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The Management of Chronic Insomnia Disorder and Obstructive Sleep Apnea: Synopsis of the 2019 U.S. Department of Veterans Affairs and U.S. Department of Defense Clinical Practice Guidelines

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Abstract

Description

In September 2019, the U.S. Department of Veterans Affairs (VA) and the U.S. Department of Defense (DoD) approved a new joint clinical practice guideline for assessing and managing patients with chronic insomnia disorder and obstructive sleep apnea (OSA). This guideline is intended to give health care teams a framework by which to screen, evaluate, treat, and manage this difficult needs and preferences of VA and DoD patients with either of these conditions.

Methods

In October 2017, the VA/DoD Evidence-Based Practice Work Group initiated a joint VA/DoD guideline development effort that included clinical stakeholders and coordinated by the Institute of Medicine's team for trustworthy clinical practice guidelines. The guideline panel developed key questions, systematically searched and evaluated the literature, created three 5-page algorithms, and advanced 41 recommendations using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system.

Recommendations

This synopsis summarizes the key recommendations of the guideline in 3 areas: diagnosis and assessment of OSA and chronic insomnia disorder, treatment and management of OSA, and treatment and management of chronic insomnia disorder. Three clinical practice algorithms are also included.

The National Institutes of Health has estimated that insomnia and obstructive sleep apnea (OSA) are 1 of the most common sleep disorders in the general U.S. population and in the military and veteran population (1). Insomnia symptoms are the most common sleep symptom among U.S. adults, occurring in approximately 20% to 30% of adults, and the prevalence of chronic insomnia disorder ranges from 4% to 10% (2–6). The prevalence of OSA ranges from 9% to 38% and is associated with older age, higher body mass index, male sex, and menopause.

Sleep disorders are more prevalent in the populations served by the U.S. Department of Veterans Affairs (VA) and the U.S. Department of Defense (DoD) than in the general civilian population. In the RAND report "Sleep in the Military: Promoting Healthy Sleep Among U.S. Servicemembers," 48.6% of military personnel surveyed had poor sleep quality (Pittsburgh Sleep Quality Index score >5) (7). The prevalence of insomnia symptoms has been reported to be as high as 45% in service members deployed to combat and 25% in noncombatants (8). In a large cohort of soldiers preparing for deployment, 19.8% met criteria for insomnia according to the Insomnia Severity Index (ISI) (9). A more recent study evaluated the incidence of insomnia and OSA in the entire population of U.S. Army soldiers from 1997 to 2012 (10) and showed unprecedented increases in the incidence of both conditions (62% and 68%, respectively) during this period. In military personnel referred for sleep evaluations, sleep-disrupted insomnia is the most frequently diagnosed disorder, and some studies have found that military personnel have higher rates of comorbid insomnia and OSA (11). Further, military personnel with sleep disorders often also have posttraumatic stress disorder (PTSD), symptoms of depression and anxiety, and traumatic brain injury, which can complicate diagnosis and management (12–15).

Sleep disturbances are also common in veterans (16–24). Similar to findings from active duty service members, the National Veteran Sleep Disorder Study found that the number of veterans diagnosed with sleep disorders increased nearly 6-fold from 2006 to 2010. In this study, 4.5% of veterans were diagnosed with sleep-disordered breathing, and 2.3% were diagnosed with insomnia. However, the actual prevalence of insomnia disorder among veterans is likely to be considerably higher (17) because it is often not documented in the medical record (18, 19). Comorbid PTSD was associated with a 7-fold greater risk for OSA and a 3.5-fold greater risk for insomnia (20). Because veterans have high rates of cardiovascular disease and PTSD, and because OSA is more prevalent in patients with these disorders (20), there is likely a large percentage of veterans who have not yet been diagnosed with OSA (21).

Guideline Development Process

To develop these recommendations, the VA/DoD followed a process developed by the VA/DoD Evidence-Based Practice Work Group that adheres to the standards of trustworthy guidelines (22). This group selected the guideline panel co-chairs, 2 from the VA and 2 from the DoD. The co-chairs, in conjunction with VA and DoD leadership, selected a multidisciplinary panel of practicing clinician stakeholders from various specialties, including sleep medicine, neurology, psychology, psychiatry, pulmonology, otolaryngology, internal medicine, dentistry, pharmacy, and nursing. The VA/DoD contracted with The Lewin Group, a third-party with expertise in clinical practice guideline development, to facilitate meetings and the development of key questions using the PICOTS (population, intervention, comparator, outcomes, timing of outcomes measurement, and setting) format. A patient and family stakeholder focus group was convened to assist in determining the scope and inform the development of key questions. The guideline panel developed 24 key questions to guide the criterion of interest. The systematic search of the peer-reviewed literature was conducted by ECRI Institute and covered the period from 1 January 2008 to 31 May 2018. The search methods and results are detailed in the full guideline (www.healthquality.va.gov/guidelines/CD/insomnia/ccs.asp). In collaboration with ECRI Institute, the guideline panel evaluated the body of evidence and developed the recommendations using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) methods (23–25).

Recommendations

This guideline represents an important step toward improving the management of patients with chronic insomnia disorder, OSA, or both in the VA and DoD. As with other clinical practice guidelines, challenges remain, including evidence gaps and the need to develop effective strategies for guideline implementation and for evaluation of the effect of guideline adherence on clinical outcomes. This guideline is intended for VA and DoD health care 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, OSA, or both.

Diagnosis and Assessment of OSA and Chronic Insomnia Disorder

Assessment of patients with sleep symptoms is the first step in identification of OSA, and evidence supports use of specific screening questionnaires. With an apnea-hypopnea index (AHI) of 5 events per hour or greater on polysomnography (PSG) as the gold standard to define OSA, our evidence review yielded data on the diagnostic accuracy of the Berlin Questionnaire, the STOP-BANG questionnaire, the STOP questionnaire, and the Epworth Sleepiness Scale (26).

After reviewing the sensitivity and specificity of each tool reported by Chiu and colleagues (26), the work group agreed that none had acceptable accuracy to definitively diagnose OSA. Because objective testing is required after screening, the work group focused on sensitivity as the metric of choice to increase the likelihood of detecting OSA on diagnostic testing. Among the 4 screening tools, STOP-BANG had the highest sensitivities. Given the performance similarities and simpler administration, the STOP questionnaire was included in our recommendation. This questionnaire consists of 4 dichotomous (yes or no) questions on snoring, tiredness, fatigue, or sleepiness during the daytime; observed apnea episodes; and history of high blood pressure. A score of 2 or higher out of a possible 4, with 1 point for each positive response, discriminates high from low risk for OSA (27).

Although in laboratory PSG is the gold standard for diagnosis of OSA, home sleep apnea testing (HSAT) is increasingly performed in clinical practice to establish the diagnosis among patients with a high pretest probability (28). Evidence supports use of a manually scored type III HSAT (unattended, ambulatory, home-based, portable monitoring) with at least 4 channels (airflow, respiratory effort, oxygen saturation, and heart rate) or higher to establish a diagnosis of moderate to severe OSA (29); however, the evidence is less clear for mild OSA (respiratory event index of 5 to 15 events per hour). For patients who have nondiagnostic HSAT (technically inadequate or AHI <5 events per hour), repeated testing with either HSAT or laboratory PSG should be done (29). In patients with an uncertain diagnosis of OSA or for whom treatment proves challenging, consultation with a sleep specialist is recommended.

In patients with suspected chronic insomnia disorder, self-reported measures are an important part of a comprehensive assessment. The ISI and the Insomnia Scale and over 2 each measures have high diagnostic accuracy for insomnia (30). A systematic review found that both were sensitive and specific for accurately distinguishing between patients with and without insomnia disorder (31). A formal diagnosis of chronic insomnia disorder requires a detailed sleep, medical, substance, and psychiatric history.

Treatment and Management of OSA

For treatment of OSA, the work group recommended positive airway pressure (PAP) therapy for the entirety of a person's sleep period. Because adherence can be challenging, the work group also suggested continuing PAP treatment for OSA even in patients using it for less than 4 hours per night (the Medicare standard) and providing supportive, educational, and behavioral interventions to improve adherence early in treatment (32). Alcohol and certain medications (such as opioids or sedative hypnotics) can worsen OSA in some patients and should be used with caution or avoided if possible.

The literature supports an association between greater PAP use and improved outcomes, although there is no definitive evidence that it prevents major adverse cardiovascular events (29, 33–35). Barbé and colleagues found no differences in the interim treatment comparisons of the trial of control, whereby patients received no active intervention. However, PAP use for 4 or more hours per night was associated with reduced risk for composite hypertension or cardiovascular events compared with controls (2.98 vs. 11.2 events per 100 person-years) (29). In a meta-analysis of 10 studies, Khan and colleagues reported a clinically nonsignificant 26% risk reduction in major adverse cardiovascular events with mean PAP use of 3.5 hours per night; however, a sensitivity analysis found that increased use was associated with a decrease in major adverse cardiovascular events that was primarily driven by a clinically significant decrease in stroke (33). In addition, several studies have reported benefits for health-related quality of life with PAP use for less than 4 hours per night. For example, the SomnoBE (Best Apnea Intervention for Research) study found that PAP therapy in patients with moderate to severe OSA without severe sleepiness improved several domains of health-related quality of life as well as daytime sleepiness (34), even though mean use was 3.5 hours per night at 6 months and 3.4 hours per night at 12 months. The safety of PAP therapy has been established across multiple cohort and interventional studies, and it is associated with primarily mild adverse effects, including nasal congestion, oronasal dryness, mask discomfort, and nocturnal awakenings (35).

After PAP therapy, the most most commonly used alternative is oral mandibular advancement devices (MADs). The work group specifically reviewed studies comparing PAP therapy and MADs for patients with mild to moderate OSA (36–40). Although all studies concluded that PAP therapy was superior in reducing AHI, none found a statistically significant difference in improvement of daytime sleepiness, cognitive function, vigilance, hypertension, or quality of life measures. One randomized crossover trial of veterans diagnosed with OSA and PTSD reported clinically significant greater patient preference and adherence to MADs versus PAP therapy (36), with an equivalent amelioration of PTSD and sleep-related quality of life symptoms. Thus, although MADs may not be as efficacious as PAP therapy in reducing AHI, their increased use, due in part to patient preference and acceptance, may result in similar overall treatment benefits.

Treatment and Management of Chronic Insomnia Disorder

Cognitive and Behavioral Interventions

Evidence suggests that cognitive behavioral therapy for insomnia (CBT-I) is effective in treating chronic insomnia. This therapy is a multimodal, multicomponent treatment focused on sleep-specific thoughts and behaviors. Behavioral components include sleep restriction therapy (limiting time in bed to sleep time, followed by a gradual increase in time to bed as sleep efficiency improves), stimulus control (strengthening the association between the sleep environment and sleep and establishing a consistent sleep pattern), relaxation therapy and counterarousal strategies, and sleep hygiene education (41, 42). Cognitive therapy components target maladaptive thoughts and beliefs about sleep. An abbreviated version of CBT-I, brief behavioral treatment for insomnia (BBT-I), focuses only on behavioral components of sleep restriction, stimulus control, and sleep hygiene only. Two systematic reviews examined the efficacy of behavioral therapies for insomnia. Trials assessed outcomes in the general adult population, subpopulations of older adults (for example, those aged >55 years), and patients with comorbid pain (41, 43). The systematic review by Bonnet and colleagues (41) included 39 trials comparing CBT-I and BBT-I with passive controls and reported outcomes favoring these treatments, including improvements in ISI scores, sleep efficiency, sleep quality, and wake time after sleep onset (41).

The work group also considered delivery methods for CBT-I. Telehealth delivery platforms include provider-directed telemedicine and self-directed Internet-based programs that have been studied in patients with chronic insomnia, and these are potential strategies for increasing access to CBT-I in VA and DoD populations (44–48). Ultimately, the group concluded that the evidence was insufficient to recommend for or against use of Internet-based or group delivery of CBT-I compared with face-to-face treatment.

Sleep hygiene education and pharmacotherapy are the most commonly offered treatments for chronic insomnia disorder (18); however, the work group concluded that these should not be considered first-line therapies (see the next 2 paragraphs). Sleep hygiene education commonly includes information about caffeine, alcohol, and nicotine use; exercise; the sleep environment; sleep-wake regularity and napp avoidance; and stress management (49). Although sleep hygiene education is a component of CBT-I, the work group evaluated the evidence for it as a standalone treatment. A systematic review by Chiang and colleagues (49) included 2 studies that compared sleep hygiene education as monotherapy versus CBT-I for treatment of poor sleep in insomnia. None of the studies that reviewed compared sleep hygiene education with no treatment or usual care, and findings favored CBT-I over sleep hygiene education for sleep onset latency, wake after sleep onset, sleep efficiency, and Pittsburgh Sleep Quality Index and ISI scores (49). In addition, a randomized controlled trial by Morgan and colleagues (50) compared self-help CBT-I (for example, 6 weekly booklets that provided information on components of CBT-I) with advice on sleep hygiene. The self-help group showed clinically significant improvements in insomnia severity, sleep efficiency, and sleep quality (50).

Although the work group acknowledged a role of sleep hygiene education as a way to promote healthy sleep practices and prevent poor sleep habits among patients without chronic insomnia disorder, it concluded that sleep hygiene education alone may be not only ineffectual but also potentially harmful if patients receiving it as treatment for chronic insomnia disorder are less receptive to referral for effective behavioral treatments, such as CBT-I or BBT-I, in the belief that they also will be ineffectual.

A systematic review by Mitchell and colleagues found that CBT-I was more effective than several pharmacotherapies (51). Compared with pharmacotherapy for chronic insomnia disorder, CBT-I seemed equivalent in short-term results (2 to 4 weeks) but was superior in long-term outcomes. The potential benefits of CBT-I outweigh the potential harms and burden of pharmacotherapy given that there are fewer adverse effects. Of note, there is a lack of clear harms data for pharmacologic treatments beyond relatively brief treatment periods, which raises concerns about potential increased risks with longer courses of pharmacotherapy. In contrast, there are lower concerns about harms associated with CBT-I given that treatment-related symptoms (dependent during the initial phase of sleep restriction therapy) resolve quickly on treatment cessation.

Pharmacotherapy

The work group recognized that nonpharmacologic behavioral interventions are more effective than pharmacologic therapies for treatment of chronic insomnia disorder. However, in patients who are unable or unwilling to receive CBT-I, the work group considered offering a short course of low-dose (1 or 4 mg) doxepin or zolpidem/zaleplon. In a benzodiazepine receptor agonists (BZRA) meta-analysis, Soehner, in a low-quality systematic review that included 5 randomized RCTs, the efficacy of low-dose doxepin (1, 3, and 6 mg) was compared with placebo in persons diagnosed with insomnia disorder (52). Scores on the ISI were improved at week 4 in 2 RCTs (in older adults, with the 3- or 6-mg doses of doxepin factored over placebo; effects varied with the 1-mg dose. Subjective sleep latency, total sleep time, and sleep quality outcomes were improved with the 3- and 6-mg doses in older adults (n=1 study). These outcomes were also improved in younger adults with the 6-mg dose. Some RCTs found statistically significant differences in adverse event rates between doxepin and placebo (for example, headache, somnolence, and fatigue), seemed to increase with longer treatment. Low-dose doxepin has no black box warning for suicide risk, but the risk for suicidal ideation associated with use of low-dose doxepin as a hypnotic agent is unknown and cannot be excluded.

A systematic review found that nonbenzodiazepine BZRAs improved the critical outcome of sleep efficiency and the important outcomes of sleep onset latency, sleep quality, total sleep time, and wake after sleep onset compared with placebo (53). This review included 11 RCTs studying the efficacy of different formulations, doses, and frequency of administration of 4 nonbenzodiazepine BZRAs: zolpidem, zolpiclone, zaleplon, and eszopiclone (the last of which is not available in the United States). The adverse events and withdrawal symptoms of nonbenzodiazepine BZRAs were also assessed in a separate systematic review (54). On the basis of these reviews, benefits seemed to outweigh potential harms, the most common (n=5, Food and Drug Administration recently released a safety announcement on the risk for serious injuries caused by sleep behaviors (sleepwalking, sleep driving, and other activities while not fully awake) associated with zolpidem use). Although the most common adverse events, a nondenzodiazepine BZRA, if prescribed, should be initiated at the lowest effective dose and for the shortest possible duration, and all patients offered these agents should be counseled on the potential risks.

The work group advised against use of benzodiazepines or trazodone for treatment of chronic insomnia disorder. This recommendation was based on 4 high-quality systematic reviews (55–58) that evaluated use of pharmacologic agents. In these reviews, benzodiazepines improved sleep efficiency, sleep onset latency, sleep quality, total sleep time, and wake after sleep onset compared with placebo. However, the widely known harms and adverse effects of benzodiazepines, including risk for dependency and diversion, falls and cognitive impairment in older patients, hypersensitivity in patients with respiratory conditions (including sleep apnea and obesity hypoventilation), and neuromuscular diseases, were deemed to substantially outweigh the benefits.

A systematic review reported no differences in sleep efficiency or rate of discontinuation due to adverse events between trazodone (first stage, 50 to 150 mg before bedtime) and placebo in patients diagnosed with chronic insomnia (57). Although trazodone was more effective at improving subjective sleep quality, there were no differences in sleep onset latency, total sleep time, or wake after sleep onset (57). The review noted limitations, including studies of very short durations of therapy (mean, 12 weeks) and follow-up of only 1 to 4 weeks. The low-quality evidence supporting the efficacy of trazodone was outweighed by its adverse effect profile.

The work group also advised against use of antihistamines and antipsychotics for treatment of chronic insomnia disorder. These drugs are often used off label because of their sedating effects; however, the systematic evidence review conducted for this guideline did not identify any studies that met inclusion criteria for their use as interventions for chronic insomnia disorder. In fact, because of the antimuscarinic adverse effect profile of antihistamines, the 2019 Beers Criteria carry a strong recommendation to avoid these drugs in older adults (59). In addition, tolerance of the sedative effects of antihistamines has been noted after 3 to 7 days of continuous use, limiting their benefit even in short-term treatment of insomnia symptoms. Antipsychotics, most commonly quetiapine, have been used to treat insomnia disorder, but the evidence supporting their use is sparse and unclear, with small sample sizes and short treatment durations, thus making any determination of efficacy inconclusive. All antipsychotics, including low-dose quetiapine, are known to cause harms (60), including increased risk for death in elderly populations with dementia-related psychosis and increased suicidal tendencies in children, adolescents, and young adults (61).

Over-the-Counter Complementary and Integrative Health Treatments

Several herbal over-the-counter therapies were found to be ineffective for treatment of chronic insomnia disorder. The reviewed studies showed no benefit for valerian root in chronic insomnia disorder, and two reviews found supporting their use in sparse and unclear, with small sample sizes and short treatment durations, thus making any determination of efficacy inconclusive. All antipsychotics, including low-dose quetiapine, are known to cause harms (60), including increased risk for death in elderly populations with dementia-related psychosis and increased suicidal tendencies in children, adolescents, and young adults (61).

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placebo, and there is a known risk for acute fatal liver toxicity with kava (62, 63). The work group noted that the U.S. Food and Drug Administration has warned health care providers and the public about the risk for acute liver damage and death associated with kava (62). Given these serious potential harms, the work group decided on a "strong against" recommendation for kava.

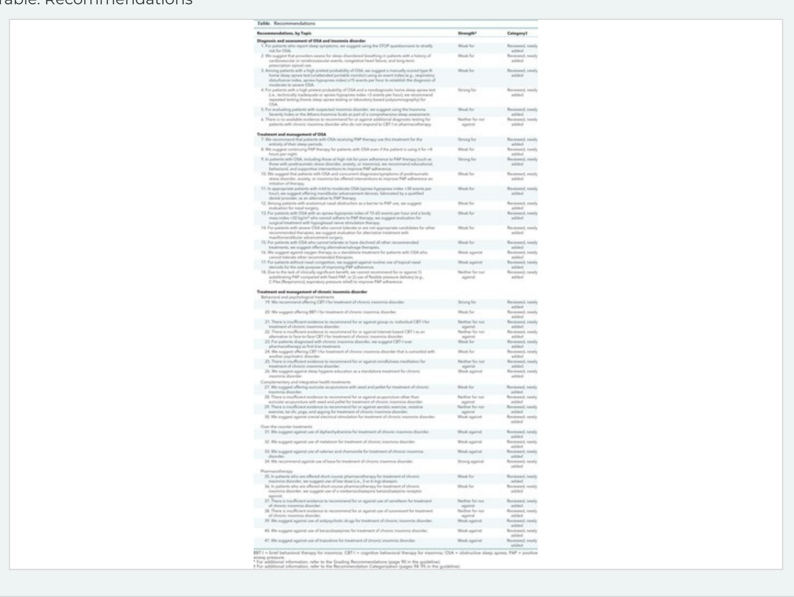
Use of valerian and chamomile for treatment of insomnia was also not supported by evidence. A systematic review by Leach and Page that included 14 trials evaluated the efficacy and safety of 3 herbal medicines (valerian, kava, and chamomile) for treatment of insomnia disorder and found no between-group differences in the critical outcomes of daytime functioning, insomnia severity, and sleep efficiency or the important outcomes of sleep onset latency, total sleep time, wake after sleep onset, and sleep quality with either valerian or chamomile (63). Specifically, no differences in either daytime functioning or insomnia severity were found for valerian or chamomile versus placebo.

The work group also did not find evidence to support use of melatonin for treatment of chronic insomnia disorder. The primary evidence base was a meta-analysis by Ferracioli-Oda and colleagues that included 19 studies of patients with primary insomnia (*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria), with highly variable treatment durations and doses of melatonin in the included studies (64). The primary outcomes were reduction in sleep latency, increase in total sleep time, and overall improvement in sleep quality. The critical outcomes of daytime functioning and ISI scores were not assessed, and adverse events were not discussed. The evidence showed an approximately 7-minute decrease in sleep latency, an 8-minute increase in total sleep time, and a very small improvement in sleep quality; however, the clinical significance of these findings was unclear. A meta-regression analysis suggested that the trials with longer treatment durations and higher doses showed greater effects on sleep latency and total sleep time but did not improve sleep quality.

Conclusion

Using a systematic, evidence-based approach, the work group identified 41 recommendations (Table) related to the diagnosis and treatment of OSA and chronic insomnia disorder, with the goal of improving outcomes for patients receiving care through the VA and DoD health care systems. Clinical practice algorithms that can assist clinicians in assessing and managing patients with chronic insomnia disorder and OSA are provided in Figures 1, 2 and 3. Evidence supports evaluation of sleep symptoms and timely diagnosis of these 2 disorders. In addition, the work group recommended specific treatments for OSA, particularly PAP therapy, with other options for patients who do not sufficiently benefit from this approach. The work group recommended CBT-I, which is supported by a large evidence base, for treatment of chronic insomnia disorder and also identified several other treatment options with emerging evidence supporting their use. Of note, the work group also recommended against several treatment approaches that are less effective (thereby diverting resources from other more effective treatments or limiting patient confidence in subsequent treatments) or that carry safety concerns. In all patients with sleep disorders, consultation with a sleep medicine specialist should be considered, especially for those in whom the diagnosis is uncertain or treatment proves challenging. Future research combining therapies for OSA and insomnia is needed, and comparative effectiveness trials evaluating the relative benefits of different approaches are warranted.

Table. Recommendations



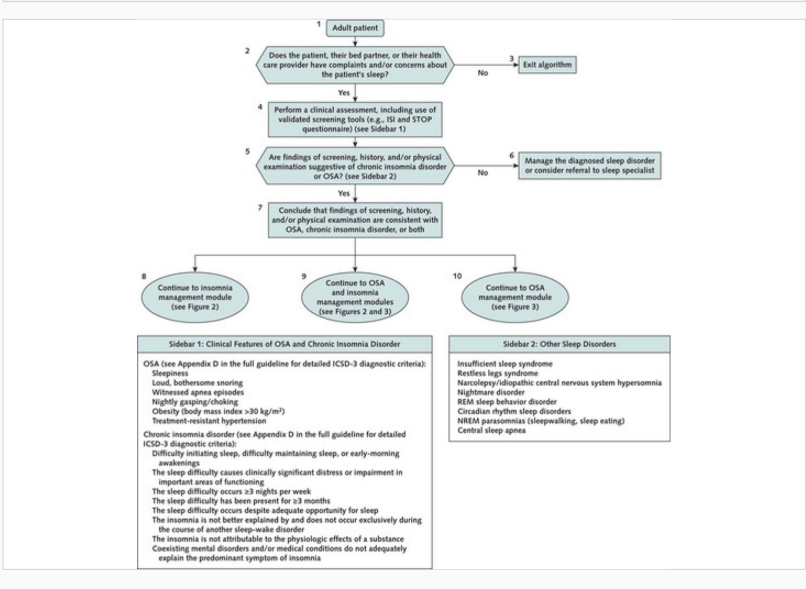


Figure 1. Module A: screening for sleep disorders.

ICSD-3 = International Classification of Sleep Disorders, Third Edition; ISI = Insomnia Severity Index; NREM = non–rapid eye movement; OSA = obstructive sleep apnea; REM = rapid eye movement.

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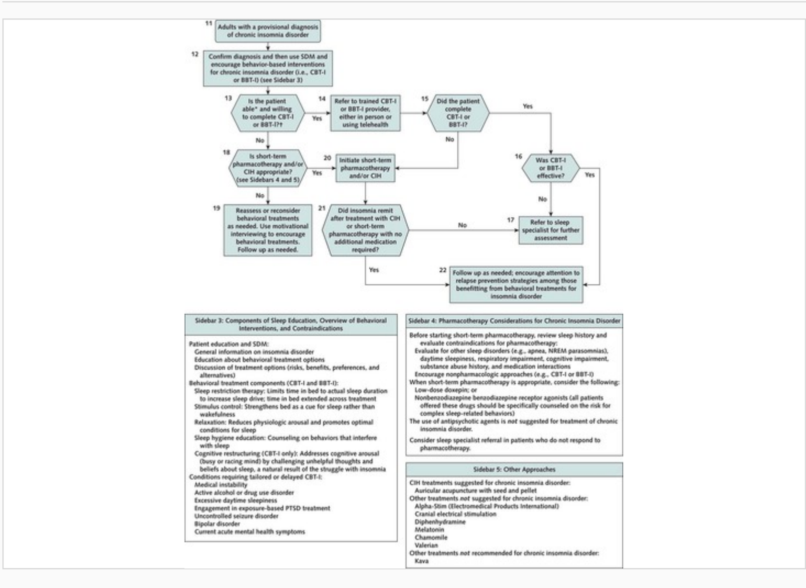

Figure 2. Module B: management of chronic insomnia disorder.

BBT-I = brief behavioral therapy for insomnia; CBT-I = cognitive behavioral therapy for insomnia; CIH = complementary and integrative health; NREM = non–rapid eye movement; PTSD = posttraumatic stress disorder; SDM = shared decision making.

* In cases where the patient requires immediate intervention, providers may exercise clinical judgment to determine whether pharmacotherapy may be safely initiated.

† CBT-I and BBT-I are not equivalent, and there is more robust evidence for CBT-I. Although 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.

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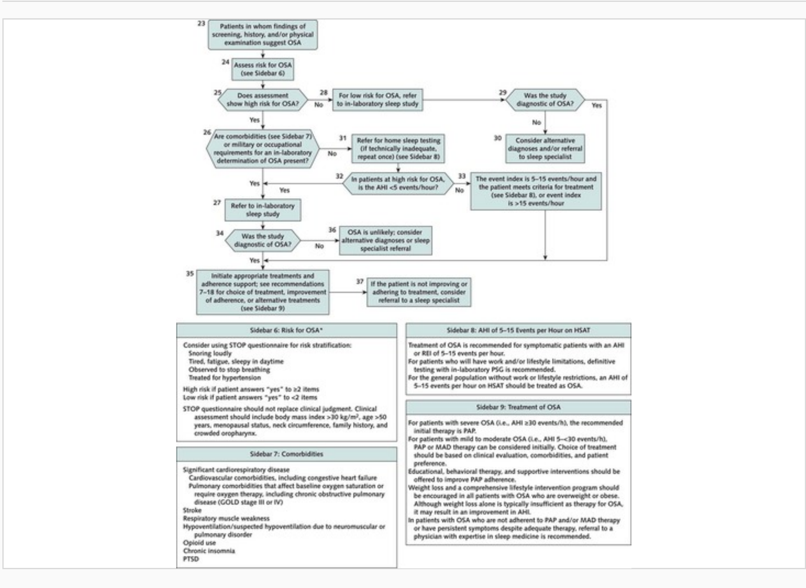

Figure 3. Module C: management of OSA.

AHI = apnea–hypopnea index; GOLD = Global Initiative for Chronic Obstructive Lung Disease; HSAT = home sleep apnea testing; MAD = mandibular advancement device; OSA = obstructive sleep apnea; PAP = positive airway pressure; PSG = polysomnography; PTSD = posttraumatic stress disorder; REI = respiratory event index.

* High risk for or high pretest probability of OSA.

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