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 and the Department of Defense guidelines are based upon the best information available at the time of publication. They 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 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 clinicians take into account the needs of individual patients, available resources, and limitations unique to an institution or type of practice. Every healthcare professional making use of these guidelines is responsible for evaluating the appropriateness of applying them in the setting of any particular clinical situation.

These guidelines are not intended to represent Department of Veterans Affairs or TRICARE policy. Further, inclusion of recommendations for specific testing and/or therapeutic interventions within these guidelines does not guarantee coverage of civilian sector care. Additional information on current TRICARE benefits may be found at www.tricare.mil or by contacting your regional TRICARE Managed Care Support Contractor.

Version 1.0 – 2019

Prepared by:

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

With support from:

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&
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Version 1.0 – 2019

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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 who are taking care of patients with chronic insomnia disorder and/or OSA along management pathways that are 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
- Minimize preventable complications and morbidity
- Emphasize the use of patient-centered care (PCC)

II. Background

A. Definitions and Scope

a. Chronic Insomnia Disorder

Insomnia is characterized by difficulty initiating and/or maintaining sleep or awakening too early, associated with significant daytime impairment.[2] In this CPG, we use the term "chronic insomnia disorder" to align with current diagnostic criteria. The International Classification of Sleep Disorders, 3rd edition (ICSD-3) specifies that insomnia disorder can be either acute or chronic, can be diagnosed when a patient experiences difficulties with sleep onset, sleep maintenance, or early morning awakenings at least three nights per week, is accompanied by daytime consequences, and occurs despite adequate opportunity and circumstances for sleep. Insomnia disorder lasting more than three months in duration is considered "chronic." The Diagnostic and Statistical Manual for Mental Disorders, 5th edition (DSM-5) uses similar criteria for Insomnia Disorder, Persistent.

The diagnosis of chronic insomnia disorder requires a clinical evaluation including a sleep, medical, and psychiatric history. Individuals with chronic insomnia often 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 measures 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 outcomes measures. In routine clinical practice, objective measures are not indicated for the evaluation of insomnia unless there is a 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 acute insomnia disorder (i.e., insomnia disorder symptoms present for <3 months), the focus of this guideline is patients experiencing insomnia disorder on a chronic basis, which DSM-5 and ICSD-3 define as three months or more. 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

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).[3] 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).[4] An apnea is a complete or near-complete (i.e., 90%) decrease in airflow that lasts at least 10 seconds. Apneas do not require a desaturation or arousal to be scored. A 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.[5] Common symptoms of OSA include daytime sleepiness, snoring, sensations of gasping or choking upon awakening from sleep, and witnessed breathing interruptions during sleep.[6] Traditionally, the diagnosis of OSA was made by an attended overnight in-lab 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.[7] Importantly, a non-diagnostic and/or negative HSAT for OSA is unable to rule out OSA and further testing is required, preferably a polysomnogram, though HSAT can be repeated.[3,7] According to the ICSD-3, OSA is 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; 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.[8-10]

B. Epidemiology and Impact in the General Population

The National Institutes of Health (NIH) estimate that roughly 30% of the general population complains of sleep disruption, and approximately 10% have the associated symptoms of daytime functional impairment.[11] Insomnia is the most common sleep complaint among adults;[12] approximately 20% to 30% of adults in the United States (U.S.) have experienced insomnia symptoms.[13,14] The prevalence of

chronic insomnia disorder is estimated to be between 6% and 10%.[14,15] OSA is one of the most common sleep disorders, with a prevalence that ranges from 9% to 38%.[16] The prevalence of OSA increases with age, body mass index (BMI), male gender, and menopause.

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

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).[17] 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] However, OSA is the most frequently diagnosed sleep disorder in military personnel.[19] Further, military personnel with sleep disorders often also have posttraumatic stress disorder (PTSD), symptoms of anxiety and depression, and traumatic brain injury (TBI).[20]

Sleep disturbances are also common in Veterans.[21-23] The National Veteran Sleep Disorder Study found that PTSD was associated with a high prevalence (7.7%) of sleep disorders among comorbid conditions evaluated.[22] In this study, the prevalence of Veterans with OSA was 3% in 2010.[22] As Veterans have high rates of CVD and PTSD, and since OSA is more prevalent in patients with these disorders,[24] there is likely a large percentage of Veterans who have not yet been diagnosed with this sleep-related breathing disorder.[25]

A study of Veterans seeking treatment at the VA San Diego Healthcare System between March 2012 and August 2013 (n=917) found that more than half had clinically significant insomnia symptoms, as measured by the Insomnia Severity Index (ISI).[26] In the subsample without military sexual trauma (n=843), 23.6% had moderate insomnia (ISI scores 15 – 21) while 9.6% reported severe insomnia (ISI scores 22 – 28).[26] In a clinical cohort study, Foster et al. compared sleep disorders rendered to active duty men and women.[27] While their scores on the Epworth Sleepiness Scale (ESS) and ISI did not differ, women were significantly more likely to have insomnia while men were more likely to have OSA.

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,[17,26] with rates as high as 50% among Veterans enrolling in VA healthcare.[26] Considering the mental and physical health risks of poor sleep (e.g., anxiety, depression, suicide, CVD) and Veterans' desire for assistance with sleep,[28,29] increased access to insomnia disorder treatment is essential. A recently published 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."[17]

To increase patient access to behaviorally-based insomnia disorder treatment, the following steps could be implemented:[17,30]

- Increased training and dissemination of evidence-based insomnia disorder treatment
- Healthcare provider education on insomnia disorder, including 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

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.[22,31] Because sleep disorders increase in prevalence with age, it affects a greater proportion of military leaders and can negatively impact military readiness. A key consideration related to OSA treatment among active duty Service Members is the requirement for military operations in austere environments.[32] Austere environments make using positive airway pressure (PAP) therapy difficult (given limited access to electricity, distilled water, etc.) as well as the inherent burden of the PAP unit. 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.[23] 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.[33] 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.[34] Considering the health-related risks of untreated OSA (e.g., degraded cognitive function, increased risk of accidents and CVD, worse outcomes in comorbid disorders), the unique military requirements, and that the military and Veteran populations are unique and have comorbid disorders that are not typically present in civilian populations, offering MAD therapy is critical to OSA management in these populations. 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

- Provide objective measures of adherence to MAD therapy by integrating rechargeable compliance chips into the device
- Standardize referral practices for MAD treatment in the DoD and VHA

III. About this Clinical Practice Guideline

This guideline represents a significant step toward improving the management of patients with chronic insomnia disorder or OSA in the VA and DoD. As with other CPGs, however, challenges remain, including evidence gaps, the need to develop effective strategies for guideline implementation, and to evaluate the effect of guideline adherence on clinical outcomes. This guideline is intended for VA and DoD healthcare practitioners including physicians, nurse practitioners, physician assistants, psychologists, social workers, nurses, clinical pharmacy specialists, dental specialists, and others involved in the care of Service Members or Veterans with chronic insomnia disorder and/or OSA.

As elaborated in the qualifying statement on page one, this CPG is not intended to serve as a standard of care. Standards of care are determined on the basis of all clinical data available for an individual patient and are subject to change as scientific knowledge and technology advance and patterns evolve. This CPG is based on information published from January 1, 2008, through May 15, 2018, and is intended to provide a general guide to best practices. A guideline can assist care providers, but the use of a CPG must always be considered as a recommendation, within the context of a provider's clinical judgment, patient values and preferences, and available resources for the care of an individual patient.

A. Methods

The methodology used in developing the 2019 CPG follows the *Guideline for Guidelines*,[35] an internal document of the VA and DoD EBPWG that was updated in January 2019. The *Guideline for Guidelines* can be downloaded from http://www.healthquality.va.gov/policy/index.asp. This document provides information regarding the process of developing guidelines, including the identification and assembly of the Guideline Champions (Champions) and other subject matter experts from within the VA and DoD, known as the Work Group and, ultimately, the development and submission of the new Chronic Insomnia Disorder and OSA CPG.

The Champions and Work Group for this CPG were charged with developing evidence-based clinical practice recommendations and writing and publishing a guideline document to be used by providers within the VA/DoD healthcare systems as well as those within the community who treat military personnel or Veterans. Specifically, the Champions and Work Group members for this guideline were responsible for identifying the key questions (KQs) of the most clinical relevance, importance, and interest for the management of patients with chronic insomnia disorder and/or OSA. The Champions and the Work Group also provided direction on inclusion and exclusion criteria for the evidence review and assessed the level and quality of the evidence. In addition, the Champions assisted in:

- Identifying appropriate disciplines of individuals to be included as part of the Work Group
- Directing and coordinating the Work Group
- Participating throughout the guideline development and review processes

The VA Office of Quality, Safety and Value, in collaboration with the Office of Evidence Based Practice, U.S. Army Medical Command, the proponent for CPGs for the DoD, identified four clinical leaders, Susmita Chowdhuri, MD, MS, FAASM and Christi Ulmer, PhD, CBSM, DBSM from the VA, and COL Vincent Mysliwiec, MD, FAASM and Christopher Spevak, MD, MPH, JD from the DoD, as Champions for the 2019 CPG.

The Lewin Team, including The Lewin Group, Duty First Consulting, ECRI Institute, and Sigma Health Consulting, LLC, was contracted by the VA and DoD to support the development of this CPG and conduct the evidence review. The first conference call was held in January 2018, with participation from the contracting officer's representative (COR), leaders from the VA Office of Quality, Safety and Value, the DoD Office of Evidence Based Practice, and the Champions. During this call, participants discussed the scope of the guideline initiative, the roles and responsibilities of the Champions, the project timeline, and the approach for developing and prioritizing specific research questions on which to base an SR about the management of patients with chronic insomnia disorder and/or OSA. The group also identified a list of clinical specialties and areas of expertise important and relevant to the management of chronic insomnia disorder and/or OSA, from which Work Group members were recruited. The specialties and clinical areas of interest included: pulmonology, neurology, psychiatry, psychology, behavioral sleep medicine, pharmacology, dental, ear, nose, and throat, surgery, and primary care.

The guideline development process for the 2019 CPG consisted of the following steps:

1. Formulating and prioritizing KQs and defining critical outcomes
2. Convening patient focus group
3. Conducting the systematic evidence review
4. Convening a face-to-face meeting with the CPG Champions and Work Group members
5. Drafting and submitting a final CPG on the management of chronic insomnia disorder and/or OSA to the VA/DoD EBPWG

Appendix A provides a detailed description of each of these tasks.

a. Grading Recommendations

The Champions and Work Group used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to assess the quality of the evidence base and assign a strength for each recommendation. The GRADE system uses the following four domains to assess the strength of each recommendation:[25]

- Balance of desirable and undesirable outcomes
- Confidence in the quality of the evidence
- Patient or provider values and preferences
- Other implications, 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"). A "Strong" recommendation generally indicates high confidence in the quality of the available scientific evidence, a clear difference in magnitude between the benefits and harms of an intervention, similarity among patient or provider values and preferences, and the apparent influence of other implications (e.g., resource use, feasibility). If the Work Group has less confidence after the assessment across these domains and believes that additional evidence may change the recommendation, it generally assigns a "Weak" recommendation. It is important to note that the GRADE terminology used to indicate the assessment across the four domains (i.e., Strong versus Weak) should not be confused with the clinical importance of the recommendation. A "Weak" recommendation may still be important to the clinical care of a patient with insomnia disorder and/or OSA.

Occasionally, instances may occur when the Work Group believes there is insufficient evidence to make a recommendation for or against a particular therapy or preventive measure. This can occur when there is an absence of studies on a particular topic that met evidence review inclusion criteria, studies included in the evidence review report conflicting results, or studies included in the evidence review report inconclusive results regarding the desirable and undesirable outcomes.

Using these elements, the grade of each recommendation is presented as part of a continuum:

- Strong for (or "We recommend offering this option …")
- Weak for (or "We suggest offering this option …")
- No recommendation for or against (or "There is insufficient evidence …")
- Weak against (or "We suggest not offering this option …")
- Strong against (or "We recommend against offering this option …")

The grade of each recommendation made in the 2019 CPG can be found in the section on Recommendations. Additional information regarding the use of the GRADE system can be found in Appendix A.

b. Peer Review Process

The CPG was developed through an iterative process in which the Work Group produced multiple drafts of the CPG. The process for developing the initial draft is described in more detail in Drafting and Submitting the Final Clinical Practice Guideline.

Once a near-final draft of the guideline was agreed upon by the Champions and Work Group members, the draft was sent out for peer review and comment. The draft was posted on a wiki website for a period of 14 business days. The peer reviewers comprised individuals working within the VA and DoD healthcare systems as well as experts from relevant outside organizations designated by the Work

Group members. Organizations designated by the Work Group to participate in the peer review and that provided feedback include:

- American Academy of Sleep Medicine

The VA and DoD Leadership reached out to both the internal and external peer reviewers to solicit their feedback on the CPG. Reviewers were provided a hyperlink to the wiki website where the draft CPG was posted. All feedback from the peer reviewers was discussed and considered by the Work Group. Modifications made throughout the CPG development process were made in accordance with the evidence.

B. Summary of Patient Focus Group Methods and Findings

When forming guideline recommendations, consideration should be given to the values of those most affected by the recommendations: patients. Patients bring perspectives, values, and preferences into their healthcare experience that can vary from those of clinicians. These differences can affect decision making in various situations, and should thus be highlighted and made explicit due to their potential to influence a recommendation's implementation.[36,37] Focus groups can be used as an efficient method to explore the ideas and perspectives of a group of individuals and collect qualitative data on a thoughtfully predetermined set of questions.

Therefore, as part of the effort to develop this CPG, VA and DoD Leadership, along with the Chronic Insomnia Disorder and OSA CPG Work Group, held a patient focus group. The patient focus group was held on March 27, 2018, at Fort Sam Houston in San Antonio, Texas. The aim of the focus group was to further understand and incorporate the perspective of patients with chronic insomnia disorder and/or OSA who are covered and/or receiving their care through the VA and/or DoD healthcare systems, as these patients are most affected by the recommendations put forth in the CPG. The focus group delved into the patients' perspectives on a set of topics related to their insomnia disorder/OSA care, including their priorities, challenges they have experienced, and the information they received regarding their care, as well as the impacts of their care on their lives.

It is important to note that the focus group was comprised of a convenience sample in one geographic region and that the Work Group recognizes the lack of generalizability and other limitations inherent in the small sample size. Fewer than 10 people in total were included in the focus group to be consistent with the requirements of the federal Paperwork Reduction Act, 1980. Five participants were men and three were women. Two of the participants were also bed partners (i.e., individuals sharing a bed). The Work Group acknowledges that the sample included in this focus group is not representative of all patients within the VA and DoD healthcare systems. Further, time limitations for the focus group prevented exhaustive exploration of all topics related to chronic insomnia disorder and/or OSA management in the VA and DoD and the patients' broader experiences with their care. Thus, the Work Group made decisions regarding the priority of topics to discuss at the focus group. These limitations, as well as others, were considered during guideline development as the information collected from the discussion was being used. Recruitment for participation in the focus group was managed by the Champions and VA and DoD Leadership, with assistance from coordinators at the facility where the focus group took place.

The following ideas and suggestions about aspects of care that are important to patients with chronic insomnia disorder and/or OSA emerged as recurring themes during the discussion (Table 1). These

concepts were important parts of the participants' care and added to the Work Group's understanding of patient values and perspectives. Additional details regarding the patient focus group methods and findings can be found in Appendix G.

Table 1. Chronic Insomnia Disorder and OSA CPG Focus Group Concepts

Chronic Insomnia Disorder/OSA CPG Patient Focus Group Concepts
A. Consider patient-specific goals, values, and preferences and use patient-centric decision making process to develop a patient-centered plan for timely diagnosis, treatment, and lifestyle adaptation.
B. Assess and screen patients for insomnia or sleep disorders in the primary care setting in order to promote early detection and treatment.
C. Discuss patient preferences regarding the use of pharmacologic and non-pharmacologic treatment options.
D. Recognize the importance of communication and collaboration among providers on an interdisciplinary care team, particularly for comorbidities.
E. Provide more detailed information and education to patients and caregivers through all stages of diagnosis and treatment.
F. Involve family caregivers to create support and motivation for patients with insomnia disorder and/or OSA. The caregivers are also directly affected by the patient's condition.
G. Reduce the stigma experienced by patients with insomnia disorder and/or OSA.
H. An important objective for patients is improving daytime functioning.

Abbreviations: CPG: clinical practice guideline; OSA: obstructive sleep apnea

C. Conflicts of Interest

At the start of this guideline development process and at other key points throughout, the project team was required to submit disclosure statements to reveal any areas of potential conflict of interest (COI) in the past 24 months. Verbal affirmations of no COI were used as necessary during meetings throughout the guideline development process. The project team was also subject to random web-based surveillance (e.g., Centers for Medicare and Medicaid Services open payments or ProPublica).

If a project team member reported a COI (actual or potential), then it was reported to the Office of Evidence Based Practice. It was also discussed with the Chronic Insomnia Disorder and OSA CPG Champions in tandem with their review of the evidence and development of recommendations. The Office of Evidence Based Practice and the Chronic Insomnia Disorder and OSA CPG Champions determined whether action, such as restricting participation and/or voting on sections related to the conflict or removal from the Work Group, was necessary. If it was deemed necessary, action to mitigate the COI was taken by the Champions and Office of Evidence Based Practice, based on the level and extent of involvement. No COIs were identified for the Chronic Insomnia Disorder and OSA CPG Work Group members or Champions. Disclosure forms are on file with the VA Evidence Based Practice Program office and available upon request.

D. Scope of this Clinical Practice Guideline

Ideally, any patient in the healthcare system should have access to the interventions that are recommended in this guideline regardless of the setting and after taking into consideration the patient's specific circumstances.

Guideline recommendations are intended to be patient-centered. Thus, treatment and care should take into account a patient's needs and preferences. Good communication between healthcare professionals and the patient is essential and should be supported by evidence-based information tailored to the patient's needs. An empathetic and non-judgmental approach facilitates discussions sensitive to gender, culture, ethnic, and other differences. The information that patients are provided about treatment and care should be culturally appropriate and also available to people with limited literacy skills. It should also be accessible to people with additional needs, such as physical, sensory, or learning disabilities. Family involvement should be considered, if appropriate.

This CPG is designed to assist providers in managing or co-managing adult patients with chronic insomnia disorder and/or OSA, as those are the most prevalent sleep disorders. Moreover, the patient population of interest for this CPG is adults with OSA and/or insomnia who are eligible for care in the VA and DoD healthcare delivery systems. It includes Veterans as well as deployed and non-deployed active duty Service, Guard, and Reserve Members and their dependents.

E. Highlighted Features of this Clinical Practice Guideline

The 2019 VA/DoD Chronic Insomnia Disorder and 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 framework for recommendations in this CPG considered factors beyond the strength of the evidence, including balancing desired outcomes with potential harms of the intervention, equity of resource availability, the potential for variation in patient values and preferences, and other considerations (e.g., resource use, subgroup considerations) as appropriate. Applicability of the evidence to VA/DoD populations was also taken into consideration. An algorithm accompanies the guideline to provide an overview of the recommendations in the context of the flow of patient care and to assist with training providers (see Algorithm). The algorithm may be used to help facilitate the translation of guideline recommendations into effective practice.

F. Patient-centered Care

VA/DoD CPGs encourage clinicians to use a PCC approach that is individualized based on patient needs, characteristics, and preferences. Regardless of the setting, all patients in the healthcare system should be able to access evidence-based care appropriate to that patient. When properly executed, PCC may decrease patient anxiety, increase trust in clinicians, and improve treatment adherence.[38-40] Improved patient-clinician communication and a PCC approach convey openness and support disclosure of current and future concerns.

As part of the PCC approach, clinicians should review the outcomes of previous healthcare experiences of patients with chronic insomnia disorder and/or OSA. Providers should ask each patient about any concerns he or she has or any perceived barriers to high quality care. In addition, they should educate the patient

about the actions that need to be taken and any decisions that need to be made and should involve the individual in decision making regarding the management of chronic insomnia disorder and/or OSA.

G. Shared Decision Making

Throughout this VA/DoD CPG, the authors encourage clinicians to focus on shared decision making (SDM). The SDM model was introduced in *Crossing the Quality Chasm,* an Institute of Medicine (IOM) (now called the National Academy of Medicine [NAM]) report, in 2001.[41] It is readily apparent that patients, together with their clinicians, make decisions regarding their plan of care and management options. Patients with chronic insomnia disorder and/or OSA require sufficient information and time to be able to make informed decisions. Clinicians must be adept at presenting information to their patients regarding individual treatments, expected outcomes, and levels and/or locations of care. Clinicians are encouraged to use SDM to individualize treatment goals and plans based on patient capabilities, needs, goals, and preferences.

H. Co-occurring Conditions

Co-occurring medical conditions and mental health disorders are important to recognize because they can modify the expression and management of chronic insomnia disorder and/or OSA, patient or provider treatment priorities, and clinical decisions. Providers should expect that many Veterans, Service Members, and their family members will have one or more co-occurring health conditions. Because the management of chronic insomnia disorder and/or OSA sometimes takes place in parallel with ongoing care for co-occurring conditions, it is generally best to manage chronic insomnia disorder and/or OSA concurrently with care for other health conditions that are being treated in primary or specialty care. Some co-occurring medical and mental health conditions may require early specialist consultation in order to discuss any necessary changes in treatment or to establish a common understanding of how care will be coordinated and delivered. Where applicable, evidence supporting specific treatment recommendations for OSA or insomnia disorder co-occurring with other medical and mental health disorders is addressed.

Insomnia disorder commonly is comorbid with other mental health and medical disorders, which should not preclude treatment with cognitive behavioral therapy for insomnia (CBT-I). In the past, insomnia generally was viewed as a symptom of other disorders and was not thought to require separate clinical attention. However, it now is recognized that the maladaptive coping strategies implemented by affected individuals often lead to an independent insomnia disorder that does not resolve simply by treating the comorbid condition. In fact, in its State of the Science Conference Statement, the NIH proposed the term "comorbid insomnia" to describe insomnia that coexists with another medical/psychiatric disorder because "there is concern that the term ‘secondary insomnia’ may promote undertreatment.”[12] CBT-I providers are trained to assess patients for the optimal sequencing of comorbid mental health disorders. However, research guiding optimal sequencing is currently limited.

I. Implementation

This CPG and algorithm are designed to be adapted by individual healthcare providers with consideration of local needs and resources. The algorithm serves as a tool to prompt providers to consider key decision points in the course of an episode of care.

Although this CPG represents the recommended practice on the date of its publication, medical practice is evolving and this evolution requires continuous updating based on published information. New technology and more research will improve patient care in the future. The CPG can assist in identifying priority areas for research and informing the optimal allocation of resources. Future studies examining the results of CPG implementation may lead to the development of new evidence particularly relevant to clinical practice.

IV. Guideline Work Group

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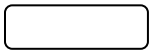
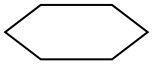
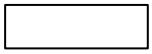
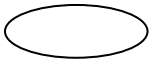
V. Algorithm

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 as a way 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:

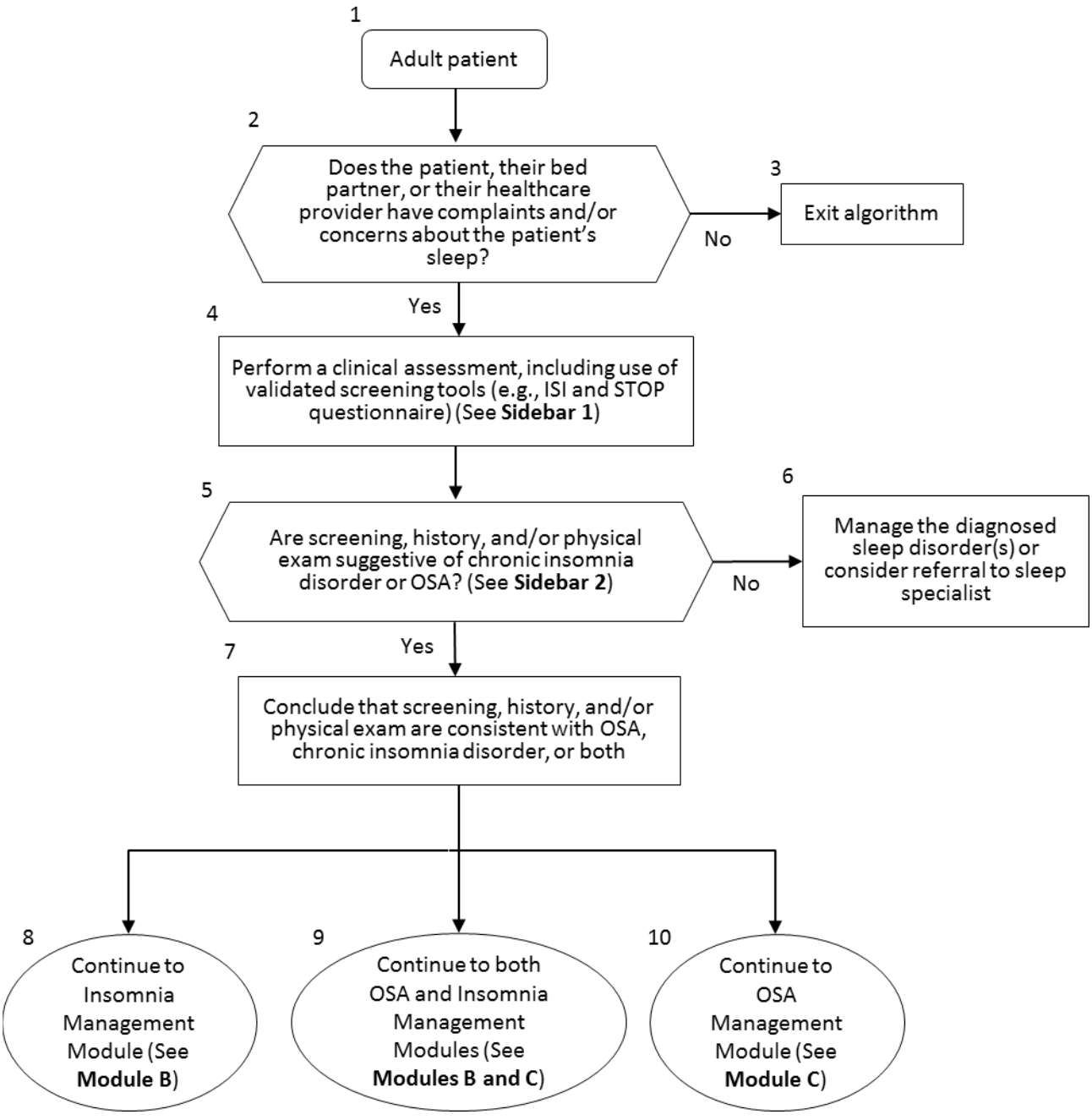
- An ordered sequence of steps of care
- Recommended observations and examinations
- Decisions to be considered
- Actions to be taken

For each VA/DoD CPG, there is a corresponding clinical algorithm that is depicted by a step-by-step decision tree. Standardized symbols are used to display each step in the algorithm, and arrows connect the numbered boxes indicating the order in which the steps should be followed.[42]

Shape	Description
	Rounded rectangles represent a clinical state or condition
	Hexagons represent a decision point in the guideline, 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 guideline

Appendix K contains alternative text descriptions of Module A, Module B, and Module C.

Module A: Screening for Sleep Disorders



Abbreviations: ISI: Insomnia Severity Index; OSA: obstructive sleep apnea; STOP: Snoring, Tiredness, Observed apnea, and high blood Pressure

Sidebar 1: Clinical Features of OSA and Chronic Insomnia Disorder

OSA (see Appendix D for detailed ICSD-3 diagnostic criteria):

- Sleepiness
- Loud, bothersome snoring
- Witnessed apneas
- Nightly gasping/choking
- Obesity (BMI >30 kg/m^2)
- Treatment resistant hypertension

Chronic Insomnia Disorder (see Appendix D for detailed ICSD-3 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
- The sleep difficulty occurs despite adequate opportunity for sleep
- The insomnia is not better explained by and does not occur exclusively during the course of another sleep-wake disorder
- The insomnia is not attributable to the physiological effects of a substance
- Coexisting mental disorders and/or medical conditions do not adequately explain the predominant complaint of insomnia

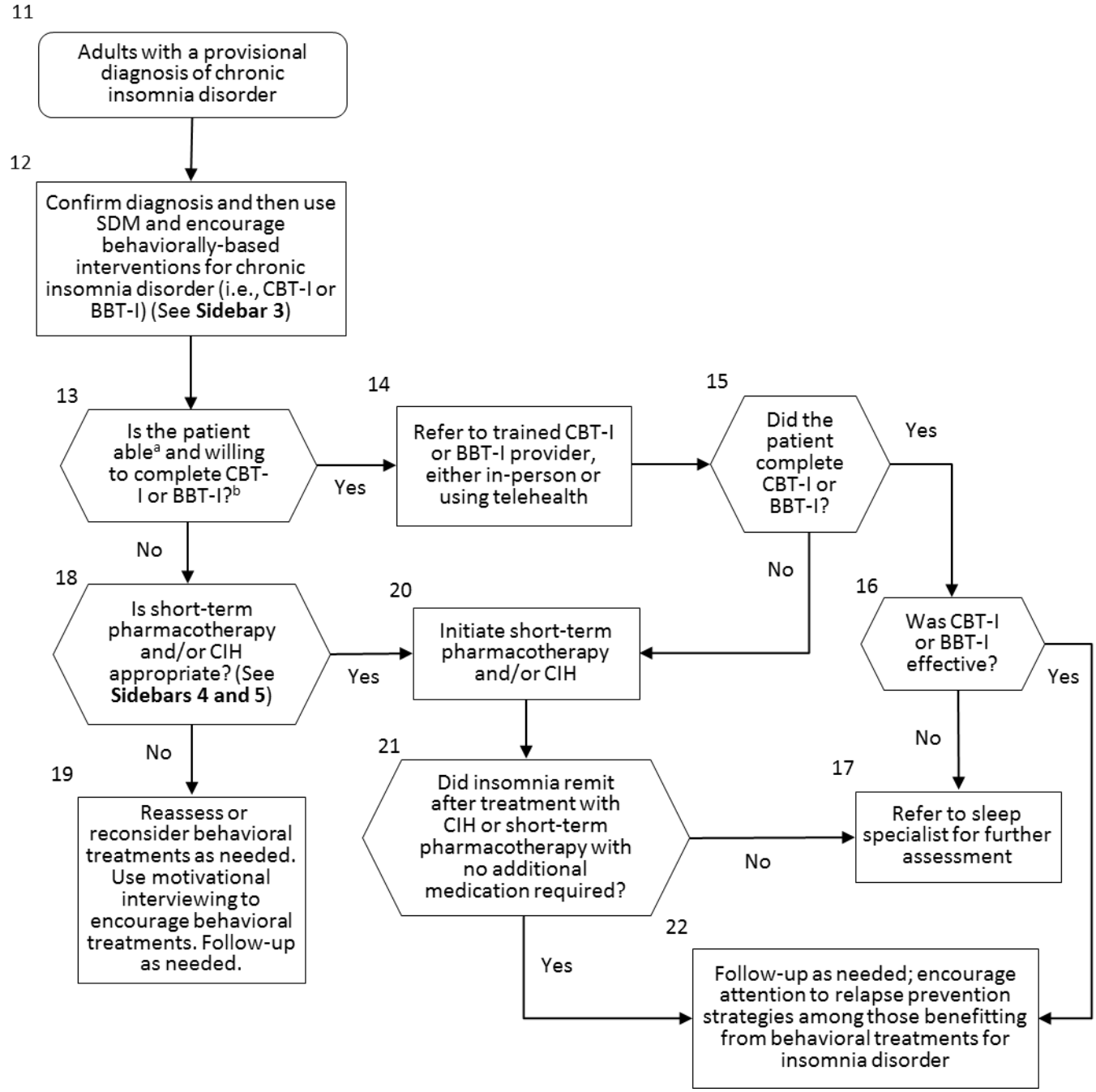
Abbreviations: BMI: body mass index; ICSD-3: International Classification of Sleep Disorders, 3rd edition; kg/m^2: kilograms per meter squared; OSA: obstructive sleep apnea

Sidebar 2: Other Sleep Disorders

- Insufficient sleep syndrome
- Restless legs syndrome
- Narcolepsy/idiopathic CNS hypersomnia
- Nightmare disorder
- REM sleep behavior disorder
- Circadian rhythm sleep disorders
- NREM parasomnias – sleepwalking/sleep eating
- Central sleep apnea

Abbreviations: CNS: central nervous system; NREM: non-rapid eye movement; REM: rapid eye movement

Module B: Management of Chronic Insomnia Disorder



[a] In cases where the patient requires immediate intervention, providers may exercise clinical judgment to determine if pharmacotherapy may be safely initiated.

[b] 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.

Abbreviations: BBT-I: brief behavioral therapy for insomnia; CBT-I: cognitive behavioral therapy for insomnia; CIH: complementary and integrative health; SDM: shared decision making

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

Patient education and SDM:

- General information on insomnia disorder
- Education about behavioral treatment options
- Discussion of treatment options (risks, benefits, preferences, and alternatives)

Behavioral treatment components (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
- Relaxation: Reduces physiological arousal and promotes optimal conditions for sleep
- Sleep Hygiene Education: Counseling regarding behaviors that interfere with sleep
- Cognitive Restructuring (CBT-I only): Addresses cognitive arousal (busy or racing mind) by challenging unhelpful thoughts and beliefs about sleep, a natural result of the struggle with insomnia

Conditions requiring tailored or delayed CBT-I:

- Medically unstable
- Active alcohol or drug use disorder
- Excessive daytime sleepiness
- Engagement in exposure-based PTSD treatment
- Uncontrolled seizure disorder
- Bipolar disorder
- Current acute mental health symptoms

Abbreviations: BBT-I: brief behavioral therapy for insomnia; CBT-I: cognitive behavioral therapy for insomnia; PTSD: posttraumatic stress disorder; SDM: shared decision making

Sidebar 4: Pharmacotherapy Considerations for Chronic Insomnia Disorder

Before starting short-term pharmacotherapy, review sleep history, 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:

- Low-dose doxepin; 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)

The use of antipsychotic agents is NOT suggested for treatment of chronic insomnia disorder.

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

Abbreviations: BBT-I: brief behavioral therapy for insomnia; CBT-I: cognitive behavioral therapy for insomnia; NREM: non-rapid eye movement

Sidebar 5: Other Approaches

CIH treatments suggested for chronic insomnia disorder:

- Auricular acupuncture with seed and pellet

Other treatments NOT suggested chronic insomnia disorder:

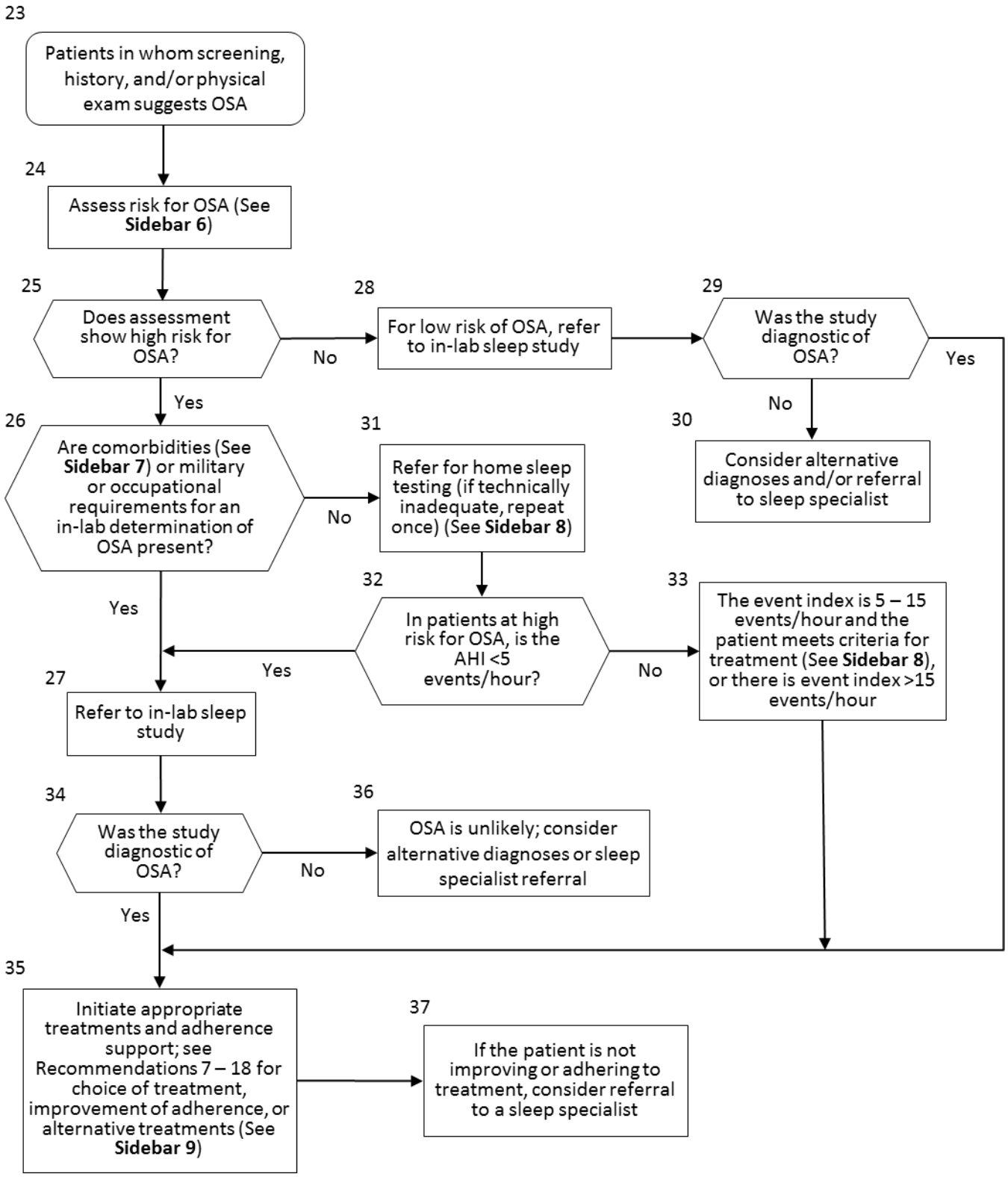
- Alpha-stim
- Cranial electrical stimulation
- Diphenhydramine
- Melatonin
- Chamomile
- Valerian

Other treatments NOT recommended for chronic insomnia disorder:

- Kava

Abbreviations: CIH: complementary and integrative health

Module C: Management of Obstructive Sleep Apnea



Abbreviations: AHI: apnea-hypopnea index; OSA: obstructive sleep apnea

Sidebar 6: Risk of OSA*

Consider using STOP questionnaire for risk stratification:

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

High risk if ≥2 items are answered "yes"

Low risk if <2 items are answered "yes"

STOP questionnaire should not replace clinical judgment; clinical assessment should include:
BMI >30 kg/m^2, age >50, menopausal status, neck circumference, family history, and crowded oropharynx

*i.e., high risk or high pretest probability of OSA

Abbreviations: BMI: body mass index; kg/m^2: kilograms per meter squared; OSA: obstructive sleep apnea; STOP: Snoring, Tiredness, Observed apnea, and high blood Pressure

Sidebar 7: Comorbidities

- Significant cardiorespiratory disease
  - Cardiovascular comorbidities including congestive heart failure
  - Pulmonary comorbidities that impact baseline oxygen saturation (or requiring oxygen therapy) including chronic obstructive pulmonary disease: GOLD Stage III or IV
- Stroke
- Respiratory muscle weakness
- Hypoventilation/suspected hypoventilation due to neuromuscular or pulmonary disorder
- Opioid use
- Chronic insomnia
- PTSD

Abbreviations: GOLD: Global Initiative for Chronic Obstructive Lung Disease; PTSD: posttraumatic stress disorder

Sidebar 8: AHI 5 – 15 on HSAT

1. Treatment for OSA is recommended for symptomatic patients with an AHI or REI of 5 – 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 – 15 events per hour on HSAT should be treated as OSA

Abbreviations: AHI: apnea-hypopnea index; HSAT: home sleep apnea testing; OSA: obstructive sleep apnea; PSG: polysomnogram; REI: respiratory event index

Sidebar 9: Treatment of OSA

1. For patients with severe OSA (i.e., AHI ≥30 events per hour), the recommended initial therapy is PAP
2. For patients with mild to moderate OSA (i.e., AHI 5 – <30 events per hour), either PAP or MAD therapy can be considered for initial therapy; choice of treatment should be based on clinical evaluation, comorbidities, and patient preference
3. Educational, behavioral therapy, and supportive interventions should be offered to improve PAP adherence
4. Weight loss and a comprehensive lifestyle intervention program should be encouraged in all patients with OSA who are overweight or obese; while weight loss alone is typically insufficient as therapy for OSA, weight loss may result in improvement of AHI
5. In those OSA patients who are not adherent to PAP and/or MAD therapy or have persistent symptoms despite adequate therapy, referral to a physician with expertise in sleep medicine is recommended

Abbreviations: AHI: apnea-hypopnea index; MAD: mandibular advancement device; OSA: obstructive sleep apnea; PAP: positive airway pressure

VI. Recommendations

Topic	Sub-topic	#	Recommendation	Strength[a]	Category[b]
Diagnosis and Assessment of Obstructive Sleep Apnea and Insomnia Disorder		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
		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
		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, apnea-hypopnea index) ≥15 events per hour to establish the diagnosis of moderate to severe obstructive sleep apnea.	Weak for	Reviewed-New-added
		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 apnea-hypopnea index <5), we recommend repeat (home sleep apnea testing or lab-based polysomnography) testing for obstructive sleep apnea.	Strong for	Reviewed, New-added
		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
		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
Treatment and Management of Obstructive Sleep Apnea		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
		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
		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
		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
		11.	In appropriate patients with mild to moderate obstructive sleep apnea (apnea-hypopnea 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
		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

Topic	Sub-topic	#	Recommendation	Strength[a]	Category[b]
Treatment and Management of Obstructive Sleep Apnea (cont.)		13.	For patients with obstructive sleep apnea with an apnea-hypopnea index of 15 – 65 per hour and a body mass index <32 kg/m^2 who cannot adhere to positive airway pressure therapy, we suggest evaluation for surgical treatment with hypoglossal nerve stimulation therapy.	Weak for	Reviewed, New-added
		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
		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
		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
		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
		18.	Due to the lack of clinically significant benefit, we cannot recommend for or against: • auto-titrating positive airway pressure when compared to fixed positive airway pressure, or • the use of flexible pressure delivery (e.g., C-Flex®, expiratory pressure relief) to improve positive airway pressure adherence.	Neither for nor against	Reviewed, New-added
Treatment and Management of Chronic Insomnia Disorder	*Behavioral and Psychological Treatments*	19.	We recommend offering CBT-I for the treatment of chronic insomnia disorder.	Strong for	Reviewed, New-added
		20.	We suggest offering brief behavioral therapy for insomnia (BBT-I) for the treatment of chronic insomnia disorder.	Weak for	Reviewed, New-added
		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
		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
		23.	For patients diagnosed with chronic insomnia disorder, we suggest CBT-I over pharmacotherapy as first-line treatment.	Weak for	Reviewed, New-added
		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
		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
		26.	We suggest against sleep hygiene education as a standalone treatment for chronic insomnia disorder.	Weak against	Reviewed, New-added

Topic	Sub-topic	#	Recommendation	Strength[a]	Category[b]
Treatment and Management of Chronic Insomnia Disorder	*Complementary and Integrative Health Treatments*	27.	We suggest offering auricular acupuncture with seed and pellet for the treatment of chronic insomnia disorder.	Weak for	Reviewed, New-added
		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
		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
		30.	We suggest against cranial electrical stimulation for the treatment of chronic insomnia disorder.	Weak against	Reviewed, New-added
	Over-the-counter Treatments	31.	We suggest against the use of diphenhydramine for the treatment of chronic insomnia disorder.	Weak against	Reviewed, New-added
		32.	We suggest against the use of melatonin for the treatment of chronic insomnia disorder.	Weak against	Reviewed, New-added
		33.	We suggest against the use of valerian and chamomile for the treatment of chronic insomnia disorder.	Weak against	Reviewed, New-added
		34.	We recommend against the use of kava for the treatment of chronic insomnia disorder.	Strong against	Reviewed, New-added
	Pharmacotherapy	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
		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
		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
		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
		39.	We suggest against the use of antipsychotic drugs for the treatment of chronic insomnia disorder.	Weak against	Reviewed, New-added
		40.	We suggest against the use of benzodiazepines for the treatment of chronic insomnia disorder.	Weak against	Reviewed, New-added
		41.	We suggest against the use of trazodone for the treatment of chronic insomnia disorder.	Weak against	Reviewed, New-added

[a] For additional information, please refer to Grading Recommendations.

[b] For additional information, please refer to Recommendation Categorization.

Abbreviations: BBT-I: brief behavioral therapy for insomnia; CBT-I: cognitive behavioral therapy for insomnia; STOP: Snoring, Tiredness, Observed apnea, and high blood Pressure

A. Diagnosis and Assessment of Obstructive Sleep Apnea and Insomnia Disorder

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)

Discussion

Using an AHI (defined as the number of apneas and hypopneas per hour of sleep) ≥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 Gender), STOP questionnaire (Snoring, Tiredness, Observed Apnea and high blood Pressure), and ESS.[43] No published literature was found for ISI, PSQI, International Restless Legs Syndrome Study Group Questionnaire (IRLSSQ), or Morningness-Eveningness Questionnaire (MEQ) as screening tools for OSA as defined above. In a recent 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.[43] 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.

The Work Group agreed that, considering all these performance measures, none of these questionnaires has sufficient accuracy in establishing a diagnosis of OSA. Because confirmatory objective testing is a requirement after screening, 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 similar to each other. Given their performance similarities and its simpler administration, STOP was included in our recommendation. This questionnaire consists 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.[44]

Evidence that was not part of the systematic evidence review conducted for this CPG has shown that VA/DoD populations are generally at high risk for OSA.[31,45] In addition, the performance of the STOP questionnaire relative to PSG has not been determined in specific populations with high prevalence of OSA, including stroke, atrial fibrillation, refractory hypertension, congestive heart failure (CHF),[46] seizures,[47] chronic obstructive airway disease, asthma,[48] pulmonary fibrosis,[49] and pregnancy. Therefore, a negative questionnaire screen should not negate the need for a sleep study in these high-risk populations.[50,51]

The Work Group's confidence in the quality of the evidence is moderate.[43] This recommendation was based on a single meta-analysis. Although it could introduce some inefficiency and possible false positive cases, the Work Group determined the benefits of OSA screening outweigh its harms or burdens. The

patient focus group expressed similar values, advocated for time efficiency in screening, and preferred early rather than delayed detection of OSA. The Work Group acknowledged that implementing screening would require additional resources and that these resources may not be available to all providers. Additionally, implementing screening would lead to increased referrals to sleep laboratories/centers. Owing to variability in resource availability, the Work Group determined that a "Strong for" recommendation could impose an unintended burden on providers with limited access to resources. Thus, the Work Group decided upon a "Weak for" recommendation.

Recommendation

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)**

Discussion

We reviewed the evidence supporting the key clinical factors that contribute to SDB, a term encompassing both obstructive and central sleep apnea (CSA) because the two conditions may present with similar clinical features, are pathophysiologically linked,[46,52] and, therefore, their measure of apnea severity (i.e., AHI, obstructive apnea index, and central apnea index [CAI]) are often reported concurrently in the epidemiology literature. In a prospective cohort study of a community-based sample of middle-aged and older adults by Chami et al. (2011), patients with incident CVD had greater levels of both obstructive and central apnea indices by 1.75 per hour, compared with participants without incident CVD, even after adjusting for multiple relevant covariates.[53] Subjects with incident CVD were more likely to experience significant SDB progression (defined as change in AHI of ≥5 events per hour) compared with subjects without incident CVD (47.4% versus 31.7%). When patients with myocardial infarction (MI) and CHF were considered separately, the association of AHI levels with incident CHF was only half as large as with incident MI.[53]

Multiple studies have demonstrated that the risk of SDB was higher in men compared to women.[16,54,55] Moreover, postmenopausal female Veterans were more likely to have both insomnia and SDB compared to their non-Veteran counterparts.[56] In the same study, women, both Veterans and non-Veterans, with insomnia and SDB had increased risk of CVD and incident diabetes.

Studies also found a significantly higher risk of OSA in patients with stroke or CHF.[54,57] A large national U.S. health claims database analysis revealed that the age- and sex-adjusted odds of ischemic heart disease, stroke, and CHF were significantly increased two- to fourfold in patients with an OSA diagnosis.[57] A significantly higher risk of both OSA and CSA was found in patients with cerebrovascular disease.[54,55,57] Similarly, a significantly higher risk of CSA was found in patients with CHF.[55]

A retrospective cohort study patients on opioid therapy for chronic spinal pain had an increased prevalence of OSA (13.8%) compared to patients without prescription opioids or benzodiazepines (10.5%).[54] The study also noted a significant correlation of OSA diagnosis with multiple comorbid conditions, including a history of CHF, stroke, atherosclerotic CVD, and increasing BMI. Additionally, a large retrospective cohort study from a national sample of U.S. Veterans reported that male gender and chronic prescription opioid use were associated with two times greater risk of CSA diagnosis compared with controls.[55] Thus, the available evidence suggests that individuals who have CVD, cerebrovascular

disease, CHF, or have a history of using prescription opioids, are at increased risk of obstructive, central, or both forms of SDB.

There was insufficient data to determine whether PTSD and OSA have a causal relationship. Studies linking PTSD and OSA are limited in that there may be selection bias due to the high prevalence of both disorders in the Veteran population. In one retrospective review in young military personnel, there was a significantly higher risk of PTSD among women with comorbid OSA and insomnia;[27] however, no additional suitable data was retrieved regarding a causal association between OSA and PTSD.

The Work Group noted that the above risk factors do not comprise an exhaustive list of possible risk factors for SDB. The Work Group also noted that the systematic evidence review did not reveal any data on TBI as a risk for OSA. Risk factors including advanced age and obesity were not part of the literature search conducted as part of the systematic evidence review for this CPG and are not discussed here.

The Work Group discussed the balance of benefits and harms in terms of assessing these high-risk patients for SDB and determined there were few harms, though there might be some cost involved in making the diagnosis. The Work Group considered that there was some variation in values and preferences; for example, some patients may not want to undergo clinical assessment for SDB or be asked about usage of opioid medications.

The Work Group's confidence in the quality of the evidence is very low, though the risks of assessment for SDB were small.[16,27,53-57] Therefore, the Work Group determined that clinical assessment for SDB is warranted for patients with a history of cardiovascular or cerebrovascular events, CHF, or chronic opioid use. Thus, the Work Group decided upon a "Weak for" recommendation.

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, apnea-hypopnea index) ≥15 events per hour to establish the diagnosis of moderate to severe obstructive sleep apnea.
   (Weak for | Reviewed, New-added)
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 apnea-hypopnea index <5), we recommend repeat (home sleep apnea testing or lab-based polysomnography) testing for obstructive sleep apnea.
   (Strong for | Reviewed, New-added)

Discussion

The gold standard test for evaluation of SDB is the attended in-lab PSG. Over the past several decades, evaluation with portable monitoring (PM) devices known as HSATs has provided an alternative, home-based method of evaluating SDB. 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. One single center RCT evaluated the validity of the ApneaLink type III PM compared to in-lab PSG.[58] In this study, 149 participants were evaluated in the laboratory with PSG and PM followed by a PM evaluation approximately one month later. PM data were scored manually as well as with two automated scoring systems (Auto, which used an 80% flow reduction for apneas and a 50% to 80% flow reduction for

hypopneas, and Auto AASM, which used a 90% flow reduction for apneas and a 30% to 90% reduction for hypopneas associated with a 3% oxygen desaturation). As the AHI cutoff value for a positive diagnosis of OSA increased from 5 to 30 events per hour, the sensitivity decreased and specificity increased in all three scoring systems. The study noted that the Auto scoring system was more sensitive at all cutoffs and that the manual scoring system and Auto AASM scoring systems were more specific at all cutoffs. At AHI cutoffs of 5, 15, and 30 events per hour, utilizing the manual scoring system for the at-home study, the sensitivity decreased from 0.93 to 0.75 and 0.63, respectively. Specificity at these cutoffs increased from 0.62 to 0.87 and 0.93 at the same cutoffs for manual scoring. The important outcome of area under the receiver operating characteristic (ROC) curve increased from 0.874 to 0.876 and 0.928 at the 5, 15, and 30 event per hour cutoffs.[58] Largely due to concerns regarding specificity of type III 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 a question, either repeat testing or a referral to a sleep specialist 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.

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.[59] Sensitivity and specificity did improve in the three studies utilizing devices with three or more channels; however, the patients evaluated with PMs had these studies conducted in a lab rather than in their home environment. The available SR did include four studies evaluating the WatchPAT®, a peripheral arterial tonometer device. All studies included less than 100 patients. A study by Garg et al. (2014), which was included in the SR by Abrahamyan et al. (2018),[59] evaluated the ROCs of WatchPAT® devices at various AHI cutoffs when compared to in-lab PSG in 75 African American patients.[60] The areas under the curve for the ROCs for WatchPAT® devices were 0.90 at an in-lab PSG AHI cutoff of 5 events per hour, 0.92 at 10 events per hour, and 0.92 at 15 events per hour. In summary, the Work Group determined there was insufficient evidence to recommend for or against the routine use of WatchPAT® devices based upon the available evidence in the systematic literature review conducted for this CPG. The Work Group's confidence in the quality of evidence is low. Given the substantial amount of data that exists on this topic, the Work Group expressed concern that only a small number of studies met inclusion criteria for the evidence review. There were also several studies that did not meet the criteria for inclusion, mostly due to small sample sizes.[61-67] However, the findings of these smaller studies are generally consistent with this recommendation.

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, Sidebar C). 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. 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 MVCs compared to the general population [68] and have a higher risk of personal injury related to those MVCs.[69,70] 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.[71] 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.[72,73] An AHI >20 events per hour confers a higher risk of stroke [74] and an AHI >30 events per hour confers a higher risk of dysrhythmias and all-cause mortality.[75,76] 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 repeat testing in patients for whom an HSAT does not confirm a diagnosis of OSA. This is also consistent with recommendations regarding evaluation with HSAT in other CPGs.[7,77] These CPGs from other organizations were not included in our evidence review and, thus, are independent from the strength of this recommendation.

Despite general consistency in the evidence supporting home testing, there is some variability in provider and patient preferences regarding this evaluation method when compared to in-lab PSG. As suggested by the patient focus group participants, patients may prefer HSAT because it enables them to sleep in their usual bed and avoid the more invasive in-lab PSG. While home testing can be burdensome to patients, particularly if repeated testing is required, there is considerable potential to enhance patient convenience with this approach. The Work Group did not find any evidence of significant patient harm regarding PM.

The Work Group's confidence in the quality of the evidence for Recommendation 3 is moderate.[58] The body of evidence had some limitations, including small sample size and certain characteristics of the patient population. Specifically, in the Cho et al. (2017) study, the mean age of 40 years may not be as relevant to VA/DoD patients.[58] Other considerations regarding this recommendation included the benefits, including increased speed of evaluation and increased patient convenience (sleeping at home instead of the sleep lab), which outweigh the negligible potential for adverse events. Patient values and preferences are likely to be somewhat varied. Thus, the Work Group decided upon a "Weak for" recommendation.

Regarding Recommendation 4, the Work Group's confidence in the quality of the evidence for this recommendation is low.[58,59] However, the Work Group believed that the risk of significant harm related to undiagnosed OSA as a result of a non-diagnostic test in a patient with high pretest probability significantly outweighed concern 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 upon a "Strong for" recommendation.

Recommendation

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)**

Discussion

The ISI and the Athens Insomnia Scale (AIS) [78] have high diagnostic accuracy for insomnia. In an SR conducted by Chiu et al. (2016), both measures were found to be both sensitive and specific for accurately classifying individuals with insomnia.[79] Chiu et al. concluded that all screening tests were effective at distinguishing between patients with and without insomnia. They found no statistically significant differences between different screening tools. They computed sensitivity and specificity for the three measures 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,[80] whereas a cutoff score of 6 correctly discriminated insomnia patients from controls on the AIS in 90% of cases.[81] These clinical samples were not included in our systematic evidence review and, thus, are independent from the strength of this recommendation.

Self-report measures for the assessment of insomnia disorder are an important part of a larger comprehensive assessment. As discussed in the Background, diagnosing insomnia disorder requires a sleep history and detailed medical, substance, and psychiatric history, and self-reported measures are recommended as part of this process for both evaluation and differential diagnosis.[82] The ISI and AIS have demonstrated accuracy for insomnia diagnosis and are recommended for this purpose.

The Work Group's confidence in the quality of the evidence is low due to limitations in the body of evidence, including publication bias, patient selection, reference standards, and study quality.[79] Several factors were considered in the Work Group's decision to recommend the ISI and AIS for insomnia disorder screening over the PSQI. First, we considered questionnaire length and scoring process. The ISI and AIS measures are comprised of only seven and eight items, respectively; scoring these measures involves only calculating a sum across items. In contrast, the PSQI is comprised of 24 items and involves a more lengthy scoring process. Second, we considered the intended purpose of each measure. 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 (e.g., sleep apnea). 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. Owing to the brevity and high accuracy of the recommended measures, the Work Group concluded that the benefits of their use outweigh any harms/burdens. As is true for all questionnaires, some patients are likely to be amenable to completing the ISI and AIS, while others will not. However, there is no cost to administering these measures and their use may increase the efficiency of patient-provider interactions. When all factors were considered, the Work Group decided upon a "Weak for" recommendation.

Recommendation

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)

Discussion

Additional diagnostic testing for patients with chronic insomnia disorder who do not respond to CBT-I or pharmacotherapy was included in the evidence search; however, there was no available evidence to make a recommendation for or against additional diagnostic testing, such as home sleep apnea testing or laboratory PSG, in this patient population. As treatment for refractory insomnia is increasingly recognized and many patients with insomnia disorder have other suspected sleep disorders (e.g., OSA), the Work Group acknowledged that further evaluation of the patient, as part of an SDM process, to include consideration of a referral to a sleep medicine specialist, should be considered.

B. Treatment and Management of Obstructive Sleep Apnea

Recommendation

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)

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)

Discussion

Evidence supports an association between increasing positive airway pressure use and improved outcomes.[83-86] The relationship between PAP usage and health outcomes (specifically daytime sleepiness, quality of life, blood pressure, and cardiovascular events) among patients with mild to severe OSA has been the subject of several RCTs.[87] A relevant SR and meta-analysis of 36 trials with 1,718 patients was outside of the systematic evidence review and, therefore, independent from the strength of this recommendation.[87] It found that PAP therapy compared to control conditions improved sleepiness, quality of life, 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.[84] These data establish that PAP therapy, when compared with no active therapy, improves patient outcomes.

Several studies provide insight into the key clinical question: what level of PAP use is associated with improvements in patient outcomes? Although the results of the studies are mixed, the data suggest that although the greatest improvements in outcomes are observed with the highest levels of PAP use, even when used less than four hours per night, PAP therapy is associated with improvement in some patient outcomes (i.e., sleepiness, functional status, and quality of life). While not included in our systematic evidence review and, thus, independent from the strength of this recommendation, Weaver et al. (2007)

examined the relationship between hours of PAP use and outcomes among 149 patients with mild to moderate sleep apnea with PAP use that ranged from 0 to 8.1 hours per night.[88] In general, patients who used PAP therapy the longest (≥7 hours per night) achieved the greatest improvements in clinical outcomes (e.g., quality of life) compared with patients with fewer hours of use (≤2 hours per night); however, even patients with PAP use ≤2 hours per night achieved some improvements in subjective (ESS) and objective sleepiness (multiple sleep latency test), and quality of life (Functional Outcomes of Sleep Questionnaire [FOSQ]). For example, although 93% of patients who used PAP for ≥7 hours per night had clinically substantial improvements in daytime sleepiness, 41% of patients with <2 hours of PAP per night similarly experienced improvement in sleepiness.[88]

An RCT by Barbé et al. (2012) examined the effect of PAP on the incidence of hypertension or cardiovascular events (n=723 patients).[83] Although they found no significant differences in the intention-to-treat (ITT) comparison of PAP versus control patients who received no active intervention, in an analysis by adherence, the authors found that PAP use of ≥4 hours per night (adherence threshold determined *a priori*) was associated with a reduced risk of new hypertension or cardiovascular events (7.90 events per 100-person-years [95% CI 5.88 – 9.91]) compared with controls (11.02 events per 100-person-years [95% CI 8.96 – 13.08]).[83] However, the PAP use of <4 hours per night group included patients with no use as well as patients with some use. Therefore, no assessment can be made of the potential dose relationship between PAP and incident cardiovascular outcomes with usage rates <4 hours per night from this study.

Several other studies have reported benefits in outcomes with PAP use of <4 hours per night. For example, the BestAir study (n=169) found that 6 to 12 months of PAP therapy improved quality of life and daytime sleepiness among patients with OSA and high cardiovascular risk.[85] These benefits were observed even though the mean PAP use was 3.8 hours per night at six months and 3.4 hours per night at 12 months. Increasing PAP use was associated with greater improvement in sleepiness.[85]

Although not included in our systematic evidence review and, thus, independent from the strength of this recommendation, Weaver et al. (2012) observed an association of improved outcomes with increasing duration of PAP use in an eight-week trial of PAP therapy versus sham, which demonstrated improved functional outcomes (e.g., quality of life) among patients with mild to moderate OSA.[89] Moreover, the authors reported a linear association between hours of PAP use and improved functional status (n=101). In another example, Rosen et al. (2016) (n=373) found that sleepiness, functional status, and quality of life improved among adults referred to a sleep center after initiating PAP therapy even with 3.7 hours use per night (SD 2.0).[90] In a final study, the Sleep Apnea cardioVascular Endpoints (SAVE) trial followed 2,687 adults with moderate to severe OSA and vascular disease for a mean of 3.7 years.[91] PAP use at 3.3 hours per night improved daytime sleepiness, quality of life, and mood but not the primary composite endpoint of fatal or non-fatal vascular events. In the secondary, propensity-adjusted analysis, use of PAP on average of ≥4 hours per night over the first two years of the study was associated with a lower risk of stroke and combined cerebrovascular events compared to usual care. A post hoc PAP dose response analysis of the SAVE data did not demonstrate a statistically significant association with cardiovascular outcomes.[91]

The evidence base for these recommendations did not include studies with concomitant therapies; therefore, no recommendations can be made related to co-therapeutic approaches.

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.[86] 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).[92] 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.[92] The mechanisms underlying the relationship between PAP use and weight gain remain unclear.

For Recommendation 7, the Work Group's confidence in the quality of the evidence is moderate.[83-86] The Work Group also considered that the benefits of treatment with PAP outweighed the minor potential harms. Some variation in patient preferences regarding the nightly duration of PAP therapy exists, and resource use issues related to reimbursement for long-term PAP therapy are relevant. Thus, the Work Group decided upon a "Strong for" recommendation.

For Recommendation 8, the Work Group's confidence in the quality of the evidence is moderate.[83-86] Based on the evidence that longer duration of nightly PAP use is associated with greater improvements in patient-centric outcomes, we recommend that patients with OSA on PAP use PAP for the entirety of their sleep periods. Based on the data that some PAP therapy is better than no PAP therapy for improving outcomes, we suggest that patients who are currently using PAP therapy for <4 hours a night should not be required to discontinue PAP treatment, but rather should be offered interventions to improve PAP adherence (see Recommendation 9) or alternative treatments (see Recommendation 11, Recommendation 13, Recommendation 14, and Recommendation 15). Thus, the Work Group decided upon a "Weak for" recommendation.

Recommendation

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)

Discussion

Based on the results of a Cochrane Review, educational, behavioral, and supportive interventions have been found to improve adherence to PAP (i.e., hours of use per night) among patients with SDB.[93] This recommendation is based on one SR by Wozniak et al. (2014) (moderate quality of evidence), which summarized findings from 40 studies, including 26 with critical outcomes of interest (n=1,890).[93] This review primarily included studies of continuous PAP-naive patients at the beginning of treatment and concluded that supportive strategies, educational therapy, and behavioral interventions were associated with significant improvements in mean hours of PAP use per night and in the proportion of patients who used PAP more than four hours per night, as compared to control conditions (typically usual care). Across studies, the follow-up time interval ranged from four to 52 weeks. The strongest evidence was for interventions that included education about sleep apnea and continuous positive airway pressure (CPAP)

therapy (rather than support alone). There was considerable variability in terms of the intervention content, delivery method, and type of provider delivering the intervention. There was no evidence that these interventions caused harm and benefits were demonstrated in multiple trials.

Evidence was largely consistent and our focus group participants also expressed the desire for support and assistance in adjusting to treatments for sleep disorders (see Appendix G). 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 in available resources and trained clinicians to provide educational, behavioral, and supportive interventions for increased PAP adherence. Because multiple types of interventions may be beneficial, effective approaches can be delivered by a variety of providers, including clinical psychologists, nurses, respiratory therapists, health educators, physicians, or sleep technicians. Nonetheless, some patients may have difficulty accessing these treatments. For example, if interventions are delivered solely face-to-face, patients with travel-related challenges may not be able to access them.

The Work Group's confidence in the quality of the evidence for this recommendation is moderate and is based on one SR.[93] Other considerations relevant to this recommendation included the benefits of improved adherence to a known effective therapy that has no identified harms, patient values and preferences for these interventions, and acceptability of the intervention by providers. The Work Group, therefore, decided upon a "Strong for" recommendation, considering the strength of the evidence and aforementioned factors favoring these approaches.

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)

Discussion

As described in Recommendation 9, educational, behavioral, and supportive interventions have been found to improve adherence to PAP therapy (i.e., hours of use per night) among patients with SDB.[93] Evidence from one RCT supported that patients with OSA plus anxiety had lower adherence to PAP than patients without anxiety.[94] One SR of three observational studies found that regular use of PAP and number of hours used per night were lower among Veterans with comorbid PTSD compared to Veterans with OSA alone.[23] There is no evidence for additional harms or reduced benefits of supportive, educational, or behavioral interventions to improve PAP adherence among patients with these comorbid conditions; however, there may be additional burden associated with identifying these comorbid conditions so that patients can be targeted for early access. Of note, the criteria used to define anxiety and insomnia were variable across studies.

There are select groups of patients at high risk for PAP non-adherence who are likely to benefit from early access to interventions to improve PAP adherence. One prospective cohort study not included in this CPG's systematic evidence review and, thus, independent from the strength of this recommendation, showed that patients with insomnia were more likely to discontinue use of PAP therapy within one year.[95] There was general consistency in the evidence demonstrating lower PAP adherence rates among individuals with

insomnia, PTSD, or anxiety. There is likely consistency in provider and patient preferences regarding supportive, educational, and behavioral interventions to improve PAP adherence based on the opinions and experience of Work Group members and the results of our patient focus group. The patient focus group revealed that patients prefer help with addressing treatment-related challenges early. There are challenges with identifying comorbid conditions such as insomnia, anxiety, and PTSD that would be required to implement adherence interventions early, which presents unique challenges for these subgroups of patients. The same challenges that apply to delivery of these adherence interventions described under Recommendation 9 through Recommendation 18 also apply here. There are likely to be variations in the delivery of these interventions across sites due to variations in the availability of resources and provider training. Since multiple types of treatments (i.e., supportive, educational, and behavioral interventions) may be beneficial, effective approaches can be delivered by a variety of providers, including clinical psychologists, nurses, respiratory therapists, health educators, physicians, or sleep technicians. Furthermore, it may be easier for some patients to access these treatments than others. For example, if interventions are delivered face-to-face, patients faced with travel-related challenges may have difficulty accessing these treatments.

The Work Group's confidence in the quality of the evidence for this recommendation is low for PTSD (due to small sample sizes) and moderate for comorbid anxiety and insomnia.[23,93,94] Other considerations for this recommendation included indirectness of evidence; challenges in screening SDB patients for comorbid conditions; the benefits of improved adherence to a known effective therapy with no identified harms; patient values and preferences that indicate many patients would desire these interventions; and acceptability of the intervention by providers. The Work Group, therefore, decided upon a "Weak for" recommendation, considering the overall low strength of the evidence.

Recommendation

11. In appropriate patients with mild to moderate obstructive sleep apnea (apnea-hypopnea 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)

Discussion

After PAP therapy, the next most studied treatment for OSA is the MAD. The MAD is also commonly referred to as "oral appliance therapy", "mandibular advancement splint", or "mandibular repositioning appliance." MAD therapy increases the size of the upper airway, primarily in the velopharynx, by advancing or stabilizing the mandible during sleep, reducing the collapsibility of the airway and the severity of OSA.[32] The Work Group specifically reviewed a number of studies comparing PAP and MAD therapy.[34,96-99] Although all studies concluded that PAP therapy was superior in AHI reduction, none of these studies found a significant difference in improvement of daytime sleepiness, cognitive function, vigilance, hypertension, or quality of life measures. One randomized cross-over trial of Veterans diagnosed with OSA and PTSD reported significantly higher patient preference for and adherence to MAD over PAP therapy.[34] In this study, there was an equivalent amelioration of PTSD severity and sleep-related quality of life improvement. Thus, while MAD 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.

There is a balance of potential risks and benefits with MAD therapy for treatment of mild-to-moderate OSA as opposed to treatment with PAP therapy. In determining if MAD therapy is appropriate for a patient with OSA, the presence or absence of comorbid diseases and patient preferences should be considered. In patients with bruxism, MAD therapy can manage both disorders. Further, if a patients' profession or lifestyle requires frequent travel or limited access to electricity, MAD therapy may be preferred. Also, MAD is intra-oral, as opposed to PAP which requires an interface (i.e., mask), and patient preference should be accounted for. Conversely, patients with significant cardiovascular or pulmonary disorders, an unstable dentition, or those who are morbidly obese may have relative contraindications to MAD and thus are better suited for PAP therapy. Another indication for MAD is in combination with PAP therapy if mask leakage or excessive PAP pressures are given as reasons for poor PAP adherence.[34]

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 on the side effects of MAD.[32,100] 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.[100] The majority of these side effects are self-limiting and the risk of tooth movement may be mitigated through material selection and avoidance of soft liners. Digitally engineered, custom milled appliances made of hard acrylic produce the least tooth movement and function similarly to orthodontic retention devices (retainers). MAD therapy has the potential to trigger temporomandibular joint or muscle pain in a small percentage of patients, but can also resolve pain associated with bruxism or teeth clenching associated with SDB. Management of MAD therapy side effects requires patient-specific strategies and treatment should not be discontinued until alternative therapies are identified by the sleep provider.[100]

These devices can be prefabricated or custom fabricated and can be either fixed or titratable. Treatment with a titratable, custom-fabricated MAD, delivered by a qualified dentist is recommended. An acceptable therapeutic outcome typically requires a maximum protrusion of >50% of the patients' mandibular range of motion. Most patients with mild and moderate OSA will respond to MAD therapy, but not all. Qualified dentists should confirm suitability for treatment and therapeutic protrusive position with a validated assessment device to quickly identify non-responders and move them to combination or alternative therapies. Gradual evaluation and titration of MAD until maximum compliance and resolution of symptoms are reported is an acceptable alternative if an assessment device is not available. In determining if a patient has achieved an appropriate therapeutic response with MAD therapy, patients with moderate or severe OSA should have a follow-up sleep study with in-lab titration of the device as indicated. In patients with mild OSA, the requirement for a follow-up sleep study is at the discretion of the treating provider.

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 blinding, objective measurements, and mitigated risk of bias.[34,96-99] However, the 30-plus year body of evidence was acceptable to render a recommendation. Other considerations regarding this recommendation included the requirement for adequate dentition (i.e., 8 – 10 teeth in both arches) and supporting bone/periodontium, patient desire or need for non-PAP alternatives, benefits of patient comfort with MAD, and the requirement for a follow-up sleep study in patients with moderate to severe OSA treated with MAD. The Work Group also considered the importance of ensuring a qualified dentist was involved in MAD selection, delivery, and follow-up care.

The RCT design weakness and variance in patient values and preference regarding this therapy led the Work Group to agree on a "Weak for" recommendation.

Recommendation

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)

Discussion

Upper airway surgery (sinonasal surgery, soft tissue pharyngeal surgery such as palatoplasty or pharyngoplasty) has been shown to improve PAP adherence in patients with 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 PAP. An 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%.[101] In another SR, Ayers et al. (2016) found a mean increase in nightly PAP use of 0.62 hours after upper airway surgery.[102] This 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.

While the evidence supporting upper airway surgery to improve PAP tolerance is consistent, there is known variability in provider and patient preferences regarding surgery. Patients' and providers' desire to pursue surgery could be based on prior experiences with surgery. Also, surgical treatment has other implications that need to be considered. Operative procedures can come at a significant financial cost to 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, not every patient is a good candidate for surgical treatment, based on comorbidity profile and general health status. These factors can limit the effectiveness of this treatment.

The Work Group's confidence in the quality of the evidence for this recommendation is very low.[101,102] This is largely due to the fact that nearly all of the studies included in the SRs are observational studies or case series of small numbers of patients, with only one RCT identified. However, as the evidence was consistent in showing benefit and the risk of adverse events is small, the benefits were deemed to slightly outweigh the risks of surgical treatment. Patient values and preferences regarding this treatment were considered to be somewhat varied. Thus, the Work Group decided upon a "Weak for" recommendation.

Recommendation

13. For patients with obstructive sleep apnea with an apnea-hypopnea index of 15 – 65 per hour and a body mass index <32 kg/m^2 who cannot adhere to positive airway pressure therapy, we suggest evaluation for surgical treatment with hypoglossal nerve stimulation therapy.
    (Weak for | Reviewed, New-added)

Discussion

Since as many as half of patients prescribed PAP therapy for the treatment of OSA will not be adherent long-term, there is a need for alternative treatment options.[103-106] Hypoglossal nerve stimulation (HGNS) therapy, alternatively termed upper airway stimulation (UAS), is a relatively new technology that has promising results in treating moderate and severe OSA in select patients. This fully-implanted neurostimulator dilates the upper airway, thereby treating OSA, by selectively stimulating branches of cranial nerve XII (the hypoglossal nerve) causing the tongue to stiffen and protrude while the device is active during sleep.

An SR by Kompelli et al. (2018) found statistically and clinically significant benefits in both objective (AHI and oxygen desaturation index [ODI]) management of OSA and subjective (ESS and FOSQ) improvement of daytime sleepiness and quality of life measures.[107] In the longest prospective cohort trial completed to date, a mean AHI reduction from 32 per hour to 12.4 per hour was demonstrated five years after device implantation, with 71 of the original 126 patients completing the follow-up PSG at five years.[108] The Work Group acknowledged that this therapy does involve surgical intervention and the use of an implanted medical device. However, the published rates of adverse events from the surgical implantation and device use are low.[108] Given the demonstrated benefit for these patients who are unable to use PAP therapy, the benefits of this therapy were deemed to outweigh the harms.

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. The other implication that needs to be considered is the resource utilization for this treatment; specifically, the cost of surgery and the device, as well as the need for a specially trained surgeon. Furthermore, this therapy has mostly been tested in a specific population of patients based on strict exclusion criteria for AHI (recommended for AHI between 15 – 65 events per hour), BMI (most rigorously tested for BMI <32 kg/m^2), and pattern of pharyngeal collapse during sleep endoscopy. In addition, not every patient is a good surgical candidate based on comorbid conditions and general health status and the consideration of this device and compatibility with magnetic resonance imaging (MRI) should be accounted for. The combination of these many factors can limit the utility of this treatment.

The Work Group's confidence in the quality of the evidence for this recommendation is low.[107,108] This is primarily because the individual studies are all either retrospective or prospective cohort studies with a small number of subjects that lack reporting on confounding variables. However, as the evidence was consistent in showing benefit, and the known risk of adverse events is low, the benefits were deemed to outweigh the risks for this treatment. Patient values and preferences regarding this treatment were considered to be somewhat varied. Thus, the Work Group decided upon a "Weak for" recommendation.

Recommendation

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)

Discussion

Maxillomandibular advancement surgery (MMA) is a subset of orthognathic surgery that has been used for over three decades to change the anatomy of the upper airway to treat OSA. Altering the facial skeleton can have a profound impact on the diameter and collapsibility of the upper airway. The surgery is commonly performed by oral and maxillofacial surgeons (OMFs) and occasionally by specially trained otolaryngologists (i.e., ear, nose, and throat specialists). The literature base regarding MMA surgery for OSA supported statistically significant improvements in several critical outcomes, including AHI, ESS scores, and FOSQ scores.[109-117] An SR including 234 patients found a mean reduction in AHI of 87% with MMA surgery in patients with a baseline mean AHI of 54 events per hour.[109] ESS score improvement was also significant, from a preoperative mean of 17.8 to 4.7 postoperatively.

Limited information was available on adverse events, although 1 – 2% of patients experience life-threatening complications.[109] The Work Group acknowledged that this therapy does involve an invasive surgical intervention that has inherent intraoperative risks as well as postoperative risks, including paresthesia, dysesthesia, infection, unaesthetic result, or failure of bones to fuse. However, the published rates of adverse events from orthognathic surgery are low. Given the demonstrated benefit for these patients who are unable to use PAP therapy, the benefits of MMA surgery were deemed to slightly outweigh the potential harms.

While the available evidence supporting the treatment of OSA with MMA surgery is consistent regarding improvement in critical outcomes, some variability is expected in provider and patient preferences regarding this extensive surgical procedure. This variability can be based on a patient's or a provider's experience with surgery. Other implications that need to be considered are the resources required for this treatment, specifically the cost of surgery and the need for a specially trained surgeon. Furthermore, this surgical treatment has inherent exclusion criteria based on patient factors such as age, comorbid conditions, status of dentition, and facial anatomy. The combination of these many factors can limit the utility of this treatment.

The Work Group's confidence in the quality of the evidence for this recommendation is very low.[109-117] This is because the individual studies are all either retrospective or prospective cohort studies with a small number of subjects and a lack of reporting on confounding variables. Also, due to limitations in study design for surgical intervention, there is no comparator group such as placebo or usual care. Patient values and preferences regarding this treatment were considered to be somewhat varied. As the evidence was consistent in showing benefit, and the benefits were deemed to slightly outweigh the risks for this treatment, the Work Group decided upon a "Weak for" recommendation.

Recommendation

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)

Discussion

Several non-surgical alternative therapies for OSA exist for those patients who cannot tolerate PAP or a MAD. If alternative/salvage therapies are being considered, consultation with a sleep specialist is

recommended to optimize treatment. Positional therapy, aimed at keeping a patient in the lateral position throughout the sleeping period, is an alternative therapy to treat OSA for patients with supine predominant disease. An SR by Barnes et al. (2017) reported that various positional therapies (e.g., tennis ball on participant's back, vibrating device when supine, alarm device when supine) significantly improved AHI and ODI at two weeks and three months, but not ESS or FOSQ scores compared to placebo or non-standard OSA therapy (sleep hygiene education, nasal decongestant).[118]

Myofunctional therapy (MT) is another alternative OSA therapy that involves specific exercises aimed at strengthening the oral and oropharyngeal muscles. An SR by Camacho et al. (2015) revealed that isolated MT for two to three months significantly improved AHI, ESS, and snoring but not ODI up to six months following completion of treatment.[119] In an RCT comparing MT to placebo MT, three 20-minute daily sessions of MT for three months significantly improved ESS and AHI but not snoring frequency or intensity.[120]

Exercise is also an alternative therapy for OSA. In patients with an AHI ≥5, an SR reported significant improvement in AHI and ESS following exercise. In this study, subjects completed a two-month exercise program of two or more sessions per week, for ≥30 minutes per session, as the sole therapy for their sleep apnea.[121] An RCT by Servantes et al. (2018) studied the effects of exercise in patients with heart failure and OSA. They found that compared to no exercise, three months of exercise therapy significantly improved AHI, New York Heart Association functional class, ESS, and quality of life in these patients.[122]

Expiratory positive airway pressure (EPAP) applies positive pressure only during the exhalation phase of breathing. One nasal EPAP device (Provent®; Provent Sleep Therapy, LLC, Manchester, New Hampshire) 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. An RCT by Berry et al. (2011) reported significant benefits of nasal EPAP compared to sham EPAP for all outcomes (AHI, ESS and ODI) at three months in individuals with mild-to-moderate OSA.[123] This study did not include 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.[124]

In the literature that was reviewed, there was insufficient evidence for weight loss, including bariatric surgery, as monotherapy for OSA. Several studies have evaluated the impact of weight loss on OSA, but none met our inclusion criteria. However, as weight loss in overweight or obese patients is beneficial in their overall clinical management, these treatments (e.g., dietary intervention, bariatric surgery) should be pursued as adjunctive therapy.

For Recommendation 15, the Work Group's confidence in the quality of the evidence is low.[118-124] Concerns with the SRs included non-consecutive enrollment of patients in some studies included in the SRs, studies being conducted at single institutions, lack of assessor blinding, and unclear randomization and allocation concealment methods.[118,119,121] Limitations of the individual trials included concerns with randomization and allocation concealment methods and lack of ITT analysis.[119,120,123] It should also be noted that none of the therapies discussed were directly compared to PAP or other recommended therapies and the included evidence did not study patients who had previously failed PAP or other recommended therapies. However, as the evidence showed benefit of alternative/salvage therapies in the treatment of OSA, and the risk of adverse events is small, the benefits were deemed to outweigh the

potential harms or burden of these therapies. Patient values and preferences regarding these treatments were considered to be somewhat varied as some patients may be unable or unwilling to tolerate these treatments. Additionally, the feasibility of using these treatments must be considered as some centers may lack resources or training for these therapies and patients with certain ailments may not be able to tolerate treatment (e.g., back/shoulder pain for positional therapy, nasal congestion for EPAP). Given these considerations, the Work Group decided upon a "Weak for" recommendation.

Recommendation

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)

Discussion

Oxygen, which may be used as a supplemental therapy in patients on 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.[125] Mehta et al. (2013) revealed that oxygen therapy improves oxygen saturation in patients with OSA but may also increase the duration of apnea-hypopnea events. This was the only evidence that met the inclusion criteria for the systematic evidence review conducted for this CPG.

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.[126] 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.[127,128] Notably, none of these studies included patients who were intolerant of CPAP and using oxygen as salvage therapy.

The Work Group's confidence in the quality of the evidence for this recommendation is low.[125] The use of home oxygen carries the small risk of adverse events, including combustion/explosion and fire. The risk of harm or burden with stand-alone oxygen therapy was deemed to outweigh potential benefits. Patient values and preferences regarding oxygen were considered to be varied since some patients may be unwilling to use oxygen therapy. The feasibility of oxygen therapy is also a consideration, for it may be difficult to obtain this treatment without evidence of nocturnal hypoxemia. With these considerations in mind, the Work Group chose a "Weak against" recommendation for oxygen therapy as a stand-alone treatment for patients with OSA who cannot tolerate other recommended therapies.

Recommendation

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)

Discussion

Topical nasal steroids are frequently prescribed to patients who have difficulty with PAP adherence. Although topical steroids are an acceptable therapy for patients with OSA and nasal congestion due to rhinitis or nasal polyps, evidence reviewed by the Work Group demonstrated that, in the absence of these associated disorders, topical nasal steroids did not improve PAP adherence. An SR by Chakhorn et al. (2017) demonstrated no improvement in either average duration of CPAP use per night or percentage of nights of CPAP use with the use of topical steroid treatment (specifically fluticasone propionate dosed at 50 micrograms twice daily) when compared to usual care.[129] Evidence also indicates some level side effects associated with nasal steroid use (e.g., epistaxis, nasal burning, nasal dryness).

The Work Group determined that there is some variability in provider and patient preferences regarding this treatment. In patients with chronic nasal obstructive symptoms, therapy with topical nasal steroids to augment PAP adherence remains a reasonable approach.

The Work Group's confidence in the quality of the evidence for this recommendation is moderate, for the body of evidence did not have concerning limitations.[129] Other considerations include the lack of proven benefit for PAP adherence and the small potential harm of adverse events in patients without nasal congestion. Thus, the Work Group decided upon a "Weak against" recommendation.

Recommendation

18. Due to the lack of clinically significant benefit, we cannot recommend for or against:
    - auto-titrating positive airway pressure when compared to fixed positive airway pressure, or
    - the use of flexible pressure delivery (e.g., C-Flex®, expiratory pressure relief)

    to improve positive airway pressure adherence.
    (Neither for nor against | Reviewed, New-added)

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. While APAP significantly increased adherence (usage of PAP) by 11 minutes compared to CPAP, this was not a clinically significant increase.[130] As both APAP and CPAP effectively treat OSA, there is a balance between the potential benefits and harms in that the evidence showed that neither modality was more efficacious. 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.

Another PAP-based therapy is flexible pressure delivery, also known as C-Flex (flexible pressure delivery with CPAP, Philips Respironics®) or A-Flex (flexible pressure delivery with APAP, Philips Respironics®) and expiratory pressure relief (EPR, RESMED®). All of these flexible pressure delivery modalities are relatively similar in that they decrease PAP upon exhalation and return to the therapeutic pressure by the start of inspiration. The SR and meta-analysis conducted by Bakker and Marshall (2011), which assessed whether flexible pressure delivery improved adherence, found no significant improvement in compliance when

flexible pressure delivery was used.[131] There is a balance of potential risks and benefits with flexible pressure therapy as opposed to not using flexible pressure therapy. In determining if flexible pressure therapy is used in conjunction with either APAP or CPAP therapy, patient preference is involved, noting that this therapy can improve comfort with PAP. The presence or absence of comorbid diseases, especially severe obstructive lung diseases, should also be considered as these patients may have increased expiratory time, leading to potential under-treatment of upper airway events.

While not included in our systematic evidence review and, thus, independent from the strength of this recommendation, Morgenthaler et al. (2008) suggested that patients on opioids and/or with comorbid disorders such as CHF, severe chronic obstructive pulmonary disease, stroke, atrial fibrillation, obesity-hypoventilation, or CSA are not necessarily ideal candidates for a home-based trial of APAP.[132]

The Work Group's confidence in the quality of the evidence for this recommendation is low.[130,131] The body of evidence was acceptable to render a recommendation. Other considerations regarding this recommendation included the benefits of increased patient comfort, decreased patient time to start treatment, and decreased resources required with APAP versus CPAP. The Work Group determined potential for harm from adverse events was unlikely if used in appropriately selected patients. Patient values and preferences were consistent. Thus, the Work Group decided upon a "Neither for nor against" recommendation.

C. Treatment and Management of Chronic Insomnia Disorder

a. Behavioral and Psychological Treatments

Recommendation

19. We recommend offering CBT-I for the treatment of chronic insomnia disorder.
    (Strong for | Reviewed, New-added)
20. We suggest offering brief behavioral therapy for insomnia (BBT-I) for the treatment of chronic insomnia disorder.
    (Weak for | Reviewed, New-added)
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)

Discussion

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.[133,134] Cognitive therapy components target maladaptive thoughts and beliefs about sleep. Brief behavioral therapy for insomnia (BBT-I) focuses on the behavioral components of sleep restriction, stimulus control, and some sleep hygiene.[133,134] For information about DoD and VA training in behavioral therapies for insomnia disorder, see Appendix F.

Two SRs examined the efficacy of CBT-I.[133,135] 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.[133,135] The SR by Brasure et al. (2015) included 59 total trials comparing psychological interventions such as CBT-I and BBT-I with passive controls.[133] 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 sleep onset latency and total sleep time (TST) (in all studied populations) and wake time after sleep onset (in adults with chronic pain).[133] 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.[133] There were no significant effects on TST. 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.[135]

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. Given the evidence for benefits of these interventions to the patient, providers are encouraged to search out area providers who are trained in CBT-I and/or BBT-I. When patients are not initially interested in CBT-I or BBT-I, or if patients do not complete CBT-I treatment, we recommend that providers work with patients to better understand and address barriers to starting or completing the intervention. Providers should empower patients in their decision making by accurately describing the interventions to patients (e.g., when applicable, letting patients know that treatments are offered by providers with additional expertise in sleep medicine who are located in primary care and that some sessions can be delivered via telephone). Providers should connect these treatments to the patient's values and circumstances using a patient-centered, motivational interviewing approach.

There is potential variation in patient values and preferences regarding behaviorally-based interventions. 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.[136]

The evidence base reviewed comparing individual versus group CBT-I consisted of one non-RCT study by Yamadera et al. (2013).[137] The study demonstrated a statistically significant improvement in sleep efficiency and sleep quality at four weeks for individual CBT-I over group CBT-I. There were no statistically significant differences in daytime functioning, sleep onset latency, TST, and WASO between individual and group CBT-I. Attrition rates were comparable in both arms.

For Recommendations 19 and 20, 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).[133,135] The quality rating for the SR of CBT-I by Johnson et al. (2016) was good overall.[135] 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.[133] In addition, an ITT analysis was performed in some, but not all, studies and several studies had high attrition.[133] 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. CBT-I and BBT-I must be delivered by professionals trained specifically in the delivery of these treatments, and the Work Group 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.

For Recommendation 21, the Work Group's confidence in the quality of the evidence is very low.[137] This is based on a lack of randomization or allocation concealment in studies. The Work Group considered the totality of the evidence as insufficient to recommend for or against group versus individual CBT-I for chronic insomnia disorder. Either individual or small group (i.e., fewer than 10 patients) approaches can be considered as appropriate based on patient preferences and local service delivery considerations. Thus, the Work Group decided upon a "Neither for nor against" recommendation.

Recommendation

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)

Discussion

Telehealth delivery platforms to include provider-directed telemedicine and self-directed internet-based programs have been studied in patients with chronic insomnia. The evidence is based on one pilot study and four additional mid-sized RCTs.[138-142] Taylor et al. (2017) studied military personnel and concluded that six weekly sessions of self-directed internet-delivered CBT-I was as effective as face-to-face CBT-I for this population.[138] However, while subjective sleep efficiency improved in both CBT-I groups, objective measures of sleep efficiency were no different from the control group. Lancee et al. (2016) studied a Dutch civilian population comprised primarily of females, so its findings are not necessarily generalizable to the active duty military or Veteran population.[140] However, it found that a guided form of internet-based CBT-I, which improved sleep efficiency and insomnia severity, was less effective than face-to-face CBT-I. In addition to internet-based treatments, telephonic CBT-I has also been studied in a very small pilot trial.[139] Because of the very low quality of studies reviewed, there was insufficient evidence to make a recommendation on the effectiveness of internet-based CBT-I relative to face-to-face treatment.

The Work Group's confidence in the quality of the evidence is very low.[138-142] The body of evidence suffered from inconsistency, imprecision, and indirectness.[140,142] Patient values and preferences were somewhat varied with the possibility of a generational variance of younger patients preferring a virtual treatment and older patients preferring face-to-face therapy. While the concept of guided or unguided internet-based CBT-I is attractive, particularly in underserved or rural areas, the magnitude of the benefit is

unclear. Internet-based CBT-I does seem to have evidence showing benefit over no treatment, and the decision to utilize this treatment delivery modality should be informed by the presence or absence of high quality face-to-face treatment in the local area. Thus, the Work Group decided upon a "Neither for nor against" recommendation.

Recommendation

23. For patients diagnosed with chronic insomnia disorder, we suggest CBT-I over pharmacotherapy as first-line treatment.
    (Weak for | Reviewed, New-added)

Discussion

CBT-I was favored over several pharmacotherapies of comparison, based upon an SR by Mitchell et al. (2012) (low quality of evidence).[143] Critical outcomes for this review included both subjective and objective measures. Mitchell et al. (2012) noted that the studies included in their SR were diverse in use of both subjective and objective sleep-related outcome measures.[143] Subjective measures included sleep diaries and questionnaires. Objective measures included PSG and actigraphy. Reports of adverse events from medications, which could include both subjective, as well as objective measures, was noted to be limited in the studies included in this SR.

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. The potential benefits of CBT-I outweigh the potential harms/burden of pharmacotherapy as there are fewer potential side effects. Of note, there is a lack of clear safety data for the majority of 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. In contrast, there are lesser concerns for harms associated with CBT-I, as treatment-related symptoms (e.g., sleepiness during the initial phase of sleep restriction therapy) resolve quickly as treatment continues.

Although not included in our systematic evidence review and, thus, independent from the strength of this recommendation, two studies provide information related to potential concerns with this treatment. Smith and Perlis (2006) found CBT-I may not be appropriate, or may need to be delayed, for some select patient groups.[144] Examples include patients with a history of mania, seizure disorder, current suicidal ideation; a temporary reduction in time allowed for sleep may exacerbate these conditions. Other potential concerns for participation in CBT-I include high-risk work duties that require sustained attention while driving or use of weapons in military training activities. However, these concerns refer to a specific component of CBT-I, sleep restriction therapy, and pertain to the potential for an associated temporary increase in sleepiness.[145] Modifications to this component within a comprehensive CBT-I treatment plan can mitigate these potential harms.

In addition to the evidence supporting CBT-I as a first-line treatment for chronic insomnia disorder over pharmacotherapy, some variation in patient values and preferences may exist. Some patients may have a preference for cognitive behavioral treatments over a pharmacologic treatment. More time is needed to achieve improvements with CBT-I approaches (which may take weeks) as compared to pharmacotherapy, (which can act quickly, sometimes with an immediate effect). This should be a consideration related to

adherence, as well as accessibility. Although CBT-I is considered a short-term cognitive behavioral treatment, it requires more frequent visits with a provider over a short period of time compared to pharmacotherapy. While pharmacotherapy requires ongoing follow-up visits, they are less frequent than a typical course of CBT-I would require. The availability of trained CBT-I providers is also a consideration. However, patients seeking treatment across the VA/DoD system are more likely to have access to a trained CBT-I provider as compared to patients seeking CBT-I in the civilian sector.

The Work Group's confidence in the overall quality of the evidence is low.[143] The body of evidence had limitations related to small sample sizes, as well as a wide variation in the follow-up periods (eight weeks to 24 months) across the included studies. Also of concern was the use of Diagnostic and Statistical Manual of Psychiatric Disorders, 4th edition (DSM-IV) criteria to diagnose chronic insomnia disorder (one-month duration of symptoms, and more stringent exclusion of those with comorbid psychiatric disorders). A one-month duration is shorter than that in the current definition of chronic insomnia disorder in DSM-5 and ICSD-3, which require three months minimum duration of insomnia symptoms. Benefits and harms were also considered. The Work Group determined the benefits of CBT-I for chronic insomnia disorder 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 upon a "Weak for" recommendation.

Recommendation

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)

Discussion

CBT-I has 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.[146-148] Based on an 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 disorders including bipolar disorder, depression, PTSD, alcohol dependence, and mixed psychiatric disorders.[147] An RCT in individuals with insomnia disorder comorbid with a schizophrenia spectrum diagnosis found improvements in insomnia severity, sleep onset latency, and sleep quality.[146] 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 gender of study participants and limited information on mental health diagnoses.[147] There was insufficient evidence to include any recommendation regarding the treatment of chronic insomnia disorder in individuals with comorbid TBI.

Although there is no evidence of harm from CBT-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.[144] 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 CBT-I. Similarly, some evidence suggests that sleep restriction may precipitate seizures in those with seizure disorders.[144] 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) was not included in our systematic evidence review and, thus, did not influence the strength of this recommendation.

The Work Group's confidence in the quality of the evidence for this recommendation varied from low (insomnia severity and sleep efficiency) to moderate (sleep onset latency, WASO, and sleep quality).[146-148] The body of evidence had some deficiencies, including limited information about patient age and gender and specifics pertaining to mental disorders.[147] Other considerations regarding the Work Group's recommendation included the benefits outweighing the potential for adverse events, which was small. Patients may have different values and preferences, and the feasibility of offering CBT-I may be limited by provider availability. Thus, the Work Group decided upon a "Weak for" recommendation.

Recommendation

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)

Discussion

This review focused on the effect of mindfulness meditation on insomnia since there was insufficient literature to examine the effects of other forms of meditation (e.g., transcendental meditation). An SR of the literature on mindfulness meditation for insomnia was conducted by Gong et al. (2016).[149] 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. Mindfulness-based therapy for insomnia (MBTI) showed the greatest precision for targeting insomnia symptoms.[149] MBTI produced significant improvements in insomnia severity and long-term remission rates, and responses for MBTI were better than those for mindfulness-based stress reduction (MBSR). Unfortunately, only one trial of MBTI was included in the Gong et al. SR.

Not all studies in the Gong et al. SR required participants to meet diagnostic criteria for chronic insomnia disorder. For example, Black et al. (2015) required that participants have only poor sleep quality based on a PSQI score >5.[150] As such, the Work Group further downgraded the confidence in the quality of this evidence base from "low" to "very low" due to diagnostic imprecision among the various interventions considered.

The Work Group's confidence in the quality of the evidence is very low.[149] Preferences for mindfulness meditation are likely to vary, with some patients being quite receptive and others declining this approach. 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. Although no direct harms were identified for mindfulness meditation, patients who are referred to this intervention for the purpose of insomnia treatment and failed to realize improvement might be discouraged from engaging in other more effective insomnia-focused behavioral interventions, such as CBT-I. As such, the harms of engaging in

mindfulness meditation for treating chronic insomnia disorder instead of CBT-I may slightly outweigh the benefits. Other concerns about the use of mindfulness meditation for the treatment of chronic insomnia disorder include resource utilization and feasibility. Few providers have been trained in mindfulness meditation and the intervention requires a considerable investment of resources on the part of not only patients but providers, as well. In light of the available evidence, resources devoted to the treatment of chronic insomnia disorder would be better directed to CBT-I training as the first-line insomnia treatment (see Recommendation 23 and Recommendation 24). In short, the available research does not demonstrate the utility of mindfulness meditation for the purpose of treating chronic insomnia disorder. Thus, the Work Group decided upon a "Neither for nor against" recommendation.

Recommendation

26. We suggest against sleep hygiene education as a standalone treatment for chronic insomnia disorder.
    (**Weak against | Reviewed, New-added**)

Discussion

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 B).[151] 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.[151] 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.[151] In addition, an 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.[152]

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 19, Recommendation 20, and Recommendation 22). 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 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. Patients who have received sleep hygiene education alone 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's confidence in the quality of the evidence is low.[151,152] The quality rating for the SR by Chung et al. (2018) was fair because of potential bias in the included studies.[151] 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.[152] Given low confidence in the quality of the evidence for the benefits of CBT-I over sleep hygiene education, the Work Group decided upon a "Weak against" recommendation for sleep hygiene education as monotherapy for the treatment of insomnia disorder.

b. Complementary and Integrative Health Treatments

Recommendation

27. We suggest offering auricular acupuncture with seed and pellet for the treatment of chronic insomnia disorder.
    (Weak for | Reviewed, New-added)

Discussion

Acupuncture has gained popularity in the U.S. in recent years although the practice has been utilized for thousands of years in China and other Asian countries. Lan et al. (2015), through an SR and meta-analysis of 15 RCTs, compared the effect of auricular acupuncture to sham acupuncture using standard points, sham auris-points methods and stimulations, pseudo plasters, and the medications estazolam or diazepam.[153] One study was conducted in the U.S., and all others were from China, Hong Kong, and Taiwan. Insomnia was defined as poor sleep quality for one month to 10 or more years. Participants measured outcomes for sleep efficiency and quality using subjective measurements (PSQI, ISI, AIS, sleep diary, Health Survey Questionnaire, Treatment Emergent Symptom Scale [TESS]). Researchers measured objective outcomes for sleep efficiency and quality with actigraphy, electroencephalogram (EEG), or PSG.

The meta-analysis of seven RCTs comparing seed and pellet auricular acupuncture to sham auris-points found increased total sleep time to six or more hours in both subjective and objective measures. In one of the seven studies, subjective PSQI results found both middle age and older age persons reported improvements in sleep quality, quantity, and sleep efficiency (80%) with auricular acupuncture compared to sham interventions.[153] The sample size and power were too small to prove efficacy over sham; however, the duration and quality of sleep showed clinical improvement for the participants.

Auricular acupuncture was compared to the medications estazolam and diazepam in eight studies.[153] Results suggested auricular acupuncture improved sleep onset latency, sleep efficiency, decreased awakenings, and increased TST (>6 hours) when compared to the medications. The auricular acupuncture intervention group had significantly fewer adverse effects (2.3%) than the comparison control group which received medications (27.4%). Participants from the treatment group reported auricle pain or redness. The

medication group reported adverse effects of headache, dizziness, fatigue, weakness, and daytime somnolence; 25 participants developed drug dependence.

The Work Group's confidence in the quality of the evidence is low.[153] Primary insomnia was not clearly defined in the studies and participants may have not met International Classification of Diseases, 10th Version (ICD-10) criteria. The body of evidence had limitations, including indirectness for the outcomes of sleep efficiency, sleep duration, sleep quality, and sleep latency. Considerable differences in methodologies, follow-up, acupuncture techniques, and points made outcomes difficult to compare. Acupuncture points were not identified, described only as standard points or prescriptions. Considerations regarding patient values and preference were recognized. Feasibility may be an issue as there may not be enough trained clinicians available. Benefits slightly outweigh harms or burdens. Thus, the Work Group decided upon a "Weak for" recommendation.

Recommendation

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)

Discussion

Shergis et al. (2016) conducted an SR and meta-analysis of 30 RCTs to compare the effects of acupuncture versus sham acupuncture, placebo acupuncture, benzodiazepines (estazolam, clonazepam, diazepam, and alprazolam), zopiclone, trazodone, and CBT-I for the treatment of primary insomnia.[154] CBT-I was not used in any of the studies retrieved. Participants reported insomnia ranging from one month to 30 years. The primary and secondary outcomes were improvements for the PSQI, ISI, and AIS measurements. Sleep parameters were measured by actigraphy, PSG, or sleep diary. Fifty-eight distinct acupuncture points were reported, with combinations of points averaging 9.3 (range 3 – 24 points) per study. All studies included at least one of the recommended acupuncture point combinations for insomnia (i.e., HT7, GV20, SP6, EX-HN1) and combinations including those points. Sham acupuncture used points not recommended for insomnia treatment; placebo acupuncture studies placed needles on the skin without penetration.

Acupuncture alone was the most frequently studied intervention (22 studies); other forms of acupuncture included electroacupuncture (three studies), acupuncture plus ear acupuncture (three studies), acupuncture plus warm needling (one study), and acupuncture plus moxa (one study). Benzodiazepines were comparators in 26 RCTs; trazodone was the comparator in one study.

Acupuncture was found to have very low to low evidence for improving chronic insomnia disorder outcomes of subjective sleep onset latency, TST, WASO, and insomnia severity as well as sleep efficiency measured by actigraphy.[154] Acupuncture was shown to be slightly superior to sham treatment. Acupuncture provided the best results when compared to pharmacotherapy, with a statistically superior effect over medication. Studies comparing acupuncture and pharmacotherapy were unable to be blinded to participants or professionals as both were able to differentiate between the two interventions allowing for a high risk of bias.

The Work Group rated its overall confidence in the existing literature for treatment of chronic insomnia disorder with acupuncture and electroacupuncture as low to very low for sleep latency, TST, and WASO as

measured by actigraphy. Acupuncture for sleep quality was rated as moderate confidence and was favored over sham or placebo acupuncture comparators.

Dong et al. (2017) through an SR of 18 RCTs compared acupuncture, sham or placebo acupuncture, and medication to evaluate the effectiveness of acupuncture for depression-related insomnia.[155] Of the 18 studies included in Dong et al. SR, only three were published in English. The primary outcome was the PSQI score; the Hamilton Depression (HAMD) score was the secondary outcome studied. The Self-Rating Depression Scale (SDS) was used in five studies, and six studies used the TESS for adverse reactions. Depression related insomnia duration ranged from one month to 22 years. More than half the studies had no blinding or allocation concealment allowing a high risk of bias.

Within the Dong et al. SR (2017), eleven studies included acupuncture as compared with the medications estazolam, fluoxetine, trazodone and Mesyre (Chinese brand of trazodone), clonazepam, and mirtazapine.[155] The subjective PSQI score improved in seven acupuncture intervention groups, while three groups did not show a significant difference between interventions with acupuncture or medication. Of the four studies that included acupuncture with medication compared to medications alone, three found a significant difference in subjective PSQI scores, favoring acupuncture with medication. Six studies evaluated outcomes with the HAMD score and found no statistical difference between interventions. Four studies reported acupuncture was more effective than medication; one study reported no significance between acupuncture and medication; and one reported the sham control group was more effective than the electroacupuncture group.

The strength of this recommendation is independent from the recommendation related to auricular acupuncture (see Recommendation 27). Additionally, battlefield acupuncture (BFA) was not included in our systematic evidence review for this CPG. BFA is designed to rapidly treat pain at the point of injury, and treatment follows by utilizing a multimodal plan of care across military treatment centers, VHA, or civilian healthcare systems.[156]

The Work Group's confidence in the quality of the evidence is very low.[154,155] Results of both studies are limited by risk of bias, heterogeneity, and serious study limitations, including inconsistency and imprecision, and lack of details or outcome data available for review. Other considerations regarding this recommendation included the balanced benefits and harms. Moreover, patient values and preferences may vary widely as some are skeptical of acupuncture and some support it. Acupuncture is not always accessible, and while some primary care providers are trained in this, it diverts their time from other treatment. Thus, the Work Group decided upon a "Neither for nor against" recommendation.

Recommendation

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)

Discussion

Exercise is very important for general health, and although there is a small risk of injury, it is generally not associated with harms. As such, exercise should be considered an important aspect of overall health

maintenance; however, the available evidence is insufficient to make a recommendation regarding exercise as a primary treatment for insomnia disorder.

Aerobic exercise, resistive exercise, tai chi, and qigong have all been studied in patients with insomnia symptoms.[157-159] An SR by Yang et al. (2012) 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.

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] Thus, the Work Group decided upon a "Neither for nor against" recommendation.

Recommendation

30. We suggest against cranial electrical stimulation for the treatment of chronic insomnia disorder. **(Weak against | Reviewed, New-added)**

Discussion

Cranial electrical stimulation (i.e., microcurrents delivered by the proprietary device Alpha-Stim through clips worn on the earlobes) was found to increase total sleep time in patients with insomnia in Lande and Gragnani (2013),[160] the only RCT of this intervention included within the SR by Shekelle et al. (2018).[161] Critical outcome measures including sleep efficiency and insomnia severity were not reported. There was little information provided on diagnostic criteria for inclusion in the RCT.[160] The length of the follow-up period was only five days. It is not known whether there may be adverse effects of this treatment other than mild skin irritation. Some patients may like the ease of administering this treatment (without scheduling office visits), but others may be skeptical. The device used to deliver the treatment is expensive, and therefore may not be accessible for most patients.

The Work Group's confidence in the quality of the evidence is very low.[161] The body of evidence had significant limitations, including small sample size, uncertainty about participants' diagnoses, and a very short follow-up period. The potential for adverse events is not clear. The one RCT included within the SR by Shekelle et al. (2018) did not include an adequate discussion of side effects.[161] Patient values and

preferences are likely to be varied. The cost of the device could be prohibitive for most patients. In addition, offering patients this treatment may direct them away from another treatment with demonstrated effectiveness. It will be important for providers and patients to understand the distinction between cranial electrical stimulation (i.e., microcurrents delivered by Alpha-Stim through clips attached to the earlobes), and transcranial electrical stimulation. Although there is insufficient evidence to determine the effectiveness of Alpha-Stim, the Work Group decided upon a "Weak against" recommendation because of the cost of the device.

c. Over-the-counter Treatments

Recommendation

31. We suggest against the use of diphenhydramine for the treatment of chronic insomnia disorder. **(Weak against | Reviewed, New-added)**

Discussion

The systematic evidence review conducted for this CPG did not identify any evidence that met inclusion criteria regarding the use of antihistamines in treating chronic insomnia disorder. The Work Group acknowledged, however, that 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, indeed, are often "prescribed" by providers as a nighttime sleep aid. However, the evidence of using these agents and other antihistamines is not supported by rigorous data for treating chronic insomnia disorder.

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.[162] All the studies were short in duration (5 – 28 days) and included adult patients with primary insomnia per DSM-IV or predominately experiencing difficulty 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.

There has also been a recently published meta-analysis comprising two randomized controlled trials.[82] 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.[163] 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) with a baseline ISI of 15.[164] The subjectively determined results from the combined trials for subjective sleep latency and subjective total sleep time (sTST), of which the quality of evidence was deemed low, 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, of which the quality of evidence was rated moderate. 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 (p=.039).

Safety data using first-generation antihistamines long-term for chronic insomnia disorder is not available. Because these antihistamines also 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 2019 Beers Criteria carries a strong recommendation to avoid using these agents in older adults.[165] 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. 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).[163] 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).[166] Moreover, the authors indicated that self-reported drowsiness was not a good predictor of impairment.

Because diphenhydramine and many other antihistamines used as sleep-aids are over-the-counter (OTC) and inexpensive, it is unlikely that any large, randomized, appropriately controlled trials evaluating their use in the treatment of chronic insomnia disorder will be conducted in the future. Because of the known harms of diphenhydramine and the lack of evidence for potential benefits, the Work Group decided upon a "Weak against" recommendation.

Recommendation

32. We suggest against the use of melatonin for the treatment of chronic insomnia disorder. **(Weak against | Reviewed, New-added)**

Discussion

The primary evidence base for this recommendation was a meta-analysis by Ferracoli-Oda et al. (2013), which included 19 studies (1,683 patients) in adults and children, of which 14 trials studied melatonin in patients with insomnia.[167] Four trials were conducted in patients with delayed sleep-wake disorder; three trials were conducted in children; and one trial studied rapid eye movement (REM) sleep. All patients were considered to have primary insomnia (DSM-IV criteria). The included studies had a highly variable treatment duration (average 50 days, range 7 – 182 days) and dosing strategies. The critical outcomes of daytime function and ISI were not assessed, nor were any adverse events discussed. However, the SR did report on the outcomes of reduction in sleep onset latency, increase in total sleep time, and overall improvement in sleep quality. The evidence demonstrated an approximately seven-minute reduction in sleep onset latency, an eight-minute increase in TST, and a very small improvement in sleep quality, all statistically significant, favoring melatonin. However, the clinical significance of these findings was unclear and the strength of the evidence was rated low.

There are no acceptable dose guidelines for melatonin related to the different sleep disorders. The melatonin doses included in the evidence ranged from 0.1 mg – 5 mg, which makes a comparison of

results difficult. It is also difficult to assess efficacy and harms because of the various formulations used, lack of reporting of the time melatonin was ingested in relation to bedtime, and the recognized, age-related decrease in melatonin production in the elderly. For circadian rhythm sleep disorders, optimal administration at the proper circadian time, based on an individual's circadian timing, is essential. While not included in our systematic evidence review and, thus, independent from the strength of this recommendation, Keijzer et al. (2014) found that when melatonin is not administered correctly, it may fail to produce the desired results or even produce opposite effects and perpetuate sleep disorders.[168] For example, if melatonin is given in the morning, it will cause a phase shift in the circadian clock to a later time and, if given in the afternoon/evening, will cause phase advances that is a shift to an earlier time. Administration of melatonin for patients with chronic insomnia disorder is often perpetuated by many factors including physical illnesses, conditioned factors, poor sleep habits, psychological factors, hormonal deficits, psychiatric disorders, and environmental factors which may worsen an underlying circadian rhythm disorder. Thus, in order to treat sleep onset insomnia, poor sleep habits must be corrected, behaviorally-based treatment applied, and melatonin used as a short-term adjunctive therapy. When taken several hours before their desired bedtime, it may help reset the sleep onset time back to normal. In the elderly population, because of their melatonin deficiency and difficulty staying asleep, a short course of long-acting melatonin at bedtime has been suggested in the literature. To determine melatonin's therapeutic effect, future research of its sleep promoting properties is needed. This research should include participants with chronic insomnia disorder and use the same melatonin dose and consistent, appropriate administration times based on the sleep/wake cycle.

The Work Group had several concerns regarding the balance of desirable and undesirable outcomes. In particular, the potential harms are largely unknown. While not included in our systematic evidence review and, thus, independent from the strength of this recommendation, Erland and Saxena (2017) found the composition of OTC melatonin variable.[169] In addition, the Work Group believed there would be differing patient and provider preferences. Many patients perceive melatonin as safe because it is marketed as an herbal or dietary supplement; therefore, they may be unaware of the potential impurities in OTC preparations. Although manufacturers are responsible for ensuring the safety of dietary supplements like melatonin, no proof of safety and effectiveness is required before dietary supplements are marketed. The Work Group discussed how the risk of impurities might be reduced by the provision of melatonin through a healthcare system that purchases products from companies that guarantee reproducibility of product quality to set specifications or good manufacturing practices (GMPs).

A recent SR by Foley et al. (2019), not included in the literature search and, thus, independent from the strength of this recommendation, evaluated the safety of oral melatonin supplementations.[170] Of the 50 studies published from 1976 to 2016, 24 trials reported one statistically significant melatonin adverse event; psychomotor and neurocognitive function, fatigue, and excessive sedation directly related the timing of melatonin being the most common. A few adverse events involving endocrine/reproductive and cardiovascular parameters potentially attributed to dosage, dose timing, and potential drug-drug interactions were reported, leading the authors to hypothesize whether melatonin – because of its phase-shifting on circadian rhythms for sleep – may also impact other circadian rhythms of other physiological functions. Overall, while the adverse effects reported were relatively minor, short lived, and associated with daytime dosing, further research is needed.

The Work Group's confidence in the overall quality of the evidence is low.[167] The evidence available did not address the critical outcomes of daytime function and ISI and suffered from a substantial risk of bias. The small improvement in some of the measures, as outlined above, did not outweigh the Work Group's concern about purity/contaminants in OTC preparations and the potential for undesired circadian consequences. The Work Group specifically acknowledged it was not addressing the use of melatonin in other sleep disorders, where it may be an indicated therapy. Thus, the Work Group decided upon a "Weak against" recommendation.

Recommendation

33. We suggest against the use of valerian and chamomile for the treatment of chronic insomnia disorder.
    (Weak against | Reviewed, New-added)

Discussion

The evidence supporting this recommendation is derived from one SR by Leach and Page (2015) that evaluated the efficacy and safety of three herbal medicines (valerian, kava, and chamomile) for the management of insomnia.[171] This SR reviewed 14 trials (n=1,602). Comparisons included valerian versus placebo, different subspecies of valerian (*V. edulis* and *V. officinalis*) versus oxazepam, chamomile individually versus placebo, and kava (evidence regarding kava is described in Recommendation 34). Mean age across trials was 37.8 to 69.4 years, and the duration of treatment was one day to six weeks, with a mean study period of three weeks.[171]

Leach and Page (2015) found no significant between-group differences in the critical outcomes of daytime functioning, insomnia severity, and sleep efficiency, or in the important outcomes of sleep onset latency, TST, WASO, and sleep quality with either valerian or chamomile for treatment of insomnia disorder.[171] Specifically, no significant differences in daytime functioning were found for valerian versus placebo (n=32) or chamomile versus placebo (n=34). Also, no significant differences in insomnia severity were found for valerian versus placebo (n=222) or chamomile versus placebo (n=34). There was no difference in sleep efficiency for valerian versus placebo (n=84), *V. edulis* versus *V. officinalis* (n=40), or chamomile versus placebo (n=34).

Results from the SR also suggest no significant differences in sleep onset latency for valerian versus placebo, *V. edulis* versus *V. officinalis*, or chamomile versus placebo; or in sleep duration (total sleep time) for valerian versus placebo, *V. edulis* versus *V. officinalis*, or chamomile versus placebo.[171] There were also no significant differences in WASO for valerian versus placebo or chamomile versus placebo, and no significant differences in sleep quality for valerian versus placebo, valerian versus oxazepam, or chamomile versus placebo.

Patient and provider preferences for use of herbal supplements for insomnia may be highly variable. While some patients may consider supplements as natural therapy, patients in the focus group acknowledged some stigma with using herbal supplements for insomnia. Moreover, patients who prefer to take OTC supplements may not report significant benefit after using them. There are also concerns about the purity and composition of these herbal supplements; however, there were no reported side effects with chamomile. These agents may also be available in various forms. Other herbal supplements were not included in the studies reviewed.

While not included in our systematic evidence review and, thus, independent from the strength of this recommendation, there are concerns, in rare instances, of the adverse events of liver toxicity and other side effects with valerian.[172]

The Work Group's confidence in the quality of the evidence for valerian and chamomile is very low.[171] The body of evidence had serious limitations, including risk of bias due to small sample size and serious imprecision. Evidence also indicates some potential harm with valerian, and there are concerns about lack of purity of these herbal supplements. Thus, there is very low quality evidence with no proven clinical efficacy for the treatment of insomnia symptoms with valerian and chamomile, and the harms attributed to valerian likely outweigh the benefits. Moreover, patient preferences and values pertaining to herbal supplements for insomnia are likely to be variable. Therefore, the Work Group decided upon a "Weak against" recommendation.

Recommendation

34. We recommend against the use of kava for the treatment of chronic insomnia disorder. **(Strong against | Reviewed, New-added)**

Discussion

The evidence supporting this recommendation is derived from one SR by Leach and Page (2015) (very low quality of evidence) that evaluated the efficacy and safety of three herbal medicines (valerian, kava, and chamomile) for the management of insomnia.[171]

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, sleep duration [TST], WASO, sleep quality) were reported in this study. Adverse events occurred with similar frequency between active and placebo groups.

The FDA has issued an advisory about the risk of liver damage associated with kava.[173] The Work Group also noted that patient preferences may be highly 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's confidence in the quality of the evidence for the use of kava in the treatment of chronic insomnia disorder is very low.[171] The body of evidence had serious limitations, including risk of bias and imprecision. The reviewed studies showed no benefit of using kava to treat chronic insomnia disorder compared to placebo, and there is a known risk for acute fatal liver toxicity with kava.[173] Considering the serious potential harm of liver failure and death, the Work Group decided upon a "Strong against" recommendation.

d. Pharmacotherapy

Recommendation

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)

Discussion

The evidence supporting the above recommendation is derived from one SR by Yeung et al. (2015), comprising six industry-sponsored RCTs of low quality evidence, that compared the efficacy of low-dose (1 mg, 3 mg, and 6 mg) doxepin versus placebo in individuals with a diagnosis of insomnia disorder, with treatment durations varying from one day to 12 weeks.[174] The SR did not combine findings from the different RCTs due to heterogeneity of study design. The critical outcome, ISI, was significantly improved at week four in two RCTs in older adults, favoring the 3 mg or 6 mg dose of doxepin over placebo; there were variable effects with the 1 mg dose. Subjective sleep latency, TST, and sleep quality outcomes were significantly improved with low-dose doxepin with the 3 mg and 6 mg doses in older adults in one study. These were also significantly improved in younger adults with the 6 mg dose. Additionally, PSG-measured sleep efficiency and TST were variably improved with both the 3 mg and 6 mg doses, but not with the 1 mg dose, in older adults. Moreover, in young and middle-aged adults, compared to placebo, doxepin 3 mg and 6 mg significantly increased PSG-defined TST, shortened latency to persistent sleep (LPS) and WASO, and improved sleep efficiency in the last quarter of the night on night one. On nights 15 and 29, the significant improvements in WASO and sleep efficiency were maintained, but TST was only improved with the 6 mg dose of doxepin.

None of the RCTs found significant differences in adverse event rates between low-dose doxepin and placebo treatment, although the SR did not combine adverse events from different RCTs and most of the studies did not monitor body weight, laboratory findings, and any cardiac adverse events. The authors of the SR indicated that the incidence of adverse events appeared to increase with longer duration of treatment. Headache and somnolence were the most common side effects reported with the low-dose doxepin. There were no significant differences between placebo and doxepin for next-day residual effects or withdrawal effects. 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. Even though low-dose doxepin, unlike the higher dose formulations, has no black box warning for suicide risk, the risk of suicidal ideation from the use of low-dose doxepin as a hypnotic agent is unknown and cannot be excluded. Moreover, the anticholinergic effects of doxepin may be additive with other anticholinergic medications. Geriatric patients are sensitive to the anticholinergic side effects of tricyclic antidepressants. According to the 2019 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 toxicity.[165]

The evidence had limitations, including the risk of bias and imprecision. Additionally, the Work Group determined that the low quality evidence supporting the efficacy of low-dose doxepin likely outweighs the harms. The adverse events were not significantly different from placebo. The lack of substantial harm is supported by other studies that did not find adverse cardiovascular consequences associated with low-

dose doxepin;[175,176] this is in contrast to the adverse effects of higher doses of doxepin when used in the treatment of depression.[177]

The Work Group's confidence in the quality of the evidence for this recommendation is low.[174] Low-dose doxepin has not been directly compared with other hypnotics for treating insomnia disorder and the optimal dose of doxepin for insomnia remains unclear. Data on low-dose doxepin, including the efficacy and safety long-term, use of 6 mg in the elderly after one month, and use in patients with comorbid conditions, are not available. Nevertheless, the Work Group determined the clinical benefits, including improved ISI, subjective sleep quality, subjective and objective TST, objective sleep efficiency, sleep onset latency, and WASO, outweighed the small potential harm. There may be some variation in provider and patient preferences regarding the use of this medication. The patient focus group revealed that there may be a stigma associated with taking an antidepressant drug for insomnia. Moreover, providers may be hesitant to use a tricyclic antidepressant medication in patients with cardiac disease or those who might be susceptible to anticholinergic side effects. Therefore, the Work Group decided upon a "Weak for" recommendation.

Recommendation

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)**

Discussion

The above recommendation is supported by one SR by Winkler et al. (2014) of moderate quality, which identified 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: zolpidem, zaleplon, eszopiclone, and zopiclone (not available in the U.S.).[178] 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 per DSM-IV-TR (Text Revision). The duration of all studies was <6 weeks except for one zolpidem (10 mg) trial lasting 224 days (range 2 – 224 days). Efficacy results were compiled and not reported for individual agents. For the critical outcome of objective sleep efficiency, a statistically significant difference favoring non-benzodiazepine benzodiazepine receptor agonists over placebo was seen based on 15 comparisons in studies of moderate quality. In addition, the non-benzodiazepine benzodiazepine receptor agonists were statistically favored over placebo for the important objective outcomes of sleep onset latency, sleep quality, TST, and WASO (moderate strength evidence).

Adverse effects of non-benzodiazepine benzodiazepine receptor agonists

Wilt et al. (2016) reported adverse events and withdrawals of non-benzodiazepine benzodiazepine receptor agonists in 18 RCTs of at least four weeks duration published between 2004 and September 2015.[179] Most studies were industry-sponsored. The incidence of adverse events was reported separately for each individual drug.

Eszopiclone 2 mg – 3 mg versus placebo

For eszopiclone versus placebo, the critical outcome of harms was studied in three RCTs (n=1,929) of moderate quality in the general population.[179] Specifically, the incidences of unpleasant taste and of somnolence were statistically higher with eszopiclone than placebo. The incidence of myalgia, which was determined from two RCTs (n=1,616) of moderate quality, was also statistically higher with eszopiclone compared to placebo. Two RCTs of moderate quality reported that participants taking eszopiclone experienced one or more adverse events compared to those taking placebo. In three RCTs of low quality, the number of withdrawals related to adverse events was not significantly different between eszopiclone and placebo.[179]

Zaleplon 5 mg – 20 mg versus placebo

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.[179] 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.

Zolpidem (various formulations and doses) versus placebo

The outcome of harm was evaluated in 11 zolpidem RCTs (n=2,779) by Wilt et al. (2016).[179] 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 is low. Based on four RCTs (n=698) of moderate quality in the general population, the incidence of somnolence was statistically higher with zolpidem 5 mg – 15 mg compared to placebo. Withdrawals due to adverse events were greater with zolpidem 5 mg – 15 mg than placebo in six trials but did not differ statistically in five trials using zolpidem 5 mg – 10 mg; however, the evidence is very low quality. 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.

Other considerations

Despite general consistency in the evidence supporting the benefits of non-benzodiazepine benzodiazepine receptor agonists for many insomnia treatment outcomes, there is some inconsistency in patient preferences regarding treatment. Nearly all of the patient focus group participants expressed a preference for non-pharmacologic treatment to a pharmacologic one. Participants in the focus group emphasized the importance of daytime functioning as an outcome measure, and this was not addressed in any of the studies reviewed. As stated in Recommendation 23, non-pharmacologic treatments should be considered first before beginning pharmacotherapy.

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, MVC, and diversion.[180,181] For military personnel on active duty depending on their military duties and response, limitation in duties and temporary medical profiles may need to be implemented if a non-benzodiazepine benzodiazepine receptor agonist is prescribed. Likewise,

the balance of potential benefits and harms needs to be considered in a patient-centric, SDM process when prescribing a non-benzodiazepine benzodiazepine receptor agonist to a Veteran or civilian who has a commercial driving license or operates heavy machinery. Similarly, there should be careful consideration of potential benefit versus harm when prescribing for patients with limited mobility, those with significant respiratory and neuromuscular conditions, and those with risk factors for fractures and falling; older adults are at particular risk.[182]

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-benzodiazepine benzodiazepine receptor agonists.[183] These complex sleep behaviors have also 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.[183] 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 the potential risks.

The Work Group's confidence in the quality of the evidence is very low.[178,179] The strength of evidence ranged from very low to moderate depending on the outcome, intervention, and formulation of the agent that was studied. The quality for the efficacy outcomes is moderate but very low to moderate for harms due to the methodological quality and imprecision of the studies.[178,179] Results from the SR by Winkler et al. (2014) suggest that patients with primary insomnia benefited from a non-benzodiazepine benzodiazepine receptor agonist compared to placebo for many of the sleep outcomes of interest, including the critical outcome sleep efficiency and the important outcomes sleep onset latency, sleep quality, TST, and WASO.[178] However, potential harms associated with this class of agents should also be of concern. Thus, the Work Group decided upon a "Weak for" recommendation.

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)

Discussion

Kuriyama et al. (2014) conducted an SR to determine the efficacy of ramelteon (n=5,812) for treating insomnia.[184] Individuals in the included studies were mostly female (62%) between 18 – 93 years old. The dose range of ramelteon was 4 – 32 mg/day and the duration of drug administration ranged from 6 – 180 days. Relative to placebo, ramelteon significantly improved sleep efficiency, sleep onset latency, TST, and WASO. The methodological quality of the studies included in the SR was rated as poor.[184] The main concerns were lack of clarity around randomization, allocation concealment, blinding of patients and investigators, and outcome assessors. Furthermore, ITT analysis was not used (9 out of 13 studies) or was unclear (2 out of 13 studies) in many of the included studies. Kuriyama et al. (2014) found somnolence as the only significant adverse event and found mixed results for sleep efficiency.

The Work Group's confidence in the quality of evidence is very low.[184] Somnolence was the only significant adverse event, and there were positive findings for important outcomes including sleep

quality, TST, and sleep onset latency. The Work Group determined that there was some variation in values and preferences of patients and providers. The drug might negatively impact daily functions including driving, and patients may experience stigma associated with taking sleep medication. The VA and DoD may have different criteria for use. Active duty Service Members may require limitations in duties. Similarly, Veterans may have a commercial driving license or operate heavy machinery. Thus, the Work Group decided upon a "Neither for nor against" recommendation based on a combination of the objective and subjective critical outcomes.

Recommendation

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)

Discussion

The limited evidence available supporting the above recommendation is derived from one SR by Kuriyama and Tabata (2017) comprising four RCTs (n=3,076) ranging from one month to one year in duration comparing the efficacy and safety of suvorexant (10 mg – 80 mg at bedtime) to placebo in patients with chronic insomnia disorder per DMS-IV-TR criteria.[185] The four industry-sponsored trials were mostly dose finding trials evaluating several doses exceeding the currently approved dose range (5 mg – 20 mg) at bedtime. The confidence in the quality of the evidence for the subjective ISI outcome was high. Comparing groups taking suvorexant doses of 40/30 mg (nonelderly/elderly) and 20/15 mg (nonelderly/elderly) to placebo, the patient-rated baseline ISI of 16 (0 – 28 scale) was significantly improved in both suvorexant groups versus placebo at both one and three months; however, a clinically meaningful improvement, prospectively defined as ≥6-point improvement, was not achieved. One SR not included in our systematic evidence review and, thus, independent from the strength of this recommendation, further analyzed the data from a trial that was included in the SR of interest.[186] The author indicated that, for the pre-specified responders taking 15 mg or 20 mg of suvorexant versus placebo, the number needed to treat (NNT) to achieve a ≥6-point improvement in the patient-rated ISI at three months was eight patients (95% CI 6 – 14).

Kuriyama and Tabata (2017) reported the outcomes of TST and sleep quality subjectively and as primary post hoc outcomes.[185] The overall confidence in the quality of evidence for sTST and subjective sleep quality was high. Significant differences favoring suvorexant compared to placebo were seen at one month, three months, and at one year for these outcomes. Moreover, the SR by Kuriyama and Tabata (2017) reported a clinically significant difference in the objective outcome of WASO (reported as a secondary post hoc outcome), favoring suvorexant compared to placebo at one and three months. A pre-specified analysis from an SR not included in our systematic evidence review, but which used data from a study reported in the SR by Kuriyama and Tabata (2017), reported for patients who responded to suvorexant doses of 15 mg or 20 mg at three months, a NNT of 13 and 16 would be required to achieve a ≥15% improvement in mean sTST and mean subjective WASO compared to placebo, respectively.[186]

In the same SR, Kuriyama and Tabata (2017) reported that, overall, patients receiving suvorexant compared to those receiving placebo were more likely to experience an adverse clinical event.[185] For the critical outcomes identified, which included somnolence (high quality evidence) and excessive daytime

sleepiness/sedation, fatigue, and abnormal dreams (moderate quality evidence), suvorexant had a higher incidence compared to placebo (all statistically significant).[185] However, the incidence of adverse effects was not stratified by dose.

Other literature not included in the systematic evidence review and, thus, independent from the strength of this recommendation, indicates that the incidence of adverse effects is strongly dose-related. For example, for common adverse events (≥2 incidences in any suvorexant group and frequency greater for suvorexant than for placebo), Citrome (2014) reported that the incidence of somnolence was 3% (31/1025) in the placebo group, 6.7% (33/493) in the suvorexant 15 mg or 20 mg group, and 10.7% (138/1291) in the suvorexant 30 mg or 40 mg group.[186] This yielded a number needed to harm (NNH) for placebo of 28 (95% CI 17 – 82) for suvorexant 15 mg or 20 mg and 13 (95% CI 11 – 18) for suvorexant 30 mg or 40 mg.

Of interest, no head-to-head trials comparing suvorexant to other sedative-hypnotic agents are available. More data on the clinical experience with suvorexant using the approved dose range (5 mg – 20 mg daily) is needed.

Suvorexant is the first in a new class of insomnia agents targeted at orexin antagonism. Despite high quality evidence supporting the use of suvorexant for many outcome measures, and the possibility that suvorexant could be useful when other sedative-hypnotic agents have been ineffective, the occurrence of adverse effects may be substantial. The most common side effect reported is somnolence. Based on suvorexant's long half-life (approximately 12 hours), there is a concerning risk of impaired next day alertness and other complex behaviors (e.g., "sleep driving") if it is taken with <7 hours of sleep before awakening. For patients taking higher than the recommended dose or a dose co-administered with other central nervous system (CNS) depressants or other drugs that increase the blood levels of suvorexant, there needs to be a patient-centric, SDM discussion before suvorexant is started (see Recommendation 23).[187] The SDM discussion should also include the potential longer exposure of the drug in women and obese patients (>30 kg/m^2).

The Work Group's confidence in the quality of the evidence is moderate.[185] The body of evidence had several limitations. For instance, the benefits and harms may have been overestimated by including studies that used a higher than recommended dose of suvorexant. Also, the evidence reviewed included exposure to suvorexant 10 mg dose in only 62 nonelderly patients for one month. Other limitations included the inconsistent reporting of similar outcomes, insufficient evidence to determine the clinical significance of a statistically significant finding, the small number of trials, the limited inclusion of older patients and patients with comorbid conditions, and variations in treatment duration. Thus, the Work Group decided upon a "Neither for nor against" recommendation.

Recommendation

39. We suggest against the use of antipsychotic drugs for the treatment of chronic insomnia disorder. **(Weak against | Reviewed, New-added)**

Discussion

The systematic evidence review conducted for this CPG did not identify any evidence that met inclusion criteria regarding the use of antipsychotics for treating chronic insomnia disorder. The Work Group

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

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.[188] Like all second-generation 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 and increased suicidal tendencies in children, adolescents, and young adults.[189] In addition, all second atypical antipsychotics carry a strong recommendation in the 2019 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.[165] Anticholinergic effects, including sedating and hypotensive effects, occur with all antipsychotics in varying frequency and severity. 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.

Because of the lack of clinical studies supporting the efficacy of antipsychotic drugs, and the potential safety concerns, the Work Group decided upon a “Weak against” recommendation.

Recommendation

40. We suggest against the use of benzodiazepines for the treatment of chronic insomnia disorder. **(Weak against | Reviewed, New-added)**

Discussion

The Work Group examined an evidence base of four SRs that compared various pharmacologic interventions to placebo in treating insomnia disorder.[178,184,190,191] The studies showed significantly improved sleep efficiency, sleep onset latency, sleep quality, TST, and WASO relative to placebo. The longest duration of follow-up was approximately seven months, but the majority of 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.[178] The methodological quality of the studies included in the SRs was generally rated as fair by the authors of the reviews.[178,190,191] 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).

The Work Group concluded that harms/burden outweighed the benefits. This was in part because of the widely known harms/adverse events of benzodiazepines. Indeed, the Work Group acknowledged the

VA/DoD Management of Opioid Therapy CPG's[1] recommendation against benzodiazepine use with opioids and the VA/DoD PTSD CPG's[2] recommendation against benzodiazepine use in the management of PTSD. Furthermore, benzodiazepines may have an adverse effect on sleep architecture (slow wave sleep suppression), be difficult to taper and discontinue, and have significant interactions with alcohol and with other drugs, notably other CNS depressants. There may be dose-related harms as described elsewhere in the CPG (see Recommendation 36).

The Work Group's confidence in the quality of evidence is moderate.[178,184,190,191] The Work Group found some variation in patient and provider values and preferences regarding benzodiazepines. This is due to factors including the negative impact of benzodiazepines on daytime function (e.g., driving) and the known adverse event profile of the drugs. The issue of stigma with taking benzodiazepines for insomnia was considered, as were the implications of acceptability, which might be affected by drug labeling. The Work Group considered 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 Members may require limitations in duties and/or a temporary restricted profile (possibly for the duration of treatment), depending on job function. Similarly, Veterans may have a commercial driving license or operate heavy machinery. Thus, the Work Group decided upon a "Weak against" recommendation based on a combination of the objective and subjective critical outcomes.

Recommendation

41. We suggest against the use of trazodone for the treatment of chronic insomnia disorder. **(Weak against | Reviewed, New-added)**

Discussion

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).[190] There is moderate quality evidence that trazodone was more effective at improving sleep quality (a subjective finding) compared to placebo, while there were no differences noted in sleep onset latency, TST, or WASO.[190] Data regarding an improvement in sleep quality were based on self-report, with patients stating that they slept better after taking trazodone. 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 a number of the trials, patients were also taking another antidepressant or methadone, which may have altered the results.

Although there is moderate quality evidence that trazodone improves sleep quality, the evidence showing benefits in other key sleep outcomes is very low quality. Additionally, there were several factors making it difficult to evaluate the safety of using trazodone for the treatment of chronic insomnia disorder. The rates

[1] See the VA/DoD Clinical Practice Guideline for the Management of Opioid Therapy for Chronic Pain (2017) (available at: https://www.healthquality.va.gov/guidelines/Pain/cot/).

[2] See the VA/DoD Clinical Practice Guideline for the Management of Posttraumatic Stress Disorder and Acute Stress Reaction (2017) (available at: https://www.healthquality.va.gov/guidelines/MH/ptsd/).

of adverse events were low overall in two of the trials in which they were reported; the other five studies did not present this data. 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).[192] 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. Most notably, it has been reported that patients will have residual morning sedation after taking trazodone at night. More research is required to fully evaluate the adverse effects of trazodone as there was limited evidence available. Additional evidence regarding potential harms may strengthen this recommendation. Thus, the limited evidence of benefits is outweighed by the potential safety concerns associated with trazodone use.

The Work Group's confidence in the quality of the evidence is very low.[190] The body of evidence had some limitations including limited evidence on benefits versus harms, use in geriatric populations, limited duration in trials, and some variation in patient preferences. There are several other implications to consider with implementing our recommendation. Our recommendation is limited to patients with chronic insomnia disorder alone and does not pertain to use of trazodone for other clinical conditions. Thus, the Work Group decided upon a "Weak against" recommendation.

D. Knowledge Gaps and Recommended Research

a. Chronic Insomnia Disorder

After reviewing the evidence that met inclusion criteria for this CPG, the Work Group identified some research gaps for future consideration. Initially, the Work Group sought evidence for effective insomnia treatment in subpopulations and an exploration of how outcomes may differ for such groups. Identified subpopulations of interest included those with chronic insomnia and comorbid conditions such as PTSD, major depressive disorder (MDD), substance use disorder (SUD), anxiety disorders, lung disease, heart disease, and pre- versus post-menopausal females. There were no studies to explore outcomes for persons within these subpopulations within the time period of our literature review, thus indicating an area for future research.

In the evidence base evaluating CBT-I and BBT-I, most studies assessing BBT-I were in patients who had not received CBT-I. The Work Group determined that there was research needed evaluating behavioral treatments; for example, studies evaluating:

- Combinations of CBT-I plus adjunctive interventions (e.g., medication, acupuncture), including their relative efficacy in the presence of comorbid conditions.
- A head-to-head comparison of CBT-I versus BBT-I and relative efficacy in the presence of comorbid conditions.
- Comparing in-person CBT-I/BBT-I versus the same therapy delivered via telehealth.
- CBT-I treatment sequencing – before or after other mental health treatments.
- The optimal "dose" and treatment length of behavioral treatment.
- Dismantling studies to better understand the efficacy of behavioral treatment components.
- CBT-I/BBT-I as implemented (e.g., pragmatic trials), including factors such as implementation barriers and facilitators.

- The relative importance of specific cognitive and behavioral components of CBT-I.
- The delivery methods and modalities associated with optimal outcomes, including face-to-face and online formats, treatment setting, and provider types and training.
- Whether patient and healthcare system factors impact the efficacy of CBT-I.

Additionally, there were research gaps identified in the evidence to support pharmacotherapy for the treatment of chronic insomnia disorder. The evidence reviewed was lacking in data regarding potential harms associated with long-term use of multiple pharmacotherapeutic medications for insomnia, largely due to the limited duration of follow-up in studies that were included in the evidence base. For most of the studies reviewed, the average duration of the study was four weeks or fewer. Studies were also limited by small sample sizes, thus affecting a more robust examination of potential benefits, as well as potential risks/harms. Overall, larger and more robust studies of increased duration are recommended as an area for future research. Well-designed RCTs are required that measure daytime functioning, insomnia severity and other critical clinical outcomes of pharmacologic treatment of chronic insomnia disorder, specifically:

- Head-to-head comparisons of the clinical efficacy of pharmacotherapeutic agents, including adverse events associated with long-term versus short-term treatment with these drugs.
- RCTs to examine the dose response of the different pharmacologic agents for the treatment of insomnia.
- Additional studies of the effect of pharmacologic and herbal agents with long-term follow-up to determine safety and efficacy, including by subgroup (e.g., gender, age, PTSD, TBI, MDD, anxiety, active duty population, and post-menopausal women).
- Large, high quality RCTs to determine the safety and efficacy of herbal supplements for insomnia.
- Studies to establish clinical benefits versus risks of suvorexant at the FDA approved doses.
- Use of suvorexant in elderly populations, patients who fail to respond to current hypnotic therapy, and for patients switching to suvorexant from current hypnotic therapy.
- Detailed studies to assess reasons, evaluation, and management strategies for chronic insomnia disorder refractory to recommended treatments.

While the Work Group members suggested against the use of melatonin for insomnia, they identified that there might be a role/need for more long-term studies with formulations produced under good manufacturing practices, using a low dose, administered ideally at the correct circadian phase, and carefully assessing sleep and circadian outcomes as well as potential harms/side effects. The concern about impurities might make studies with controlled batches of melatonin not generalizable to routine practice in the U.S.

Additional research on MBTI is recommended to strengthen the literature base. More generally, additional, high quality research is needed examining the effects of manual-based mindfulness meditation on patients who have chronic insomnia disorder that has been diagnosed in accordance with consensus nosologies (i.e., ICSD-3 or the DSM-5).

Additional research is needed for self-reported insomnia measures. Chiu et al. (2016) found lower diagnostic accuracy for the ISI and PSQI in studies using the International Classification of Sleep Disorders, 2nd edition (ICSD-2) insomnia diagnostic criteria relative to those using the DSM-IV, DSM-IV-TR, or various combinations of DSM and ICSD.[79] They concluded that this was due to inconsistent diagnostic criteria across nosologies employed in studies within the SR. Specifically, unlike the ICD-10 and DSM-IV nosologies, the ICSD-2 also requires that insomnia occurs despite adequate opportunity for sleep. There is greater consistency between the recently revised DSM-5 and ICSD-3 diagnostic criteria for insomnia disorder. Future research should evaluate the accuracy of the ISI and AIS against these newer nosologies. In addition, future research is needed to develop insomnia disorder measures designed for use in the general population and primary care setting, including brief screening measures having high predictive validity for insomnia disorder.

Research is required to define treatment refractory insomnia and identify the appropriate steps for evaluation after treatment failure. It is increasingly recognized that patients do not necessarily respond to CBT-I, BBT-I, and/or pharmacotherapy, and it is clinically challenging to identify how to proceed. In this population, the following areas require research:

- Is the refractory nature of the insomnia due to comorbid disorders or lack of adherence to behavioral tenets?
- Should a PSG be obtained in patients with refractory insomnia disorder for purposes of identifying other occult sleep disorders?
- Do novel or technology-based treatments have a role in the management of patients with refractory chronic insomnia?
- Is intensive sleep retraining, which is currently performed in a sleep lab, an appropriate next step for patients who have not responded to CBT-I, BBT-I, and/or pharmacotherapy?[193]

b. Obstructive Sleep Apnea

To address OSA in the active duty Service Members and Veterans who suffer from this disorder, it is important to acknowledge the inherent differences in these populations as compared to civilian populations. Military personnel with OSA tend to be younger, less obese, and have sleepiness at least in part due to insufficient sleep,[194] whereas Veterans with OSA have high rates of comorbid disorders, such as PTSD and TBI.[195,196] In order to appropriately screen, diagnose, and treat military personnel and Veterans with OSA, it is essential to understand that the recommendations are primarily based on evidence from civilian populations.

Regarding risk stratification for sleep apnea, the Work Group determined that the STOP questionnaire has evidence to support a weak for recommendation. However, all studies assessed were in non-military, non-Veteran populations. For example, a study assessing the STOP-BANG in a military population referred for PSG with a mean AHI of 12.9 events per hour reported a sensitivity, specificity, positive and negative predictive values (PPV, NPV) of 83.8, 18.0, 64.4, and 38.0%, respectively.[197] The ability to apply current evidence to these distinct populations is not necessarily accurate and, thus, further studies validating sleep questionnaires in these specific populations are required.

As clinical practice advances, home sleep apnea testing is increasingly utilized. In order to appropriately diagnose OSA, well-designed studies with larger sample sizes, specifically including military and Veteran populations, are needed. These studies should determine the sensitivity and specificity of HSATs for different clinical populations, as well as comparing different types of HSATs in terms of accuracy and usability. In addition, there was a lack of evidence to support a recommendation for specific patient populations that should have HSAT versus in-lab PSG, as well as a lack of evidence to determine the best approach to repeat evaluation after a technically inadequate HSAT.

The Work Group members agreed that the current nosology for determining OSA severity is somewhat arbitrary as it does not account for oxygen desaturation, sleepiness, and other relevant comorbid disorders. There are also recent advances in different phenotypes of patients with OSA. These OSA phenotypes include those with primarily airway collapse as opposed to those with a low arousal threshold, which has been found highly prevalent in both active duty [198] and Veterans [199] with OSA. How these phenotypes present and how disorders of interest to the military and Veteran population act as risk factors are areas in which further research is required.

The impact of PTSD and TBI on sleep and if they are independent risk factors for OSA has limited evidence. The Work Group determined that prospective longitudinal studies would be helpful in making recommendations and evaluating these disorders as risk factors for OSA. This is certainly of concern for military and Veteran populations.

Future research should examine how the relationship between PAP use and outcomes vary according to the number of hours and timing of sleep, number of hours of PAP use and baseline and residual AHI while using PAP. The impact of other clinically relevant factors such as functional status, sleepiness, comorbid disorders (cardiovascular, pulmonary, neurologic, psychiatric) quality of life, and neurocognitive performance should also be assessed. Study authors should report effects for a full range of PAP usability factors. Studies evaluating adherence to PAP have consistently reported that civilians, active duty Service Members, and Veterans with OSA and PTSD have lower adherence.[195,200,201] Methods to understand and optimize adherence to OSA therapies or determine other treatment options are also priority research topics. Important areas for future research include:

- Large-scale studies to effectively characterize the severity of OSA in order to optimally target those patients who require therapy and for those whom less aggressive treatment regimens may be appropriate.
- Research to determine if PTSD or TBI are independent risk factors for OSA.
- Comparative effectiveness of different approaches to OSA treatment, including comparative effectiveness of PAP therapy to mandibular advancement therapy at different disease severity levels. These studies should assess short-term outcomes such as sleepiness, cognitive performance, and biomarkers as well as long-term outcomes, including cardiovascular, neurologic, and biomarkers.
- PAP use in various settings (e.g., for deployed military personnel, inpatient settings) and associated clinical- and performance-related outcomes.
- Adherence to PAP therapy among different subgroups (e.g., age, gender, comorbid conditions).

- In the military and Veteran populations with OSA, whether long-term PAP adherence is associated with improved health outcomes (e.g., coronary artery and cerebrovascular disease) and health-related quality of life.
- The degree to which PAP usage is required for optimal benefit in terms of sleepiness, cognitive performance, and cardiovascular outcomes.
- Research to identify a standardized approach to patients who are intolerant to PAP and/or MAD and determine an appropriate surgical approach to 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.
- Studies to evaluate the treatment of comorbid insomnia and OSA.
- Future studies in military personnel and Veterans are required to address the low arousal threshold OSA phenotype, especially as this related to comorbid disorders and PAP adherence.[199]
- Regarding PAP adherence in patients with OSA, well-designed trials, assessing different OSA phenotypes, are required to determine which of the following interventions, either alone or in combination, can improve PAP adherence: cognitive, behavioral, motivational, and pharmacologic.
- For patients with inadequate PAP adherence, studies addressing the combination of PAP and mandibular advancement devices in the same sleep period to determine if this improves the overall effective AHI and the associated effect on sleep, quality of life, biomarkers, and long-term health outcomes.
- For patients with OSA and PTSD who are intolerant of PAP therapy, whether more advanced, non-invasive airway pressure modalities are associated with improved acceptance, adherence, and clinical outcomes.

In military personnel with mild OSA, further research is required to determine the following:

- Are there distinct OSA phenotypes to include those who have airway collapse or a low arousal threshold as the etiology of their sleep disordered breathing?
- Whether treating mild OSA improve outcomes, including cognitive/performance and health-related outcomes (e.g., cardiovascular, behavioral medicine disorders).
- Whether adherence differs between PAP versus MAD therapy.

Appendix A: Evidence Review Methodology

A. Developing the Key Questions

The CPG Champions, along with the Work Group members, were tasked with identifying KQs to guide the SR of the literature on sleep disorders. These questions, which were developed in consultation with the Lewin team, addressed clinical topics of the highest priority for the VA and DoD populations. The KQs follow the population, intervention, comparison, outcome, timing and setting (PICOTS) framework for evidence questions, as established by the Agency for Healthcare Research and Quality (AHRQ). Table A-1 provides a brief overview of the PICOTS typology.

Table A-1. PICOTS [202]

PICOTS Element	Description
Population, Patients, or Problem	A description of the patients of interest. It includes the condition(s), populations or sub-populations, disease severity or stage, co-occurring conditions, and other patient characteristics or demographics.
Intervention or Exposure	Refers to the specific treatments or approaches used with the patient or population. It includes doses, frequency, methods of administering treatments, etc.
Comparison	Describes the interventions or care that is being compared with the intervention(s) of interest described above. It includes alternatives such as placebo, drugs, surgery, lifestyle changes, standard of care, etc.
Outcome	Describes the specific results of interest. Outcomes can include short, intermediate, and long-term outcomes, or specific results such as quality of life, complications, mortality, morbidity, etc.
Timing, if applicable	Describes the duration of time that is of interest for the particular patient intervention and outcome, benefit, or harm to occur (or not occur).
Setting, if applicable	Describes the setting or context of interest. Setting can be a location (such as primary, specialty, or inpatient care).

The Champions, Work Group, and evidence review team carried out several iterations of this process, each time narrowing the scope of the CPG and the literature review by prioritizing the topics of interest. Due to resource constraints, all developed KQs were not able to be included in the systematic evidence review. Thus, the Champions and Work Group determined which questions were of highest priority, and those were included in the review. Table A-2 contains the final set of KQs used to guide the SR for this CPG.

Once the KQs were finalized, the Work Group prioritized the outcomes they had defined for each KQ based on how important the Work Group judged each outcome to be. Ranking outcomes by their relative importance can help focus attention on those outcomes that are considered most important for clinical decision making when making judgements regarding the overall quality of the evidence to support a recommendation.[203]

Using GRADE methodology, 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 outcomes judged to be critical were used to determine the overall quality of evidence (see Grading Recommendations).

a. Population(s)

- Adults 18 years or older treated in any VA/DoD primary care setting who have experienced sleep disorders.

b. Interventions

- Key Question 1

  Pharmacotherapy:

  - Orexin receptor agonist
    - Suvorexant
  - Non-benzodiazepine benzodiazepine receptor agonists
    - Eszopiclone
    - Zaleplon
    - Zolpidiem (various formulations)
  - Benzodiazepines
    - Estazolam
    - Quazepam
    - Flurazepam
    - Oxazepam
    - Triazolam
    - Temazepam
  - Melatonin agonist
    - Ramelteon
  - Antidepressants
    - Doxepin
    - Trazodone
    - Paroxetine
    - Trimipramine
  - Anticonvulsants
    - Gabapentin
  - Over-the-counter preparations
    - Diphenhydramine
    - Melatonin
    - L-tryptophan
    - Valerian
  - Atypical antipsychotics
    - Quetiapine

- Key Question 2
  - Behavioral therapy
    - CBT-I
    - BBT-I
  - Intensity and components of behavioral therapy
- Key Question 3
  - CPAP
- Key Question 4
  - Individual CBT-I
- Key Question 5
  - CPAP
- Key Question 6

  Pharmacotherapy:
  - Non-benzodiazepine benzodiazepine receptor agonists
    - Zolpidiem
    - Eszopiclone
    - Zaleplon
  - Benzodiazepines
    - Flurazepam
    - Quazepam
    - Triazolam
    - Estazolam
    - Temazepam
  - Antidepressants
    - Trazodone
    - Amitriptyline
    - Doxepin
  - Melatonin receptor agonist
    - Ramelteon
  - Other medications used off label:
    - Mirtazapine
    - Quetiapine (or other atypical antipsychotics)
    - Prazosin
    - Over-the-counter antihistamines

- Key Question 7
    - Use of CPAP with one duration (e.g., hours per day) and one intensity (e.g., 30-day average of number of days of use per week) (e.g., 4 hours/night 70% of days)
- Key Question 8

  Methods intended to improve adherence with CPAP:
    - CBT
    - Motivational therapy
    - Other behavioral therapies (e.g., multicomponent, incentive-based, support groups, desensitization programs)
    - Mask type (e.g., nasal pillow, half face mask)
    - Education (any education program)
    - Remote support (e.g., web-based support, mobile apps)
    - Remote CPAP monitoring (e.g., Remote Veterans Apnea Management Platform [REVAMP] program)
    - Titrated CPAP pressure versus APAP
    - Dental devices (TAP PAP)
    - Humidification
    - Pharmacotherapy (e.g., eszopiclone, zolpidem)
    - Nasal surgery/sinus surgery/septoplasty/turbinate reduction surgery
    - Expiratory pressure relieve
    - Individual versus group interventions
- Key Question 9
    - Management of comorbid sleep conditions (e.g., OSA)
    - Alternative therapies for insomnia
        - Intensive sleep retraining
- Key Question 10

  Diagnostic work-up:
    - Polysomnography
    - Medical work-up
    - Behavioral health work-up
- Key Question 11

  Herbals/supplements:
    - Melatonin
    - Valerian
    - Kava
    - L-Theanine
    - 5-HTP

  - GABA
  - Passion flower
- Key Question 12

  Complementary and alternative medicine treatments:
  - Meditation
  - Mindfulness
  - Yoga
  - Tai-chi
  - Alpha Stim
  - Acupuncture
  - Physical activity (e.g., any exercise program for insomnia)
- Key Question 13
  - Home sleep testing or non-PSG (unattended versus attended)
  - Type 2, 3, or 4 devices (e.g., WatchPat®)
- Key Question 14
  - Chronic opioid use/opioid analgesics
  - Other medications (i.e., benzodiazepines, muscle relaxants)
  - Gender (menopause)
  - Veterans or military Service Members (shift work or short sleep)
  - TBI
  - Heart failure
  - Cerebrovascular accident
- Key Question 15
  - CBT-I in addition to usual care for co-occurring mental health condition
- Key Question 16
  - Adults with OSA with comorbidities (PTSD, TBI) and receiving CPAP
- Key Question 17
  - Telehealth delivery of intervention for insomnia
  - Telehealth delivery includes:
    - Asynchronous: Patient-only, no provider interaction (web-based, phone applications)
    - Synchronous: Involving a provider (telephone or video telehealth)
  - Interventions also include mobile apps or web-based CBT-I
- Key Question 18
  - Sleep hygiene education

- Key Question 19
  - Screening questionnaires
- Key Question 20
  - Screening questionnaires

c. Comparators

- Key Question 1
  - CBT-I
- Key Question 2
  - Treatment as usual, no treatment
  - Different behavioral therapy
  - Different intensity or different components of behavioral therapy
- Key Question 3
  - Other interventions
    - EPAP (Provent)
    - Inspire hypoglossal stimulator and other surgical treatments
    - Weight loss
    - Myofunctional treatments
    - Positional therapies
    - Oxygen
    - Exercise therapy
- Key Question 4
  - Group CBT-I
- Key Question 5
  - Dental/oral appliances
- Key Question 6
  - No treatment, usual care, education, sleep hygiene
  - Different medication
  - CBT-I
  - Placebo
- Key Question 7
  - Other durations and intensities
- Key Question 8
  - No intervention/no therapy/usual care/education
  - Different method to improve adherence to CPAP
- Key Question 9
  - No treatment, usual care

    - CBT-I
    - Pharmacotherapy
    - Other alternative therapy for insomnia
- Key Question 10
    - Different diagnostic test or management option
- Key Question 11
    - No treatment/usual care (including CBT-I)
    - Placebo
    - A different herbal remedy or dietary supplement
    - Pharmacotherapy (e.g., benzodiazepines)
- Key Question 12
    - No treatment/usual care
    - Placebo or sham intervention
    - Different type of complementary and alternative medicine
- Key Question 13
    - Polysomnography
- Key Question 14
    - Absence of these exposures
- Key Question 15
    - Treatment as usual
- Key Question 16
    - Adults with OSA without co-occurring conditions and receiving CPAP
- Key Question 17
    - Face-to-face delivery of interventions for insomnia, usual care
- Key Question 18
    - No treatment
    - CBT-I
- Key Question 19
    - Clinical interview
- Key Question 20
    - Polysomnography

d. Outcomes

- Key Questions 1, 2, 4, 6, 9, 10, 11, 12, 15, 17, 18
    - Critical Outcomes
        - Daytime functioning
        - Insomnia severity

        - Sleep efficiency
        - Harms (for KQ 1, 6, and 11, see below)
    - Important Outcomes
        - Sleep onset latency
        - Wake after sleep onset
        - Sleep quality
        - Quality of life
        - Total sleep time
- Key Questions 3, 5, 7
    - Critical Outcomes
        - Daytime sleepiness/functioning
        - Reduction of apnea-hypopnea index
        - O^2 desaturation index
        - Quality of life/sleep-related quality of life
        - Neurocognitive (e.g., attention, memory, reaction time, concentration, executive function)
        - Increased mortality
        - Functional outcomes (includes FOSQ or other outcomes)
    - Important Outcomes
        - Snoring
        - Cardiovascular (e.g., myocardial infarction, stroke)
        - Hypertension (e.g., elevated blood pressure)
- Key Question 13, 19, 20
    - Critical outcomes
        - Sensitivity and specificity
        - Positive and negative predictive values (PPV, NPV)
        - Diagnostic accuracy (KQ 13 only)
    - Important outcomes
        - Area under the ROC curve (AUC)
- Key Question 8, 16
    - Critical outcomes
        - Adherence with CPAP (defined by any number of hours/night and percent of the time)
- Key Question 14
    - Critical outcomes
        - Incidence/prevalence of OSA

- Key Question 1, 6, 11
    - Critical outcomes unique to these KQs
        - Quality of life: EQ-5D, SF-36, SIS, SS-QOL
        - Harms, including side effects (e.g., drug-drug interaction) increased motor vehicle accidents, falls due to medication, hypersomnia, night walking/driving, occupational effects, dependency or addiction, worsened sleep disordered breathing

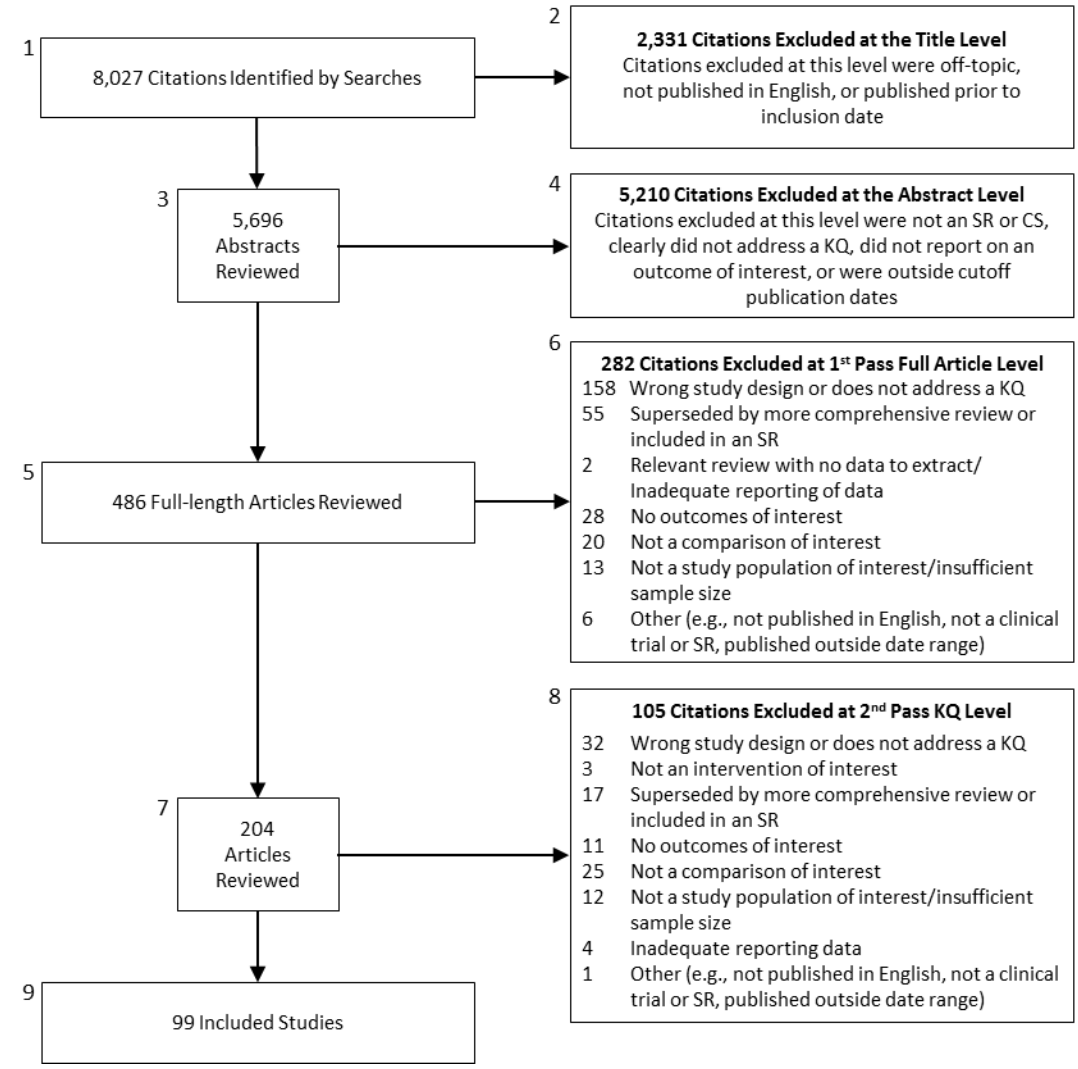
B. Conducting the Systematic Review

Based on the decisions made by the Champions and Work Group members regarding the scope, the KQs, and the PICOTS statements, the Lewin Team produced a systematic review protocol prior to conducting the review. The protocol was reviewed and approved by the Champions and Work Group members. It described in detail the final set of KQs, the methodology to be used during the systematic review process, and the inclusion/exclusion criteria to be applied to each potential study, including, but not limited to, study type, sample size, and PICOTS criteria.

Extensive literature searches identified 8,027 citations potentially addressing the KQs of interest to this evidence review. Of those, 2,331 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, 5,696 abstracts were reviewed with 5,210 of those being excluded for the following reasons: not an SR or an accepted study design (see the General Criteria for Inclusion in Systematic Review and Key Question Specific Criteria), did not address a KQ of interest to this review, did not report on an outcome of interest, or published outside cut-off publication dates. A total of 486 full-length articles were reviewed. Of those, 282 were excluded at a first pass review for the following: not addressing a KQ of interest, not enrolling the population of interest, not meeting inclusion criteria for study design, not meeting inclusion criteria for any KQ, or being a duplicate. A total of 204 full-length articles were thought to address one or more KQs and were further reviewed. Of these, 105 were ultimately excluded. Reasons for their exclusion are presented in Figure A-1 below.

Overall, 99 studies addressed one or more of the KQs and were considered as evidence in this review. Table A-2 indicates the number of studies that addressed each of the questions.

Figure A-1. Study Flow Diagram



Abbreviations: CS: clinical study; KQ: key question; SR: systematic review

Alternative Text Description of Study Flow Diagram

Figure D-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: 8,027 citations identified by searches
    a. Right to Box 2: 2,331 citations excluded at the title level
        i. Citations excluded at this level were off-topic, not published in English, or published prior to inclusion date
    b. Down to Box 3

2. Box 3: 5,696 abstracts reviewed
    a. Right to Box 4: 5,210 citations excluded at the abstract level
        i. Citations excluded at this level were not an SR or CS, clearly did not address a KQ, did not report on an outcome of interest, or were outside cutoff publication dates
    b. Down to Box 5
3. Box 5: 486 full-length articles reviewed
    a. Right to Box 6: 282 citations excluded at 1st pass full article level
        i. 158 wrong study design or does not address a KQ
        ii. 55 superseded by more comprehensive review or included in an SR
        iii. 2 relevant review with no data to extract/inadequate reporting of data
        iv. 28 no outcomes of interest
        v. 20 not a comparison of interest
        vi. 13 not a study population of interest/insufficient sample size
        vii. 6 other (e.g., not published in English, not a clinical trial or SR, published outside date range)
    b. Down to Box 7
4. Box 7: 204 articles reviewed
    a. Right to Box 8: 105 citations excluded at 2nd pass KQ level
        i. 32 wrong study design or does not address a KQ
        ii. 3 not an intervention of interest
        iii. 17 superseded by more comprehensive review or included in an SR
        iv. 11 no outcomes of interest
        v. 25 not a comparison of interest
        vi. 12 not a study population of interest/insufficient sample size
        vii. 4 inadequate reporting data
        viii. 1 other (e.g., not published in English, not a clinical trial or SR, published outside date range)
    b. Down to Box 9
5. Box 9: 99 included studies

Table A-2. Evidence Base for KQs

Question Number	Question	Number of Studies & Type of Studies
1	What is the long-term efficacy on sleep outcomes, comparative effectiveness, and harms of pharmacotherapy versus CBT-I?	1 SR
2	What is the effectiveness of behavioral therapy (i.e., CBT-I and BBT-I) in improving sleep outcomes?	2 SRs
3	In adults with OSA who cannot tolerate CPAP, what is the effectiveness of alternative therapies in improving sleep outcomes?	6 SRs, 5 RCTs, 12 non-RCTs
4	What is the comparative effectiveness of individual versus group CBT-I therapy on improving sleep outcomes?	1 non-RCT
5	What is the comparative effectiveness of CPAP versus dental/oral appliances in improving sleep outcomes?	2 SRs, 3 RCTs
6	What is the effectiveness of pharmacotherapy (FDA approved for insomnia and off-label) on sleep outcomes?	8 SRs
7	What is the relationship between intensity of use of/adherence to CPAP and health outcomes?	1 SR, 4 RCTs, 2 cohort studies
8	What methods improve adherence with CPAP?	7 SRs
9	In adult patients with insomnia who do not respond to CBT-I or pharmacotherapy, what treatments or management strategies lead to better sleep outcomes?	4 RCTs
10	In adult patients with insomnia who do not respond to CBT-I or pharmacotherapy, what is the effectiveness and yield of additional diagnostic testing in improving sleep outcomes?	No evidence
11	What is the effectiveness of herbal remedies or dietary supplements (e.g., melatonin, Valerian, kava) to improve sleep outcomes?	2 SRs, 2 RCTs
12	What is the efficacy of complementary and alternative treatments (e.g., meditation, mindfulness, yoga, acupuncture, Alpha Stim, etc.) to improve sleep outcomes?	7 SRs
13	In adults with suspected OSA, what is the comparative effectiveness of polysomnography versus home sleep testing on accuracy of diagnosis?	2 SRs, 3 cohort studies
14	What factors increase the risk for sleep disordered breathing (OSA/CSA)?	1 SR, 6 cohort studies
15	In adults with co-occurring mental health conditions (e.g., PTSD, GAD, mood disorders including depression and bipolar, TBI, substance use disorders, psychotic disorders), is CBT-I effective in treating insomnia?	1 SR, 2 RCTs
16	In adults with OSA and comorbid disorders (PTSD, TBI, depression, insomnia, anxiety) being treated with CPAP, what is the adherence rate among those with and without comorbidities?	1 SR, 1 RCT, 1 cohort study
17	In adults with chronic insomnia, what is the effectiveness of telehealth (provider directed or self-directed, including mobile apps) versus face-to-face healthcare delivery?	5 RCTs
18	What is the efficacy of sleep hygiene education as a monotherapy for insomnia symptoms?	1 SR, 2 RCTs
19	In adults with sleep complaints, what screening questionnaires are accurate for assessment of insomnia?	1 SR
20	In adults with suspected sleep apnea, what screening questionnaires are accurate for assessment of OSA (e.g., ISI, ESS, STOP-BANG, Berlin, PSQI, IRLSS, MEQ)?	1 SR, 2 cohort studies
	Total Evidence Base	**99 studies**

a. General Criteria for Inclusion in Systematic Review

- Clinical studies or systematic reviews published on or after January 1, 2008, to May 15, 2018. If multiple systematic reviews addressed a key question, we selected the most recent and/or comprehensive review. Systematic reviews were supplemented with clinical studies published subsequent to the systematic review.
- Studies must have been published in English.
- Publication must have been a full clinical study or systematic review; abstracts alone were not included. Similarly, letters, editorials, and other publications that are not full-length clinical studies were not accepted as evidence.
- Systematic reviews must 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 AHRQ). If an existing review did not assess the overall quality of the evidence, evidence from the review must be 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.
- Intervention studies must have assessed pharmacologic or non-pharmacologic treatment, care management approach, or community-based interventions and be a prospective, RCT with an independent control group. Crossover trials were not included.
- Study must have enrolled at least 20 patients (10 per study group) unless otherwise noted (see Key Question Specific Criteria).
- Study must have enrolled at least 85% of patients who meet the study population criteria: adults aged 18 years or older who might be experiencing sleep disorders.
- Study must have reported on at least one outcome of interest.

b. Key Question Specific Criteria

- For KQs 2, 5, 6, 8, 11, 12, and 17, systematic reviews of acceptable study designs (RCTs).
- For KQs 1, 3, 4, 9, 15, and 18, systematic reviews of acceptable study designs (RCTs) and RCTs.
- For KQs 7, 14, and 16, only systematic reviews of comparative observational studies, such as large prospective (>100 patients/arm) or retrospective (>200 patients/arm) cohort or case-controlled studies, or individual comparative observational studies were used.
- For KQs 10, 13, and 19, systematic reviews of diagnostic cohort studies that compare a diagnostic screening instrument to a valid reference standard report on the diagnostic characteristics of the screening instrument (e.g., sensitivity, specificity, repeatability), or individual diagnostic cohort studies.
- For KQ 20, only systematic reviews of diagnostic cohort studies with a minimum enrollment of 1,500 patients that compare a diagnostic screening instrument to a valid reference standard

report on the diagnostic characteristics of the screening instrument (e.g., sensitivity, specificity, repeatability), or similar individual diagnostic cohort studies.

Information regarding the bibliographic databases, date limits, and platform/provider can be found in Table A-3, below. Additional information on the search strategies, including topic-specific search terms and search strategies can be found in Appendix J.

Table A-3. Bibliographic Database Information

Name	Date Limits	Platform/Provider
Cochrane Database of Systematic Reviews (Cochrane Reviews)	January 1, 2008 to May 15, 2018	Wiley
Database of Abstracts of Reviews of Effects	January 1, 2008 to May 15, 2018	Wiley
EMBASE (Excerpta Medica)	January 1, 2008 to May 15, 2018	Elsevier
MEDLINE	January 1, 2008 to May 15, 2018	OvidSP
PsycINFO	January 1, 2008 to May 15, 2018	OvidSP
PubMed (In-process and Publisher records)	January 1, 2008 to May 15, 2018	National Library of Medicine

C. Convening the Face-to-face Meeting

In consultation with the COR, the Champions, and the Work Group, the Lewin Team convened a three and one-half day face-to-face meeting of the CPG Champions and Work Group members on November 6 – 9, 2018. These experts gathered to develop and draft the clinical recommendations for the 2019 Chronic Insomnia Disorder and OSA CPG. Lewin presented findings from the evidence review in order to facilitate and inform the process.

Under the direction of the Champions, the Work Group members were charged with interpreting the results of the evidence review and were asked to develop new clinical practice recommendations based on the 2018 evidence review. The subject matter experts were divided into three smaller subgroups at this meeting.

As the Work Group members drafted clinical practice recommendations, they also assigned a grade for each recommendation based on a modified GRADE and USPSTF methodology. Each recommendation was graded by assessing the quality of the overall evidence base, the associated benefits and harms, the variation in values and preferences, and other implications of the recommendation.

D. Grading Recommendations

This CPG uses the GRADE methodology to assess the quality of the evidence base and assign a strength for each recommendation. The GRADE system uses the following four domains to assess the strength of each recommendation:[204]

- Balance of desirable and undesirable outcomes
- Confidence in the quality of the evidence
- Values and preferences

- Other implications, as appropriate, e.g.,:
    - Resource use
    - Equity
    - Acceptability
    - Feasibility
    - Subgroup considerations

The following sections further describe each domain.

Balance of desirable and undesirable outcomes refers to the size of anticipated benefits (e.g., increased longevity, reduction in morbid event, resolution of symptoms, improved quality of life, decreased resource use) and harms (e.g., decreased longevity, immediate serious complications, adverse event, impaired quality of life, increased resource use, inconvenience/hassle) relative to each other. This domain is based on the understanding that the majority of clinicians will offer patients therapeutic or preventive measures as long as the advantages of the intervention exceed the risks and adverse effects. The certainty or uncertainty of the clinician about the risk-benefit balance will greatly influence the strength of the recommendation.

Some of the discussion questions that fall under this domain include:

- Given the best estimate of typical values and preferences, are you confident that the benefits outweigh the harms and burden or vice versa?
- Are the desirable anticipated effects large?
- Are the undesirable anticipated effects small?
- Are the desirable effects large relative to undesirable effects?

Confidence in the quality of the evidence reflects the quality of the evidence base and the certainty in that evidence. This second domain reflects the methodological quality of the studies for each outcome variable. In general, the strength of recommendation follows the level of evidence, but not always, as other domains may increase or decrease the strength. The evidence review used for the development of recommendations, conducted by ECRI, assessed the confidence in the quality of the evidence base using GRADE methodology and assigned a rating of "High," "Moderate," "Low," or "Very Low." The outcomes judged to be critical were used to determine the overall quality of evidence. Per GRADE, if the quality of evidence differs across the critical outcomes, the lowest quality of evidence for any of the relevant critical outcomes determines the overall quality of the evidence for a recommendation; the overall confidence cannot be higher than the lowest confidence in effect estimates for any outcome that is determined to be critical for clinical decision making.[37,203]

The elements that go into the confidence in the quality of the evidence include:

- Is there high or moderate quality evidence that answers this question?
- What is the overall certainty of this evidence?

Values and preferences is an overarching term that includes patients' perspectives, beliefs, expectations, and goals for health and life. More precisely, it refers to the processes that individuals use in considering the potential benefits, harms, costs, limitations, and inconvenience of the therapeutic or preventive measures in relation to one another. For some, the term "values" has the closest connotation to these processes. For others, the connotation of "preferences" best captures the notion of choice. In general, values and preferences increase the strength of the recommendation when there is high concordance and decrease it when there is great variability. In a situation in which the balance of benefits and risks are uncertain, eliciting the values and preferences of patients and empowering them and their surrogates to make decisions consistent with their goals of care becomes even more important. A recommendation can be described as having "similar values," "some variation," or "large variation" in typical values and preferences between patients and the larger populations of interest.

Some of the discussion questions that fall under the purview of values and preferences include:

- Are you confident about the typical values and preferences and are they similar across the target population?
- What are the patient's values and preferences?
- Are the assumed or identified relative values similar across the target population?

Other implications consider the practicality of the recommendation, including resource use, equity, acceptability, feasibility, and subgroup considerations. Resource use is related to the uncertainty around the cost-effectiveness of a therapeutic or preventive measure. For example, statin use in the frail elderly and others with multiple co-occurring conditions may not be effective and, depending on the societal benchmark for willingness to pay, may not be a good use of resources. Equity, acceptability, feasibility, and subgroup considerations require similar judgments around the practicality of the recommendation.

The framework below (Table A-4) was used by the Work Group to guide discussions on each domain.

Table A-4. GRADE Evidence to Recommendation Framework

Decision Domain	Questions to Consider	Judgment
Balance of desirable and undesirable outcomes	• Given the best estimate of typical values and preferences, are you confident that the benefits outweigh the harms and burden or vice versa? • Are the desirable anticipated effects large? • Are the undesirable anticipated effects small? • Are the desirable effects large relative to undesirable effects?	• Benefits outweigh harms/burden • Benefits slightly outweigh harms/ burden • Benefits and harms/burden are balanced • Harms/burden slightly outweigh benefits • Harms/burden outweigh benefits
Confidence in the quality of the evidence	• Is there high or moderate quality evidence that answers this question? • What is the overall certainty of this evidence?	• High • Moderate • Low • Very low
Values and preferences	• Are you confident about the typical values and preferences and are they similar across the target population? • What are the patient's values and preferences? • Are the assumed or identified relative values similar across the target population?	• Similar values • Some variation • Large variation
Other implications (e.g., resource use, equity, acceptability, feasibility, subgroup considerations)	• Are the resources worth the expected net benefit from the recommendation? • What are the costs per resource unit? • Is this intervention generally available? • Is this intervention and its effects worth withdrawing or not allocating resources from other interventions? • Is there lots of variability in resource requirements across settings?	• Various considerations

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 combines the four domains.[205] GRADE methodology does not allow for recommendations to be made based on expert opinion alone. While strong recommendations are usually based on high or moderate confidence in the estimates of effect (quality of the evidence) there may be instances where strong recommendations are warranted even when the quality of evidence is low.[204] In these types of instances where the balance of desirable and undesirable outcomes and values and preferences played large roles in determining the strength of a recommendation, this is explained in the discussion section for the recommendation.

The GRADE of a recommendation is based on the following elements:

- Four decision domains used to determine the strength and direction (described above)
- Relative strength (Strong or Weak)
- Direction (For or Against)

The relative strength of the recommendation is based on a binary scale, "Strong" or "Weak." A strong recommendation indicates that the Work Group is highly confident that desirable outcomes outweigh undesirable outcomes. If the Work Group is less confident in the balance between desirable and undesirable outcomes, they present a weak recommendation.

Similarly, a recommendation for a therapy or preventive measure indicates that the desirable consequences outweigh the undesirable consequences. A recommendation against a therapy or preventive measure indicates that the undesirable consequences outweigh the desirable consequences.

Occasionally, instances may occur when the Work Group feels there is insufficient evidence to make a recommendation for or against a particular therapy or preventive measure. This can occur when there is an absence of studies on a particular topic that met evidence review inclusion criteria, studies included in the evidence review report conflicting results, or studies included in the evidence review report inconclusive results regarding the desirable and undesirable outcomes.

Using these elements, the grade of each recommendation is presented as part of a continuum:

- Strong For (or "We recommend offering this option …")
- Weak For (or "We suggest offering this option …")
- No recommendation for or against (or "There is insufficient evidence …")
- Weak Against (or "We suggest not offering this option …")
- Strong Against (or "We recommend against offering this option …")

Note that weak (For or Against) recommendations may also be termed "Conditional," "Discretionary," or "Qualified." Recommendations may be conditional based upon patient values and preferences, the resources available, or the setting in which the intervention will be implemented. Recommendations may be at the discretion of the patient and clinician or they may be qualified with an explanation about the issues that would lead decisions to vary.

E. Recommendation Categorization

a. Recommendation Categories and Definitions

A set of recommendation categories was adapted from those used by the National Institute for Health and Care Excellence (NICE).[206,207] These categories, along with their corresponding definitions, are used to account for the various ways in which CPG recommendations can be developed or updated from a previous version of a CPG. The categories and definitions can be found in Table A-5.

Table A-5. Recommendation Categories and Definitions

Evidence Reviewed*	Recommendation Category*	Definition*
Reviewed	New-added	New recommendation following review of the evidence
	New-replaced	Recommendation from the previous CPG that has been carried forward to the updated CPG and has been changed following review of the evidence
	Not changed	Recommendation from the previous CPG that has been carried forward to the updated CPG where the evidence has been reviewed but the recommendation is not changed
	Amended	Recommendation from the previous CPG that has been carried forward to the updated CPG where the evidence has been reviewed and a minor amendment has been made
	Deleted	Recommendation from the previous CPG that has been removed based on review of the evidence
Not reviewed	Not changed	Recommendation from the previous CPG that has been carried forward to the updated CPG, but for which the evidence has not been reviewed
	Amended	Recommendation from the previous CPG that has been carried forward to the updated CPG where the evidence has not been reviewed and a minor amendment has been made
	Deleted	Recommendation from the previous CPG that has been removed because it was deemed out of scope for the updated CPG

*Adapted from the NICE guideline manual (2012) [206] and Garcia et al. (2014) [207]
Abbreviation: CPG: clinical practice guideline

b. Categorizing Recommendations

Because the Chronic Insomnia Disorder and OSA CPG is a new CPG, all recommendations were categorized as "Reviewed, New-added." "Reviewed, New-added" recommendations are original, new recommendations.

F. Drafting and Submitting the Final Clinical Practice Guideline

Following the face-to-face meeting, the Champions and Work Group members were given writing assignments to craft discussion sections to support each of the new recommendations. During this time, the Champions and Work Group also made additional revisions to the algorithms, as necessary.

After developing the initial draft of the CPG, an iterative review process was used to solicit feedback on and make revisions to the CPG. Once they were developed, the first two drafts of the CPG were posted on a wiki website for a period of 14 – 20 business days for internal review and comment by the Work Group. All feedback submitted during each review period was reviewed and discussed by the Work Group and appropriate revisions were made to the CPG.

Draft 3 of the CPG was made available for peer review and comment. This process is described in the section titled Peer Review Process. After revisions were made based on the feedback received during the peer review and comment period, the Champions presented the CPG to the EBPWG for their approval. Changes were made based on feedback from the EBPWG and the guideline was finalized.

The Work Group also produced a set of guideline toolkit materials which included a provider summary, pocket card, and patient summary. The final 2019 Chronic Insomnia Disorder and OSA CPG was submitted to the EBPWG in August 2019.

Appendix B: 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 [208] 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 provider 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 actually 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 have not experienced insomnia for a long time, the strategies you have 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 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 the 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 sleep inducing medications have NOT been found to be as effective for treatment of chronic insomnia, and, in fact, behavioral therapy is more likely to be effective than sleep medications in the long run."

"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 in order 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. Their minds and bodies end up associating the bed with a place to be awake rather than a place to be asleep. What sorts of things has (*name of CBT-I or BBT-I provider*) discussed with you to do that may improve this? How difficult has this been 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 complete a two week sleep diary, when recommended by your healthcare provider, to allow the provider to get a more accurate estimate of your sleep schedule."

Appendix C: 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 either reviewing a PAP therapy download in patients using either auto-adjustable 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, to specifically include sleepiness, are adequately addressed. Examples are provided in the following sections.

A. General Information on Obstructive Sleep Apnea

"Sleep apnea is a very common, 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 sleepiness, morning headaches, using the bathroom frequently at night, a dry sore mouth, and daytime fatigue. If you are experiencing any of these symptoms, you may have sleep apnea."

"What defines sleep apnea are pauses in breathing – either a partial pause (hypopnea) or complete absence of breathing (apnea) – that occur while an individual is sleeping. During these periods of little to no breathing, oxygen levels can decrease (hypoxia) and carbon dioxide levels can increase (hypercapnia). Many of the serious medical consequences, such as hypertension, heart failure, cerebrovascular disease, and death, result from the frequent episodes of hypoxia. Frequent 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 obtaining a diagnosis of sleep apnea: (1) a home sleep apnea test, which is only used to confirm a highly suspected diagnosis of sleep apnea, and (2) an in-lab sleep study, which provides more information. Both studies measure your oxygen levels and the number of times per hour you stop breathing, which is called the apnea-hypopnea index. 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 is required."

C. Describing Sleep Apnea Treatment to Patients

"The primary and most efficacious treatment for sleep apnea is PAP therapy. PAP is delivered from a machine connected to a mask that you wear while sleeping. There are 2 types of PAP: (1) an auto-adjustable PAP, which determines how much pressure is required to keep your airway open, or (2) a fixed-pressure PAP (continuous PAP, or CPAP), which uses one pressure level only (i.e., it doesn't vary over time). You should use PAP whenever you sleep or take a nap 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 sleep apnea."

"MADs are another treatment for sleep apnea. Depending on your teeth and severity of sleep apnea, this may be a reasonable treatment. This device works by moving your jaw forward – to open your airways – and maintaining it in this position while you wear it during your sleep. In order to obtain a MAD, you will need to see a dentist who is experienced in making these devices."

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

"Overall, men have a higher prevalence of sleep apnea than women. Moreover, post-menopausal status in women also increases the risk of having sleep apnea. There are some areas of your lifestyle you can change to either improve or worsen sleep apnea. Having a regular sleep schedule and making sure you receive 7 – 8 hours of sleep on a regular, nightly basis can improve your sleep and sleep apnea. Not sleeping, or sleeping too little, can worsen your sleep apnea. Also, alcohol and certain medications (e.g., opioids/pain medications, sleeping medications) can make sleep apnea worse. Weight loss can improve sleep apnea while weight gain can make sleep apnea worse. Also, what position you sleep in can improve sleep apnea in some patients as sleeping on your back typically makes 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 MVCs and mistakes on duty or at work. If you are sleepy, you should neither drive nor perform dangerous or critical tasks."

F. Addressing Adherence to Positive Airway Pressure

"The following are interventions that can help with PAP adherence:

- Use of heated humidification for PAP therapy
- Ensuring the appropriate mask choice, noting nasal masks are associated with higher adherence
- Educational strategies to include an overview of OSA and their treatment modality
- Cognitive behavioral therapies addressing distorted views of sleep and sleep apnea, promoting positive associations with PAP, and enlisting social support
- Investigate and address issues of high leak
- Close follow-up (at least at 4-weeks, if not sooner) after initial PAP prescription to evaluate usage"

Appendix D: ICSD-3 Diagnostic Criteria

A. Chronic Insomnia Disorder [2]

ICD-9-CM code: 307.42

ICD-10-CM code: F51.01

a. Alternate Names

Chronic insomnia, primary insomnia, secondary 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. Waking up 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. Attention, concentration, or memory impairment
    3. Impaired social, family, occupational, or academic performance
    4. Mood disturbance/irritability
    5. 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., enough time is allotted for sleep) or inadequate circumstances (i.e., the environment is safe, dark, 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/wake difficulty is not better explained by another sleep disorder

B. Obstructive Sleep Apnea [2]

ICD-9-CM code: 327.23

ICD-10-CM code: G47.33

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 satisfy the criteria

A. The presence of one or more of the following:
    1. The patient complains of sleepiness, nonrestorative sleep, fatigue, or insomnia symptoms
    2. The patient wakes with breath holding, gasping, or choking
    3. The bed partner or other observer reports habitual snoring, breathing interruptions, or both during the patient's sleep
    4. The patient has been diagnosed with hypertension, a mood disorder, cognitive dysfunction, coronary artery disease, stroke, congestive heart failure, atrial fibrillation, or type 2 diabetes mellitus

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)

OR

C. PSG or HSAT demonstrates:
    1. Fifteen or more predominantly obstructive respiratory events (apneas, hypopneas, or RERAs) per hour of sleep during a PSG or per hour of monitoring (HSAT)

Appendix E: ISI and STOP Questionnaire Scoring Criteria

A. ISI [209]

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)

B. STOP Questionnaire [44]

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

Appendix F: DoD and VA Training in Behavioral Therapies for Insomnia Disorder

Both the DoD and VA are disseminating clinician training in evidence-based, behavioral treatments for insomnia disorders. The VA has disseminated and implemented evidence-based psychotherapies throughout VA to make these treatments widely available to Veterans. As part of this initiative, the VA has developed a national training program in CBT-I to promote competency-based training for VA providers. As of June 30, 2019, more than 850 VA providers had been trained to deliver individualized, face-to-face CBT-I. This training program is delivered in 2 phases. Phase 1 involves 10 hours of didactic training, 7.5 hours of experiential training (e.g., role-playing), and 2.5 hours of independent study. Phase 2 involves four months of weekly 90-minute phone calls with a training consultant. Therapy sessions are recorded and provided to training consultants for review. Successful completion of the program requires at least one full course of CBT-I completed with at least one patient, obtaining a minimum score on assessment and therapy rating scales, and demonstrated competency with assessment measures and electronic health record progress note templates. In late 2018, the VA also began disseminating a training program in group-based CBT-I. The VA does not currently offer formal training in brief behavioral therapy for insomnia.

DoD is implementing a training program in BBT-I for internal behavioral health consultants (i.e., psychologists and social workers integrated into patient-centered medical homes). The training was developed by the Center for Deployment Psychology (CDP) in collaboration with the Department of the Army and is delivered by CDP. Previous experience with CBT-I or sleep assessment and treatment is not required to be trained in BBT-I. Providers first participate in an online workshop consisting of eight hours of didactic training then four hours of interactive, experiential role-plays and exercises the following day. Providers then join 12, one-hour, weekly consultation calls, which include didactic training and discussion and problem-solving of cases brought by the providers. Providers must participate in at least 9 of the 12 consultation calls to successfully complete the training.

Across the DoD, accessibility to a provider with BBT-I and/or CBT-I training varies. Sites located at or near larger military treatment facilities, typically those with a clinical health psychology service, have providers trained in CBT-I. Examples include Madigan Army Medical Center at Joint Base Lewis-McChord, Joint Base San Antonio, and Walter Reed National Military Medical Center; all with programs that provide ongoing training and supervision in CBT-I. Other sites across the DoD may have providers (i.e., typically clinical psychologists) who have received training in CBT-I and/or other aspects of behavioral sleep medicine at one of the aforementioned sites, or independently, and offer this treatment. At this time, the DoD does not have an organizational level formal training and consultation process for CBT-I.

Both BBT-I and CBT-I have demonstrated efficacy,[133-135] but prior research has not directly compared BBT-I to CBT-I. The choice of which intervention to offer is routinely based on clinical setting, provider expertise, and patient characteristics. With its shorter treatment duration and lesser contact time, BBT-I is presumed to be more feasible in the primary care setting,[210] whereas a full course of CBT-I is frequently offered within specialty mental health or sleep clinics. Patients having significant medical and/or mental health comorbidities may need a more tailored treatment approach and are thus presumed to fare better with the greater provider contact of CBT-I. Since BBT-I is more widely available within the DoD, patients are frequently offered BBT-I as an initial course of treatment and non-responders may be “stepped up” to a higher level of care. A host of self-management insomnia

treatment resources are available, as well, with varying levels of empirical support and expense (e.g., CBT-I Coach, Path to Better Sleep, Sleepio, and Shut-i).

Appendix G: Patient Focus Group Methods and Findings

A. Methods

As part of the effort to update this CPG, VA and DoD Leadership held a patient focus group. The aim of the focus group was to further understand and incorporate the perspective of patients receiving treatment for chronic insomnia disorder and/or OSA within the VA and/or DoD healthcare systems, as these patients are most affected by the recommendations put forth in the CPG. The patient focus group was held on March 27, 2018, at Fort Sam Houston in San Antonio, Texas. The focus group delved into the patients' perspectives on a set of topics related to their insomnia/OSA care, including their priorities, challenges they have experienced, the information they received regarding their care, as well as the impact of their care on their lives.

Participants for the focus group were recruited by VA and DoD Leadership as well as by the Chronic Insomnia Disorder and OSA CPG Champions. Patient focus group participants were not designed to be a representative sample of VA and DoD patients. However, recruitment focused on eliciting a range of perspectives likely to be relevant and informative in the guideline development process. Patients were not incentivized for their participation or reimbursed for travel expenses.

The Chronic Insomnia Disorder and OSA CPG Champions and Work Group, with support from Lewin, developed a set of questions to help guide the focus group. The focus group facilitator led the discussion using the previously prepared questions as a general guide to elicit the most important information from the patients regarding their experiences and views about their treatment and overall care. Given the limited time and the range of interests of the focus group participants, not all of the listed questions were addressed. Eight patients participated in the focus group.

B. Patient Focus Group Findings

a. Consider patient-specific goals, values, and preferences and use patient-centric decision making process to develop a patient-centered plan for timely diagnosis, treatment, and lifestyle adaptation.

- Identify patient-specific goals and preferences associated with diagnosis and treatment of OSA and insomnia.
- Understand the importance that patients place on timely diagnosis, enabling them to begin treatment for their sleep disorder.
- Discuss the harms, benefits, and likely outcomes of different diagnostic and treatment options, particularly imaging tests, and potential treatments.

b. Assess and screen patients for insomnia or sleep disorders in the primary care setting in order to promote early detection and treatment.

- Assess patients for symptoms of sleep disorders in the primary care setting and refer patients to specialty sleep care for early interventions.

c. Discuss patient preferences regarding the use of pharmacologic and non-pharmacologic treatment options.

- Discuss pharmacologic options in depth with the patient; seek to understand patient preference regarding reducing or eliminating certain medicines from their treatment plan.
- Provide information regarding non-pharmacologic treatment options to patients who prefer alternatives to medication.
- Be prepared to adjust or otherwise change treatment subject to patient response, preferences, and changes in priorities and goals.

d. Recognize the importance of communication and collaboration among providers on an interdisciplinary care team, particularly for comorbidities.

- Patients benefit when specialists are aware of their comorbidities and adapt a treatment plan to their particular needs.
- Providers should work together to ensure each patient receives timely referrals and smooth transitions between different members of their care team.

e. Provide more detailed information and education to patients and caregivers through all stages of diagnosis and treatment.

- Provide information to patients and their caregivers throughout all stages of diagnosis and treatment.
- Inform patients about the process and objectives of a PSG.

f. Involve family caregivers to create support and motivation for patients with insomnia disorder and/or OSA. The caregivers are also directly affected by the patient's condition.

- Include family members early in discussions about what to expect during each stage of diagnosis and treatment, especially with regards to lifestyle adaptation and self-care.
- Build and maintain trust, respect, and support with the patient and their family.

g. Reduce the stigma experienced by patients with insomnia disorder and/or OSA.

- Clinicians should acknowledge the potential difficulty military personnel face when reporting their sleep disorder.
- Patients may experience workplace stigma, particularly military personnel, who may struggle with feeling they are no longer able to perform their duties.
- Active duty populations may be particularly concerned about affecting their careers and being sent for a medical board once they are being treated for a sleep disorder.

h. An important objective for patients is improving daytime functioning.

- Patients feel that their sleep disorder makes it difficult to perform daily activities, and treatment goals should include improving daytime functioning for patients with insomnia/OSA.

Appendix H: Evidence Table

Exhibit H-1: Evidence Table[a, b, c]

Recommendation	Evidence	Strength of Recommendation	Recommendation Category
1. For patients who report sleep complaints, we suggest using the STOP questionnaire to stratify the risk of obstructive sleep apnea.	[43] **Additional References**: [31,44-51]	Weak for	Reviewed, New-added
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.	[16,27,53-57] **Additional References**: [46,52]	Weak for	Reviewed, New-added
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, apnea-hypopnea index) ≥15 events per hour to establish the diagnosis of moderate to severe obstructive sleep apnea.	[58]	Weak for	Reviewed, New-added
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 apnea-hypopnea index <5), we recommend repeat (home sleep apnea testing or lab-based polysomnography) testing for obstructive sleep apnea.	[58,59] **Additional References**: [7,60-77]	Strong for	Reviewed, New-added
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.	[79] **Additional References**: [78,80-82]	Weak for	Reviewed, New-added

[a] Evidence column: The first set of references listed in each row in the evidence column constitutes the evidence base for the recommendation. To be included in the evidence base for a recommendation, a reference needed to be identified through the 2018 evidence review. The second set of references in the evidence column (called "Additional References") includes references that provide additional information related to the recommendation, but which were not systematically identified through a literature review. These references were not included in the evidence base for the recommendation and therefore did not influence the strength and direction of the recommendation.

[b] Strength of Recommendation column: Refer to the Grading Recommendations section for more information on how the strength of the recommendation was determined using GRADE methodology.

[c] Recommendation Category column: Refer to the Recommendation Categorization section for more information on the description of the categorization process and the definition of each category.

Recommendation	Evidence	Strength of Recommendation	Recommendation Category
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.	Not applicable	Neither for nor against	Reviewed, New-added
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).	[83-86] **Additional References**: [87-92]	Strong for	Reviewed, New-added
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.	[83-86] **Additional References**: [87-92]	Weak for	Reviewed, New-added
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.	[93]	Strong for	Reviewed, New-added
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.	[23,93,94] **Additional References**: [95]	Weak for	Reviewed, New-added
11. In appropriate patients with mild to moderate obstructive sleep apnea (apnea-hypopnea index <30 per hour), we suggest offering mandibular advancement devices, fabricated by a qualified dental provider, as an alternative to positive airway pressure therapy.	[34,96-99] **Additional References**: [32,100]	Weak for	Reviewed, New-added
12. Among patients with anatomical nasal obstruction as a barrier to positive airway pressure use, we suggest evaluation for nasal surgery.	[101,102]	Weak for	Reviewed, New-added
13. For patients with obstructive sleep apnea with an apnea-hypopnea index of 15 – 65 per hour and a body mass index <32 kg/m^2 who cannot adhere to positive airway pressure therapy, we suggest evaluation for surgical treatment with hypoglossal nerve stimulation therapy.	[107,108] **Additional References**: [103-106]	Weak for	Reviewed, New-added
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.	[109-117]	Weak for	Reviewed, New-added

Recommendation	Evidence	Strength of Recommendation	Recommendation Category
15. For patients with obstructive sleep apnea who cannot tolerate or who have declined all other recommended treatments, we suggest offering alternative/salvage therapies.	[118-124]	Weak for	Reviewed, New-added
16. We suggest against oxygen therapy as a standalone treatment for patients with obstructive sleep apnea who cannot tolerate other recommended therapies.	[125] **Additional References**: [126-128]	Weak against	Reviewed, New-added
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.	[129]	Weak against	Reviewed, New-added
18. Due to the lack of clinically significant benefit, we cannot recommend for or against: • auto-titrating positive airway pressure when compared to fixed positive airway pressure, or • the use of flexible pressure delivery (e.g., C-Flex®, expiratory pressure relief) to improve positive airway pressure adherence.	[130,131] **Additional References**: [132]	Neither for nor against	Reviewed, New-added
19. We recommend offering CBT-I for the treatment of chronic insomnia disorder.	[133,135] **Additional References**: [134,136]	Strong for	Reviewed, New-added
20. We suggest offering brief behavioral therapy for insomnia (BBT-I) for the treatment of chronic insomnia disorder.	[133] **Additional References**: [134]	Weak for	Reviewed, New-added
21. There is insufficient evidence to recommend for or against group versus individual CBT-I for the treatment of chronic insomnia disorder.	[137]	Neither for nor against	Reviewed, New-added
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.	[138-142]	Neither for nor against	Reviewed, New-added
23. For patients diagnosed with chronic insomnia disorder, we suggest CBT-I over pharmacotherapy as first-line treatment.	[143] **Additional References**: [144,145]	Weak for	Reviewed, New-added

Recommendation	Evidence	Strength of Recommendation	Recommendation Category
24. We suggest offering CBT-I for the treatment of chronic insomnia disorder that is comorbid with another psychiatric disorder.	[146-148] **Additional References**: [144]	Weak for	Reviewed, New-added
25. There is insufficient evidence to recommend for or against mindfulness meditation for the treatment of chronic insomnia disorder.	[149] **Additional References**: [150]	Neither for nor against	Reviewed, New-added
26. We suggest against sleep hygiene education as a standalone treatment for chronic insomnia disorder.	[151,152]	Weak against	Reviewed, New-added
27. We suggest offering auricular acupuncture with seed and pellet for the treatment of chronic insomnia disorder.	[153]	Weak for	Reviewed, New-added
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.	[154,155] **Additional References**: [156]	Neither for nor against	Reviewed, New-added
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.	[157,159] **Additional References**: [158]	Neither for nor against	Reviewed, New-added
30. We suggest against cranial electrical stimulation for the treatment of chronic insomnia disorder.	[161] **Additional References**: [160]	Weak against	Reviewed, New-added
31. We suggest against the use of diphenhydramine for the treatment of chronic insomnia disorder.	**Additional References**: [82,162-166]	Weak against	Reviewed, New-added
32. We suggest against the use of melatonin for the treatment of chronic insomnia disorder.	[167] **Additional References**: [168-170]	Weak against	Reviewed, New-added
33. We suggest against the use of valerian and chamomile for the treatment of chronic insomnia disorder.	[171] **Additional References**: [172]	Weak against	Reviewed, New-added

Recommendation	Evidence	Strength of Recommendation	Recommendation Category
34. We recommend against the use of kava for the treatment of chronic insomnia disorder.	[171] **Additional References**: [173]	Strong against	Reviewed, New-added
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.	[174] **Additional References**: [165,175-177]	Weak for	Reviewed, New-added
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.	[178,179] **Additional References**: [180-183]	Weak for	Reviewed, New-added
37. There is insufficient evidence to recommend for or against the use of ramelteon for the treatment of chronic insomnia disorder.	[184]	Neither for nor against	Reviewed, New-added
38. There is insufficient evidence to recommend for or against the use of suvorexant for the treatment of chronic insomnia disorder.	[185] **Additional References**: [186,187]	Neither for nor against	Reviewed, New-added
39. We suggest against the use of antipsychotic drugs for the treatment of chronic insomnia disorder.	**Additional References**: [165,188,189]	Weak against	Reviewed, New-added
40. We suggest against the use of benzodiazepines for the treatment of chronic insomnia disorder.	[178,184,190,191]	Weak against	Reviewed, New-added
41. We suggest against the use of trazodone for the treatment of chronic insomnia disorder.	[190] **Additional References**: [192]	Weak against	Reviewed, New-added

Abbreviations: BBT-I: brief behavioral therapy for insomnia; CBT-I: cognitive behavioral therapy for insomnia; STOP: Snoring, Tiredness, Observed apnea, and high blood Pressure

Appendix I: Participant List

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Appendix J: Literature Review Search Terms and Strategy

A. Embase.com Syntax

a. Insomnia

Question	Set #	Concept	Strategy
Questions 1,2,5, and 15 – CBT-I for insomnia	#1	Population (adults with chronic insomnia)	insomnia/exp OR parasomnia/exp OR nightmare/exp OR 'sleep disorder'/mj OR (insomnia* OR dyssomnia* OR hypersomnia* OR parasomnia* OR dream* OR nightmare* OR sleepless* OR (sleep* NEAR/3 initiat*) OR (sleep* NEAR/3 onset*) OR (sleep* NEAR/3 quality*) OR (sleep* NEAR/3 maintenance) OR (sleep* NEAR/3 disorder*) OR (sleep* NEAR/3 disturb*) OR COMISA):ti
	#2	Intervention (CBT-I/BBT-I)	'cognitive behavioral therapy'/exp OR 'cognitive therapy'/exp OR 'behavior therapy'/exp OR (((cognitive OR behavior* OR behaviour*) NEAR/3 (therap* OR treatment*)) OR "CBT" or "CBTI" or "CBT-I" or "BBT" OR "BBT-I" OR BBTI):ti OR ((sleep NEAR/2 (restrict* OR hygien*)) OR (stimul* NEAR/2 control*) OR relaxation OR mindful* OR restructure*):ti
	#3	Combine sets	#1 AND #2
	#4	Apply Limits	See Search Limits at the end of the table
Question 6 – Pharmacotherapy for insomnia	#1	Population (adults with chronic insomnia – controlled terms limited to major concepts for increased specificity)	insomnia/exp/mj OR parasomnia/exp/mj OR nightmare/exp/mj OR 'sleep disorder'/mj OR (insomnia* OR dyssomnia* OR hypersomnia* OR parasomnia* OR dream* OR nightmare* OR sleepless* OR (sleep* NEAR/3 initiat*) OR (sleep* NEAR/3 onset*) OR (sleep* NEAR/3 quality*) OR (sleep* NEAR/3 maintenance) OR (sleep* NEAR/3 disorder*) OR (sleep* NEAR/3 disturb*) OR COMISA):ti
	#2	Broad intervention (drug therapy)	'drug therapy'/exp OR 'drug therapy'/lnk OR (pharmacotherap* OR medicine* OR medicat* OR (drug* NEAR/2 (therap* OR treat OR treatment*))):ti
	#3	Focused intervention (drug classes and generic/brand names)	'antidepressant agent'/exp OR hypnotic sedative agent'/exp OR 'sedative agent'/exp OR 'benzodiazepine receptor affecting agent'/exp OR 'benzodiazepine'/exp OR 'melatonin receptor agonist'/exp OR 'melatonin'/exp OR 'melatonin receptor agonist'/exp OR Benzodiazepin* OR hypnotic* OR sedative* OR antidepressive* OR antidepressant* OR (anti* ADJ1 depress*) OR zolpidem OR ambien OR eszopiclone OR lunesta OR zaleplon OR sonata* OR flurazepam OR dalmane OR quazepam OR doral OR triazolam OR halcion OR estazolam OR prosom OR temazepam OR restoril OR trazodone OR oleptro OR desyrel OR amitriptyline OR elavil OR doxepin OR sinequan OR ramelton OR rozerem OR mirtazapine OR remeron OR quetiapine OR Seroquel OR prazosin OR minipress OR melatonin
	#4	Combine sets	#1 AND (#2 OR #3)
	#5	Apply Limits	See Search Limits at the end of the table

Question	Set #	Concept	Strategy
Questions 9 and 10 – Management and additional diagnostic testing for refractory insomnia (not responding to CBT-I or pharmacotherapy)	#1	Population (adults with insomnia)	insomnia/exp OR parasomnia/exp OR nightmare/exp OR 'sleep disorder'/mj OR (insomnia* OR dyssomnia* OR hypersomnia* OR parasomnia* OR dream* OR nightmare* OR sleepless* OR (sleep* NEAR/3 initiat*) OR (sleep* NEAR/3 onset*) OR (sleep* NEAR/3 quality*) OR (sleep* NEAR/3 maintenance) OR (sleep* NEAR/3 disorder*) OR (sleep* NEAR/3 disturb*) OR COMISA):ti,ab
	#2	Population (refractory insomnia)	'treatment failure'/exp
	#3	Combine sets	#1 AND #2
	#4	Population (adults with refractory insomnia) – keyword title search	((Insomnia* OR dyssomnia* OR hypersomnia* OR parasomnia* OR dream* OR nightmare* OR sleepless* OR (sleep* NEAR/3 initiat*) OR (sleep* NEAR/3 onset*) OR (sleep* NEAR/3 quality) OR (sleep NEAR/3 maintenance) OR (sleep NEAR/3 disorder*) OR (sleep NEAR/3 disturb*) OR COMISA) AND (intractable OR persist* OR refractory OR nonrespon* OR (non NEAR/1 respon*) OR ((therap* OR treatment* OR pharmacotherapy*) NEAR/6 (fail* OR resist*)))):ti
	#5	Population (adults with refractory insomnia) – keyword title/abstract search with insomnia terms adjacent to treatment failure terms	((Insomnia* OR dyssomnia* OR hypersomnia* OR parasomnia* OR dream* OR nightmare* OR sleepless* OR COMISA) NEAR/4 (intractable OR persist* OR refractory OR nonrespon* OR “non responsive” OR non-responsive)):ti,ab
	#6	Combine sets – population	#3 OR #4 OR #5
	#7	Intervention (alternative therapies, management of comorbid conditions [KQ9]) – broad search for RCTs, SRs and Meta-analyses pertaining to treatment refractory insomnia	Randomized controlled trials/systematic review/meta-analysis hedge [see Search Limits at the end of this table]
	#8	Intervention (diagnostic work-up [KQ10]	'diagnostic test accuracy':de OR 'diagnosis':lnk OR 'differential diagnosis'/exp OR 'receiver operating characteristic':de OR 'roc curve'/exp OR 'roc curve' OR 'sensitivity and specificity':de OR 'sensitivity' OR 'specificity' OR 'accuracy':de OR 'precision'/exp OR precision OR 'prediction and forecasting'/exp OR 'prediction and forecasting' OR 'diagnostic error'/exp OR 'diagnostic error' OR 'maximum likelihood method':de OR 'likelihood' OR 'predictive value'/exp OR 'predictive value' OR ppv OR ((false OR true) NEAR/1 (positive OR negative))
	#9	Other study types [KQ 10]	'latin square design'/de OR 'controlled study'/exp OR 'clinical trial'/exp OR 'comparative study'/exp OR 'cohort analysis'/de OR 'follow up'/de OR 'intermethod comparison'/de OR 'parallel design'/de OR 'control group'/de OR 'prospective study'/de OR 'retrospective study'/de OR 'case control study'/exp OR 'major clinical study'/de OR 'evaluation study'/exp OR (cohort* OR longitudinal OR prospective OR retrospective OR "case control" OR compar* OR "control group" OR "controlled study" OR "controlled trial" OR "cross over" OR crossover OR "double blind" OR "double blinded" OR "matched controls" OR placebo* OR random* OR sham):ti,ab OR ((versus OR vs):ti)
	#10	Combine sets	#6 AND (#7 OR #8 OR #9)
	#11	Apply limits	See Search Limits at the end of the table

Question	Set #	Concept	Strategy
Question 11, 12, 17, 18 – Selected treatments for insomnia (herbal remedies, complementary therapies, sleep hygiene)	#1	Population (adults with chronic insomnia – controlled terms limited to major concepts and keywords limited to titles for increased specificity)	insomnia/exp/mj OR parasomnia/exp/mj OR nightmare/exp/mj OR 'sleep disorder'/mj OR (insomnia* OR dyssomnia* OR hypersomnia* OR parasomnia* OR dream* OR nightmare* OR sleepless* OR (sleep* NEAR/3 initiat*) OR (sleep* NEAR/3 onset*) OR (sleep* NEAR/3 quality*) OR (sleep* NEAR/3 maintenance) OR (sleep* NEAR/3 disorder*) OR (sleep* NEAR/3 disturb*) OR COMISA):ti
	#2	Intervention (herbal remedies/dietary supplements [KQ11])	'dietary supplement'/exp OR 'natural products and their synthetic derivatives'/exp OR 'plant medicinal product'/exp OR 'melatonin'/exp OR 'Chinese drug'/exp OR 'vitamin'/exp OR 'valerian'/exp OR 'kava'/exp OR 'kava extract'/exp OR '5 hydroxytryptophan'/exp OR 'GABAergic receptor affecting agent'/exp OR 'Passiflora'/exp OR 'Passiflora incarnata extract'/exp OR (diet OR dietary OR herb OR herbs OR herbal* OR plant OR plants OR vitamin* OR melatonin* OR valerian* OR kava* OR "l-theanine" OR "l theanine" OR "5-htp" OR "5 htp" OR "5-Hydroxytryptophan" OR hydroxytryptophan* OR GABA OR (gamma NEXT/1 Aminobutyric) OR "passion flower" OR passiflora* OR (Chinese NEAR/2 (medicin* OR medication* OR therap* OR treatment* OR remedy OR remedies))):ti
	#3	Intervention (Complementary and alternative therapies [KQ 12])	'alternative medicine'/exp OR 'meditation'/exp OR 'mindfulness'/exp OR 'yoga'/exp OR 'Tai Chi'/exp OR 'acupuncture'/exp OR 'relaxation training'/exp OR 'exercise'/exp OR 'electrostimulation'/exp OR 'cranial electrotherapy stimulator'/exp OR 'electrotherapy'/exp OR (((Complement* or alternative* or "CAM") NEAR/5 (therap* or treatment* or remedy or remedies or medicin*)) or meditat* or mindful* or yoga* or "tai chi" or "tai ji" or acupunctur* or exercis* or relaxation* or (physical NEAR/3 activit*) or (alpha NEAR/1 stim) or (electr* NEAR/3 stimulat*) or electrotherapy* or electrosleep*):ti
	#4	Intervention (treatment delivery via telehealth [KQ 17])	'computer assisted therapy'/exp OR 'telemedicine'/exp OR 'mobile phone'/exp OR 'smartphone'/exp OR 'Internet'/exp OR 'mobile application'/exp OR 'telecommunication'/exp OR 'social media'/exp OR (Cellphone* or ((Cell or cellular) NEXT/1 phone*) or computer* or ehealth or internet or mhealth or (mobile NEAR/1 (application or app)) or digital* or smartphone* or (smart NEXT/1 phone*) or "social media" or telecommunications or telehealth or telemedicine or "telemental health" or website* OR (web NEXT/1 based) OR online OR web):ti
	#5	Intervention (sleep hygiene education [KQ 18])	'sleep hygiene'/exp OR (Sleep* NEAR/4 (hygien* OR educat*)):ti,ab,de
	#6	Combine sets	#1 AND (#2 OR #3 OR #4 OR #5)
	#7	Apply limits	See Search Limits at the end of the table

Question	Set #	Concept	Strategy
Question 19 – Questionnaires for the assessment of insomnia	#1	Population (adults with chronic insomnia)	insomnia/exp OR parasomnia/exp OR nightmare/exp OR 'sleep disorder'/mj OR (Insomnia* OR dyssomnia* OR hypersomnia* OR parasomnia* OR dream* OR nightmare* OR sleepless* OR (sleep* NEAR/3 initiat*) OR (sleep* NEAR/3 onset*) OR (sleep* NEAR/3 quality*) OR (sleep* NEAR/3 maintenance) OR (sleep* NEAR/3 disorder*) OR (sleep* NEAR/3 disturb*) OR COMISA):ti
	#2	Intervention (screening questionnaires)	'questionnaire'/exp AND ('mass screening'/exp OR 'screening test'/exp) OR ((survey* or questionnaire* OR scale or scales or index or indices or tool*) AND (screen* OR assess* OR suspect* OR confirm*)):ti OR (ISI or "insomnia severity index" or ESS or "Epworth sleepiness scale" or "stop bang" or "berlin questionnaire" or "sleep quality index" or PSQI or "international restless legs syndrome" or IRLSS OR (morningness NEAR/2 eveningness) or MEQ):ti
	#3	Combine sets	#1 AND #2
	#4	RCTs/Meta Analyses/Systematic Reviews	Randomized controlled trials/systematic review/meta-analysis hedge [see Search Limits at the end of this table]
	#5	Diagnostic test study types	'diagnostic test accuracy':de OR 'diagnosis':lnk OR 'differential diagnosis'/exp OR 'receiver operating characteristic':de OR 'roc curve'/exp OR 'roc curve' OR 'sensitivity and specificity':de OR ('sensitivity' AND 'specficity') OR 'accuracy':de OR 'precision'/exp OR precision OR 'prediction and forecasting'/exp OR (prediction and forecasting) OR 'diagnostic error'/exp OR 'diagnostic error' OR 'maximum likelihood method':de OR 'likelihood' OR 'predictive value'/exp OR 'predictive value' OR ppv OR ((false OR true) NEAR/1 (positive OR negative)) OR diagnos* or PPV OR "receiver operating characteristic" or (area NEXT/1 under NEXT/3 curve) OR AUC or "diagnostic accuracy"
	#6	Other study types	'latin square design'/de OR 'controlled study'/exp OR 'clinical trial'/exp OR 'comparative study'/exp OR 'cohort analysis'/de OR 'follow up'/de OR 'intermethod comparison'/de OR 'parallel design'/de OR 'control group'/de OR 'prospective study'/de OR 'retrospective study'/de OR 'case control study'/exp OR 'major clinical study'/de OR 'evaluation study'/exp OR 'validation study'/exp OR 'longitudinal study'/exp
	#7	Combine Sets	#3 AND (#4 OR #5 OR #6)
	#8	Apply limits	See Search Limits at the end of the table

b. Obstructive Sleep Apnea

Question	Set #	Concept	Strategy
Question 3 and 5 – Alternative therapies for CPAP	#1	Population (adults with obstructive sleep apnea)	'sleep disordered breathing'/exp OR (Sleep* NEAR/4 (apnea* or apnoea* OR breathing* OR hypoventilat*)) OR OSA OR OSAS OR OSAHS OR COMISA
	#2	Intervention (CPAP)	'positive end expiratory pressure'/exp OR 'CPAP device'/exp OR APAP OR A-PAP OR (positive next/1 airway next/1 pressure) OR autopap* OR auto-pap OR autoCPAP OR auto-cpap OR bipap OR bi-pap OR vpap OR v-pap OR CPAP OR c-pap OR PAP
	#3	Intervention (alternative therapies to CPAP [KQ3] including dental/oral appliances [KQ5])	'alternative medicine'/exp OR 'dental therapeutic device'/exp OR 'snoring device'/exp OR 'dental device'/exp OR 'mandibular advancement'/exp OR 'oral appliance'/exp OR 'mandibular advancement device'/exp OR 'oxygen therapy'/exp OR 'muscle training'/exp OR 'body weight loss'/exp OR 'weight loss program'/exp OR 'exercise'/exp OR 'electrostimulation'/exp OR ((Dental OR snore OR snoring OR oral) NEAR/5 (appliance* OR device*)) OR EPAP* OR (expiratory next/1 positive next/1 airway next/1 pressure) OR provent* OR inspire* OR (hypogloss* AND stimulat*) OR electrostimulat* OR (electric* AND stimulat*) OR position* OR ((Oxygen OR "O2") NEAR/5 (therap* OR treatment* OR supplement* OR device* OR cannula*)) OR (weight AND (loss OR losing OR reduc*)) OR diet* OR (mandibul* NEAR/2 advance*) OR monoblock OR twinblock OR myotherap* OR myo-therap* OR ((myofunctional OR myofascial OR orofacial OR oropharyngeal OR "upper airway") AND (exercis* OR therap* OR remodel* OR reeducat* OR re-educat*))
	#4	Intervention (alternative therapies – CPAP terms adjacent to keywords for alternative therapies)	(APAP OR A-PAP OR "positive airway pressure" OR autopap* OR auto-pap OR autoCPAP OR auto-cpap OR bipap OR bi-pap OR vpap OR v-pap OR CPAP OR c-pap OR PAP) NEAR/3 (alternat* OR complement* OR compare* OR comparison OR instead* OR tolerate* OR tolerance* OR adher*)
	#5	Combine sets	#1 AND #2 AND (#3 OR #4)
	#6	Apply limits	See Search Limits at the end of the table
Question 7, 8, 16 – Intensity of use and adherence to CPAP (including adherence in adults with comorbid conditions)	#1	Population (adults with obstructive sleep apnea)	'sleep disordered breathing'/exp OR (Sleep* NEAR/4 (apnea* or apnoea* OR breathing* OR hypoventilat*)) OR OSA OR OSAS OR OSAHS OR COMISA
	#2	Intervention (CPAP)	'positive end expiratory pressure'/exp OR 'CPAP device'/exp OR APAP OR A-PAP OR (positive next/1 airway next/1 pressure) OR autopap* OR auto-pap OR autoCPAP OR auto-cpap OR bipap OR bi-pap OR vpap OR v-pap OR CPAP OR c-pap OR PAP
	#3	Combine Sets	#1 AND #2
	#4	Apply limits	See Search Limits at the end of the table

Question	Set #	Concept	Strategy
Question 13 – Polysomnography versus Home sleep testing	#1	Population (adults with obstructive sleep apnea)	'sleep disordered breathing'/exp OR ((Sleep* NEAR/4 (apnea* or apnoea* OR breathing* OR hypoventilat*)) OR OSA OR OSAS OR OSAHS OR COMISA)
	#2	Intervention (polysomnography)	'polysomnography'/exp OR polysomnogra* OR polygraph* OR PSG
	#3	Intervention (home sleep testing)	'ambulatory monitoring'/exp OR 'home use apnea monitor'/exp OR HST or ((home or ambulatory or portable or unattended or nonattended or "un-attended" or "non-attended") NEAR/3 (test* or monitor* or study or studies)) or watchpat or "sleep profiler" or medibyte or sleepview or ezsleep or zmachine or embletta or nomad or oxyholter or "lx sleep" or accusom or "nox-t3" or nightone or apnealink or ARES or bwmini or somnotouch or somte
	#4	Combine sets	#1 AND #2 AND #3
	#5	RCTs/Meta Analyses/Systematic Reviews	Randomized controlled trials/systematic review/meta-analysis hedge [see Search Limits at the end of this table]
	#6	Diagnostic test study types	'diagnostic test accuracy':de OR 'diagnosis':lnk OR 'differential diagnosis'/exp OR 'receiver operating characteristic':de OR 'roc curve'/exp OR 'roc curve' OR 'sensitivity and specificity':de OR ('sensitivity' AND 'specficity') OR 'accuracy':de OR 'precision'/exp OR precision OR 'prediction and forecasting'/exp OR (prediction and forecasting) OR 'diagnostic error'/exp OR 'diagnostic error' OR 'maximum likelihood method':de OR 'likelihood' OR 'predictive value'/exp OR 'predictive value' OR ppv OR ((false OR true) NEAR/1 (positive OR negative)) OR diagnos* or PPV OR "receiver operating characteristic" or (area NEXT/1 under NEXT/3 curve) OR AUC or "diagnostic accuracy"
	#7	Other Study types	'latin square design'/de OR 'controlled study'/exp OR 'clinical trial'/exp OR 'comparative study'/exp OR 'cohort analysis'/de OR 'follow up'/de OR 'intermethod comparison'/de OR 'parallel design'/de OR 'control group'/de OR 'prospective study'/de OR 'retrospective study'/de OR 'case control study'/exp OR 'major clinical study'/de OR 'evaluation study'/exp OR 'validation study'/exp OR 'longitudinal study'/exp
	#8	Combine Sets	#4 AND (#5 OR #6 OR #7)
	#9	Apply limits	See Search Limits at the end of this table

Question	Set #	Concept	Strategy
Question 14 – Factors that increase the risk for sleep disordered breathing (OSA/CSA)	#1	Population (adults with sleep apnea – narrow focus using major concepts and title words)	'sleep disordered breathing'/exp/mj OR 'central sleep apnea syndrome'/exp/mj OR (Sleep* NEAR/4 (apnea* or apnoea* OR breathing* OR hypoventilat*)):ti OR (OSA OR OSAS OR OSAHS OR COMISA OR CSA):ti
	#2	Intervention (Risk exposure – narrow, limited to major concepts and title keywords)	'risk factor'/exp/mj OR 'risk assessment'/exp/mj OR 'risk'/exp/mj OR 'prevalence'/exp/mj OR 'incidence'/exp/mj OR 'epidemiology'/exp/mj OR 'prediction and forecasting'/exp/mj OR (Risk* OR epidemiolog* OR incidence OR prevalen* OR predict* OR etiolog* OR comorbid*).ti. OR (risk* NEAR/3 factor*)
	#3	Intervention (Risk exposure – broad, not limited to major concepts, but still limited to titles in the keyword)	'risk factor'/exp OR 'risk assessment'/exp OR 'risk'/exp OR 'prevalence'/exp OR 'incidence'/exp OR 'epidemiology'/exp OR 'prediction and forecasting'/exp OR (Risk* OR epidemiolog* OR incidence OR prevalen* OR predict* OR etiolog* OR comorbid*).ti. OR (risk* NEAR/3 factor*)
	#4	Intervention (named risk factor– opioid/medication use)	'antidepressant agent'/exp OR hypnotic sedative agent'/exp OR 'sedative agent'/exp OR 'benzodiazepine receptor affecting agent'/exp OR 'benzodiazepine'/exp OR opiate* OR opioid* OR narcotic* OR analgesic* OR Benzodiazepin* OR hypnotic* OR sedative* OR antidepressive* OR antidepressant* OR (anti* NEXT/1 depress*)
	#5	Intervention (named risk factor – gender)	'women`s health'/exp OR 'men`s health'/exp OR 'menopause and climacterium'/exp OR male OR female OR women OR woman OR men OR man OR menopaus* OR gender OR transgender
	#6	Intervention (named risk factor – veteran/military populations)	'military medicine'/exp OR 'military phenomena'/exp OR 'veteran'/exp OR 'veterans health'/exp OR "active duty" OR "air force" OR "armed forces" OR army OR battle* OR combat OR deployed OR navy OR naval OR marine OR marines OR soldier OR veteran* OR military
	#7	Intervention (other named risk factors)	'heart failure'/exp OR (heart NEXT/1 failure) OR 'traumatic brain injury'/exp OR (traumatic NEAR/2 brain NEAR/2 injur*) OR TBI OR 'cerebrovascular accident'/exp OR stroke* OR (cerebrovascular NEXT/1 accident*) OR CVA OR 'posttraumatic stress disorder'/exp OR 'mental disease'/exp OR 'behavior disorder'/exp (traumatic NEAR/2 stress) OR PTSD OR depression OR depressive OR ((mental OR behavior*) NEAR/4 (disorder* OR health))
	#8	Combine sets	(#1 AND #2) OR (#1 AND #3 AND (#4 OR #5 OR #6 OR #7))
	#9	RCTs/Meta Analyses/Systematic Reviews	Randomized controlled trials/systematic review/meta-analysis hedge [see Search Limits at the end of this table]
	#10	Other Study types	'latin square design'/de OR 'controlled study'/exp OR 'clinical trial'/exp OR 'comparative study'/exp OR 'cohort analysis'/de OR 'follow up'/de OR 'intermethod comparison'/de OR 'parallel design'/de OR 'control group'/de OR 'prospective study'/de OR 'retrospective study'/de OR 'case control study'/exp OR 'major clinical study'/de OR 'evaluation study'/exp OR 'validation study'/exp OR 'longitudinal study'/exp
	#11	Combine sets	#8 AND (#9 OR #10)
	#12	Apply limits	See Search Limits at the end of this table

Question	Set #	Concept	Strategy
Question 20 – Screening questionnaires for OSA	#1	Population (adults with obstructive sleep apnea)	'sleep disordered breathing'/exp OR ((Sleep* NEAR/4 (apnea* or apnoea* OR breathing* OR hypoventilat*)) OR OSA OR OSAS OR OSAHS OR COMISA)
	#2	Intervention (screening questionnaires)	'questionnaire'/exp AND ('mass screening'/exp OR 'screening test'/exp) OR ((survey* or questionnaire* OR scale or scales or index or indices or tool*) AND (screen* OR assess* OR suspect* OR confirm*)):ti OR (ISI or "insomnia severity index" or ESS or "Epworth sleepiness scale" or "stop bang" or "berlin questionnaire" or "sleep quality index" or PSQI or "international restless legs syndrome" or IRLSS OR (mornigness NEAR/2 eveningness) or MEQ):ti
	#3	Combine sets	#1 AND #2
	#4	RCTs/Meta Analyses/Systematic Reviews	Randomized controlled trials/systematic review/meta-analysis hedge [see Search Limits at the end of this table]
	#5	Diagnostic test study types	'diagnostic test accuracy':de OR 'diagnosis':lnk OR 'differential diagnosis'/exp OR 'receiver operating characteristic':de OR 'roc curve'/exp OR 'roc curve' OR 'sensitivity and specificity':de OR ('sensitivity' AND 'specficity') OR 'accuracy':de OR 'precision'/exp OR precision OR 'prediction and forecasting'/exp OR (prediction and forecasting) OR 'diagnostic error'/exp OR 'diagnostic error' OR 'maximum likelihood method':de OR 'likelihood' OR 'predictive value'/exp OR 'predictive value' OR ppv OR ((false OR true) NEAR/1 (positive OR negative)) OR diagnos* or PPV OR "receiver operating characteristic" or (area NEXT/1 under NEXT/3 curve) OR AUC or "diagnostic accuracy"
	#6	Other study types	'latin square design'/de OR 'controlled study'/exp OR 'clinical trial'/exp OR 'comparative study'/exp OR 'cohort analysis'/de OR 'follow up'/de OR 'intermethod comparison'/de OR 'parallel design'/de OR 'control group'/de OR 'prospective study'/de OR 'retrospective study'/de OR 'case control study'/exp OR 'major clinical study'/de OR 'evaluation study'/exp OR 'validation study'/exp OR 'longitudinal study'/exp
	#7	Combine Sets	#3 AND (#4 OR #5 OR #6)
	#8	Apply limits	See Search Limits at the end of this table
Search Limits Applied to Each Search		Limit to English language, humans and publication year	AND (english language AND humans AND yr="2008 - 2018")
		Exclude conference publications, books, letters, editorials, case studies, etc.	(abstract:nc OR annual:nc OR book/de OR 'case report'/de OR 'case study'/de OR conference:nc OR 'conference abstract':it OR 'conference paper'/de OR 'conference paper':it OR 'conference proceeding':pt OR 'conference review':it OR congress:nc OR editorial/de OR editorial:it OR erratum/de OR letter:it OR note/de OR note:it OR meeting:nc OR sessions:nc OR 'short survey'/de OR symposium:nc) .
		Limit to meta-analyses and systematic reviews	AND ('research synthesis' OR 'systematic review'/exp OR 'systematic review' OR 'meta analysis'/exp OR 'meta analysis' OR Cochrane)
		Limit to randomized controlled trials	'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)

B. MEDLINE Syntax

a. Insomnia

Question	Set #	Concept	Strategy
Questions 1,2,5, and 15 – CBT-I for insomnia	#1	Population (adults with chronic insomnia)	exp "sleep initiation and maintenance disorders"/ OR exp parasomnias/ OR exp night terrors/ OR exp dreams/ OR Sleep Wake Disorders/ OR (insomnia* OR dyssomnia* OR hypersomnia* OR parasomnia* OR dream* OR nightmare* OR sleepless* OR (sleep* ADJ3 initiat*) OR (sleep* ADJ3 onset*) OR (sleep* ADJ3 quality) OR (sleep ADJ3 maintenance) OR (sleep ADJ3 disorder*) OR (sleep ADJ3 disturb*) OR COMISA).ti,ab.
	#2	Intervention (CBT-I/BBT-I)	Exp behavior therapy/ OR exp cognitive therapy/ OR (((cognitive OR behavior* or behaviour*) ADJ3 (therap* or treatment*)) OR "CBT" OR "CBTI" OR "CBT-I" OR "BBT" OR "BBT-I" OR "BBTI" OR ((sleep ADJ2 (restrict* OR hygien*)) OR (stimul* ADJ2 control*) OR relaxation OR mindful* OR restructur*).ti,ab.
	#3	Combine sets	#1 AND #2
	#4	Apply Limits	See Search Limits at the end of the table
Question 6 – Pharmacotherapy for insomnia	#1	Population (adults with chronic insomnia – keywords limited to titles for increased specificity)	exp "sleep initiation and maintenance disorders"/ OR exp parasomnias/ OR exp night terrors/ OR exp dreams/ OR Sleep Wake Disorders/ OR (insomnia* OR dyssomnia* OR hypersomnia* OR parasomnia* OR dream* OR nightmare* OR sleepless* OR (sleep* ADJ3 initiat*) OR (sleep* ADJ3 onset*) OR (sleep* ADJ3 quality) OR (sleep ADJ3 maintenance) OR (sleep ADJ3 disorder*) OR (sleep ADJ3 disturb*) OR COMISA).ti.
	#2	Broad intervention (drug therapy)	Exp drug therapy/ OR dt.fs. OR pharmacotherap*.ti. OR medicine*.ti. OR medicat*.ti. OR (drug* ADJ2 (therap* OR treat OR treatment*)).ti.
	#3	Focused intervention (drug classes and generic/brand names)	exp "Hypnotics and Sedatives"/ OR exp Benzodiazepines/ OR exp Antidepressive Agents/ OR exp Receptors, Melatonin/ OR Benzodiazepin* OR hypnotic* OR sedative* OR antidepressive* OR antidepressant* OR (anti* ADJ1 depress*) OR zolpidem OR ambien OR eszopiclone OR lunesta OR zaleplon OR sonata* OR flurazepam OR dalmane OR quazepam OR doral OR triazolam OR halcion OR estazolam OR prosom OR temazepam OR restoril OR trazodone OR oleptro OR desyrel OR amitriptyline OR elavil OR doxepin OR sinequan OR ramelton OR rozerem OR mirtazapine OR remeron OR quetiapine OR Seroquel OR prazosin OR minipress OR melatonin
	#4	Combine sets	#1 AND (#2 OR #3)
	#5	Apply Limits	See Search Limits at the end of the table

Question	Set #	Concept	Strategy
Questions 9 and 10 – Management and additional diagnostic testing for refractory insomnia (not responding to CBT-I or pharmacotherapy)	#1	Population (adults with insomnia)	exp "sleep initiation and maintenance disorders"/ OR exp parasomnias/ OR exp night terrors/ OR exp dreams/ OR Sleep Wake Disorders/ OR (insomnia* OR dyssomnia* OR hypersomnia* OR parasomnia* OR dream* OR nightmare* OR sleepless* OR (sleep* ADJ3 initiat*) OR (sleep* ADJ3 onset*) OR (sleep* ADJ3 quality) OR (sleep ADJ3 maintenance) OR (sleep ADJ3 disorder*) OR (sleep ADJ3 disturb*)OR COMISA).ti,ab.
	#2	Population (refractory insomnia)	exp treatment failure/
	#3	Combine sets	#1 AND #2
	#4	Population (adults with refractory insomnia) – keyword title search	(Insomnia* OR dyssomnia*OR hypersomnia* OR parasomnia* OR dream* OR nightmare* OR sleepless* OR (sleep* ADJ3 initiat*) OR (sleep* ADJ3 onset*) OR (sleep* ADJ3 quality) OR (sleep ADJ3 maintenance) OR (sleep ADJ3 disorder*) OR (sleep ADJ3 disturb*) OR COMISA).ti. AND (intractable OR persist* OR refractory OR nonrespon* OR (non ADJ1 respon*) OR ((therap* OR treatment* OR pharmacotherapy*) ADJ6 (fail* OR resist*))).ti.
	#5	Population (adults with refractory insomnia) – keyword title/abstract search with insomnia terms adjacent to treatment failure terms	(Insomnia* OR dyssomnia*OR hypersomnia* OR parasomnia* OR dream* OR nightmare* OR sleepless* OR (sleep* ADJ3 initiat*) OR (sleep* ADJ3 onset*) OR (sleep* ADJ3 quality) OR (sleep ADJ3 maintenance) OR (sleep ADJ3 disorder*) OR (sleep ADJ3 disturb*) OR COMISA) ADJ4 (intractable OR persist* OR refractory OR nonrespon* OR (non ADJ1 respon*) OR ((therap* OR treatment* OR pharmacotherapy*) ADJ3 (fail* OR resist*))).ti,ab.
	#6	Combine sets – population	#3 OR #4 OR #5
	#7	Intervention (alternative therapies, management of comorbid conditions [KQ9]) – broad search for RCTs, SRs and Meta-analyses pertaining to treatment refractory insomnia	Randomized controlled trials/systematic review/meta-analysis hedge [see Search Limits at the end of this table]
	#8	Intervention (diagnostic work-up [KQ10])	exp diagnosis/ OR di.fs. OR receiver operating characteristic/ OR ROC curve/ OR (sensitivity/ and specificity/) OR accuracy/ OR diagnostic accuracy/ OR precision OR (prediction and forecasting) OR likelihood OR ((false OR true) ADJ (positive OR negative)) OR predictive value of tests/ OR exp diagnostic errors/ OR exp diagnostic error/ OR diagnostic accuracy/ OR positive predictive value OR PPV OR diagnos* OR workup OR "work-up" OR "work up" OR test OR testing OR tests OR psychometric* OR polysomnograph* OR "sleep study" OR "sleep studies" OR "sleep lab" OR "sleep lab" OR (predictive value of tests OR receiver operating characteristic OR ROC curve OR (sensitivity and specificity) OR accuracy OR diagnostic accuracy OR precision OR likelihood).de. OR ((false OR true) ADJ (positive OR negative)).mp.
	#9	Other study types [KQ 10]	exp cohort studies/ OR exp longitudinal studies/ OR exp retrospective studies/ OR exp prospective studies OR exp controlled study/ or exp clinical trial/ or exp comparative study/ OR major clinical study/ OR cross-over studies/ or crossover procedure/ or cross over studies/ OR (cohort* OR longitudinal OR prospective OR retrospective OR "case control" OR compar* OR "control group" OR "controlled study" OR "controlled trial" OR "cross over" OR crossover OR "double blind" OR "double blinded" OR "matched controls" OR placebo* OR random* OR sham OR validat*).ti,ab. OR ((versus OR vs).ti.)
	#10	Combine sets	#6 AND (#7 OR #8 OR #9)
	#11	Apply limits	See Search Limits at the end of the table

Question	Set #	Concept	Strategy
Question 11, 12, 17, 18 – Selected treatments for insomnia (herbal remedies, complementary therapies, sleep hygiene)	#1	Population (adults with chronic insomnia - keywords limited to titles for increased specificity)	exp "sleep initiation and maintenance disorders"/ OR exp parasomnias/ OR exp night terrors/ OR exp dreams/ OR Sleep Wake Disorders/ OR (Insomnia* OR dyssomnia* OR hypersomnia* OR parasomnia* OR dream* OR nightmare* OR sleepless* OR (sleep* ADJ3 initiat*) OR (sleep* ADJ3 onset*) OR (sleep* ADJ3 quality) OR (sleep ADJ3 maintenance) OR (sleep ADJ3 disorder*) OR (sleep ADJ3 disturb*) OR COMISA).ti.
	#2	Intervention (herbal remedies/dietary supplements [KQ11])	exp dietary supplements/ OR exp drugs, chinese herbal/ OR exp herbal medicine/ OR exp melatonin/ OR exp plants, Medicinal/ OR exp vitamins/ OR exp valerian/ OR exp kava/ OR exp plant extracts/ OR exp 5-Hydroxytryptophan/ OR exp gaba agents/ OR exp passiflora/ OR diet OR dietary OR herb OR herbs OR herbal* OR plant OR plants OR vitamin* OR melatonin* OR valerian* OR kava* OR "l-theanine" OR "l theanine" OR "5-htp" OR "5 htp" OR "5-Hydroxytryptophan"OR hydroxytryptophan* OR GABA OR (gamma ADJ1 Aminobutyric) OR "passion flower" OR passiflora* OR (Chinese ADJ2 (medicin* OR medication* OR therap* OR treatment* OR remedy OR remedies))
	#3	Intervention (Complementary and alternative therapies [KQ 12])	exp complementary therapies/ OR exp meditation/ OR exp mindfulness/ OR exp yoga/ OR exp Tai Ji/ OR exp acupuncture points/ OR exp acupuncture/ or exp acupuncture therapy/ OR exp relaxation therapy/ OR exp exercise OR exp electric stimulation therapy/ OR (((Complement* OR alternative* OR "CAM") ADJ5 (therap* OR treatment* OR remedy OR remedies OR medicin*)) OR meditat* OR mindful* OR yoga* OR "tai chi" OR "tai ji" OR acupunctur* OR exercis* OR relaxation* OR (physical ADJ3 activit*) OR (alpha ADJ1 stim) OR (electr* ADJ3 stimulat*) or electrotherapy* OR electrosleep*).mp
	#4	Intervention (treatment delivery via telehealth [KQ 17])	exp cell phone/ OR exp computer-assisted instruction/ OR exp Internet/ OR exp Mobile applications/ OR exp social media/ OR exp smartphone/ OR exp telecommunications/ OR exp Telemedicine/ OR Cellphone* OR ((Cell OR cellular) ADJ1 phone*) OR computer* OR ehealth OR internet OR mhealth OR (mobile ADJ1 (application OR app)) OR digital* OR smartphone* OR (smart ADJ1 phone*) OR "social media" OR telecommunications OR telehealth OR telemedicine OR "telemental health" OR website* OR (web ADJ1 based) OR online.ti. OR web.ti.
	#5	Intervention (sleep hygiene education [KQ 18])	Exp Sleep Hygiene/ OR ((Sleep* ADJ4 (hygien* OR educat*)) OR (sleep ADJ2 restrict*) OR (stimul* ADJ2 control*) OR relaxation OR mindful* OR restructur*).ti,ab.
	#6	Combine sets	#1 AND (#2 OR #3 OR #4 OR #5)
	#7	Apply limits	See Search Limits at the end of the table

Question	Set #	Concept	Strategy
Question 19 – Questionnaires for the assessment of insomnia	#1	Population (adults with chronic insomnia)	exp "sleep initiation and maintenance disorders"/ OR exp parasomnias/ OR exp night terrors/ OR exp dreams/ OR Sleep Wake Disorders/ OR (insomnia* OR dyssomnia*OR hypersomnia* OR parasomnia* OR dream* OR nightmare* OR sleepless* OR (sleep* ADJ3 initiat*) OR (sleep* ADJ3 onset*) OR (sleep* ADJ3 quality) OR (sleep ADJ3 maintenance) OR (sleep ADJ3 disorder*) OR (sleep ADJ3 disturb*) OR COMISA).ti.ab.
	#2	Intervention (screening questionnaires)	exp "Surveys and Questionnaires"/ AND exp "mass screening"/ OR (((survey* or questionnaire* OR scale or scales or index or indices or tool*) AND (screen* OR assess* OR suspect* OR confirm*)) OR ISI OR "insomnia severity index" OR ESS OR "Epworth sleepiness scale" OR "stop bang" OR "berlin questionnaire" OR "sleep quality index" OR PSQI OR "international restless legs syndrome" OR IRLSS OR (morningness ADJ2 eveningness) OR MEQ).ti.
	#3	Combine sets	#1 AND #2
	#4	RCTs/Meta Analyses/Systematic Reviews	Randomized controlled trials/systematic review/meta-analysis hedge [see Search Limits at the end of this table]
	#5	Diagnostic study types	exp diagnosis/ OR di.fs. OR receiver operating characteristic/ OR ROC curve/ OR (sensitivity/ and specificity/) OR accuracy/ OR diagnostic accuracy/ OR predictive value of tests/ OR exp diagnostic errors/ OR exp diagnostic error/ OR diagnos* OR "predictive value" OR PPV OR "receiver operating characteristic" OR "ROC curve" OR (area ADJ1 under ADJ3 curve) OR AUC OR (sensitivity and specificity) OR accuracy OR "diagnostic accuracy" OR (prediction and forecasting) OR precision OR likelihood OR ((false OR true) ADJ (positive OR negative))
	#6	Other study types	exp cohort studies/ OR exp longitudinal studies/ OR exp retrospective studies/ OR exp prospective studies OR exp controlled study/ or exp clinical trial/ or exp comparative study/ OR major clinical study/ OR cross-over studies/ or crossover procedure/ or cross over studies/ OR observational study/ OR validation studies/ OR (cohort* OR longitudinal OR prospective OR retrospective OR "case control" OR compar* OR "control group" OR "controlled study" OR "controlled trial" OR "cross over" OR crossover OR "double blind" OR "double blinded" OR "matched controls" OR placebo* OR random* OR sham OR validat*).ti,ab. OR ((versus OR vs).ti.)
	#7	Combine Sets	#3 AND (#4 OR #5 OR #6)
	#8	Apply limits	See Search Limits at the end of the table

b. Obstructive Sleep Apnea

Question	Set #	Concept	Strategy
Question 3 and 5 – Alternative therapies for CPAP	#1	Population (adults with obstructive sleep apnea)	Exp sleep apnea syndromes/ OR exp sleep apnea, obstructive/ OR (Sleep* ADJ4 (apnea* or apnoea* OR breathing* OR hypoventilat*) OR OSA OR OSAS OR OSAHS OR COMISA).ti,ab.
	#2	Intervention (CPAP)	exp positive-pressure respiration/ OR exp continuous positive airway pressure/ OR exp intermittent positive-pressure breathing/ OR APAP OR A-PAP OR (positive ADJ1 airway ADJ1 pressure) OR autopap* OR auto-pap OR autoCPAP OR auto-cpap OR bipap OR bi-pap OR vpap OR v-pap OR CPAP OR c-pap OR PAP
	#3	Intervention (alternative therapies to CPAP [KQ3] including dental/oral appliances [KQ5])	exp complementary therapies/ OR exp occlusal splints/ OR exp orthodontic appliances/ OR exp mandibular advancement/ OR oxygen/tu, th OR exp oxygen inhalation therapy/ OR exp patient positioning/ OR exp weight loss/ OR exp myofunctional therapy/ OR exp electric stimulation therapy/ OR exp exercise/ or exp exercise therapy/ OR ((Dental OR snore OR snoring OR oral) ADJ5 (appliance* OR device*)) OR EPAP* OR (expiratory ADJ1 positive ADJ1 airway ADJ1 pressure) OR provent* OR inspire* OR (hypogloss* AND stimulat*) OR electrostimulat* OR (electric* ADJ3 stimulat*) OR position* OR ((Oxygen OR "O2") ADJ5 (therap* OR treatment* OR supplement* OR device* OR cannula*)) OR (weight AND (loss OR losing OR reduc*)) OR diet* OR (mandibul* ADJ2 advance*) OR monoblock OR twinblock OR myotherap* OR myo-therap* OR ((myofunctional OR myofascial OR orofacial OR oropharyngeal OR "upper airway") AND (exercis* OR therap* OR remodel* OR reeducat* OR re-educat*)) OR exercis*
	#4	Intervention (alternative therapies – CPAP terms adjacent to keywords for alternative therapies)	(APAP OR A-PAP OR (positive ADJ1 airway ADJ1 pressure) OR autopap* OR auto-pap OR autoCPAP OR auto-cpap OR bipap OR bi-pap OR vpap OR v-pap OR CPAP OR c-pap OR PAP) ADJ3 (alternat* OR complement* OR compare* OR comparison OR instead* OR tolerate* OR tolerance* OR adher*)
	#5	Combine sets	#1 AND #2 AND (#3 OR #4)
	#6	Apply limits	See Search Limits at the end of the table
Question 7, 8, 16 – Intensity of use and adherence to CPAP (including adherence in adults with comorbid conditions)	#1	Population (adults with obstructive sleep apnea)	Exp sleep apnea syndromes/ OR exp sleep apnea, obstructive/ OR (Sleep* ADJ4 (apnea* or apnoea* OR breathing* OR hypoventilat*) OR OSA OR OSAS OR OSAHS OR COMISA).ti,ab.
	#2	Intervention (CPAP)	exp positive-pressure respiration/ OR exp continuous positive airway pressure/ OR exp intermittent positive-pressure breathing/ OR APAP OR A-PAP OR (positive ADJ1 airway ADJ1 pressure) OR autopap* OR auto-pap OR autoCPAP OR auto-cpap OR bipap OR bi-pap OR vpap OR v-pap OR CPAP OR c-pap OR PAP
	#3	Combine Sets	#1 AND #2
	#4	Apply limits	See Search Limits at the end of the table

Question	Set #	Concept	Strategy
Question 13 – Polysomnography versus Home sleep testing	#1	Population (adults with obstructive sleep apnea)	Exp sleep apnea syndromes/ OR exp sleep apnea, obstructive/ OR (Sleep* ADJ4 (apnea* or apnoea* OR breathing* OR hypoventilat*) OR OSA OR OSAS OR OSAHS OR COMISA).ti,ab.
	#2	Intervention (polysomnography)	Exp polysomnography/ OR polysomnogra* OR polygraph* OR PSG
	#3	Intervention (home sleep testing)	exp monitoring ambulatory/ OR HST OR ((home OR ambulatory OR portable OR unattended OR nonattended OR "un-attended" OR "non-attended") ADJ3 (test* OR monitor* OR study OR studies)) OR watchpat OR "sleep profiler" OR medibyte OR sleepview OR ezsleep OR zmachine OR embletta OR nomad OR oxyholter OR "lx sleep" OR accusom OR "nox-t3" OR nightone OR apnealink OR ARES OR bwmini OR somnotouch OR somte
	#4	Combine sets	#1 AND #2 AND #3
	#5	RCTs/Meta Analyses/Systematic Reviews	Randomized controlled trials/systematic review/meta-analysis hedge [see Search Limits at the end of this table]
	#6	Diagnostic test study types	exp diagnosis/ OR di.fs. OR receiver operating characteristic/ OR ROC curve/ OR (sensitivity/ and specificity/) OR accuracy/ OR diagnostic accuracy/ OR predictive value of tests/ OR exp diagnostic errors/ OR exp diagnostic error/ OR diagnos* OR "predictive value" OR PPV OR "receiver operating characteristic" OR "ROC curve" OR (area ADJ1 under ADJ3 curve) OR AUC OR (sensitivity and specificity) OR accuracy OR "diagnostic accuracy" OR (prediction and forecasting) OR precision OR likelihood OR ((false OR true) ADJ (positive OR negative))
	#7	Other Study types	exp cohort studies/ OR exp longitudinal studies/ OR exp retrospective studies/ OR exp prospective studies OR exp controlled study/ OR exp clinical trial/ OR exp comparative study/ OR major clinical study/ OR cross-over studies/ or crossover procedure/ or cross over studies/ OR observational study/ OR validation studies/
	#8	Combine Sets	#4 AND (#5 OR #6 OR #7)
	#9	Apply limits	See Search Limits at the end of this table

Question	Set #	Concept	Strategy
Question 14 – Factors that increase the risk for sleep disordered breathing (OSA/CSA)	#1	Population (adults with sleep apnea – narrow focus using major concepts and title words)	Exp *sleep apnea syndromes/ OR exp *sleep apnea, obstructive/ OR exp *Sleep Apnea, Central/ OR (Sleep* ADJ4 (apnea* or apnoea* OR breathing* OR hypoventilat*) OR OSA OR OSAS OR OSAHS OR CSA OR COMISA).ti.
	#2	Intervention (Risk exposure – narrow, limited to major concepts and title keywords)	(exp *risk/ OR exp *risk factors/ OR exp *prevalence/ OR exp *incidence/ OR exp *epidemiology/ OR exp *comorbidity/ OR (Risk* OR epidemiolog* OR incidence OR prevalen* OR predict* OR etiolog* OR comorbid*).ti. OR (risk* ADJ3 factor*)
	#3	Intervention (Risk exposure – broad, not limited to major concepts, but still limited to titles in the keyword)	exp risk/ OR exp risk factors/ OR prevalence/ OR exp incidence/ OR exp epidemiology/ OR comorbidity/ OR (Risk* OR epidemiolog* OR incidence OR prevalen* OR predict* OR etiolog* OR comorbid*).ti. OR (risk* ADJ3 factor*)
	#4	Intervention (named risk factor – opioid/medication use)	exp "Hypnotics and Sedatives"/ OR exp Benzodiazepines/ OR exp Antidepressive Agents/ OR exp opioid-related disorders/ OR exp Analgesics, Opioid/ OR exp narcotics/ OR opiate* OR opioid* OR narcotic* OR analgesic* OR Benzodiazepin* OR hypnotic* OR sedative* OR antidepressive* OR antidepressant* OR (anti* ADJ1 depress*)
	#5	Intervention (named risk factor – gender)	exp Women's Health/ OR exp Men's Health/ OR exp menopause/ OR Male OR female OR women OR woman OR men OR man OR menopaus* OR gender OR transgender
	#6	Intervention (named risk factor – veteran/military populations)	exp military personnel/ OR exp military facilities/ OR exp military medicine/ OR exp veterans/ OR exp veterans health/ OR exp hospitals, veterans/ OR exp hospitals, military/ OR exp "united states department of veterans affairs"/ OR “active duty” OR “air force” OR “armed forces” OR army OR battle* OR combat OR deployed OR navy OR naval OR marine OR marines OR soldier OR veteran* OR military
	#7	Intervention (other named risk factors)	exp Heart Failure/ OR (heart ADJ1 failure) OR exp Brain Injuries, Traumatic/ OR (traumatic ADJ2 brain ADJ2 injur*) OR TBI OR exp stroke/ OR stroke* OR (cerebrovascular ADJ1 accident*) OR CVA OR exp Stress Disorders, Post-Traumatic/ or exp Combat Disorders/ or Mental Disorders/ or exp Depression/ OR (traumatic ADJ2 stress) OR PTSD OR depression OR depressive OR ((mental OR behavior*) ADJ4 (disorder* OR health))
	#8	Combine sets	(#1 AND #2) OR (#1 AND #3 AND (#4 OR #5 OR #6 OR #7))
	#9	RCTs/Meta Analyses/Systematic Reviews	Randomized controlled trials/systematic review/meta-analysis hedge [see Search Limits at the end of this table]
	#10	Other Study types	exp cohort studies/ OR exp longitudinal studies/ OR exp retrospective studies/ OR exp prospective studies OR exp controlled study/ OR exp clinical trial/ OR exp comparative study/ OR major clinical study/ OR cross-over studies/ or crossover procedure/ or cross over studies/ OR observational study/ OR validation studies/
	#11	Combine sets	#8 AND (#9 OR #10)
	#12	Apply limits	See Search Limits at the end of this table

Question	Set #	Concept	Strategy
Question 20 – Screening questionnaires for OSA	#1	Population (adults with obstructive sleep apnea)	Exp sleep apnea syndromes/ OR exp sleep apnea, obstructive/ OR (Sleep* ADJ4 (apnea* or apnoea* OR breathing* OR hypoventilat*) OR OSA OR OSAS OR OSAHS OR COMISA).ti,ab.
	#2	Intervention (screening questionnaires)	exp "Surveys and Questionnaires"/ and exp "mass screening"/ OR (((survey* OR questionnaire* OR scale OR scales OR index OR indices OR tool*) AND (screen* OR assess* OR suspect* OR confirm*)) OR ISI OR "insomnia severity index" OR ESS OR "Epworth sleepiness scale" OR "stop bang" OR "berlin questionnaire" OR "sleep quality index" OR PSQI OR "international restless legs syndrome" OR IRLSS OR (morningness ADJ2 eveningness) OR MEQ).ti.
	#3	Combine sets	#1 AND #2
	#4	RCTs/Meta Analyses/Systematic Reviews	Randomized controlled trials/systematic review/meta-analysis hedge [see Search Limits at the end of this table]
	#5	Diagnostic test study types	exp diagnosis/ OR di.fs. OR receiver operating characteristic/ OR ROC curve/ OR (sensitivity/ and specificity/) OR accuracy/ OR diagnostic accuracy/ OR predictive value of tests/ OR exp diagnostic errors/ OR exp diagnostic error/ OR diagnos* OR "predictive value" OR PPV OR "receiver operating characteristic" OR "ROC curve" OR (area ADJ1 under ADJ3 curve) OR AUC OR (sensitivity and specificity) OR accuracy OR "diagnostic accuracy" OR (prediction and forecasting) OR precision OR likelihood OR ((false OR true) ADJ (positive OR negative))
	#6	Other study types	exp cohort studies/ OR exp longitudinal studies/ OR exp retrospective studies/ OR exp prospective studies OR exp controlled study/ OR exp clinical trial/ OR exp comparative study/ OR major clinical study/ OR cross-over studies/ or crossover procedure/ or cross over studies/ OR observational study/ OR validation studies/
	#7	Combine Sets	#3 AND (#4 OR #5 OR #6)
	#8	Apply limits	See Search Limits at the end of this table
Search Limits Applied to Each Search		Limit to English language, humans and publication year	AND (english language AND humans AND yr="2008 - 2018")
		Exclude conference publications, books, letters, editorials, case studies, etc..	NOT ((("column/opinion" OR "comment/reply" OR dissertation OR editorial OR letter OR book).dt. OR book.pt.) OR (letter/ or editorial/ OR news/ OR comment/ OR case report OR case reports/ OR note/ OR conference paper/) OR (letter OR editorial OR news OR comment OR case reports OR conference abstract$).pt.
		Limit to meta-analyses and systematic reviews	AND (meta analysis/ OR (systematic review OR meta analysis).mp. OR (meta-analysis OR systematic review).ti.)
		Limit to randomized controlled trials	AND (Randomized controlled trials OR random allocation OR double-blind method OR single-blind method OR placebos OR cross-over studies).de. OR placebo$.mp. OR random$.ti. OR randomized controlled trial.pt. OR crossover$.mp. OR cross over.mp. OR ((singl* OR doubl* OR tripl* OR trebl*) ADJ3 (blind* OR mask* OR sham*)).mp. OR latin square.mp. OR ISRTCN OR ACTRN* OR (NCT* not NCT) OR (clinical trials/ AND random*.ti.)

C. PsycINFO with Ovid Syntax

a. Insomnia

Question	Set #	Concept	Strategy
Questions 1,2,5, and 15 – CBT-I for insomnia	#1	Population (adults with chronic insomnia)	Exp insomnia/ OR exp parasomnias/ OR exp nightmares/ OR Sleep Disorders OR (Insomnia* OR dyssomnia*OR hypersomnia* OR parasomnia* OR dream* OR nightmare* OR sleepless* OR (sleep* ADJ3 initiat*) OR (sleep* ADJ3 onset*) OR (sleep* ADJ3 quality) OR (sleep ADJ3 maintenance) OR (sleep ADJ3 disorder*) OR (sleep ADJ3 disturb*) OR COMISA).ti,ab.
	#2	Intervention (CBT-I/BBT-I)	exp cognitive behavior therapy/ OR exp behavior therapy/ OR exp cognitive therapy/ OR (((cognitive OR behavior* or behaviour*) ADJ3 (therap* or treatment*)) OR "CBT" OR "CBTI" OR "CBT-I" OR "BBT" OR "BBT-I" OR "BBTI" OR ((sleep ADJ2 (restrict* OR hygien*)) OR (stimul* ADJ2 control*) OR relaxation OR mindful* OR restructur*).ti,ab.
	#3	Combine sets	#1 AND #2
	#4	Apply limits	See Search Limits at the end of the table
Question 6 – Pharmacotherapy for insomnia	#1	Population (adults with chronic insomnia – keywords limited to titles for increased specificity)	Exp insomnia/ OR exp parasomnias/ OR exp nightmares/ OR Sleep Disorders/ OR (Insomnia* OR dyssomnia* OR hypersomnia* OR parasomnia* OR dream* OR nightmare* OR sleepless* OR (sleep* ADJ3 initiat*) OR (sleep* ADJ3 onset*) OR (sleep* ADJ3 quality) OR (sleep ADJ3 maintenance) OR (sleep ADJ3 disorder*) OR (sleep ADJ3 disturb*) OR COMISA).ti.
	#2	Broad intervention (drug therapy)	Exp drug therapy/ OR dt.fs. OR pharmacotherap*.ti. OR medicine*.ti. OR medicat*.ti. OR (drug* ADJ2 (therap* OR treat OR treatment*)).ti.
	#3	Focused intervention (drug classes and generic/brand names)	exp Hypnotic Drugs/ or exp Sedatives/ or exp Benzodiazepines/ OR exp Antidepressant drugs/ OR exp melatonin/ OR Benzodiazepin* OR hypnotic* OR sedative* OR antidepressive* OR antidepressant* OR (anti* ADJ1 depress*) OR zolpidem OR ambien OR eszopiclone OR lunesta OR zaleplon OR sonata* OR flurazepam OR dalmane OR quazepam OR doral OR triazolam OR halcion OR estazolam OR prosom OR temazepam OR restoril OR trazodone OR oleptro OR desyrel OR amitriptyline OR elavil OR doxepin OR sinequan OR ramelton OR rozerem OR mirtazapine OR remeron OR quetiapine OR Seroquel OR prazosin OR minipress OR melatonin
	#4	Combine	#1 AND (#2 OR #3)
	#5	Apply limits	See Search Limits at the end of the table

Question	Set #	Concept	Strategy
Questions 9 and 10 – Management and additional diagnostic testing for refractory insomnia (not responding to CBT-I or pharmacotherapy)	#1	Population (adults with refractory insomnia)	Exp insomnia/ OR exp parasomnias/ OR exp nightmares/ OR Sleep Disorders/ OR (Insomnia* OR dyssomnia* OR hypersomnia* OR parasomnia* OR dream* OR nightmare* OR sleepless* OR (sleep* ADJ3 initiat*) OR (sleep* ADJ3 onset*) OR (sleep* ADJ3 quality) OR (sleep ADJ3 maintenance) OR (sleep ADJ3 disorder*) OR (sleep ADJ3 disturb*) OR COMISA).ti,ab.
	#2	Population (refractory insomnia)	exp Treatment Resistant Disorders/ OR (exp treatment/ AND exp failure/)
	#3	Combine sets	#1 AND #2
	#4	Population (adults with refractory insomnia) – keyword title search	(Insomnia* OR dyssomnia*OR hypersomnia* OR parasomnia* OR dream* OR nightmare* OR sleepless* OR (sleep* ADJ3 initiat*) OR (sleep* ADJ3 onset*) OR (sleep* ADJ3 quality) OR (sleep ADJ3 maintenance) OR (sleep ADJ3 disorder*) OR (sleep ADJ3 disturb*) OR COMISA).ti. AND (intractable OR persist* OR refractory OR nonrespon* OR (non ADJ1 respon*) OR ((therap* OR treatment* OR pharmacotherapy*) ADJ6 (fail* OR resist*))).ti.
	#5	Population (adults with refractory insomnia) – keyword title/abstract search with insomnia terms adjacent to treatment failure terms	(Insomnia* OR dyssomnia*OR hypersomnia* OR parasomnia* OR dream* OR nightmare* OR sleepless* OR (sleep* ADJ3 initiat*) OR (sleep* ADJ3 onset*) OR (sleep* ADJ3 quality) OR (sleep ADJ3 maintenance) OR (sleep ADJ3 disorder*) OR (sleep ADJ3 disturb*) OR COMISA) ADJ4 (intractable OR persist* OR refractory OR nonrespon* OR (non ADJ1 respon*) OR ((therap* OR treatment* OR pharmacotherapy*) ADJ3 (fail* OR resist*))).ti,ab.
	#6	Combine sets – population	#3 OR #4 OR #5
	#7	Intervention (alternative therapies, management of comorbid conditions [KQ9]) – broad search for RCTs, SRs and Meta-analyses pertaining to treatment refractory insomnia	Randomized controlled trials/systematic review/meta-analysis hedge [see Search Limits at the end of this table]
	#8	Intervention (diagnostic work-up [KQ10])	(exp Psychometrics/ or exp Screening Tests/ or exp Medical Diagnosis/ or exp Test Validity/ or exp Diagnosis/ or exp Test Reliability/exp OR exp differential diagnosis/ OR exp diagnostic criteria/ OR (diagnos* or workup or "work-up" or "work up" or test or testing or tests or psychometric* or polysomnograph* or "sleep study" or "sleep studies" or "sleep lab" or "sleep lab").mp. OR (predictive value of tests or receiver operating characteristic or ROC curve or (sensitivity and specificity) or accuracy or diagnostic accuracy or precision or likelihood).de. OR ((false or true) adj (positive or negative)).mp.
	#9	Other Study types	exp Cohort Analysis/ OR exp longitudinal studies/ OR exp prospective studies/ OR exp retrospective studies/ OR exp clinical trials/ OR (cohort* OR longitudinal OR prospective OR retrospective OR "case control" OR compar* OR "control group" OR "controlled study" OR "controlled trial" OR "cross over" OR crossover OR "double blind" OR "double blinded" OR "matched controls" OR placebo* OR random* OR sham OR validat*).ti,ab. OR ((versus OR vs).ti.)
	#10	Combine sets	#6 AND (#7 OR #8 OR #9)
	#11	Apply limits	See Search Limits at the end of the table

Question	Set #	Concept	Strategy
Question 11, 12, 17, 18 – Selected treatments for insomnia (herbal remedies, complementary therapies, sleep hygiene)	#1	Population (adults with chronic insomnia – keywords limited to titles for increased specificity)	Exp insomnia/ OR exp parasomnias/ OR exp nightmares/ OR Sleep Disorders/ OR (insomnia* OR dyssomnia* OR hypersomnia* OR parasomnia* OR dream* OR nightmare* OR sleepless* OR (sleep* ADJ3 initiat*) OR (sleep* ADJ3 onset*) OR (sleep* ADJ3 quality) OR (sleep ADJ3 maintenance) OR (sleep ADJ3 disorder*) OR (sleep ADJ3 disturb*) OR COMISA).ti.
	#2	Intervention (herbal remedies/dietary supplements [KQ11])	exp Dietary Supplements/ OR exp melatonin/ OR exp "Medicinal Herbs and Plants"/ OR exp vitamins/ OR diet OR dietary OR herb OR herbs OR herbal* OR plant OR plants OR vitamin* OR melatonin* OR valerian* OR kava* OR "l-theanine" OR "l theanine" OR "5-htp" OR "5 htp" OR "5-Hydroxytryptophan"OR hydroxytryptophan* OR GABA OR (gamma ADJ1 Aminobutyric) OR "passion flower" OR passiflora* OR (Chinese ADJ2 (medicin* OR medication* OR therap* OR treatment* OR remedy OR remedies))
	#3	Intervention (Complementary and alternative therapies [KQ 12])	Exp Alternative Medicine/ OR exp meditation/ or exp mindfulness/ or exp relaxation therapy/ OR exp yoga/ OR exp exercise/ OR exp acupuncture/ OR exp physical activity/ OR exp electrical stimulation/ OR (((Complement* OR alternative* OR "CAM") ADJ5 (therap* OR treatment* OR remedy OR remedies OR medicin*)) OR meditat* OR mindful* OR yoga* OR "tai chi" OR "tai ji" OR acupunctur* OR exercis* OR relaxation* OR (physical ADJ3 activit*) OR (alpha ADJ1 stim) OR (electr* ADJ3 stimulat*) or electrotherapy* OR electrosleep*).mp
	#4	Intervention (treatment delivery via telehealth [KQ 17])	Exp Cellular Phones/ OR exp Computer Applications/ OR exp computer mediated communication/ OR exp electronic learning/ OR exp internet OR exp Mobile Devices/ OR exp online therapy/ OR exp social media/ OR exp telecommunications media/ OR exp telemedicine/ OR exp websites/ OR Cellphone* OR ((Cell OR cellular) ADJ1 phone*) OR computer* OR ehealth OR internet OR mhealth OR (mobile ADJ1 (application OR app)) OR digital* OR smartphone* OR (smart ADJ1 phone*) OR "social media" OR telecommunications OR telehealth OR telemedicine OR "telemental health" OR website* OR (web ADJ1 based) OR online.ti. OR web.ti.
	#5	Intervention (sleep hygiene education [KQ 18])	(exp Sleep/ AND exp Hygiene/) OR ((Sleep* ADJ4 (hygien* OR educat*)) OR (sleep ADJ2 restrict*) OR (stimul* ADJ2 control*) OR relaxation OR mindful* OR restructur*).ti,ab.
	#6	Combine sets	#1 AND (#2 OR #3 OR #4 OR #5)
	#7	Apply limits	See Search Limits at the end of the table

Question	Set #	Concept	Strategy
Question 19 – Questionnaires for the assessment of insomnia	#1	Population (adults with chronic insomnia)	Exp insomnia/ OR exp parasomnias/ OR exp nightmares/ OR Sleep Disorders/ OR (insomnia* OR dyssomnia* OR hypersomnia* OR parasomnia* OR dream* OR nightmare* OR sleepless* OR (sleep* ADJ3 initiat*) OR (sleep* ADJ3 onset*) OR (sleep* ADJ3 quality) OR (sleep ADJ3 maintenance) OR (sleep ADJ3 disorder*) OR (sleep ADJ3 disturb*) OR COMISA).ti.ab.
	#2	Intervention (screening questionnaires)	(Exp questionnaires/ AND (exp screening tests/ or exp screening/)) OR (((survey* or questionnaire* OR scale or scales or index or indices or tool*) AND (screen* OR assess* OR suspect* OR confirm*)) OR ISI OR "insomnia severity index" OR ESS OR "Epworth sleepiness scale" OR "stop bang" OR "berlin questionnaire" OR "sleep quality index" OR PSQI OR "international restless legs syndrome" OR IRLSS OR (morningness ADJ2 eveningness) OR MEQ).ti.
	#3	Combine sets	#1 AND #2
	#4	RCTs/Meta Analyses/Systematic Reviews	Randomized controlled trials/systematic review/meta-analysis hedge [see Search Limits at the end of this table]
	#5	Diagnostic test study types	exp Psychometrics/ OR exp Medical Diagnosis/ OR exp Test Validity/ OR exp Diagnosis/ OR exp Test Reliability/exp OR exp differential diagnosis/ OR exp diagnostic criteria/ OR diagnos* OR "predictive value" OR PPV OR "receiver operating characteristic" OR "ROC curve" OR (area ADJ1 under ADJ3 curve) OR AUC OR (sensitivity and specificity) OR accuracy OR "diagnostic accuracy" OR (prediction and forecasting) OR precision OR likelihood OR ((false OR true) ADJ (positive OR negative))
	#6	Other study types	exp Cohort Analysis/ OR exp longitudinal studies/ OR exp prospective studies/ OR exp retrospective studies/ OR exp clinical trials/ OR (cohort* OR longitudinal OR prospective OR retrospective OR "case control" OR compar* OR "control group" OR "controlled study" OR "controlled trial" OR "cross over" OR crossover OR "double blind" OR "double blinded" OR "matched controls" OR placebo* OR random* OR sham OR validat*).ti,ab. OR ((versus OR vs).ti.)
	#7	Combine sets	#3 AND (#4 OR #5 OR #6)
	#8	Apply limits	See Search Limits at the end of the table

b. Obstructive Sleep Apnea

Question	Set #	Concept	Strategy
Question 7, 8, 16 – Intensity of use and adherence to CPAP (including adherence in adults with comorbid conditions)	#1	Population (adults with obstructive sleep apnea)	exp Sleep Apnea/ OR (Sleep* ADJ4 (apnea* or apnoea* OR breathing* OR hypoventilat*) OR OSA OR OSAS OR OSAHS OR COMISA).ti,ab.
	#2	Intervention (CPAP)	APAP OR A-PAP OR (positive ADJ1 airway ADJ1 pressure) OR autopap* OR auto-pap OR autoCPAP OR auto-cpap OR bipap OR bi-pap OR vpap OR v-pap OR CPAP OR c-pap OR PAP
	#3	Combine Sets	#1 AND #2
	#4	Apply Limits	See Search Limits at the end of the table
Search Hedges Applied to Each Strategy		Limit to English language, humans and publication year	AND (english language AND humans AND yr="2008 - 2018")
		Exclude conference publications, books, letters, editorials, case studies, etc..	NOT ((("column/opinion" OR "comment/reply" OR dissertation OR editorial OR letter OR book).dt. OR book.pt.) OR (letter/ or editorial/ OR news/ OR comment/ OR case report OR case reports/ OR note/ OR conference paper/) OR (letter OR editorial OR news OR comment OR case reports OR conference abstract$).pt.
		Limit to meta-analyses and systematic reviews	AND (meta analysis/ OR (systematic review OR meta analysis).mp. OR (meta-analysis OR systematic review).ti.)
		Limit to randomized controlled trials	AND (Randomized controlled trials OR random allocation OR double-blind method OR single-blind method OR placebos OR cross-over studies).de. OR placebo$.mp. OR random$.ti. OR randomized controlled trial.pt. OR crossover$.mp. OR cross over.mp. OR ((singl* OR doubl* OR tripl* OR trebl*) ADJ3 (blind* OR mask* OR sham*)).mp. OR latin square.mp. OR ISRTCN OR ACTRN* OR (NCT* not NCT) OR (clinical trials/ AND random*.ti.)

Appendix K: Alternative Text Descriptions of Algorithms

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 begins with Box 1, in the shape of a rounded rectangle: "Adult patient"
2. Box 1 connects to 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 questionnaire) (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: "Manage the diagnosed sleep disorder(s) or consider referral 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[a] and willing to complete CBT-I or BBT-I?[b]"
    a. Note: [a]In cases where the patient requires immediate intervention, providers may exercise clinical judgment to determine if pharmacotherapy may be safely initiated.
    b. Note 2: [b]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 to trained CBT-I or BBT-I provider, either in-person or using telehealth"

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 and/or CIH appropriate? (see Sidebars 4 and 5)"

   i. If the answer is "Yes" to Box 18, then Box 20, in the shape of a rectangle: "Initiate short-term pharmacotherapy treatment and/or CIH"

   ii. If the answer is "No" to Box 18, then Box 19, in the shape of a rectangle: "Reassess or reconsider behavioral treatments as needed. Use motivational interviewing to encourage behavioral treatments. Follow-up as needed"

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 "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 22, in the shape of a rectangle: "Follow-up as needed; encourage attention to relapse prevention strategies among those benefitting from behavioral treatments for insomnia disorder"

      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"

   b. If the answer is "No" to Box 15, then Box 20, in the shape of a rectangle: "Initiate short-term pharmacotherapy treatments and/or CIH"

5. Box 20 connects to Box 21, in the shape of a hexagon, asks the question: "Did insomnia remit after treatment with CIH or short-term pharmacotherapy with no additional medication required?"

   a. If the answer is "Yes" to Box 21, then Box 22, in the shape of a rectangle: "Follow-up as needed; encourage attention to relapse prevention strategies among those benefitting from behavioral treatments for insomnia disorder"

   b. If the answer is "No" to Box 21, then Box 17, in the shape of a rectangle: "Refer to sleep specialist for further assessment"

Module C: Management of Obstructive Sleep Apnea

1. Module C begins with Box 23, in the shape of a rounded rectangle: "Patient in whom screening, history, and/or physical exam suggests OSA"

2. Box 23 connects to Box 24, in the shape of a rectangle: "Assess risk for OSA (see Sidebar 6)"

3. Box 24 connects to Box 25, in the shape of a hexagon, asks the question: "Does assessment show high risk for OSA?"

   a. If the answer is "Yes" to Box 25, then Box 26, in the shape of a hexagon, asks the question: "Are comorbidities (see Sidebar 7) or military or occupational requirements for an in-lab determination of OSA present?"

1. If the answer is "Yes" to Box 26, then Box 27, in the shape of a rectangle: "Refer to in-lab sleep study"
2. If the answer is "No" to Box 26, then Box 31, in the shape of a rectangle: "Refer for home sleep testing (if technically inadequate, repeat once) (see Sidebar 8)"

b. If the answer is "No" to Box 25, then Box 28, in the shape of a rectangle: "For low risk of OSA, refer to in-lab sleep study"

4. Box 28 connects to Box 29, in the shape of a hexagon, asks the question: "Was the study diagnostic of OSA?"
    a. If the answer is "Yes" to Box 29, then Box 36, in the shape of a rectangle: "Initiate appropriate treatments and adherence support; see Recommendations 7 – 18 for choice of treatment, improvement of adherence, or alternative treatments (see Sidebar 9)"
    b. If the answer is "No" to Box 29, then Box 30, in the shape of a rectangle: "Consider alternative diagnoses and/or referral to sleep specialist"
5. Box 31 connects to Box 32, in the shape of a hexagon, asks the question: "In patients at high risk for OSA, is the AHI <5 events/hour?"
    a. If the answer is "Yes" to Box 32, then Box 27, in the shape of a rectangle: "Refer to in-lab sleep study"
    b. If the answer is "No" to Box 32, then Box 33, in the shape of a rectangle: "The event index is 5 – 15 events/hour and the patient meets criteria for treatment (see Sidebar 8), or there is event index >15 events/hour"
6. Box 33 connects to Box 35, in the shape of a rectangle: "Initiate appropriate treatments and adherence support. See Recommendations 7-18 for choice of treatment, improvement of adherence, or alternative treatments (see Sidebar 9)"
7. Box 27 connects to Box 34, in the shape of a hexagon, asks the question: "Was the study diagnostic of OSA?"
    a. If the answer is "Yes" to Box 34, then Box 35, in the shape of a rectangle: "Initiate appropriate treatments and adherence support; see Recommendations 7-18 for choice of treatment, improvement of adherence, or alternative treatments (see Sidebar 9)"
    b. If the answer is "No" to Box 34, then Box 36, in the shape of a rectangle: "OSA is unlikely. Consider alternative diagnoses or sleep specialist referral"
8. Box 35 connects to Box 37, in the shape of a rectangle: "If the patient is not improving or adhering to treatment, consider referral to a sleep specialist"

Appendix L: Abbreviation List

Abbreviation	Definition
AE	adverse event
AHI	apnea-hypopnea index
AHRQ	Agency for Healthcare Research and Quality
AIS	Athens Insomnia Scale
APAP	auto-titrating positive airway pressure
BBT-I	brief behavioral therapy for insomnia
BFA	battlefield acupuncture
BMI	body mass index
BQ	Berlin Questionnaire
CAI	central apnea index
CBT-I	cognitive behavioral therapy for insomnia
CDP	Center for Deployment Psychology
CHF	congestive heart failure
CI	confidence interval
CNS	central nervous system
COI	conflict of interest
COR	Contracting Officer's Representative
CPAP	continuous positive airway pressure
CPG	clinical practice guideline
CSA	central sleep apnea
CVD	cardiovascular disease
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
DoD	Department of Defense
EBPWG	Evidence-Based Practice Work Group
EEG	electroencephalogram
EPAP	expiratory positive airway pressure
ESS	Epworth Sleepiness Scale
FDA	Food and Drug Administration
FOSQ	Functional Outcomes of Sleep Questionnaire
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

Abbreviation	Definition
ISI	Insomnia Severity Index
ITT	intention-to-treat
kg/m²	kilograms per meter squared
KQ	key question
LPS	latency to persistent sleep
MAD	mandibular advancement device
MBSR	mindfulness-based stress reduction
MBTI	mindfulness-based therapy for insomnia
MDD	major depressive disorder
MEQ	Morningness-Eveningness Questionnaire
MHS	Military Health System
MI	myocardial infarction
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
NPV	negative predictive values
ODI	oxygen desaturation index
OMF	oral and maxillofacial surgeon
OSA	obstructive sleep apnea
OTC	over-the-counter
PAP	positive airway pressure
PCC	patient-centered care
PICOTS	population, intervention, comparison, outcome, timing, and setting
PM	portable monitoring
PPV	positive predictive value
PSG	polysomnography
PSQI	Pittsburgh Sleep Quality Index
PTSD	posttraumatic stress disorder
RCT	randomized controlled trial
REI	respiratory event index
RERA	respiratory effort related arousal
ROC	receiver operating characteristic
SAVE	Sleep Apnea cardioVascular Endpoints
SDB	sleep disordered breathing
SDM	shared decision making
SDS	Self-Rating Depression Scale
Se	sensitivity
Sp	specificity
SR	systematic review
STOP	Snoring, Tiredness, Observed apnea, and high blood Pressure

Abbreviation	Definition
STOP-BANG	Snoring, Tiredness, Observed apnea, high blood Pressure, Body mass index, Age, Neck circumference, male Gender
sTST	subjective total sleep time
SUD	substance use disorder
TBI	traumatic brain injury
TESS	Treatment Emergent Symptom Scale
TST	total sleep time
U.S.	United States
UAS	upper airway stimulation
UPPP	uvulopalatopharyngoplasty
VA	Department of Veterans Affairs
VHA	Veterans Health Administration
WASO	wake after sleep onset

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