorder, we suggest against the use of cannabis and/or its derivatives. | NA | (146,147,149) | Weak against | Reviewed, New-added |

| # | Recommendation | 2019 Strength of Recommendation | Evidence | 2025 Strength of Recommendation | 2025 Recommendation Category |
|---|---|---|---|---|---|
| 14. | For treatment of chronic insomnia disorder, we suggest against the use of:<br>• Chamomile<br>• Melatonin<br>• Passionflower<br>• Saffron<br>• Valerian | Weak against | (150-153)<br>**Additional References**<br>(144,154) | Weak against | Reviewed, Amended |
| 15. | For treatment of chronic insomnia disorder, there is insufficient evidence to recommend for or against the use of magnesium. | NA | (155)<br>**Additional References**<br>(156) | Neither for nor against | Reviewed, New-added |
| 16. | For treatment of chronic insomnia disorder, there is insufficient evidence to recommend for or against:<br>• Aerobic exercise<br>• Mindfulness meditation<br>• Qigong<br>• Resistive exercise<br>• Tai chi<br>• Yoga | Neither for nor against | **Additional References**<br>(157-160) | Neither for nor against | Not reviewed, Amended |
| 17. | For treatment of obstructive sleep apnea, we recommend one or more of the following evidence-based therapies, depending on patient values and characteristics:<br>• Mandibular advancement devices<br>• Positive airway pressure (PAP)<br>• Referral for surgical evaluation | NA | **Additional References**<br>(161-172) | Strong for | Reviewed, New-added |

| # | Recommendation | 2019 Strength of Recommendation | Evidence | 2025 Strength of Recommendation | 2025 Recommendation Category |
|---|---|---|---|---|---|
| 18. | For treatment of mild to moderate obstructive sleep apnea (Event Index <30 per hour), we suggest either mandibular advancement devices or positive airway pressure as first line therapy options. | Weak for | (52,55,174,177,182-184) | Weak for | Reviewed, Amended |
| 19. | For treatment of newly diagnosed obstructive sleep apnea, we suggest initiating auto-titrating over fixed continuous positive airway pressure to facilitate usage. | Weak against | (185) | Weak for | Reviewed, New-replaced |
| 20. | For treatment of obstructive sleep apnea in patients with overweight or obesity, we suggest evidence-based weight management in combination with other treatments for obstructive sleep apnea. (See VA/DOD CPG on Management of Overweight and Obesity) | NA | (186,187) **Additional References** (188-190) | Weak for | Reviewed, New-added |
| 21. | For treatment of positional obstructive sleep apnea, we suggest positional therapy. | NA | (191) | Weak for | Reviewed, New-added |
| 22. | For treatment of obstructive sleep apnea in appropriate* patients (including with an apnea hypopnea index of 15 or greater per hour) who have not been successful with positive airway pressure therapy, we suggest referral for evaluation for hypoglossal nerve stimulation therapy.<br><br>*Note FDA criteria for appropriate patients in the narrative. | Weak for | (192-196,198) | Weak for | Reviewed, Amended |
| 23. | For treatment of obstructive sleep apnea in patients who cannot tolerate other recommended therapies, we suggest against oxygen therapy as a standalone treatment. | Weak against | **Additional References** (199-202) | Weak against | Not reviewed, Amended |
| 24. | For treatment of obstructive sleep apnea, we suggest against atomoxetine or a combination of atomoxetine and oxybutynin. | NA | (203,204) | Weak against | Reviewed, New-added |

| # | Recommendation | 2019 Strength of Recommendation | Evidence | 2025 Strength of Recommendation | 2025 Recommendation Category |
|---|---|---|---|---|---|
| 25. | For treatment of obstructive sleep apnea there is insufficient evidence to suggest for or against these interventions:<br>• Expiratory positive airway pressure (EPAP)<br>• Inspiratory muscle therapy<br>• Intra-oral negative airway pressure<br>• Myofunctional exercise<br>• Neuromuscular electrical stimulation<br>• Transcutaneous electrical nerve stimulation (TENS) | NA | (205-210)<br>**Additional References**<br>(211,212) | Neither for nor against | Reviewed, New-replaced |
| 26. | For treatment of obstructive sleep apnea in patients who are prescribed positive airway pressure therapy, we suggest the use of in-person or telehealth educational, behavioral, and supportive interventions to improve PAP usage. | Strong for (educational, behavioral, and supportive interventions)<br><br>Weak for (interventions to improve PAP adherence) | (215-219) | Weak for | Reviewed, New-replaced |
| 27. | For treatment of obstructive sleep apnea in appropriate patients, we suggest up to a two-week course of eszopiclone to improve positive airway pressure usage. | NA | **Additional References**<br>(220) | Weak for | Reviewed, New-added |
| 28. | For treatment of obstructive sleep apnea in patients with anatomical nasal obstruction as a barrier to positive airway pressure use, we suggest evaluation for nasal surgery. | Weak against | **Additional References**<br>(221,222,232) | Weak for | Reviewed, Not changed |

| # | Recommendation | 2019 Strength of Recommendation | Evidence | 2025 Strength of Recommendation | 2025 Recommendation Category |
|---|---|---|---|---|---|
| 29. | For treatment of obstructive sleep apnea-related residual excessive daytime sleepiness in patients who are optimally treated with sufficient therapy use, we suggest adding:<br>• Armodafinil<br>• Modafinil<br>• Solriamfetol. | NA | (223-226)<br>**Additional References**<br>(227,228) | Weak for | Reviewed, New-added |

# Appendix C: 2019 Recommendation Categorization Table

**Table C-1. 2019 VA/DOD Insomnia/OSA CPG Recommendation Categorization Table[a,b,c,d,e,f]**

| 2019 CPG Recommendation # | 2019 CPG Recommendation Text | 2019 CPG Strength of Recommendation | 2019 CPG Recommendation Category | 2025 CPG Recommendation Category | 2025 CPG Recommendation # |
|---|---|---|---|---|---|
| 1. | For patients who report sleep complaints, we suggest using the STOP questionnaire to stratify the risk of obstructive sleep apnea. | Weak for | Reviewed, New-added | Not reviewed, Amended | 1 |
| 2. | We suggest that providers assess for sleep disordered breathing in patients with a history of cardiovascular or cerebrovascular events, congestive heart, and chronic prescription opioid use. | Weak for | Reviewed, New-added | Not reviewed, Deleted | N/A |

[a] 2019 CPG Recommendation # column: This indicates the recommendation number of the recommendation in the 2019 VA/DOD Insomnia/OSA CPG.
[b] 2019 CPG Recommendation Text column: This contains the wording of each recommendation from the 2019 VA/DOD Insomnia/OSA CPG.
[c] 2019 CPG Strength of Recommendation column: The 2019 VA/DOD Insomnia/OSA CPG used the GRADE approach to determine the strength of each recommendation.
[d] 2019 CPG Recommendation Category column: This is the recommendation category assigned during the development of the 2019 VA/DOD Insomnia/OSA CPG. Refer to the Recommendation Categorization section for more information on the description of the categorization process and the definition of each category.
[ee] 2025 CPG Recommendation Category column: This is the recommendation category assigned during the development of the 2025 VA/DOD Insomnia/OSA CPG. Refer to the Recommendation Categorization section for more information on the description of the categorization process and the definition of each category.
[f] 2025 CPG Recommendation # column: For recommendations that were carried forward to the 2019 VA/DOD Insomnia/OSA CPG, this column indicates the new recommendation(s) to which they correspond.

| 2019 CPG Recommendation # | 2019 CPG Recommendation Text | 2019 CPG Strength of Recommendation | 2019 CPG Recommendation Category | 2025 CPG Recommendation Category | 2025 CPG Recommendation # |
|---|---|---|---|---|---|
| 3. | Among patients with a high pretest probability for obstructive sleep apnea, we suggest a manually-scored type III home sleep apnea test (unattended portable monitor) using an event index (i.e., respiratory disturbance index, apneahypopnea index) ≥15 events per hour to establish the diagnosis of moderate to severe obstructive sleep apnea. | Weak for | Reviewed, New-added | Reviewed, New-replaced | 3 |
| 4. | For patients with a high pretest probability for obstructive sleep apnea and a non-diagnostic home sleep apnea test (i.e., technically inadequate or apneahypopnea index <5), we recommend repeat (home sleep apnea testing or labbased polysomnography) testing for obstructive sleep apnea. | Strong for | Reviewed, New-added | Reviewed, New-replaced | 4 |
| 5. | For evaluating patients suspected of having insomnia disorder, we suggest using the Insomnia Severity Index or Athens Insomnia Scale as part of a comprehensive sleep assessment. | Weak for | Reviewed, New-added | Not reviewed, Amended | 1 |
| 6. | There is no available evidence to recommend for or against additional diagnostic testing for patients with chronic insomnia disorder who do not respond to cognitive behavioral therapy for insomnia (CBT-I) or pharmacotherapy. | Neither for nor against | Reviewed, New-added | Not reviewed, Deleted | NA |
| 7. | We recommend that patients with obstructive sleep apnea on positive airway pressure therapy use this treatment for the entirety of their sleep period(s). | Strong for | Reviewed, New-added | Not reviewed, Deleted | NA |
| 8. | We suggest continuing positive airway pressure therapy for patients with obstructive sleep apnea even if the patient is using this treatment for <4 hours per night. | Weak for | Reviewed, New-added | Not reviewed, Deleted | NA |
| 9. | In patients with obstructive sleep apnea, including those at high-risk for poor positive airway pressure adherence, such as those with posttraumatic stress disorder, anxiety, or insomnia, we recommend educational, behavioral, and supportive interventions to improve positive airway pressure adherence. | Strong for | Reviewed, New-added | Reviewed, New-replaced | 26 |

| 2019 CPG Recommendation # | 2019 CPG Recommendation Text | 2019 CPG Strength of Recommendation | 2019 CPG Recommendation Category | 2025 CPG Recommendation Category | 2025 CPG Recommendation # |
|---|---|---|---|---|---|
| 10. | We suggest that patients with obstructive sleep apnea and concurrent diagnoses/symptoms of posttraumatic stress disorder, anxiety, or insomnia be offered interventions to improve positive airway pressure adherence upon initiation of therapy. | Weak for | Reviewed, New-added | Reviewed, New-replaced | 26 |
| 11. | In appropriate patients with mild to moderate obstructive sleep apnea (apneahypopnea index <30 per hour), we suggest offering mandibular advancement devices, fabricated by a qualified dental provider, as an alternative to positive airway pressure therapy. | Weak for | Reviewed, New-added | Reviewed, Amended | 18 |
| 12. | Among patients with anatomical nasal obstruction as a barrier to positive airway pressure use, we suggest evaluation for nasal surgery. | Weak for | Reviewed, New-added | Reviewed, Not changed | 29 |
| 13. | For patients with obstructive sleep apnea with an apnea-hypopnea index of 15 – 65 per hour and a body mass index <32 kg/m2 who cannot adhere to positive airway pressure therapy, we suggest evaluation for surgical treatment with hypoglossal nerve stimulation therapy. | Weak for | Reviewed, New-added | Reviewed, Amended | 22 |
| 14. | For patients with severe obstructive sleep apnea who cannot tolerate or are not appropriate candidates for other recommended therapies, we suggest evaluation for alternative treatment with maxillomandibular advancement surgery. | Weak for | Reviewed, New-added | Not reviewed, Deleted | NA |
| 15. | For patients with obstructive sleep apnea who cannot tolerate or who have declined all other recommended treatments, we suggest offering alternative/salvage therapies. | Weak for | Reviewed, New-added | Not reviewed, Deleted | NA |
| 16. | We suggest against oxygen therapy as a standalone treatment for patients with obstructive sleep apnea who cannot tolerate other recommended therapies. | Weak against | Reviewed, New-added | Not reviewed, Amended | 23 |
| 17. | For patients without nasal congestion, we suggest against the routine use of topical nasal steroids for the sole purpose of improving positive airway pressure adherence. | Weak against | Reviewed, New-added | Not reviewed, Deleted | NA |

| 2019 CPG Recommendation # | 2019 CPG Recommendation Text | 2019 CPG Strength of Recommendation | 2019 CPG Recommendation Category | 2025 CPG Recommendation Category | 2025 CPG Recommendation # |
|---|---|---|---|---|---|
| 18. | Due to the lack of clinically significant benefit, we cannot recommend for or against:<br>• auto-titrating positive airway pressure when compared to fixed positive airway pressure, or<br>• the use of flexible pressure delivery (e.g., C-Flex®, expiratory pressure relief) to improve positive airway pressure adherence. | Weak against | Reviewed, New-added | Reviewed, New-replaced | 19 |
| 19. | We recommend offering CBT-I for the treatment of chronic insomnia disorder. | Strong for | Reviewed, New-added | Not reviewed, Amended | 5 |
| 20. | We suggest offering brief behavioral treatment for insomnia (BBT-I) for the treatment of chronic insomnia disorder. | Weak for | Reviewed, New-added | Not reviewed, Not changed | 6 |
| 21. | There is insufficient evidence to recommend for or against group versus individual CBT-I for the treatment of chronic insomnia disorder. | Neither for nor against | Reviewed, New-added | Not reviewed, Deleted | NA |
| 22. | There is insufficient evidence to recommend for or against internet-based CBT-I as an alternative to face-to-face based CBT-I for the treatment of chronic insomnia disorder. | Neither for nor against | Reviewed, New-added | Not reviewed, Deleted | NA |
| 23. | For patients diagnosed with chronic insomnia disorder, we suggest CBT-I over pharmacotherapy as first-line treatment. | Weak for | Reviewed, New-added | Reviewed, Amended | 8 |
| 24. | We suggest offering CBT-I for the treatment of chronic insomnia disorder that is comorbid with another psychiatric disorder. | Weak for | Reviewed, New-added | Not reviewed, Deleted | NA |
| 25. | There is insufficient evidence to recommend for or against mindfulness meditation for the treatment of chronic insomnia disorder. | Neither for nor against | Reviewed, New-added | Not reviewed, Deleted | NA |
| 26. | We suggest against sleep hygiene education as a standalone treatment for chronic insomnia disorder. | Weak against | Reviewed, New-added | Not reviewed, Not changed | 7 |

| 2019 CPG Recommendation # | 2019 CPG Recommendation Text | 2019 CPG Strength of Recommendation | 2019 CPG Recommendation Category | 2025 CPG Recommendation Category | 2025 CPG Recommendation # |
|---|---|---|---|---|---|
| 27. | We suggest offering auricular acupuncture with seed and pellet for the treatment of chronic insomnia disorder. | Weak for | Reviewed, New-added | Not reviewed, Deleted | NA |
| 28. | There is insufficient evidence to recommend for or against acupuncture other than auricular acupuncture with seed and pellet for the treatment of chronic insomnia disorder. | Neither for nor against | Reviewed, New-added | Not reviewed, Deleted | NA |
| 29. | There is insufficient evidence to recommend for or against aerobic exercise, resistive exercise, tai chi, yoga, and qigong for the treatment of chronic insomnia disorder. | Neither for nor against | Reviewed, New-added | Not reviewed, Amended | 16 |
| 30. | We suggest against cranial electrical stimulation for the treatment of chronic insomnia disorder. | Weak against | Reviewed, New-added | Not reviewed, Deleted | NA |
| 31. | We suggest against the use of diphenhydramine for the treatment of chronic insomnia disorder. | Weak against | Reviewed, New-added | Reviewed, New-replaced | 10 |
| 32. | We suggest against the use of melatonin for the treatment of chronic insomnia disorder. | Weak against | Reviewed, New-added | Reviewed, Amended | 14 |
| 33. | We suggest against the use of valerian and chamomile for the treatment of chronic insomnia disorder. | Weak against | Reviewed, New-added | Reviewed, Amended | 14 |
| 34. | We recommend against the use of kava for the treatment of chronic insomnia disorder. | Strong Against | Reviewed, New-added | Reviewed, Amended | 12 |
| 35. | In patients who are offered a short-course of pharmacotherapy for the treatment of chronic insomnia disorder, we suggest use of low-dose (i.e., 3 mg or 6 mg) doxepin. | Weak for | Reviewed, New-added | Reviewed, New-replaced | 9 |
| 36. | In patients who are offered a short-course of pharmacotherapy for the treatment of chronic insomnia disorder, we suggest the use of a non-benzodiazepine benzodiazepine receptor agonist. | Weak for | Reviewed, New-added | Reviewed, New-replaced | 9 |

| 2019 CPG Recommendation # | 2019 CPG Recommendation Text | 2019 CPG Strength of Recommendation | 2019 CPG Recommendation Category | 2025 CPG Recommendation Category | 2025 CPG Recommendation # |
|---|---|---|---|---|---|
| 37. | There is insufficient evidence to recommend for or against the use of ramelteon for the treatment of chronic insomnia disorder. | Neither for nor against | Reviewed, New-added | Reviewed, Amended | 11 |
| 38. | There is insufficient evidence to recommend for or against the use of suvorexant for the treatment of chronic insomnia disorder. | Neither for nor against | Reviewed, New-added | Reviewed, New-replaced | 9 |
| 39. | We suggest against the use of antipsychotic drugs for the treatment of chronic insomnia disorder. | Weak against | Reviewed, New-added | Reviewed, New-replaced | 10 |
| 40. | We suggest against the use of benzodiazepines for the treatment of chronic insomnia disorder. | Weak against | Reviewed, New-added | Reviewed, New-replaced | 10 |
| 41. | We suggest against the use of trazodone for the treatment of chronic insomnia disorder. | Weak against | Reviewed, New-added | Reviewed, New-replaced | 10 |

# Appendix D: Provider Guide to Sleep Education for Insomnia Disorder

Primary care providers are encouraged to provide patient education that includes general information on insomnia disorder, treatment goal setting, and an accurate description of behaviorally based treatments. To effectively communicate with patients about chronic insomnia disorder, providers are encouraged to become familiar with the 3 Ps Model of Insomnia(233) to understand the process by which insomnia disorder develops and why chronic insomnia disorder is driven less by what caused one's insomnia symptoms, but rather by the strategies enacted to cope with insomnia symptoms. For patients who have already initiated CBT-I and BBT-I treatments, primary care providers are encouraged to inquire about their ability to adhere to the intervention components by identifying and helping patients' problem-solve to overcome any barriers to continuing with their plan of care. Examples of these provide education and support conversations and activities are provided in the following sections.

## A. General Information on Insomnia Disorder

"I'm glad you let me know about the sleep problems you've been having. From all that you've told me; it sounds like you are suffering from insomnia disorder. Insomnia disorder can be a difficult experience. While it can impact how you feel during the day, your mood and concentration, your general health, and your enjoyment of activities, it doesn't have to. There are treatments that are effective."

"Insomnia symptoms are usually first brought on because of stressful life events, such as military training, deployment, trauma, emotional distress, or illness. During that stressful period, it is understandable that your habits may change to cope with not getting enough sleep. During this time, even thoughts and beliefs about sleep can change. But after the stressful period ends, your sleep difficulties can persist due to the coping strategies used that were unhelpful. Ironically, these unhelpful strategies turn into the cause of the ongoing insomnia. So, no matter what caused your insomnia, the solution must address the unhelpful coping strategies that cause your insomnia to persist."

**If also treating a comorbid condition:** "I want to emphasize that insomnia is not merely a symptom of another condition. Just as we are treating your (comorbid condition [e.g., pain, depression]), we should treat the insomnia as well."

**If insomnia symptoms have been of short duration:** "Although you've only been struggling with insomnia for a short while, certain strategies you've adopted to cope with insomnia can promote a chronic problem if we don't correct these unhelpful strategies. I'd like to get you started with a behavioral treatment to avoid that happening if possible."

## B. Goals of Insomnia Treatment

"Not everyone will be able to achieve, or even needs, a solid eight hours of sleep every night. Everyone is different and sleep patterns change as people age. That said, you've told me that you are struggling with (e.g., falling asleep, staying asleep, feeling rested when you wake), and you're concerned about how these issues are impacting you during the daytime. We can work together to help you sleep better and feel better during the day. What do you most hope to achieve with insomnia treatment? What would you like to change about your sleep?"

## C. Describing CBT-I and BBT-I to Patients

"CBT-I and BBT-I are primarily behavioral treatments for insomnia. There is good evidence that these are the treatments of choice for people with insomnia that has lasted a few months or longer. For example, they are more effective than if I just gave you some sleep strategies to help your sleep which we call 'sleep hygiene.' Also, the effects of CBT-I and BBT-I are longer lasting than if we treated insomnia with sleep medication, and these behavioral treatments do not have the risk of medication interactions and side effects. I also want you to know that, in the short run, sleep-inducing medications are less effective than behavioral therapies for chronic insomnia. In the long run, sleep medications seem to be even less effective than behavioral therapies, suggesting that behavioral therapies may address the underlying cause of chronic insomnia."

"In addition to including the sleep hygiene education I mentioned, CBT-I and BBT-I use multiple techniques to target factors that maintain insomnia, and they provide you with skills that will help you to regulate when you are asleep and awake. For example, a technique called 'stimulus control' will help make the bed and the bedroom stronger cues for your brain to know that it is time to be asleep. Another technique will help you figure out how much time you should spend in bed to sleep well. You may also learn skills to help you relax at bedtime and techniques to address thoughts and beliefs that interfere with your sleep. The provider will work with you to create an individualized plan to best suit your needs. What questions do you have about this? Could I set you up with an initial appointment (or provide a referral) to learn more about it?"

## D. Examples of Supporting Self-management Goals Related to the Stimulus Control and Sleep Restriction Components of CBT-I/BBT-I

**Associating bed with sleep:** "Many patients who have trouble sleeping spend a lot of time in bed hoping they fall asleep. Over time, their minds and bodies end up associating the bed with wakefulness rather than asleep. What sorts of things has (name of CBT-I or BBT-I provider) discussed with you to help you to strengthen the association between your bed and sleep? Has this been difficult for you?" (Note: Alert the CBT-I or BBT-I provider if the patient is unsure of how they are approaching this.)

**Keeping a schedule:** "I saw that Dr. (name of CBT-I or BBT-I provider) has talked with you about an earlier bedtime and when to get out of bed each day. It is important to stick to that schedule. How has this been for you? Some patients tell me it is a challenge. (Note: Alert the CBT-I or BBT-I provider if the patient is unable to stick to their prescribed sleep schedule so adjustments can be made.) Please be sure to complete your sleep diary as recommended by your healthcare provider, to allow them to get a more accurate estimate of your sleep schedule."

# Appendix E: Provider Guide to Sleep Education for Obstructive Sleep Apnea

Primary care providers are encouraged to provide patient education that includes general information on OSA, an accurate description of PAP and/or MAD therapy and setting treatment goals. In addition, primary care providers are encouraged to support adherence to the patient's OSA therapy of choice by reviewing a PAP therapy download in patients using either auto-adjusting PAP or continuous (fixed pressure) PAP, or in the case of patients using MAD therapy, inquiring about their usage of the device. Primary care providers should assess for any treatment-related side effects, identify barriers to adherence, and determine if the patient's presenting symptoms, specifically including sleepiness, are adequately addressed. Examples are provided in the following sections.

## A. General Information on Obstructive Sleep Apnea

"Obstructive sleep apnea is a very common and serious sleep disorder which affects many military personnel and Veterans. Snoring is one common symptom of sleep apnea, but not all patients with sleep apnea snore. Other common sleep apnea symptoms include pauses in breathing while asleep, trouble staying asleep, using the bathroom frequently at night, morning headaches, morning dry mouth, morning sore throat, and daytime sleepiness. If you are experiencing any of these symptoms, you may have sleep apnea."

"What defines sleep apnea is decreased breathing – either a partial (hypopnea) or complete absence of breathing (apnea) – that occurs while sleeping. During these periods of little to no breathing, oxygen levels can decrease (hypoxia) and carbon dioxide levels can increase (hypercapnia). Many serious medical consequences result from the frequent episodes of hypoxia, such as high blood pressure, heart failure, irregular heart rhythms, stroke, memory impairment, and death. Multiple awakenings during the night also lead to excessive daytime sleepiness and increased risk for motor vehicle accidents. We will need to obtain a sleep study to confirm this diagnosis. There are effective treatments for sleep apnea."

## B. Diagnosing Sleep Apnea: Sleep Studies

“There are two options for diagnosing obstructive sleep apnea: (1) a home sleep apnea test, which is only used to confirm a highly suspected case of obstructive sleep apnea, and (2) an in-lab sleep study (polysomnography), which provides more comprehensive information. Both studies measure your oxygen levels and the number of times per hour your breathing decreases or stops, which is called the apnea-hypopnea index (AHI). If you have sleep apnea symptoms and your AHI is >5 events per hour, you have sleep apnea. If a home sleep apnea test does not confirm a diagnosis of sleep apnea, then additional testing may be required.”

## C. Describing Sleep Apnea Treatment to Patients

“The primary and most efficacious treatment for obstructive sleep apnea is positive airway pressure (PAP) therapy. PAP is gentle air pressure that is delivered by a small bedside machine connected to a mask that you wear while sleeping. There are 2 types of PAP: (1) an auto-adjusting PAP (APAP), which automatically adjusts how much pressure is delivered to keep your airway open, or (2) a continuous PAP (CPAP), which delivers one set pressure (i.e., it does not vary over time). You should use PAP whenever you sleep, including naps, and for the longest possible duration. Longer use of PAP is better for your sleep and overall health.”

“For a variety of reasons, some patients may choose other treatments for obstructive sleep apnea. One alternative is a mandibular advancement device (MAD). Depending on your teeth and severity of sleep apnea, this may be a reasonable treatment. This device works by moving your lower jaw forward to open your airway and maintaining it in this position while you wear it during sleep. In order to obtain a MAD, you will need to see a dentist who is experienced in making these devices."

“There are other less common medical devices and surgeries that can be considered for treatment of your sleep apnea. However, you will need to speak with a sleep specialist to determine the appropriateness of these therapies.”

## D. Other Areas that Can Make Sleep Apnea Better or Worse

“Overall, men have a higher prevalence of sleep apnea than women. In women, post-menopausal status increases their risk of having sleep apnea. Weight loss can improve sleep apnea while weight gain can make sleep apnea worse. Avoiding sleep on your back can improve sleep apnea in some patients as sleeping on your back typically makes sleep apnea worse. Using certain substances and medications (i.e., alcohol, opioids/pain medications, sleeping medications) can make sleep apnea worse.”

## E. Addressing Sleepiness

"Sleepiness is one of the primary symptoms of sleep apnea. Patients with untreated sleep apnea are at increased risk of motor vehicle accidents and mistakes on duty or at work. If you are sleepy, you should not drive nor perform dangerous or critical tasks."

## F. Addressing Adherence to Positive Airway Pressure

The following are interventions that can help with PAP adherence:

- Provide education that includes an overview of OSA and the patient's treatment modality
- Use heated humidification to help with nasal dryness and congestion with PAP usage
- Ensure the appropriate mask choice, noting nasal masks are associated with higher adherence
- Investigate and address issues of high mask leak
- Refer to cognitive behavioral therapies that address unhelpful thoughts and/or behaviors related to sleep and sleep apnea therapy, and unhelpful behaviors related to PAP
- Encourage interventions that involve peer, caregiver, and/or other social support
- Arrange close follow-up (at least at 4-weeks, if not sooner) after PAP initiation to evaluate usage

# Appendix F: ICSD-3-TR Diagnostic Criteria(234)

## A. Chronic Insomnia Disorder

### *a. Alternate Names*

Chronic insomnia, primary insomnia, secondary insomnia, persistent insomnia, comorbid insomnia, disorder of initiating and maintaining sleep, behavioral insomnia of childhood, sleep-onset association disorder, limit-setting sleep disorder

### *b. Diagnostic Criteria*

*Criteria A-F must be met*

A. The patient reports, or the patient's parent or caregiver observes, one or more of the following:
    1. Difficulty initiating sleep
    2. Difficulty maintaining sleep
    3. Final awakening earlier than desired
    4. Resistance to going to bed on appropriate schedule
    5. Difficulty sleeping without parent or caregiver intervention

B. The patient reports, or the patient's parent or caregiver observes, one or more of the following related to the nighttime sleep difficulty:
    1. Fatigue/malaise
    2. Impaired attention, concentration, or memory
    3. Impaired social, family, occupational, or academic performance
    4. Mood disturbance/irritability
    5. Subjective daytime sleepiness
    6. Behavioral problems (e.g., hyperactivity, impulsivity, aggression)
    7. Reduced motivation/energy/initiative
    8. Proneness for errors/accidents
    9. Concerns about or dissatisfaction with sleep

C. The reported sleep/wake complaints cannot be explained purely by inadequate opportunity (i.e., time allotted for sleep) or inadequate circumstances (i.e., safety, darkness, quiet, and comfortable) for sleep

D. The sleep disturbance and associated daytime symptoms occur at least three times per week

E. The sleep disturbance and associated daytime symptoms have been present for at least three months

F. The sleep disturbance and associated daytime symptoms are not solely due to another current sleep disorder, medical disorder, mental disorder, or medication/substance use.

## B. Obstructive Sleep Apnea

### *a. Alternate Names*

OSA syndrome, sleep apnea, sleep apnea syndrome, obstructive apnea, sleep disordered breathing, obstructive sleep apnea hypopnea syndrome

### *b. Diagnostic Criteria*

((A and B) or C) + D must be met

A. The presence of one or more of the following:
    1. The patient complains of sleepiness, fatigue, insomnia, or other symptoms leading to impaired sleep-related quality of life.
    2. The patient wakes with breath holding, gasping, or choking
    3. The bed partner or other observer reports habitual snoring or breathing interruptions during the patient's sleep

B. PSG or HSAT demonstrates:
    1. Five or more predominantly obstructive respiratory events (obstructive and mixed apneas, hypopneas, or respiratory effort related arousals [RERAs]) per hour of sleep during a PSG or per hour of monitoring (HSAT)

C. PSG or HSAT demonstrates:
    1. Fifteen or more predominantly obstructive respiratory events (obstructive and mixed apneas, hypopneas, or respiratory effort related arousals [RERAs]) per hour of sleep during a PSG or per hour of monitoring (HSAT)

D. The symptoms are not better explained by another current sleep disorder, medical disorder, medication or substance use.

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See the ICSD-3-TR Diagnostic Criteria 2. American Academy of Sleep Medicine. *The International Classification of Sleep Disorders, Diagnostic and Coding Manual*. 3 ed. American Academy of Sleep Medicine; 2023., 234.
American Academy of Sleep Medicine. *The International Classification of Sleep Disorders, Diagnostic and Coding Manual.* 3 ed. American Academy of Sleep Medicine; 2014.

# Appendix G: ISI and STOP Questionnaire Scoring Criteria

## A. ISI

Subject ID: _____ Date: _____

For each question below, please circle the number corresponding most accurately to your sleep patterns in the LAST MONTH.

For the first three questions, please rate the **SEVERITY** of your sleep difficulties.

1. Difficulty falling asleep:

| None | Mild | Moderate | Severe | Very severe |
|---|---|---|---|---|
| 0 | 1 | 2 | 3 | 4 |

2. Difficulty staying asleep:

| None | Mild | Moderate | Severe | Very severe |
|---|---|---|---|---|
| 0 | 1 | 2 | 3 | 4 |

3. Problem waking up too early in the morning:

| None | Mild | Moderate | Severe | Very severe |
|---|---|---|---|---|
| 0 | 1 | 2 | 3 | 4 |

4. How **SATISFIED**/dissatisfied are you with your current sleep pattern?

| Very Satisfied | Satisfied | Neutral | Dissatisfied | Very Dissatisfied |
|---|---|---|---|---|
| 0 | 1 | 2 | 3 | 4 |

5. To what extent do you consider your sleep problem to **INTERFERE** with your daily functioning (e.g., daytime fatigue, ability to function at work/daily chores, concentration, memory, mood).

| Not at all Interfering | A Little Interfering | Somewhat Interfering | Much Interfering | Very Much Interfering |
|---|---|---|---|---|
| 0 | 1 | 2 | 3 | 4 |

6. How **NOTICEABLE** to others do you think your sleeping problem is in terms of impairing the quality of your life?

| Not at all Noticeable | A little Noticeable | Somewhat Noticeable | Much Noticeable | Very Much Noticeable |
|---|---|---|---|---|
| 0 | 1 | 2 | 3 | 4 |

7. How **WORRIED**/distressed are you about your current sleep problem?

| Not at all | A Little | Somewhat | Much | Very Much |
|---|---|---|---|---|
| 0 | 1 | 2 | 3 | 4 |

**Guidelines for Scoring/Interpretation:**

Add scores for all seven items =_____ Total score ranges from 0-28

0-7 = No clinically significant insomnia
8-14 = Subthreshold insomnia
15-21 = Clinical insomnia (moderate severity)
22-28 = Clinical insomnia (severe)

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## B. STOP Questionnaire

Height _____ inches/cm
Weight _____ lb/kg
Age _____
Male/Female
BMI _____
Collar size of shirt: S, M, L, XL, or _____ inches/cm
Neck circumference* _____ cm

1. **S**noring
   Do you **s**nore loudly (louder than talking or loud enough to be heard through closed doors)?
   Yes No

2. **T**ired
   Do you often feel **t**ired, fatigued, or sleepy during daytime?
   Yes No

3. **O**bserved
   Has anyone **o**bserved you stop breathing during your sleep?
   Yes No

4. Blood **p**ressure
   Do you have or are you being treated for high blood **p**ressure?
   Yes No

* Neck circumference is measured by staff.
*High risk of OSA:* answering yes to two or more questions
*Low risk of OSA:* answering yes to less than two questions

See the ISI and STOP Questionnaire Scoring Criteria 79. Chung F, Yegneswaran B, Liao P, et al. STOP Questionnaire: a tool to screen patients for obstructive sleep apnea. *Anesthesiology*. May 2008;108(5):812-21. doi:10.1097/ALN.0b013e31816d83e4, (221)

# Appendix H: Patient Focus Group Methods and Findings

## A. Methods

Recruitment of Patient Focus Group participants was led by VA and DOD Leadership, with support from various Insomnia/OSA Work Group members. The goal of recruitment for this Patient Focus Group was to have a group of engaging, diverse patients, who would be able to cogently explain their experience with insomnia and OSA receiving VA or DOD healthcare services. Thirteen individuals participated in the Patient Focus Group, which included five women and eight men. Eight participants had OSA as a diagnosis, one had insomnia, and four patients had a combination of insomnia and OSA. Participants were mixed in receiving care from VA or DOD. Participants received care both virtually and in person from the VA and DOD.

The VA/DOD Insomnia/OSA CPG Champions and Work Group members, with support from the Sigma Team, determined Patient Focus Group discussion topics and moderators' questions for the participants. The Sigma Team created an interview guide for Patient Focus Group meeting facilitation, to aid in the flow of the call. Input from the VA/DOD Insomnia/OSA Champions and Work Group members were incorporated into the final interview guide. Frances Murphy, MD, MPH moderated the Patient Focus Group; she engaged and encouraged participants' participation, which allowed for continuous flow of discussion between the participants. Due to this, not all the questions that are included in the Moderators Guide for Insomnia/OSA Patient Focus Group were addressed, but between the moderator encouraging conversation and the participants utilizing the Zoom for Government chat space, most topics were covered. Multiple notetakers attended the call and supported the management of the Patient Focus Group.

## B. Patient Focus Group Findings

### *a. Participants discussed the value of having a multi-disciplinary team approach for their treatment plan.*

- Participants would like their care to be more team-based and include all providers who play a role in their treatment plan, including dental providers.

### *b. Participants with insomnia/OSA emphasized the importance of providers sharing and discussing different treatment options.*

- Participants wanted their providers to discuss the likelihood of each treatment helping and meeting their needs.
- Participants desired the ability to switch between treatments to find the most effective options.

### *c. Participants discussed the need for offering education to providers about insomnia/OSA.*

- Providers must increase their awareness of insomnia and OSA.

- Participants discussed that a range of sleep resources are needed for primary care providers.

***d. Participants emphasized the impact that insomnia/OSA has on their quality of life and daily activities.***

- Participants reported an improvement in quality of life due to their treatments.
- Participants discussed alternative activities they do to contribute to an improved quality of life.
- Participants explained the limitations they continue to face as a result of insomnia/OSA related to their treatments.

***e. Participants value effective patient-provider communication, self-advocacy, and coordination of care.***

- Participants valued clear and concise communication by providers.
- Participants expressed the need for self-advocacy when discussing treatment needs with providers and partnering with providers to choose treatment options.

***f. Participants discussed the value of family and social support during treatment.***

- Participants valued the engagement of their support network in their treatment.
- Participants expressed the negative impact that insomnia/OSA had on their family members and loved ones

# Appendix I: Participant List

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# Appendix J: Literature Review Search Terms and Strategy

## A. Topic-specific Search Terms

The search strategies employed combinations of free-text keywords as well as controlled vocabulary terms including (but not limited to) the following concepts. Strategies for each bibliographic database follow this table.

**Table K-1. Key Question Specific Concept Tables for Populations, PubMed and EMBASE**

| Concept | Thesaurus Term | Keywords |
|---|---|---|
| **Population** | | |
| **KQ1, KQ4, KQ8, KQ10 Insomnia**<br><br>**KQ 11 Suspected Insomnia** | **Embase (EMTREE)**<br>insomnia<br><br>**PubMed (Mesh)**<br>sleep initiation and maintenance disorders<br><br>**PsycINFO**<br>insomnia | insomnia |
| **KQ2, KQ3, KQ6, KQ7, KQ12 Obstructive Sleep Apnea**<br><br>**KQ9 Suspected Sleep Apnea** | **Embase (EMTREE)**<br>obstructive sleep apnea<br><br>**PubMed (Mesh)**<br>sleep apnea, obstructive<br><br>**PsycINFO**<br>sleep apnea | obstructive-sleep-apnea |
| **KQ5 Comorbid Insomnia and Sleep Apnea** | **Embase (EMTREE)**<br>comorbidity<br>insomnia<br>obstructive sleep apnea<br><br>**PubMed (MeSH)**<br>comorbidity<br>sleep apnea, obstructive<br>sleep initiation and maintenance disorders | co-occur*<br>comorbid*<br>insomnia<br>obstructive-sleep-apnea<br><br>*Word variations searched |
| **KQ6 Hypersomnia** | **Embase (EMTREE)**<br>hypersomnia<br><br>**PubMed (MeSH)**<br>Disorders of excessive somnolence | excessive-somnolence<br>hypersomnia<br>residual-daytime-sleepiness |
| **KQ11 Sleep complaints** | **Embase (EMTREE)**<br>insomnia<br><br>**PsycINFO**<br>insomnia | insomnia |

**Table K-2. Key Question Specific Concept Table for Interventions, PubMed and EMBASE**

| Concept | Thesaurus Term | Keywords |
|---|---|---|
| **Interventions** | | |
| **KQ1**<br>**Pharmacotherapy for insomnia** | | daridorexant<br>lemborexant<br>suvorexant<br>eszopiclone<br>zaleplon<br>zolpidem<br>alprazolam<br>clonazepam<br>diazepam<br>estazolam<br>flurazepam<br>gabapentin<br>lorazepam<br>oxazepam<br>quazepam<br>temazepam<br>triazolam<br>ramelteon<br>amitriptyline<br>doxepin<br>mirtazapine<br>paroxetine<br>trazodone<br>diphenhydramine<br>hydroxyzine<br>doxylamine<br>l-tryptophan<br>melatonin<br>valerian<br>quetiapine |
| **KQ1**<br>**CBT-I for insomnia** | **Embase (EMTREE)**<br>cognitive behavioral therapy<br><br>**PubMed (Mesh)**<br>cognitive behavioral therapy | CBT-I<br>cognitive-behavioral-therapy-insomnia |
| **KQ2**<br>**Interventions for OSA** | **Embase (EMTREE)**<br>body weight loss<br>occlusant splint<br>oxygen<br>weight loss programs<br><br>**PubMed (MeSH)** | EPAP<br>expiratory-positive-airway-pressure<br>excite-OSA<br>exercise-therapy<br>iNAP<br>mandibular-device*<br>mouth-tap* |

| Concept | Thesaurus Term | Keywords |
|---|---|---|
| **Interventions** | | |
| | exercise therapy<br>occlusal splints<br>oxygen<br>weight loss<br>weight reduction programs | myofunctional-treatment*<br>oral-appliance-therapy<br>oxygen<br>PAP<br>positive-airway-pressure<br>positional -therap*<br>tongue-retaining -device*<br>weight-loss<br>winx<br>ultepap<br><br>*Word variations searched |
| **KQ2**<br>**Pharmacotherapy for OSA** | | atomoxetine<br>desipramine<br>reboxetine<br>(atomoxetine and fesoterodine)<br>(atomoxetine and oxybutynin)<br>(atomoxetine and r-oxybutynin)<br>(duloxetine and oxybutynin)<br>(milnacipran and oxybutynin)<br>(reboxetine and hyoscine butylbromide)<br>(reboxetine and oxybutynin) |
| **KQ3**<br>**CPAP for OSA** | **Embase (EMTREE)**<br>automatic positive airway pressure<br>bilevel positive airway pressure<br>BiPAP device<br>continuous positive airway pressure<br>CPAP device<br>expiratory positive airway pressure<br>positive end expiratory pressure ventilation<br>positive pressure respiration<br><br>**PubMed (Mesh)**<br>continuous positive airway pressure<br>positive airway pressure | BPAP<br>BIPAP<br>CPAP<br>positive-airway-pressure<br>positive-end-expiratory-pressure<br>positive-pressure-respiration |
| **KQ3** | **Embase (EMTREE)**<br>orthodontic device | dental-appliance*<br>mandibular-advancement device* |

| Concept | Thesaurus Term | Keywords |
|---|---|---|
| **Interventions** | | |
| **Dental/oral appliances for OSA** | **PubMed (Mesh)**<br>orthodontic appliances, removable | occlusal-splint*<br>oral-appliance*<br>orthodontic-appliance*<br>orthodontic-device* |
| **KQ4 Pharmacotherapy for insomnia** | | daridorexant<br>lemborexant<br>suvorexant<br>eszopiclone<br>zaleplon<br>zolpidem<br>alprazolam<br>clonazepam<br>diazepam<br>estazolam<br>flurazepam<br>gabapentin<br>hydroxyzine<br>lorazepam<br>oxazepam<br>quazepam<br>temazepam<br>triazolam<br>ramelteon<br>amitriptyline<br>doxepin<br>mirtazapine<br>paroxetine<br>trazodone<br>diphenhydramine<br>doxylamine<br>l-tryptophan<br>valerian<br>quetiapine |
| **KQ5 (List also for KQ7) Pharmacotherapy for OSA with insomnia** | | eszopiclone<br>zaleplon<br>zolpidem<br>daridorexant<br>gabapentin<br>hydroxyzine<br>lemborexant<br>suvorexant |

| Concept | Thesaurus Term | Keywords |
|---|---|---|
| **Interventions** | | |
| | | doxepin<br>trazodone<br>ramelteon |
| **KQ6**<br>**Pharmacotherapy for Hypersomnia (OSA)** | | armodafinil<br>methylphenidate<br>modafinil<br>solriamfetol<br>pitolisant<br>sodium-oxybate |
| **KQ7**<br>**CPAP adherence**<br>**Include list of pharmacotherapies from KQ5** | **Embase (EMTREE)**<br>automatic positive airway pressure<br>cognitive behavioral therapy<br>orthodontic device<br>psychotherapy<br><br>**PubMed (Mesh)**<br>cognitive behavioral therapy<br>psychotherapy<br>orthodontic appliances, removal<br>nasal surgical procedures<br><br>**PsycINFO**<br>cognitive behavioral therapy | apps**<br>automatic-positive-airway-pressure***<br>behavioral-therap*<br>continuous-positive-airway-pressure<br>cognitive-behavior-therapy<br>dental-devices<br>education<br>expiratory-pressure-relief<br>group-intervention*<br>mask*<br>motivational-therap*<br>nasal-surger*<br>oral appliance*<br>psychotherapy<br>remote-cpap-monitoring<br>remote<br>sinus-surger*<br>SMS**<br>text**<br>titrated-continuous positive-airway-pressure***<br>web**<br><br>eszopiclone<br>zaleplon<br>zolpidem<br>daridorexant<br>gabapentin<br>hydroxyzine<br>lemborexant<br>suvorexant<br>doxepin<br>trazodone |

| Concept | Thesaurus Term | Keywords |
|---|---|---|
| **Interventions** | | |
| | | ramelteon<br><br>*Word variations searched<br>** These terms will be searched near remote<br>***These terms will be searched in conjunction |
| **KQ8**<br>**Herbal supplements for insomnia** | | herbal-medicine<br>ashwagandha<br>cannabis<br>cannabidiol<br>chamomile<br>ginger<br>glycine<br>i-tryptophan<br>lavender and oral<br>magnesium<br>sage-supplement*<br>spearmint<br>tart-cherry<br>5-htp<br>5-hydroxytryptophan<br>gabapentin<br>gamma-aminobutyric acid<br>l-theanine<br>melatonin<br>passion-flower<br>reishi-mushroom<br>Ganoderma-lucidum<br>tetrahydrocannabinol<br>delta-8-THC<br>delta-9-THC<br>valerian-root |
| **KQ9**<br>**Home testing for OSA** | **Embase (EMTREE)**<br>polysomnography<br>sleep study<br><br>**PubMed (Mesh)**<br>polysomnography | IN HOME<br>home-sleep-test*<br>peripheral-arterial-technology<br>wearable-technolog*<br>IN-LAB<br>polysomnogra*<br>sleep lab*<br>sleep stud* |
| **KQ10** | **Embase (EMTREE)** | behavior*-intervention* |

| Concept | Thesaurus Term | Keywords |
|---|---|---|
| **Interventions** | | |
| **Behavioral Treatments for insomnia** | cognitive behavioral therapy<br><br>**PubMed (Mesh)**<br>cognitive behavioral therapy<br><br>**PsycINFO**<br>cognitive behavioral therapy | behavior*-treatment*<br>CBT-I<br>cognitive-behavioral-therapy-insomnia<br>delivery **<br>group **<br>individual **<br>internet **<br>on-line course **<br>phone **<br>telehealth **<br>workbook **<br><br>** These terms will be searched near therapies. |
| **KQ11 Screening Questionnaires for insomnia** | **Embase (EMTREE)**<br>questionnaire<br><br>**PubMed (Mesh)**<br>surveys and questionnaires<br><br>**PsycINFO**<br>psychodiagnostic Interview questionnaires | clinical interview*<br>questionnaire*<br><br>*Variations of these terms will be searched |
| **KQ12 Hypoglossal nerve stimulation for OSA** | | hypoglossal nerve stimulat* |
| **KQ1, KQ3, KQ9, KQ11**<br>**Comparative Effectiveness** | **Embase**<br>comparative effectiveness<br><br>**PubMed**<br>comparative effectiveness research<br>pragmatic clinical trial" | comparative effectiveness<br>head-to-head-study<br>pragmatic clinical trial" |

## B. Search Strategies

**Table K-3. Embase**

| Set # | Description | Strategy |
|---|---|---|
| **#1** | Insomnia | 'insomnia'/exp OR insomnia:ti,ab |
| **#2** | Pharmacotherapy | daridorexant:ti,ab OR lemborexant:ti,ab OR suvorexant:ti,ab OR eszopiclone:ti,ab OR zaleplon:ti,ab OR zolpidem:ti,ab OR alprazolam:ti,ab OR clonazepam:ti,ab OR diazepam:ti,ab OR estazolam:ti,ab OR flurazepam:ti,ab OR lorazepam:ti,ab OR oxazepam:ti,ab OR quazepam:ti,ab OR temazepam:ti,ab OR triazolam:ti,ab OR rameleteon:ti,ab OR amitriptyline:ti,ab OR doxepin:ti,ab OR mirtazapine:ti,ab OR paroxetine:ti,ab OR trazodone:ti,ab OR diphenhydramine:ti,ab OR doxylamine:ti,ab OR 'l tryptophan':ti,ab OR melatonin:ti,ab OR valerian:ti,ab OR gabapentin:ti,ab OR hydroxyzine:ti,ab OR quetiapine:ti,ab |
| **#3** | Cognitive Behavioral Therapy | 'cognitive behavioral therapy'/exp OR 'cognitive behavioral therapy insomnia':ti,ab OR 'cbt i':ti,ab |
| **#4** | Combine Sets | #1 AND #2 AND #3 |
| **#5** | Obstructive Sleep Apnea | 'obstructive sleep apnea'/exp OR 'obstructive sleep apnea':ti,ab |
| **#6** | Interventions | 'body weight loss'/exp OR 'occlusal splint'/exp OR 'oxygen'/exp OR 'weight loss programs'/exp OR epap:ti,ab OR 'expiratory positive airway pressure':ti,ab OR 'excite osa':ti,ab OR 'exercise therapy':ti,ab OR 'inap':ti,ab OR 'mandibular device*':ti,ab OR 'mouth tap*':ti,ab OR 'myofunctional treatment*':ti,ab OR 'oral-appliance':ti,ab OR oxygen:ti,ab OR pap:ti,ab OR 'positive airway pressure':ti,ab OR 'positional therap*':ti,ab OR 'tongue retaining device':ti,ab OR ultepap:ti,ab OR 'weight loss':ti,ab OR winx:ti,ab |
| **#7** | Pharmacotherapy | atomoxetine:ti,ab OR desipramine:ti,ab OR reboxetine:ti,ab OR (atomoxetine:ti,ab AND fesoterodine:ti,ab) OR (atomoxetine:ti,ab AND oxybutynin:ti,ab) OR (atomoxetine:ti,ab AND 'r oxybutynin':ti,ab) OR (duloxetine:ti,ab AND oxybutynin:ti,ab) OR (milnacipran:ti,ab AND oxybutynin:ti,ab) OR (reboxetine:ti,ab AND 'hyoscine butylbromide:ti,ab') OR (reboxetine:ti,ab AND oxybutynin:ti,ab) |
| **#8** | Combine Sets | #5 AND (#6 OR #7) |
| **#9** | Obstructive Sleep Apnea | 'obstructive sleep apnea'/exp OR 'obstructive sleep apnea':ti,ab |
| **#10** | CPAP | 'automatic positive airway pressure'/exp OR 'bilevel positive airway pressure'/exp OR 'continuous positive airway pressure'/exp OR 'expiratory positive airway pressure'/exp OR 'positive end expiratory pressure ventilation'/exp OR 'positive pressure respiration'/exp OR apap:ti,ab OR bpap:ti,ab OR bipap:ti,ab OR cpap:ti,ab OR 'positive airway pressure':ti,ab OR 'positive end expiratory pressure':ti,ab OR 'positive pressure respiration':ti,ab |

| Set # | Description | Strategy |
|---|---|---|
| **#11** | Dental Devices | 'orthodontic device'/exp OR 'dental appliance*':ti,ab OR 'mandibular advancement device*':ti,ab OR 'occlusal splint*':ti,ab OR 'oral appliance*':ti,ab OR 'orthodontic appliance*':ti,ab OR 'orthodontic device*':ti,ab |
| **#12** | Combine Sets | #9 AND #10 AND #11 |
| **#13** | Insomnia | 'insomnia'/exp OR insomnia:ti,ab |
| **#14** | Pharmacotherapy | daridorexant:ti,ab OR lemborexant:ti,ab OR suvorexant:ti,ab OR eszopiclone:ti,ab OR zaleplon:ti,ab OR zolpidem:ti,ab OR alprazolam:ti,ab OR clonazepam:ti,ab OR diazepam:ti,ab OR estazolam:ti,ab OR flurazepam:ti,ab OR lorazepam:ti,ab OR oxazepam:ti,ab OR quazepam:ti,ab OR temazepam:ti,ab OR triazolam:ti,ab OR ramelteon:ti,ab OR amitriptyline:ti,ab OR doxepin:ti,ab OR mirtazapine:ti,ab OR paroxetine:ti,ab OR trazodone:ti,ab OR diphenhydramine:ti,ab OR doxylamine:ti,ab OR 'l tryptophan':ti,ab OR valerian:ti,ab OR gabapentin:ti,ab OR hydroxyzine:ti,ab OR quetiapine:ti,ab |
| **#15** | Combine Sets | #13 AND #14 |
| **#16** | Comorbid Insomnia and OSA | ('obstructive sleep apnea'/exp OR 'obstructive sleep apnea':ti,ab) AND ('insomnia'/exp OR insomnia:ti,ab) |
| **#17** | Comorbid Insomnia and OSA | 'comorbidity'/exp OR comorbid*:ti,ab OR 'co occur*':ti,ab |
| **#18** | Combine Sets | #16 AND #17 |
| **#19** | Pharmacology | eszopiclone:ti,ab OR zaleplon:ti,ab OR zolpidem:ti,ab OR daridorexant:ti,ab OR gabapentin:ti,ab OR hydroxyaine:ti,ab OR lemborexant:ti,ab OR suvorexant:ti,ab OR doxepin:ti,ab OR trazodone:ti,ab OR ramelteon:ti,ab |
| **#20** | Combine Sets | #18 AND #19 |
| **#21** | Obstructive Sleep Apnea | 'obstructive sleep apnea'/exp OR 'obstructive sleep apnea':ti,ab |
| **#22** | Hypersomnia | 'hypersomnia'/exp OR 'excessive somnolence':ti,ab OR hypersomnia:ti,ab OR 'residual daytime sleepiness':ti,ab |
| **#23** | Pharmacology | armodafinil:ti,ab OR methylphenidate:ti,ab OR modafinil:ti,ab OR solriamfetol:ti,ab OR pitolisant:ti,ab OR 'sodium oxybate':ti,ab |
| **#24** | Combine Sets | #21 AND #22 AND #23 |
| **#25** | Obstructive Sleep Apnea | 'obstructive sleep apnea'/exp OR 'obstructive sleep apnea':ti,ab |

| Set # | Description | Strategy |
|---|---|---|
| **#26** | CPAP | 'automatic positive airway pressure'/exp OR 'bilevel positive airway pressure'/exp OR 'continuous positive airway pressure'/exp OR 'expiratory positive airway pressure'/exp OR 'positive end expiratory pressure ventilation'/exp OR 'positive pressure respiration'/exp OR apap:ti,ab OR bpap:ti,ab OR bipap:ti,ab OR cpap:ti,ab OR 'positive airway pressure':ti,ab OR 'positive end expiratory pressure':ti,ab OR 'positive pressure respiration':ti,ab |
| **#27** | Pharmacology | eszopiclone:ti,ab OR zaleplon:ti,ab OR zolpidem:ti,ab OR daridorexant:ti,ab OR gabapentin:ti,ab OR hydroxyaine:ti,ab OR lemborexant:ti,ab OR suvorexant:ti,ab OR doxepin:ti,ab OR trazodone:ti,ab OR ramelteon:ti,ab |
| **#28** | Interventions | 'cognitive behavioral therapy'/exp OR 'orthodontic device'/exp OR 'psychotherapy'/exp OR apps:ti,ab OR 'behavioral therap*':ti,ab OR 'cognitive behavior therapy':ti,ab OR 'dental devices':ti,ab OR education:ti,ab OR 'expiratory pressure relief':ti,ab OR 'group intervention*':ti,ab OR mask*:ti,ab OR 'motivational therap*':ti,ab OR 'nasal surger*':ti,ab OR 'oral appliance*':ti,ab OR psychotherapy:ti,ab OR 'remote cpap monitoring':ti,ab OR 'sinus surger*':ti,ab OR (titrat* NEAR/5 pressure) OR (support NEAR/5 (text OR sms OR internet OR web)) |
| **#29** | | #27 OR #28 |
| **#30** | Combine Sets | #25 AND #26 AND #29 |
| **#31** | Insomnia | 'insomnia'/exp OR insomnia:ti,ab |
| **#32** | Herbal Medicines | 'herbal medicine':ti,ab OR ashwagandha:ti,ab OR cannabis:ti,ab OR cannabidiol:ti,ab OR cbd:ti,ab OR chamomile:ti,ab OR glycine:ti,ab OR 'i tryptophan':ti,ab OR (lavender:ti,ab AND oral:ti,ab) OR magnesium:ti,ab OR 'tart cherry':ti,ab OR '5 htp':ti,ab OR '5 hydroxytryptophan':ti,ab OR gaba:ti,ab OR 'gamma amniobutyric acid':ti,ab OR 'l theanine':ti,ab OR melatonin:ti,ab OR 'passion flower':ti,ab OR 'reishi mushroom':ti,ab OR tetrahydrocannabinol:ti,ab OR 'delta 8 thc':ti,ab OR 'delta 9 thc':ti,ab OR 'valerian root':ti,ab |
| **#33** | Combine Sets | #31 AND #32 |
| **#34** | Obstructive Sleep Apnea | 'obstructive sleep apnea'/exp OR 'obstructive sleep apnea':ti,ab |
| **#35** | Home Sleep Testing | (home NEAR/3 ('sleep test*' OR 'sleep study')) OR 'peripheral arterial technology':ti,ab OR 'wearable technolog*':ti,ab |
| **#36** | Lab Sleep Studies | 'polysomnography'/exp OR 'sleep study'/exp OR polysomnogra*:ti,ab OR 'sleep lab':ti,ab OR 'sleep study':ti,ab |
| **#37** | Combine Sets | #34 AND #35 AND #36 |
| **#38** | Insomnia | 'insomnia'/exp OR insomnia:ti,ab |

| Set # | Description | Strategy |
|---|---|---|
| **#39** | Delivery of Behavioral Treatments | ('behavior* intervention*' OR behavior*treatment* OR 'cbt i' OR 'cognitive behavioral therapy insomnia') NEAR/5 (delivery OR individual OR group OR telehealth OR internet OR 'on-line course' OR phone OR workbook*) |
| **#40** | Combine Sets | #38 AND #39 |
| **#41** | Insomnia | 'insomnia'/exp OR insomnia:ti,ab |
| **#42** | Questionnaire/Interview | 'questionnaire'/exp OR questionnaire:ti,ab OR 'clinical interview*':ti,ab OR 'psychodiagnostic interview*':ti,ab |
| **#43** | Combine Sets | #41 AND #42 |
| **#44** | Obstructive Sleep Apnea | 'obstructive sleep apnea'/exp OR 'obstructive sleep apnea':ti,ab |
| **#45** | Hypoglossal Nerve Stimulator | 'hypoglossal nerve stimulator'/exp OR 'hypoglossal nerve stimulat*':ti,ab |
| **#46** | Combine Sets | #44 AND #45 |
| **#47** | Combine Sets | #4 OR #12 |
| **#48** | CER | 'comparative effectiveness'/exp OR (comparative NEAR/3 effectiveness) OR 'pragmatic randomized controlled trial*':ti,ab OR 'head-to-head study':ti,ab |
| **#49** | Combine Sets | #47 AND #48 |
| **#50** | Combine Sets | #8 OR #15 OR #20 OR #24 OR #30 OR #33 OR #40 OR #46 |
| **#51** | Study Design | 'systematic review'/exp OR 'systematic review':ti,ab OR 'meta analysis'/exp OR 'meta analysis':ti,ab OR 'randomized controlled trial'/exp OR 'randomization'/de OR 'double blind procedure'/de OR 'single blind procedure'/de OR 'placebo'/de OR 'crossover procedure'/de OR placebo* OR random*:de,ti OR crossover* OR 'cross over' OR ((singl* OR doubl* OR tripl* OR trebl*) NEAR/3 (blind* OR mask* OR sham*)) OR 'latin square' OR isrtcn* OR actrn* OR (nct* NOT nct) |
| **#52** | Combine Sets | #50 AND #51 |
| **#53** | Combine Sets | #37 OR #43 |

| Set # | Description | Strategy |
|---|---|---|
| **#54** | Exclude Study Designs | 'editorial'/exp OR 'letter'/exp OR 'medical illustration'/exp OR 'book'/exp OR 'poster'/exp OR 'conference abstract'/exp OR 'conference paper'/exp OR 'conferences and congresses'/exp OR 'conference review'/exp OR 'erratum'/exp OR 'symposium'/exp OR 'short survey'/exp OR 'note'/exp OR 'chapter'/it OR 'conference abstract'/it OR 'conference paper'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it OR abstract:nc OR annual:nc OR conference:nc OR 'conference proceeding':pt OR 'conference review':it OR congress:nc OR meeting:nc OR sessions:nc OR symposium:nc OR [conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [editorial]/lim OR [letter]/lim OR [note]/lim OR [short survey]/lim OR comment:ti OR book:pt OR comment:ab,ti OR annual:ab,ti OR 'conference proceeding':ab,ti OR note:ab,ti OR meeting:ab,ti OR sessions:ab,ti OR 'short survey':ab,ti OR animal:ab,ti OR rat:ab,ti OR rats:ab,ti OR mouse:ab,ti OR mice:ab,ti OR goat:ab,ti OR goats:ab,ti OR pig:ab,ti OR pigs:ab,ti OR cadaver:ab,ti OR dog:ab,ti OR dogs:ab,ti OR monkey:ab,ti OR monkeys:ab,ti OR ape:ab,ti OR apes:ab,ti |
| **#55** | Combine Sets | #53 NOT #54 |
| **#56** | Combine Sets | #49 OR #52 OR #55 |
| **#57** | Exclude Pediatric | adolescen*:ti,ab OR babies:ti,ab OR baby:ti,ab OR boy*:ti,ab OR child*:ti,ab OR girl* OR infan*:ti,ab OR juvenile:ti,ab OR neonat*:ti,ab OR newborn*:ti,ab OR nicu:ti,ab OR nurser*:ti,ab OR paediatric*:ti,ab OR pediatric*:ti,ab OR preschool:ti,ab OR pubesc*:ti,ab OR pubert*:ti,ab OR 'school age*':ti OR schoolchildren:ti,ab OR teen*:ti,ab OR toddler*:ti,ab OR young*:ti,ab OR youth*:ti,ab |
| **#58** | | #56 NOT #57 |
| **#59** | | #58 AND [humans]/lim AND [english]/lim AND [2018-2024]/py |

**Table K-3. PubMed**

| Set # | Description | Strategy |
|---|---|---|
| | Filters | Humans, English, from 2018/5/17-2024 |
| **#1** | Insomnia | "sleep initiation maintenance disorders"[mesh] OR insomnia[tiab] |

| Set # | Description | Strategy |
|---|---|---|
| **#2** | Pharmacology | daridorexant[tiab] OR lemborexant[tiab] OR suvorexant[tiab] OR eszopiclone[tiab] OR zaleplon[tiab] OR zolpidem[tiab] OR alprazolam[tiab] OR clonazepam[tiab] OR diazepam[tiab] OR estazolam[tiab] OR flurazepam[tiab] OR lorazepam[tiab] OR oxazepam[tiab] OR quazepam[tiab] OR temazepam[tiab] OR triazolam[tiab] OR ramelteon[tiab] OR amitriptyline[tiab] OR doxepin[tiab] OR mirtazapine[tiab] OR paroxetine[tiab] OR trazodone[tiab] OR diphenhydramine[tiab] OR doxylamine[tiab] OR "l tryptophan"[tiab] OR melatonin[tiab] OR valerian[tiab] OR hydroxyzine[tiab] OR gabapentine[tiab] OR quetiapine[tiab] |
| **#3** | Cognitive Behavioral Therapy | "Cognitive Behavioral Therapy"[Mesh] OR "cognitive behavioral therapy insomnia"[tiab] OR "cbt i"[tiab] |
| **#4** | Combine Sets | #1 AND #2 AND #3 |
| **#5** | Combine Sets | #1 AND #2 |
| **#6** | Herbal Medicine | "herbal medicine"[tiab] OR ashwagandha[tiab] OR cannabis[tiab] OR cannabidiol[tiab] OR cbd[tiab] OR chamomile[tiab] OR glycine[tiab] OR "i tryptophan"[tiab] OR (lavender[tiab] AND oral[tiab]) OR magnesium[tiab] OR "tart cherry"[tiab] OR "5 htp"[tiab] OR "5 hydroxytryptophan"[tiab] OR gaba[tiab] OR "gamma amniobutyric acid"[tiab] OR "l theanine"[tiab] OR melatonin[tiab] OR "passion flower"[tiab] OR "reishi mushroom"[tiab] OR tetrahydrocannabinol[tiab] OR "delta 8 thc"[tiab] OR "delta 9 thc"[tiab] OR "valerian root"[tiab] |
| **#7** | | #1 AND #6 |
| **#8** | Delivery of Behavioral Health Treatments | ("Cognitive Behavioral Therapy"[Mesh] OR "behavior* intervention*"[tiab] OR behavior*treatment*[tiab] OR "cbt i"[tiab] OR "cognitive behavioral therapy insomnia"[tiab]) AND (delivery[tiab] OR individual[tiab] OR group[tiab] OR telehealth[tiab] OR internet[tiab] OR "on-line course"[tiab] OR phone[tiab] OR workbook*[tiab]) |
| **#9** | | #1 AND #8 |
| **#10** | Questionnaires | "Surveys and Questionnaires"[Mesh] OR questionnaire[tiab] OR "clinical interview*"[tiab] OR "psychodiagnostic interview*"[tiab] |

| Set # | Description | Strategy |
|---|---|---|
| **#11** | Combine Sets | #1 AND #10 |
| **#12** | | "Sleep Apnea, Obstructive"[Mesh] OR "obstructive sleep apnea"[tiab] |
| **#13** | Interventions | "Orthodontic Appliances, Removable"[Mesh] OR "Oxygen"[Mesh] OR "Weight Reduction Programs"[Mesh]OR epap[tiab] OR "expiratory positive airway pressure"[tiab] OR "excite osa"[tiab] OR "exercise therapy"[tiab] OR "inap"[tiab] OR "mandibular device*"[tiab] OR "mouth tap*"[tiab] OR "myofunctional treatment*"[tiab] OR "oral appliance"[tiab] OR oxygen[tiab] OR pap[tiab] OR "positive airway pressure"[tiab] OR "positional therap*"[tiab] OR "weight loss"[tiab] OR winx[tiab] OR "tongue retaining device"[tiab] OR "oral appliance*"[tiab] OR ultepap[tiab] |
| **#14** | Pharmacology | atomoxetine[tiab] OR desipramine[tiab] OR reboxetine[tiab] OR (atomoxetine[tiab] AND fesoterodine[tiab]) OR (atomoxetine[tiab] AND oxybutynin[tiab]) OR (atomoxetine[tiab] AND 'r oxybutynin'[tiab]) OR (duloxetine[tiab] AND oxybutynin[tiab]) OR (milnacipran[tiab] AND oxybutynin[tiab]) OR (reboxetine[tiab] AND 'hyoscine butylbromide[tiab]') OR (reboxetine[tiab] AND oxybutynin[tiab]) |
| **#15** | Combine Sets | #12 AND (#13 OR #14) |
| **#16** | CPAP | "Continuous Positive Airway Pressure"[Mesh] OR apap[tiab] OR bpap[tiab] OR bipap[tiab] OR cpap[tiab] OR "positive airway pressure"[tiab] OR "positive end expiratory pressure"[tiab] OR "positive pressure respiration"[tiab] |
| **#17** | Dental Devices | "Orthodontic Appliances, Removable"[Mesh]OR "dental appliance*"[tiab] OR "mandibular advancement device*"[tiab] OR "occlusal splint*"[tiab] OR "orthodontic appliance*"[tiab] OR "oral appliance*"[tiab] OR "orthodontic device*"[tiab] |
| **#18** | Combine Sets | #12 AND #16 AND #17 |
| **#19** | Hypersomnia | "Disorders of Excessive Somnolence"[Mesh]OR "excessive somnolence"[tiab] OR hypersomnia[tiab] OR "residual daytime sleepiness"[tiab] |

| Set # | Description | Strategy |
|---|---|---|
| **#20** | Pharmacology | armodafinil[tiab] OR methylphenidate[tiab] OR modafinil[tiab] OR solriamfetol[tiab] OR pitolisant[tiab] OR "sodium oxybate"[tiab] |
| **#21** | Combine Sets | #12 AND #19 AND #20 |
| **#22** | Interventions | "Cognitive Behavioral Therapy"[Mesh]OR "Orthodontic Appliances, Removable"[Mesh]OR "Psychotherapy"[Mesh]OR "behavioral therap*"[tiab] OR class*[tiab] OR "cognitive behavior therapy"[tiab] OR "dental devices"[tiab] OR education[tiab] OR "expiratory pressure relief"[tiab] OR "group intervention*"[tiab] OR mask*[tiab] OR "motivational therap*"[tiab] OR "nasal surger*"[tiab] OR psychotherapy[tiab] OR "remote cpap monitoring"[tiab] OR "sinus surger*"[tiab] OR (titrat*[tiab] AND pressure[tiab]) OR (support[tiab] AND (text[tiab] OR sms[tiab] OR internet[tiab] OR web[tiab])) |
| **#23** | Pharmacology | eszopiclone[tiab] OR zaleplon[tiab] OR zolpidem[tiab] OR daridorexant[tiab] OR gabapentin[tiab] OR hydroxyzine[tiab] OR lemborexant[tiab] OR suvorexant[tiab] OR doxepin[tiab] OR trazodone[tiab] OR ramelteon[tiab] |
| **#24** | Combine Sets | #22 OR #23 |
| **#25** | Combine Sets | #12 AND #16 AND #24 |
| **#26** | Home Sleep Tests | (home[tiab] AND ("sleep test*"[tiab] OR "sleep study"[tiab])) OR "peripheral arterial technology"[tiab] OR "wearable technolog*"[tiab] |
| **#27** | Lab Sleep Studies | "Polysomnography"[Mesh] OR polysomnogra*[tiab] OR "sleep study"[tiab] OR "sleep lab"[tiab] |
| **#28** | Combine Sets | #12 AND #26 AND #27 |
| **#29** | Hypoglossal Nerve Stimulator | "hypoglossal nerve stimulat*"[tiab] |
| **#30** | Combine Sets | #12 AND #29 |
| **#31** | COMISA | "Comorbidity"[Mesh]OR comorbid*[tiab] OR "co-occur*"[tiab] |
| **#32** | COMISA | #1 AND #12 AND #31 |
| **#33** | Combine Sets | #23 AND #32 |
| **#34** | Combine Sets | #4 OR #11 |
| **#35** | CER | "Comparative Effectiveness Research"[Mesh] OR "comparative effectiveness"[tiab] OR "Pragmatic Clinical Trial" [Publication Type] OR "pragmatic clinical trial"[tiab] OR "head-to-head study"[tiab] |
| **#36** | Combine Sets | #34 AND #35 |
| **#37** | Combine Sets | #5 OR #7 OR #9 OR #15 OR #21 OR #25 OR #30 OR #33 |
| **#38** | LIMIT to Study Designs | meta-analysis/exp OR systematic review/exp OR "systematic review*"[tiab] OR "meta analysis"[tiab] OR "meta analyses"[tiab] |

| Set # | Description | Strategy |
|---|---|---|
| **#39** | LIMIT to Study Designs | random allocation[mh] OR "randomized controlled trials"[pt] OR random*[tiab] OR RCT[tiab] |
| **#40** | Combine Sets | #37 AND (#38 OR #39) |
| **#41** | Combine Sets | #11 OR #18 |
| **#42** | Exclude Study Designs | comment[pt] OR editorial[pt] OR letter[pt] OR news[pt] OR "Book Illustrations"[pt] OR congress[pt] OR annual[tiab] OR book[tiab] OR comment[tiab] OR chapter[tiab] OR note[tiab] OR review[tiab] OR symposium[tiab] OR poster[tiab] OR abstract[tiab] OR "conference paper"[tiab] OR "conference proceeding"[tiab] OR "conference review"[tiab] OR congress[tiab] OR editorial[tiab] OR erratum[tiab] OR letter[tiab] OR note[tiab] OR meeting[tiab] OR sessions[tiab] OR "short survey"[tiab] OR symposium[tiab] OR animal[tiab] OR rat[tiab] OR rats[tiab] OR mouse[tiab] OR mice[tiab] OR goat[tiab] OR goats[tiab] OR pig[tiab] OR pigs[tiab] OR cadaver[tiab] OR dog[tiab] OR dogs[tiab] OR monkey[tiab] OR monkeys[tiab] OR ape[tiab] OR apes[tiab] |
| **#43** | Combine Sets | #41 NOT #42 |
| **#44** | Combine Sets | #36 OR #40 OR #43 |
| **#45** | Exclude Pediatrics | adolescen*[ti] OR babies[ti] OR baby[ti] OR boy[ti] OR boys[ti] OR child*[ti] OR girl*[ti] OR infancy[ti] OR infant*[ti] OR juvenile*[ti] OR neonat*[ti] OR newborn*[ti] OR nurser*[ti] OR paediatric*[ti] OR pediatric*[ti] OR preschool*[ti] OR "school age*"[ti] OR schoolchildren*[ti] OR teen*[ti] OR toddler*[ti] OR youth*[ti] |
| **#46** | Exclude Publication Types | booksdocs[Filter] OR "case reports"[pt] OR comment[pt] OR congress[pt] OR editorial[pt] OR letter[pt] OR "case report"[ti] OR comment*[ti] OR editorial[ti] OR letter[ti] OR news[ti] |
| **#47** | | #47 OR #46 |
| **#48** | | #44 NOT #47 |

**Table K-4. PsycINFO**

| Set # | Description | Strategy |
|---|---|---|
| | Filters | Humans, English, from 2018/5/17-2024 |
| **#1** | Insomnia | TI insomnia OR AB insomnia OR SU insomnia |

| Set # | Description | Strategy |
|---|---|---|
| **#2** | Pharmacology | TI ( daridorexant OR lemborexant OR suvorexant OR eszopiclone OR zaleplon OR zolpidem OR alprazolam OR clonazepam OR diazepam OR estazolam OR flurazepam OR lorazepam OR oxazepam OR quazepam OR temazepam OR triazolam OR ramelteon OR amitriptyline OR doxepin OR mirtazapine OR paroxetine OR trazodone OR diphenhydramine OR doxylamine OR "l tryptophan" OR gabapentin OR hydroxyzine OR valerian OR quetiapine ) OR AB (daridorexant OR lemborexant OR suvorexant OR eszopiclone OR zaleplon OR zolpidem OR alprazolam OR clonazepam OR diazepam OR estazolam OR flurazepam OR lorazepam OR oxazepam OR quazepam OR temazepam OR triazolam OR ramelteon OR amitriptyline OR doxepin OR mirtazapine OR paroxetine OR trazodone OR diphenhydramine OR doxylamine OR "l tryptophan" OR gabapentin OR hydroxyzine OR valerian OR quetiapine ) |
| **#3** | Cognitive Behavioral Therapy | TI "cognitive behavioral therapy" OR AB "cognitive behavioral therapy" OR- SU "cognitive behavioral behavioral therapy: |
| **#4** | Herbal Medicine | TI("herbal medicine" OR ashwagandha OR cannabis OR cannabidiol OR cbd OR chamomile OR glycine OR "i tryptophan" OR (lavender AND oral ) OR magnesium OR "tart cherry" OR "5 htp" OR "5 hydroxytryptophan" OR gaba OR "gamma amniobutyric acid" OR "l theanine" OR melatonin OR "passion flower" OR "reishi mushroom" OR tetrahydrocannabinol OR "delta 8 thc" OR "delta 9 thc" OR "valerian root") OR AB ("herbal medicine" OR ashwagandha OR cannabis OR cannabidiol OR cbd OR chamomile OR glycine OR "i tryptophan" OR (lavender AND oral ) OR magnesium OR "tart cherry" OR "5 htp" OR "5 hydroxytryptophan" OR gaba OR "gamma amniobutyric acid" OR "l theanine" OR melatonin OR "passion flower" OR "reishi mushroom" OR tetrahydrocannabinol OR "delta 8 thc" OR "delta 9 thc" OR "valerian root") |
| **#5** | Delivery of Behavioral Treatments | TI ( ("Cognitive Behavioral Therapy" OR "behavior* intervention*" OR behavior* treatment* OR "cbt i" OR "cognitive behavioral therapy insomnia") AND (delivery OR individual OR group OR telehealth OR internet OR "on-line course" OR phone OR workbook*) ) OR AB( ("Cognitive Behavioral Therapy" OR "behavior* intervention*" OR behavior* treatment* OR "cbt i" OR "cognitive behavioral therapy insomnia") AND (delivery OR individual OR group OR telehealth OR internet OR "on-line course" OR phone OR workbook*) ) |
| **#6** | Questionnaire | TI ( questionnaire OR "clinical interview*" OR "psychodiagnostic interview*" ) OR AB TI ( questionnaire OR "clinical interview*" OR "psychodiagnostic interview*" ) OR SU (questionnaire OR "psychodiagnostic interview" |
| **#7** | Combine Sets | #1 AND (#2 OR (#2 AND #3) OR #4 OR #5 OR #6) |

| Set # | Description | Strategy |
|---|---|---|
| **#8** | EXCLUDE Publication Types/Pediatrics | comment OR editorial OR letter OR news OR "Book Illustrations" OR congress OR annual OR book OR comment OR chapter OR note OR review OR symposium OR poster OR abstract OR "conference paper" OR "conference proceeding" OR "conference review" OR congress OR editorial OR erratum OR letter OR note OR meeting OR sessions OR "short survey" OR symposium OR animal OR rat OR rats OR mouse OR mice OR goat OR goats OR pig OR pigs OR cadaver OR dog OR dogs OR monkey OR monkeys OR ape OR apes OR adolescen* OR babies OR baby OR boy OR boys OR child* OR girl* OR infancy OR infant* OR juvenile* OR neonat* OR newborn* OR nurser* OR paediatric* OR pediatric* OR preschool* OR "school age*" OR schoolchildren* OR teen* OR toddler* OR youth |
| **#9** | Combine Sets | #7 NOT #8 |

# Appendix K: Alternative Text Descriptions of Algorithm

The following outlines narratively describe Module A, Module B, and Module C. An explanation of the purpose of the algorithms and description of the various shapes used within the algorithms can be found in the Algorithm section. The sidebars referenced within these outlines can also be found in the Algorithm section.

## Module A: Screening for Sleep Disorders

1. Module A of the algorithm begins with Box 1, in the shape of a rounded rectangle: “Adult Patient” that connects to Box 2.
2. Box 2: In the shape of a hexagon, asks the question: “Does the patient, their bed partner, or their healthcare provider have complaints and/or concerns about the patient’s sleep?”
    a. If the answer is “Yes” to Box 2, then Box 4, in the shape of a rectangle: “Perform a clinical assessment, including use of validated screening tools (e.g., ISI and STOP questionnaires) (See Sidebar 1)”
    b. If the answer is “No” to Box 2, then Box 3, in the shape of a rectangle: “Exit algorithm”
3. Box 4 connects to Box 5, in the shape of a hexagon, asks the question: “Are screening, history, and/or physical exam suggestive of chronic insomnia disorder or OSA? (See Sidebar 2)”
    a. If the answer is “Yes” to Box 5, then Box 7, in the shape of a rectangle: “Conclude that screening, history, and/or physical exam are consistent with OSA, chronic insomnia disorder, or both”
    b. If the answer is “No” to Box 5, then Box 6, in the shape of a rectangle: “Address sleep complaint and/or refer to sleep specialist

4. Box 7 connects to:
    a) Box 8, in the shape of an oval: “Continue to Insomnia Management Module (See Module B)”
    b) Box 9, in the shape of an oval: “Continue to both OSA and Insomnia Management Modules (See Modules B and C)”
    c) Box 10, in the shape of an oval: “Continue to OSA Management Module (See Module C)”

## Module B: Management of Chronic Insomnia Disorder

1. Module B begins with Box 11, in the shape of a rounded rectangle: “Adults with a provisional diagnosis of chronic insomnia disorder”
2. Box 11 connects to Box 12, in the shape of a rectangle: “Confirm diagnosis and then use SDM and encourage behaviorally based interventions for chronic insomnia disorder (i.e., CBT-I or BBT-I) (See Sidebar 3)”
3. Box 12 connects to Box 13, in the shape of a hexagon, asks the question: “Is the patient able and willing to complete CBT-I or BBT-I?”
    a. Note: In cases where the patient requires immediate intervention, providers may exercise clinical judgment to determine if pharmacotherapy may be safely initiated.
    b. Note 2: CBT-I and BBT-I are not equivalent, and there is more robust evidence for CBT-I. While this algorithm uses CBT-I and BBT-I similarly, providers referring patients for these treatments should consider availability of the treatment, the complexity and comorbidities of the patient, and the training of the provider.
    c. If the answer is “Yes” to Box 13, then Box 14, in the shape of a rectangle: “Refer for CBT-I or BBT-I (See Sidebar 3)”
    d. If the answer is “No” to Box 13, then Box 18, in the shape of a hexagon, asks the question: “Is short-term pharmacotherapy appropriate? (See Sidebars 4 and 5)”
        i. If the answer is “Yes” to Box 18, then Box 21, in the shape of a rectangle: “Initiate short-term pharmacotherapy” then to Box 22 which states, “Did insomnia remit after short-term pharmacotherapy?”
        ii. If the answer is “No” to Box 18, then Box 19, in the shape of a rectangle: “Refer to sleep specialist”
4. Box 14 connects to Box 15, in the shape of a hexagon, asks the question: “Did the patient complete CBT-I or BBT-I?”

a) If the answer is “No” to Box 15, then Box 20, in the shape of a hexagon: “Patient is willing to consider a different CBT-I/BBT-I modality

b) If the answer is “Yes” to Box 15, then Box 16, in the shape of a hexagon, asks the question: “Was CBT-I or BBT-I effective?”

   i. If the answer is “Yes” to Box 16, then Box 24, in the shape of a rectangle: “Follow-up and reassess as necessary”

   ii. If the answer is “No” to Box 16, then Box 17, in the shape of a rectangle: “Refer to sleep specialist for further assessment”

5. Box 18 is in the shape of a hexagon, asks the question: “Is short-term pharmacotherapy appropriate? (See Sidebars 4 and 5)”

   a. If the answer is “Yes” to Box 18, then Box 21, which states, “Initiate short-term pharmacotherapy” then to Box 22, “Did insomnia remit after short-term pharmacotherapy?”

   b. If the answer is “No” to Box 18, then Box 19 “Refer to sleep specialist” and then to Box 24 “Follow-up and reassess as necessary”

6. Box 20 is in the shape of a hexagon, asks the question: “Patient is willing to consider a different CBT-I/BBT-I modality.”

   a. If the answer is “Yes” to Box 20, then Box 14.

   b. If the answer is “No” to Box 20, then Box 18, in the shape of a hexagon: “Is short-term pharmacotherapy appropriate? (See Sidebars 4 and 5)”

7. Box 22 is in the shape of a hexagon, asks the question: “Did insomnia remit after short-term pharmacotherapy?”

   a. If the answer is “Yes” then to Box 23 that says, “Discontinue pharmacotherapy” and then to Box 24 that says, “Follow up and reassess as necessary.”

   b. If the answer is “No” then Box 17 “Refer to sleep specialist for further assessment.” Then to Box 24 “Follow-up and reassess as necessary”

## Module C: Management of Obstructive Sleep Apnea

1. Module C of the algorithm begins with Box 25 which states, “Patients in whom screening, history, and/or physical exam suggests OSA.
2. Box 25 then goes to Box 26, “Assess risk for OSA (See Sidebar 6)”
3. Box 26 connects to Box 27, in the shape of a hexagon, asks the question: “Does assessment show high risk for OSA?”
    a. If the answer is “Yes” then to Box 28 which states “Is the patient appropriate for home sleep apnea testing (HSAT)? (See Sidebar 7)”
    b. If the answer is “No” then to Box 30: “For low risk of OSA, refer to in-lab sleep study”
4. Box 30 connects to Box 31, in the shape of a hexagon: “Was the study diagnostic of OSA?”
    a. If the answer to Box 31 is “Yes”, then Box 35, in a shape of a rectangle, “Develop an individualized treatment plan for obstructive sleep apnea (See Sidebars 8 and 9).” Then to Box 40, “Follow-up and reassess as necessary”
    b. If the answer to Box 31 is No, then Box 32, a rectangle: “Consider alternative diagnoses and/or refer to sleep specialist.”
5. Box 28 in the shape of hexagon: “Is the patient appropriate for home sleep apnea testing (HSAT)? (See Sidebar 7)
    a. If the answer is “Yes”, then to Box 33, “Refer for HSAT (if technically inadequate, repeat once) then to Box 34, a hexagon: “Was the study diagnostic of OSA?”
    b. If the answer is “No”, then to Box 29, “Refer to in-lab sleep study or refer to sleep specialist.”
6. Box 34 in a shape of a hexagon, “Was the study diagnostic of OSA?”
    a. If the answer is “Yes”, then to Box 35, stating “Develop an individualized treatment plan for obstructive sleep apnea (See Sidebars 8 and 9)”. Then to Box 40, a rectangle “Follow-up and reassess as necessary”
    b. If the answer is “No”, then to Box 29 that states “Refer to in-lab sleep study or refer to sleep specialist”
7. Box 29 connects to Box 36 which says, “Was the study diagnostic of OSA?”
    a. If the answer is “Yes”, then Box 38, a rectangle: “Initiate appropriate treatments and provide interventions to support use; See Recommendations 17-29 (See Sidebars 8 and 9)”

   b. If the answer is “No”, then Box 37, a rectangle: “OSA is unlikely; consider alternative diagnoses and/or refer to sleep specialist” then connects to Box 40, “Follow-up and reassess as necessary”

8. Box 38, “Initiate appropriate treatments and provide interventions to support use, see recommendations 17-29 (See Sidebars 8 and 9)”
   a. Box 38 connects to Box 39, “If the patient is not improving or is not using therapy, consider referral to a sleep specialist and/or behavioral sleep medicine provider”, which then connects to Box 40, “Follow-up and reassess as necessary”

# Appendix L: Abbreviations

| Abbreviation | Definition |
|---|---|
| **AE** | Adverse event |
| **AHI** | Apnea-hypopnea index |
| **AHRQ** | Agency for Healthcare Research and Quality |
| **AI** | artificial intelligence |
| **AIS** | Athens Insomnia Scale |
| **APAP** | Auto-titrating positive airway pressure |
| **BBT-I** | Brief behavioral treatment for insomnia |
| **BDI** | Beck Depression Inventory |
| **BIC** | brief intervention and contact |
| **BiPAP** | bilevel positive airway pressure |
| **BMI** | body mass index |
| **BPD** | borderline personality disorder |
| **BQ** | Berlin Questionnaire |
| **CAI** | central apnea index |
| **CBD** | cannabidiol |
| **CBT** | cognitive behavioral therapy |
| **CBT-I** | cognitive behavioral therapy for insomnia |
| **CDC** | Centers for Disease Control and Prevention |
| **CDP** | Center for Deployment Psychology |
| **CHF** | congestive heart failure |
| **CI** | confidence interval |
| **CID** | Chronic insomnia disorder |
| **CNS** | central nervous system |
| **COI** | conflict of interest |
| **COMISA** | Comorbid insomnia and obstructive sleep apnea |
| **COR** | Contracting Officer's Representative |
| **CPAP** | continuous positive airway pressure |
| **COPD** | chronic obstructive pulmonary disease |
| **CPG** | clinical practice guideline |
| **CSA** | central sleep apnea |
| **CVD** | cardiovascular disease |
| **DBT** | dialectical behavior therapy |
| **DHA** | Defense Health Agency |

| Abbreviation | Definition |
|---|---|
| **DOD** | Department of Defense |
| **DODI** | Department of Defense Instructions |
| **DOR** | diagnostic odds ratio |
| **DSM-IV** | Diagnostic and Statistical Manual of Psychiatric Disorders, 4th edition |
| **DSM-IV-TR** | Diagnostic and Statistical Manual of Psychiatric Disorders, 4th edition (Text Revision) |
| **DSM-5** | Diagnostic and Statistical Manual for Mental Disorders, 5th edition |
| **EBPWG** | Evidence-Based Practice Work Group |
| **EEG** | electroencephalogram |
| **EPAP** | expiratory positive airway pressure |
| **ESS** | Epworth Sleepiness Scale |
| **ETAU** | enhanced treatment as usual |
| **FAIR** | Findable, Accessible, Interoperable, Reusable |
| **FDA** | Federal Drug Administration |
| **FOSQ** | Functional Outcomes of Sleep Questionnaire |
| **GABA** | Gamma-Aminobutyric Acid |
| **GMP** | good manufacturing practice |
| **GRADE** | Grading of Recommendations Assessment, Development, and Evaluation |
| **HAMD** | Hamilton Depression Rating Scale |
| **HEC** | Health Executive Committee |
| **HGNS** | hypoglossal nerve stimulation |
| **HSAT** | home sleep apnea testing |
| **ICD-10** | International Classification of Diseases, 10th Version |
| **ICSD-2** | International Classification of Sleep Disorders, 2nd edition |
| **ICSD-3** | International Classification of Sleep Disorders, 3rd edition |
| **IOM** | Institute of Medicine |
| **IRLSS** | International Restless Legs Syndrome Study Group |
| **ISI** | Insomnia Severity Index |
| **ITT** | intention-to-treat |
| **kg/m2** | kilograms per meter squared |
| **KQ** | key question |
| **LMS** | lethal means safety |
| **LPS** | latency to persistent sleep |
| **MA** | meta-analysis |
| **MAD** | mandibular advancement device |

| Abbreviation | Definition |
|---|---|
| **MBSR** | mindfulness-based stress reduction |
| **MBTI** | mindfulness-based therapy for insomnia |
| **MD** | Mean difference |
| **MDD** | major depressive disorder |
| **MEQ** | Morningness-Eveningness Questionnaire |
| **MHS** | Military Health System |
| **MI** | myocardial infarction |
| **MIRECC** | Mental Illness, Research, Education, and Clinical Center |
| **MMA** | maxillomandibular advancement surgery |
| **MOS** | military occupational specialty |
| **MRI** | magnetic resonance imaging |
| **MT** | myofunctional therapy |
| **MVC** | Motor vehicle crash |
| **NAM** | National Academy of Medicine |
| **NICE** | National Institute for Health and Care Excellence |
| **NIH** | National Institutes of Health |
| **Non-BZD BzRAs** | Non-benzodiazepine benzodiazepine receptor agonists |
| **NPV** | negative predictive values |
| **ODI** | oxygen desaturation index |
| **OMF** | oral and maxillofacial surgeon |
| **OR** | odds ratio |
| **OSA** | obstructive sleep apnea |
| **OTC** | over the counter |
| **OUD** | opioid use disorder |
| **PAP** | positive airway pressure |
| **PCC** | patient-centered care |
| **PHQ-9** | Patient Health Questionnaire-9 |
| **PICOTS** | population, intervention, comparison, outcome, timing, and setting |
| **PM** | portable monitoring |
| **PPV** | positive predictive value |
| **PSG** | polysomnography |
| **PSQI** | Pittsburgh Sleep Quality Index |
| **PST** | problem-solving therapy |
| **P2P** | peer-to-peer |

| Abbreviation | Definition |
|---|---|
| **QoL** | quality of life |
| **RCT** | randomized controlled trial |
| **REI** | respiratory event index |
| **REMS** | Risk Evaluation and Mitigation Strategy |
| **RERA** | respiratory effort related arousal |
| **RDoC** | Research Domain Criteria |
| **ROC** | receiver operating characteristic |
| **rTMS** | repetitive transcranial magnetic stimulation |
| **SAQLI** | Sleep Apnea Quality of Life Index |
| **SAVE** | Sleep Apnea cardioVascular Endpoints |
| **SDB** | sleep disordered breathing |
| **SDM** | shared decision making |
| **SDS** | Self-Rating Depression Scale |
| **Se** | sensitivity |
| **SES** | socioeconomic status |
| **SoE** | Strength of evidence |
| **Sp** | specificity |
| **SPI** | Safety Planning Intervention |
| **SR** | systematic review |
| **STOP** | Snoring, Tiredness, Observed apnea, and high blood Pressure |
| **STOP-BANG** | Snoring, Tiredness, Observed apnea, high blood Pressure, Body mass index, Age, Neck circumference, male |
| **sTST** | subjective total sleep time |
| **TAP** | Transition assistance program |
| **TAU** | treatment as usual |
| **TBI** | traumatic brain injury |
| **TCAs** | Tricyclic antidepressants |
| **TENS** | Transcutaneous electrical nerve stimulation |
| **TESS** | Treatment Emergent Symptom Scale |
| **THC** | tetrahydrocannabinol |
| **TJC** | The Joint Commission |
| **TST** | total sleep time |
| **U.S.** | United States |
| **UAS** | upper airway stimulation |
| **UPPP** | uvulopalatopharyngoplasty |

| Abbreviation | Definition |
|---|---|
| **USPSTF** | U.S. Preventive Services Task Force |
| **VA** | Department of Veterans Affairs |
| **VHA** | Veterans' Health Administration |
| **UAS** | upper airway stimulation |
| **WASO** | wake after sleep onset |
| **WHO** | World Health Organization |

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