AJMC® SUPPLEMENT
THE AMERICAN JOURNAL OF MANAGED CARE®

March 2020
Vol. 26 • No. 4, Sup.

A Managed Care Review on Insomnia: Treatment Guidelines, Emerging Therapies, and the Need for Safe, Effective Options

HIGHLIGHTS

Supplement to *The American Journal of Managed Care®*

A Managed Care Review on Insomnia: Treatment Guidelines, Emerging Therapies, and the Need for Safe, Effective Options

Release date: March 11, 2020

Expiration date: March 11, 2021

Estimated time to complete activity: 3.0 hours

Type of activity: Application

Medium: Print with Internet-based posttest, evaluation, and request for credit

Fee: Free

This activity is supported by an educational grant from Eisai.

Intended Audience

Pharmacists and managed care professionals

Activity Overview

Up to 40 million Americans are estimated to have some form of insomnia. Factors that contribute to making insomnia a substantial public health burden include high healthcare costs, impaired quality of life, and exacerbation of coexisting medical and psychiatric conditions. It has an especially negative impact on vulnerable patient groups, including menopausal women, the elderly population, active military personnel and veterans, and those with coexisting depression or anxiety. Despite guideline recommendations to provide cognitive behavioral therapy for insomnia (CBTI) as first-line treatment, a lack of trained providers has limited patient access to it. Digital CBTI products are beginning to fill that void. Prescription treatment options include benzodiazepines, benzodiazepine receptor agonist hypnotics, doxepin, and orexin receptor antagonists. Factors that should be considered in pharmacotherapy selection include the type of insomnia, patient factors, adverse effect potential, and drug interactions. This activity will help increase awareness among managed care professionals about the impact of insomnia on vulnerable patient groups, CBTI and pharmacologic treatment options to manage insomnia, the economic implications of various treatment options, and strategies for optimizing patient care through education and therapy monitoring.

Statement of Educational Need

Insomnia comes with many comorbidities, both physiological and psychological, creating a heavy financial healthcare burden. In addition, lack of adequate sleep due to insomnia can have profound negative effects on many aspects of a patient's quality of life. Treatment guidelines are a multifaceted approach of cognitive behavioral therapy and prescription medications. Treatment should be individualized, especially in vulnerable populations that cannot tolerate certain insomnia medications, such as elderly individuals, due to respiratory issues. Dialogue on the current treatment landscape with promising emerging therapies is needed to improve clinical practice guidelines and increase access to cost-effective therapies. Continuing education on the available options, efficacy, and safety of drugs used in insomnia will allow managed care professionals and payers to provide quality pharmaceutical care to patients and to analyze cost-effectiveness of therapies.

Educational Objectives

Upon completion of this activity, participants should be able to:

- Characterize the burden of insomnia and its associated comorbidities.
- Examine treatment guidelines and differentiate current and emerging treatments, including efficacy and safety considerations.
- Explore costs associated with insomnia and patient population needs to identify potential management strategies.

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OVERVIEW

Through this supplement to *The American Journal of Managed Care®*, managed care professionals will increase their knowledge of the burden of insomnia and of current and emerging therapies.

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EDITORIAL SUPPORT DISCLOSURES

Jill E. Allen, PharmD, BCPS; David Modrak, PhD; Patrick Stone; and **Jenna Wood, PharmD,** have no relevant financial relationships with commercial interests to disclose.

The American Journal of Managed Care®

Publishing Staff: Ida Delmendo, Ted Pigeon, Angelia Szwed, Monica Tran, Elizabeth Kukielka, and Andrea Szeszko have no relevant financial relationships with commercial interests to disclose.

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REPORT

Insomnia Overview: Epidemiology, Pathophysiology, Diagnosis and Monitoring, and Nonpharmacologic Therapy

Julie A. Dopheide, PharmD, BCPP, FASHP

Introduction

Insomnia, the most common sleep disorder, is a substantial burden for the US healthcare system and vulnerable patient groups.[1] Combined direct and indirect costs for insomnia in the United States exceed $100 billion annually.[2] Because it is so common, the annual loss of quality-adjusted life-years from insomnia appears to be greater than the loss from other medical and psychiatric conditions, including arthritis, depression, and hypertension.[3] Between 1993 and 2015, the diagnosis of insomnia during office visits in the United States increased 11-fold, from 800,000 to 9.4 million.[4] Further, insomnia is linked to higher healthcare utilization and costs, especially in patients with coexisting medical or psychiatric disorders,[5,6] illustrating why it is an important managed care issue. In a recent study of a managed care population, an 80% increase in healthcare costs after a diagnosis of insomnia was attributed to management of insomnia and coexisting conditions.[7]

Insomnia: Classification, Diagnosis, and Monitoring

In 2014, the third edition of the *International Classification of Sleep Disorders* (*ICSD-3*), the most widely used classification system for sleep disorders, revised how insomnia is defined.[8] It now subclassifies insomnia as short-term, chronic, or other. The previous subclassification of chronic insomnia as primary or comorbid was eliminated because it did not improve diagnostic accuracy or differentiate treatment options. The underlying rationale for removal was that calling insomnia comorbid may misleadingly imply that it is a secondary concern that will resolve with adequate treatment of the comorbid condition. To the contrary, the maladaptive cognitions and behaviors that perpetuate insomnia must be addressed regardless of coexisting medical or psychiatric disorders.[8]

Diagnostic criteria for insomnia include difficulty getting to sleep or staying asleep and results in daytime dysfunction in a patient who has an adequate opportunity to sleep.[8] It is short-term if symptoms occur for less than 3 months and chronic if symptoms occur 3 or more times per week for 3 months or longer. Insomnia is often precipitated by a significant life stressor (eg, acute pain, traumatic event). It may end when the stressor resolves or the patient learns

ABSTRACT

Insomnia, whether short-term or chronic, is a common condition. It has a negative impact on vulnerable patient groups, including active military personnel and veterans, patients with coexisting psychiatric and medical disorders, those in life transitions such as menopause, and elderly persons. Although cognitive behavioral therapy for insomnia (CBTI) is first-line treatment for insomnia, its high cost and a lack of trained providers has prevented widespread uptake. Now, digital CBTI (dCBTI) is emerging as a scalable option with the potential to overcome these barriers in managed care. The first part of this article reviews the epidemiology and pathophysiology of insomnia with a focus on vulnerable patient groups. The second part explores the rapidly evolving landscape of nondrug therapy for insomnia. The underlying concepts and supporting evidence for CBTI and dCBTI are presented, including their utility in vulnerable patient groups.

***Am J Manag Care*. 2020;26:S76-S84**

For author information and disclosures, see end of text.

To view the *Patient Perspective* interview accompanying this supplement, please visit **www.pharmacytimes.org/go/insomnia-suppl.**

to cope, or it may evolve into chronic insomnia.[9] Short-term and chronic insomnia may be inferred from a patient's language. No longer mentioning a precipitating life stressor and talking about insomnia as "the problem" may mark the transition from short-term to chronic insomnia.[9]

Chronic insomnia is a clinical diagnosis that relies heavily on patient history about sleep, medical and psychiatric conditions, and substance use.[10] The sleep history should characterize how sleep is disturbed and document the daytime consequences of insomnia. Descriptors that measure and characterize sleep disturbances are shown in **Table 1**.[11-16] When patients report complaints of excessive daytime sleepiness, a diagnosis of a hypersomnolence disorder, narcolepsy, or a sleep-related breathing disorder should be considered.[17] The Epworth Sleepiness Scale (ESS) can be used to differentiate between fatigue and significant daytime sleepiness that indicates the potential for another sleep disorder.[16] Questionnaires, such as the Insomnia Severity Index (ISI) and Dysfunctional Beliefs and Attitudes About Sleep scale, and sleep diaries, such as the Consensus Sleep Diary, are useful to identify behaviors that perpetuate insomnia and to monitor treatment effects (see Table 1[11-16]).[12-14] A general questionnaire can identify comorbidities that contribute to insomnia or affect its management.[10] A medication and substance use history, including over-the-counter drugs and dietary supplements, identifies drugs and substances that interfere with sleep.

Insomnia can occur as a primary sleep disorder, a symptom of another sleep disorder (eg, obstructive sleep apnea [OSA], restless legs syndrome [RLS]), periodic leg movements during sleep [PLMS]), or a comorbid sleep disorder.[8,16,18] An estimated 39% to 55% of patients already diagnosed with OSA or sleep disordered breathing have reported symptoms of insomnia.[19] Conversely, approximately 30% of elderly patients already diagnosed with insomnia have been found to have moderate OSA based on an apnea-hypopnea index of 15 or greater.[19] In a large cross-sectional survey, almost 30% of participants with insomnia reported having RLS symptoms 3 or more nights per week, and 85% to 95% of patients with RLS also have PLMS.[18,20]

The sleep history may suggest the presence of another sleep disorder. For example, snoring or breathing pauses suggest OSA, whereas a sleeping partner getting kicked during the night suggests RLS and/or PLMS. Concerns about OSA should be heightened in patients with obesity or a thick neck.[16] Because symptoms of RLS can be difficult for patients to describe, it may help to ask about symptoms that involuntarily make them want to move their legs, improve by moving, and worsen at night.[21] Polysomnography is not necessary for the diagnosis of chronic insomnia, but it is indicated if another sleep disorder is suspected. As part of the Choose Wisely initiative, the American Academy of Sleep Medicine (AASM) recommends against polysomnography in patients with chronic insomnia unless symptoms suggest a comorbid sleep disorder (eg, OSA, RLS, PLMS).[22]

Pathophysiology of Insomnia

Insomnia is a complex interaction of psychological cognitive arousal and altered circadian and homeostatic mechanisms. Decreased function of the sleep-wake switch may also contribute to insomnia. During sleep, there is a slow transition through stages of non–rapid-eye

TABLE 1. Common Terms and Definitions Used in Diagnosis and Monitoring of Insomnia[11-16]

Term	Definition
Tools Used in Diagnosis and Monitoring of Insomnia	
Consensus Sleep Diary (CSD)	A standardized sleep diary with patient-collected sleep data including 10 morning and 5 nighttime items
Dysfunctional Beliefs and Attitudes about Sleep (DBAS) scale	28-item screening tool that provides detailed information about cognitive components that contribute to disturbed sleep; a shorter 16-item tool scores items on a 10-point Likert scale
Epworth Sleepiness Scale (ESS)	8-item self-report questionnaire that assesses subjective sleepiness (score range of 0-24; normal <10)
Insomnia Severity Index (ISI)	7-item screening tool for insomnia that is used as an outcome assessment tool for insomnia treatment; score range of 0-28 with a decrease of >7 points indicating a response to therapy
Pittsburgh Sleep Quality Index (PSQI)	19-item questionnaire about sleep quality with 7 component scores: (1) subjective sleep quality, (2) sleep latency, (3) sleep duration, (4) habitual sleep efficiency, (5) sleep disturbances, (6) hypnotic use, and (7) daytime dysfunction (poor sleep: global score >5)
Sleep Descriptors	
Nonrestorative sleep	Sleep that is restless, light, or of poor quality, although the duration may appear normal
Sleep efficiency (SE)	Percentage of time in bed when sleep actually takes place
Sleep-onset latency (SOL)	Amount of time it takes to transition from being awake to the beginnings of non-REM sleep (ie, sleep onset)
Sleep quality	Definitions vary, but self-measured indicators of sleep quality may include sleep latency, number of awakenings >5 minutes, wake after sleep onset, and SE
Wake time after sleep onset (WASO)	Amount of time spent awake after initial sleep onset; measures the level of sleep fragmentation

movement (non-REM) sleep to cycles of rapid-eye movement (REM) sleep.[23] The AASM classifies sleep into 5 progressive stages[23]:

1. Stage W (wakefulness)
2. Stage N1 (relaxed wakefulness)
3. Stage N2 (light sleep)
4. Stage N3 (deep or slow-wave sleep)
5. Stage R (REM sleep or dreaming)

Stages N1-N3 are phases of non-REM sleep in which cortical activity is low, whereas the brain is highly active during REM sleep.[23]

Multiple brain centers work in concert to promote sleep or wakefulness. The sleep-wake cycle is a complex process in which wakefulness and sleep are switched on and off by reciprocal systems in a feedback loop.[23,24] Wakefulness results from ascending activity in a number of brainstem and posterior hypothalamic nuclei in what is referred to as the ascending reticular activation system (ARAS). This system projects widely into the cerebral cortex. Hypocretin/orexin-containing neurons in the lateral hypothalamus (orexin) project to hypothalamic and brainstem arousal centers and functionally reinforce their activity during wakefulness.

This model of the sleep-wake cycle is often called the flip-flop switch because it permits one to either be awake or asleep, but not both, at the same time. Via the switching mechanism, the active state suppresses the other state until circadian rhythms induce a switch to the reciprocal state. The cerebral cortex and the limbic system further modify wakefulness. Sleep-promoting centers in the anterior hypothalamus project into the brainstem and posterior arousal centers and function with the lateral hypothalamus as a sleep-wake switch.

Circadian factors promote wakefulness on a roughly 24-hour biological clock, whereas homeostatic factors respond to accumulated wakefulness with the drive for sleep.[11] In the brain, the ARAS promotes wakefulness and the ventrolateral preoptic region (VLPR) promotes sleep. During wakefulness, the ARAS inhibits the VLPR via activation of cholinergic neurons, monoaminergic cell bundles, and orexin nuclei in the lateral hypothalamus. The orexin system promotes wakefulness and alertness and works to balance sleep and wakefulness. Orexin system activation maintains the fully awake state for longer periods of time; conversely, deactivation of the orexin system allows for consolidated sleep during the night. Orexinergic signaling by 2 distinct forms, orexin A and orexin B, maintains wakefulness via continuous depolarization in wake-promoting brain nuclei. Sleep is cued by a homeostatic sleep drive inhibition of orexins. During sleep, the ventrolateral preoptic nucleus inhibits the ARAS via 2 inhibitory neurotransmitters, γ-aminobutyric acid (GABA) and galanin.[23,24] GABA is the neurotransmitter that most widely promotes sleep, whereas norepinephrine and dopamine promote wakefulness; serotonin is necessary for both optimal sleep and wakefulness.[23,24] Flip-flop switching also regulates the transition from non-REM to REM sleep.[25] Within regions of the brainstem, REM-off and REM-on areas inhibit each other.[25]

The 3P behavioral model of insomnia helps to explain how acute insomnia becomes chronic and lays the groundwork for assessing insomnia in individual patients.[26] The 3Ps, which occur in temporal order, are factors that:

- Predispose an individual to insomnia
- Precipitate an acute episode of insomnia
- Perpetuate insomnia from acute to chronic

Predisposing factors, which are generally not modifiable, include genetics and personality traits (eg, being a worrier; family history of poor sleep) that lead to physiologic and cognitive hyperarousal. As shown in **Table 2**,[27-33] precipitating factors that trigger insomnia are typically stressful life events. Patients usually identify problems related to health, family, work, or school as precipitating factors for insomnia.[34] Perpetuating factors are the maladaptive behaviors, thoughts, and coping strategies that allow insomnia to continue after original triggers have resolved.[35] Physical examples of maladaptive behaviors include daytime napping or spending too much time in bed. Less quantifiable perpetuators include dysfunctional beliefs, expectations, and attributions about sleep as well as an intense desire to solve the sleep problem.

TABLE 2. Selected Factors That Contribute to Insomnia[27-33]

Life Events and Social/ Societal Factors	Medical and Psychiatric Disorders and Symptoms
• Displacement due to traumatic events • Traffic noise • Owing money • Unemployment • Racial discrimination • Homelessness • Traumatic childhood experiences • Divorce • Military deployment	• Anxiety • Depression • Posttraumatic stress disorder • Substance abuse • Pain • Nocturia • Dyspnea • Irritable bowel syndrome • Traumatic brain injury • Other sleep disorders

Insomnia Burden: Epidemiology and Vulnerable Patient Groups

The burden of insomnia in the United States was extensively characterized in 2008-2009 by the American Insomnia Survey, a nationwide survey of more than 10,000 members in a national health plan.[36-38] More than one-half of adults had difficulty sleeping, and 22.1% met *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* diagnostic criteria for insomnia. The prevalence of insomnia based on other diagnostic criteria in place at the time was 14.7% for

ICSD-2 and 3.9% for *International Statistical Classification of Diseases and Related Health Problems, 10th Revision*.[36] The most prevalent symptom was difficulty maintaining sleep (61%), followed by early morning awakening (2.2%), difficulty initiating sleep (7.7%), and nonrestorative sleep (25.2%).[38] Although the overall prevalence of insomnia in working people was 23.2%, it was significantly higher in women than men (27.1% vs 19.7%; $P = .001$).[37] The higher prevalence of insomnia in women begins in adolescence, and it is especially high during menopause.[32] In addition to women, insomnia has higher prevalence in the elderly population, individuals with low socioeconomic status, and those with poor health or low quality of life (QOL).[39,40] As shown in Table 2,[27-33] many social or societal stressors are associated with insomnia. For example, results of a recent study showed the incidence of insomnia in homeless people was twice that of the general population (41% vs 19%).[31]

Approximately 30% to 40% of adults in the United States report symptoms of insomnia at some point in a given year.[17] Short-term insomnia has an estimated prevalence of 9.5% in the United States, but about 1 in 5 cases of short-term insomnia transitions to chronic insomnia, which can persist for years.[41] In longitudinal studies, insomnia continued in 40% to 70% of patients for as long as 4 years.[42-44] Although symptoms persist in some patients, insomnia may have a waxing and waning course in others.[44]

The incidence of insomnia appears to be increasing in the United States.[45] Based on National Health Interview Survey data, the unadjusted prevalence of insomnia or trouble sleeping increased by 8% over a decade, from 17.5% (37.5 million adults) in 2002 to 19.2% (46.2 million adults) in 2012.[45] National Ambulatory Medical Care Survey data showed that the number of office visits for insomnia increased by 13% over 10 years, from 4.9 million visits in 1999 to 5.5 million visits in 2010.[46] Based on Medicare data, physician-diagnosed insomnia increased from 3.9% in 2006 to 6.2% in 2013.[47] An increase in insomnia has also been noted in Canada, where data collected with similar methodology showed an increase in adults with insomnia symptoms from 13.4% in 2002 to 23.8% in 2015.[39]

Insufficient sleep has been linked to poor outcomes across many disease states, including cardiovascular and cerebrovascular disease, cancer, hypertension, and diabetes.[48] Epidemiologic studies have linked insomnia symptoms to the development of other diseases, including type 2 diabetes (hazard ratio [HR], 1.28; 95% CI, 1.24-1.33), dementia (relative risk, 1.53; 95% CI, 1.07-2.18), stroke (HR, 1.54; 95% CI, 1.38-1.72), and chronic kidney disease (HR, 1.39; 95% CI, 1.34-1.44).[49-52] Specific symptoms of insomnia have been linked to an increase in total cardiovascular disease (CVD) incidence.[53] Respective HRs for increased risk of total CVD incidence for difficulty initiating or maintaining sleep, early morning awakening, and daytime dysfunction were 1.09 (95% CI, 1.07-1.11), 1.07 (95% CI, 1.05-1.09), and 1.13 (95% CI, 1.09-1.18).[53] The most recent evidence does not indicate a link between insomnia and mortality,[54] although insomnia is also linked to higher rates of workplace injuries and traffic accidents.[37,55]

Vulnerable Patient Groups

Insomnia has bidirectional effects with coexisting medical and mental disorders, especially depression.[17] Insomnia is a significant predictor for subsequent onset of psychiatric disorders, including depression (odds ratio [OR], 2.83; 95% CI, 1.55-5.17), anxiety (OR, 3.23; 95% CI, 1.52-6.85), and alcohol abuse (OR, 1.35; 95% CI, 1.08-1.67).[56]

Military Personnel and Veterans

Active military personnel and veterans are extremely vulnerable to insomnia. Most veterans report sleep disturbances and about half meet the diagnosis of insomnia.[57,58] Since 2001, when the longest overseas conflict in US history began, insomnia in military service members has skyrocketed and has been linked to deployment and combat exposure. In a retrospective cohort study of more than 1.3 million active duty US Army soldiers, the incidence of insomnia increased by 652% between 2003 and 2011.[59] Comorbid conditions with a 2- or 3-fold higher risk of insomnia included sleep-related movement disorders, posttraumatic stress disorder (PTSD), anxiety, adjustment reaction, and acute reaction to stress. The incidence of OSA also increased by 600% over this period. Medical conditions linked to more than a 2-fold risk of OSA included hypertension, gastroesophageal reflux, diabetes, PTSD, and being overweight or obese.[59] More than 90% of veterans with PTSD report sleep disturbances, primarily insomnia and nightmares.[60] The current thinking is that insomnia helps drive the suicide epidemic in veterans by exacerbating depression and PTSD.[61,62] Suicide prevention is part of the rationale for a Veterans Affairs public health campaign that offers CBTI.[63]

Traumatic Brain Injury

Almost 2.9 million traumatic brain injury (TBI)-related emergency department visits, hospitalizations, and deaths occurred in the United States in 2014.[64] Insomnia occurs in 30% to 65% of patients with chronic TBI symptoms.[65] In patients with mild TBI, insomnia appears to have a relationship with other TBI complications, including PTSD, depression, and chronic pain.[65] A recent longitudinal study correlated the impact of sleep disturbances on functional impairment in adults with mild TBI.[66] Functional impairment was highest among those with both insomnia and short sleep (43%-79%), followed by insomnia alone (33%-64%), those with short sleep of less than 6 hours (29%-33%), and good sleepers (15%-25%). The relationship between sleep quality and global functioning was also bidirectional, with greater sleep disturbance predicting greater functional impairment months later and vice versa. This raises the possibility that early detection and management of sleep disturbances may both identify patients with a poor prognosis and improve recovery from TBI.[66]

Depression and Anxiety Disorders

A key concern for clinicians is that insomnia strongly predicts the occurrence of depression. About 90% of patients with major depressive disorder (MDD) report difficulty sleeping.[67] Although sleep disturbances are part of the diagnostic criteria for MDD and generalized anxiety disorder, insomnia also occurs as a coexisting disorder that worsens the mood disorder prognosis.[17] In one of the earliest studies to investigate the relationship between insomnia and psychiatric disorders, 40% of patients with insomnia had a psychiatric disorder, most commonly an anxiety disorder (24%) or depression (14%).[68] In this study, people with insomnia had a substantial risk of developing depression over the following year (OR, 39.8; 95% CI, 19.8-80.0). The risk of developing an anxiety disorder was also increased (OR, 6.3; 95% CI, 3.6-10.9).[68] Results of a meta-analysis of 34 prospective cohort studies found that insomnia more than doubled the risk of developing depression.[69] This is supported by new evidence from the Sequenced Treatment Alternatives to Relieve Depression trial in which improvements in sleep occurred independently from MDD remission.[67] Insomnia increases the risk of suicide in depressed patients (OR, 2.29; 95% CI, 1.69-3.10),[70] and persistent insomnia also increases the risk of depression relapse.[10]

Alcohol and Substance Use

Alcohol use and insomnia have a complex relationship. The prevalence of insomnia in alcohol dependence is estimated at 36% to 91%.[71] Chronic insomnia increases the risk of relapse in alcoholism.[10] Approximately 15% to 30% of people report drinking to manage insomnia,[32,72] and because people can rapidly develop tolerance to the sedative effects of alcohol, self-treating insomnia with alcohol has been proposed as a gateway to problem drinking.[72] A similar theme has been suggested for cannabis in that initial improvements in sleep may be followed by tolerance.[73] Daily cannabis users report high rates of sleep disturbances, given that a tolerance often develops to the sleep-inducing effects of cannabis. Further, cannabis withdrawal can cause severe insomnia characterized by trouble falling asleep and staying asleep, as well as vivid dreams, all of which make it difficult to quit.[73]

TABLE 3. Elements of Sleep Hygiene Education[10,16,80,81]

- Ensure the sleep environment is quiet, pleasant, and at the best temperature for sleeping (15.5°C-19.4°C [60°F-67°F])
- Establish a bedtime routine
- Ensure adequate exposure to sunlight
- Exercise during the day
- Avoid exercise, excessive fluids, alcohol, or nicotine close to bedtime
- Avoid caffeine in the afternoon and evening
- Avoid or limit naps to 30 minutes
- Limit screen time or interactive technology in the 1 or 2 hours before bed

Menopause and Aging

Vasomotor symptoms are an important precipitating factor for chronic insomnia in peri- and postmenopausal women. In a cross-sectional study, the prevalence of chronic insomnia symptoms increased with the severity of vasomotor symptoms, reaching greater than 80% in women with severe vasomotor symptoms.[74] Similar to other scenarios, insomnia and depression appear to have a bidirectional relationship in perimenopausal women, with insomnia contributing to depressive symptoms and vice versa.[75]

In a longitudinal study of community-living persons aged in their mid-80s with a burden of medical conditions and taking multiple medications, the prevalence of insomnia was 43%[76]; however, the mean ISI score was 12.3, suggesting mild severity. Insomnia was associated with depressive symptoms (OR, 8.34; 95% CI, 4.49-15.47) and RLS (OR, 2.49; 95% CI, 1.48-4.21). Biological factors related to aging that are thought to predispose elderly persons to insomnia include circadian rhythm changes that lead to less deep sleep, more sleep fragmentation, and early morning awakening.[77] Precipitating factors may include an increasing burden of health problems with sleep-disruptive symptoms (eg, nocturia, dyspnea, pain), lifestyle changes after retirement, poor physical function, and polypharmacy, whereas perpetuating factors may include social isolation, caregiving, and bereavement.[76,78]

Nonpharmacologic Therapy of Insomnia

Since the mid-1970s when sleep hygiene education was conceived, nondrug therapy has evolved to target both physiologic and cognitive hyperarousal factors that contribute to insomnia.[79] CBTI, the most effective and comprehensive nondrug approach to treating insomnia, combines cognitive therapy, behavioral interventions, and sleep hygiene education.[10,16] The most recent iteration of CBTI is fully automated digital CBTI (dCBTI) and does not require clinician involvement. dCBTI has the scalability to address insomnia as a public health issue.[5] Other nondrug approaches that may have benefit for some patients include relaxation techniques and mindfulness interventions.[10,16]

Sleep Hygiene Education

Teaching patients about behavioral and environmental factors that improve sleep (see **Table 3**[10,16,80,81]) can improve sleep over baseline. Practice guidelines recommend against sleep hygiene education (SHE) as a stand-alone intervention because it is less effective than CBTI or mindfulness training[16]; however, sleep hygiene education is still commonly used in primary care.[79,82] The newest aspect of sleep hygiene education is limiting bedtime screen use, because bright light from devices stimulates wakefulness.[81] Short-wavelength blue

light from electronics interferes with natural melatonin secretion. Study results show children and adolescents are particularly sensitive to insomnia worsened by light from electronics, with almost twice the magnitude of melatonin suppression compared with adults.[83]

Behavioral Treatment of Insomnia

The goal of behavioral treatment is to break the maladaptive connection between going to sleep and hyperarousal using 2 retraining strategies: (1) sleep restriction and (2) stimulus control.[16] Sleep restriction aims to increase sleep drive by reducing the time spent awake in bed. Time in bed is limited to align with the patient's sleep duration and requires monitoring of daily sleep and wake times. Stimulus control aims to break the association between being in bed and negative aspects of insomnia, such as wakefulness, frustration, and worry. The underlying rationale is that eliminating these activities allows the bed to be re-associated with sleep rather than arousal. Both strategies may increase daytime sleepiness in the short term. Sleep specialists recommend against sleep restriction in patients with coexisting conditions that sleep deprivation can exacerbate, such as untreated sleep apnea or seizure disorders.[84] Sleep restriction in a person with bipolar disorder may risk triggering mania.[84]

Brief Behavioral Treatment for Insomnia

This streamlined 4-session approach, which focuses on stimulus control and sleep restriction, can be delivered by healthcare providers without specialized training.[85] In a clinical trial of older adults, brief behavioral treatment for insomnia was more effective than sleep hygiene education at improving sleep onset latency (SOL), wake time after sleep onset (WASO), sleep efficiency, and sleep quality.[86]

Cognitive Treatment of Insomnia

The goal of cognitive therapy for insomnia is to identify and challenge myths and negative beliefs about sleep that perpetuate insomnia, and then replace them with rational thoughts and facts.[16] Cognitive treatment of insomnia includes setting realistic expectations about the amount and quality of sleep any person should expect.[87]

Cognitive Behavioral Therapy for Insomnia

Based on robust evidence from many clinical trials, practice guidelines recommend cognitive behavioral therapy for insomnia (CBTI) as first-line treatment of chronic insomnia.[10,16,88,89] The rationale is that CBTI has more durable benefit and fewer adverse effects than drug therapy. In comparative studies, the efficacy of CBTI was comparable with benzodiazepines or benzodiazepine receptor agonists during acute use; however, sedative hypnotics did not have continued benefit after discontinuation.[10] CBTI has demonstrated efficacy for insomnia in patients with coexisting medical conditions, including chronic pain, fibromyalgia, and breast cancer, as well as in perimenopausal women with vasomotor symptoms.[90,91] Efficacy has also been demonstrated for patients with coexisting psychiatric conditions, such as alcohol dependence, PTSD, and MDD.[91]

An important CBTI side benefit is improvement in symptoms of coexisting psychiatric conditions, particularly depression.[92] The benefit for depression symptoms appears to be moderated by improvements in sleep quality. Longitudinal data from the Veterans Affairs CBTI program suggest that it reduces suicidal ideation.[93] The proportion of patients endorsing suicidal ideation dropped from 32% at baseline to 21% after CBTI ($P < .001$). Each 7-point decrease in ISI score achieved with CBTI was linked to a 65% reduction in the odds of suicidal ideation (OR, 0.35; 95% CI, 0.24-0.52).

Despite guideline recommendations and robust evidence of benefit, few patients receive CBTI. The key access barrier is the lack of trained clinicians. A recent international survey identified 752 CBTI specialists, with almost 90% located in the United States and almost 60% of them concentrated in 12 states.[94]

dCBTI

dCBTI products make up the consumer sleep technology (CST) landscape and have the potential to resolve some of the barriers that have prevented widespread uptake of CBTI. Over the last decade, CST (eg, Fitbit) has become ubiquitous. There are more than 10,000 behavioral health apps, most of which focus on relaxation, mindfulness, and meditation.[95] About 10% of adults in the United States may use sleep tracking devices.[87] Analogous to dietary supplements, a software application that makes a wellness claim (eg, better sleep) does not require FDA approval, whereas one that makes a medical claim (eg, treating insomnia) does. The AASM position is that CST must be FDA approved and rigorously tested before adoption into clinical practice.[96] Among the dCBTI products studied most extensively in clinical trials, Sleepio and CBT-i Coach have not sought FDA approval, whereas Somryst (formerly Shuti) is currently being considered for FDA approval.[97-102]

How dCBTI compares with in-person CBTI is an important question. In a small randomized controlled trial (n = 90), dCBTI and in-person CBTI had significantly larger treatment effects on the ISI than a waitlist group.[103] However, in-person CBTI outperformed dCBTI on ISI scores and posttreatment depression and anxiety symptoms. In a clinical trial of active military personnel with insomnia, in-person CBTI outperformed online delivery for self-reported sleep quality (d = 0.80), dysfunctional beliefs and attitudes about sleep (d = −0.58), and total sleep time (d = −0.55 to −0.60).[104]

Nonprescription dCBTI

As part of a wider initiative to provide digital therapeutics as a health plan benefit, CVS Health is encouraging employers to offer Sleepio as an employee benefit.[105] It is already offered to 10.3 million patients in the United Kingdom's National Health Service and at

least 2 million Americans through their employers.[106] Sleepio has the format of a single-player video game in six 20-minute sessions. In the Digital Insomnia Therapy to Assist Your Life as Well as Your Sleep (DIALS) trial, more than 1700 people with self-reported insomnia were randomized to Sleepio or online SHE.[97] Compared with SHE, Sleepio had a large improvement in sleep-related QOL at week 24 (−18.72; 95% CI, −22.04 to −15.41). Improvements in functional health and psychological well-being were more modest, with respective adjusted differences of 1.76 (95% CI, 1.22-2.30) and 2.95 (95% CI, 2.13-3.76). Almost 20% of participants randomized to dCBTI did not attend the first session, and fewer than 50% completed all sessions.[97]

The DIALS trial is one of the few large-scale clinical trials to evaluate potential adverse effects of dCBTI.[97] At week 8 posttreatment, participants randomized to Sleepio or sleep education were asked to rate adverse effects. Patients who received Sleepio had higher rates of fatigue and/or exhaustion (46.3% vs 27.0%; P <.0001); extreme sleepiness (30.8% vs 14.2%; P <.0001); headache or migraine (18.8% vs 12.6%; P = .0084); difficulty with concentration or focus (33.2% vs 19.1%; P <.0001); reduced motivation and/or energy (32.8% vs 24.1%; P = .0032); and irritability (28.2% vs 17.9%; P = .0002) compared with the sleep education group.

Prescription dCBTI

The FDA is considering approval of Somryst (formerly Shuti) as the first prescription dCBTI to treat adults with chronic insomnia and depression.[100] It is also the first product submitted for FDA approval through the Software Pre-certification Pilot Program. Somryst is a software application that provides CBTI and sleep restriction in 6 sessions.[101,102]

Clinicians should not assume all dCBTI programs are equal. Programs with a longer duration and more personal clinical support may have greater benefit.[107] Recent data suggest that specific traits of affect and personality influence whether a person responds to dCBTI.[108] These observations highlight how much we need to learn about adherence, predictors of response, drop-out rates, and the clinical infrastructure needed to deliver dCBTI in managed care.[109]

Conclusions

Insomnia is a heterogenous and almost ubiquitous disorder with unique predisposing and precipitating factors in vulnerable patient groups. Successful management requires that managed care clinicians understand the factors that drive insomnia in these groups. CBTI effectively treats chronic insomnia in most patients with coexisting medical and psychiatric conditions, in the elderly population, and in those in life transitions, such as menopause. A decade ago, understanding the subtleties of CBTI was a moot point because access barriers, primarily high cost and a lack of trained providers, prevented widespread adoption. Today, managed care clinicians face a vastly different challenge—the relatively unexplored landscape of digital therapeutics. However, dCBTI is here to stay, and it is a scalable option that is being launched in managed care. Now, the issues are which dCBTI product to provide, how to deliver it, how to manage nonresponders and adherence issues, and overall, what role dCBTI will play in the step-care of chronic insomnia. ■

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Funding source: This activity is supported by an educational grant from Eisai.

Author disclosure: Dr Dopheide has no relevant financial relationships with commercial interests to disclose.

Authorship information: Substantial contributions to the intellectual content including acquisition of data, analysis and interpretation of data, drafting of the manuscript, and critical revision of the manuscript for intellectual content.

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Medical writing and editorial support provided by: Jill E. Allen, PharmD, BCPS.

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REPORT

Current and Emerging Therapies for Insomnia

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ABSTRACT

Up to 10% of the US adult population will experience chronic insomnia, with women and elderly individuals at particularly high risk. Cognitive behavioral therapy is the core treatment for insomnia. When cognitive behavioral therapy is not enough, medications can help patients overcome the barriers and learned behaviors that prevent a good night's sleep. Benzodiazepines and nonbenzodiazepine GABA-A receptor agonists are the traditional medications used to treat insomnia. More recently, orexin inhibitors have been introduced that may have fewer adverse effects, including the development of dependence. To date, only suvorexant and lemborexant have been approved for the treatment of insomnia. However, several other agents are in later stages of development. This article will review the available pharmacotherapeutic options for treating insomnia.

***Am J Manag Care*. 2020;26:S85-S90**

For author information and disclosures, see end of text.

Introduction

Insomnia is a condition of unsatisfactory sleep in terms of sleep onset, sleep maintenance, or early waking.[1-5] It impairs daytime well-being and subjective abilities and functioning. Insomnia is pervasive in the United States and other Western societies. Insomnia can occur over either a short period of time (acute) or a longer period (chronic). This article will discuss chronic insomnia primarily.

Chronic insomnia is associated with numerous adverse effects (AEs) on a person's well-being, including fatigue, poor cognitive function, mood disturbance, and distress or interference with personal functioning.[1-7] Older adults more often have difficulty maintaining sleep (wake time after sleep onset [WASO]), whereas younger adults report more difficulty falling asleep (sleep onset latency [SOL]).

Guideline Recommendations for the Treatment of Insomnia

Insomnia can be treated with pharmacologic and nonpharmacologic approaches, individually or in combination. Several groups have published guidelines for the management of insomnia, including:

- American Academy of Sleep Medicine (AASM) (2017)[1]
- American College of Physicians (ACP) (2016)[2]
- Agency for Healthcare Research and Quality (AHRQ) (US Department of Health and Human Services) (2017)[3]
- British Association for Psychopharmacology (2019)[5]

Clinical Assessment

The diagnosis of insomnia is usually based on patient self-reporting. Insomnia may be a condition in and of itself or a symptom of another underlying medical or behavioral condition.[1-5] The patient evaluation of comorbid conditions should exclude:

- Medical conditions (eg, obstructive sleep apnea [OSA], pulmonary disease, heart failure, chronic pain, restless legs syndrome, hyperthyroidism)
- Psychiatric disorders (eg, depression, anxiety, posttraumatic stress disorder)

To view the *Patient Perspective* interview accompanying this supplement, please visit **www.pharmacytimes.org/go/insomnia-suppl.**

- Substance abuse/misuse (eg, alcohol, caffeine, drug and herbal stimulants)
- Behavioral contributions (eg, excessive screen time, exercise, or fluids before bed; poor sleep hygiene)
- Other factors contributing to sleep disruption (eg, circadian rhythm sleep-wake disorders)

Many individuals may experience insomnia and comorbid disorder(s) concurrently. For instance, insomnia may lead to anxiety about insomnia, which could further exacerbate sleep fragmentation. Questionnaires, at-home sleep logs, and actigraphy can all be helpful tools for the assessment of insomnia in the absence of other apparent etiologies.

Treatment Guidance

The guidelines vary in their recommendations of specific pharmacologic treatments. However, they follow a general approach[1-5,8]:

- Evaluate insomnia characteristics.
  - » Determine how sleep is deficient.
  - » Optimize treatment for any comorbid disorders.
- Initiate treatment with cognitive behavioral therapy (CBT) with/without relaxation therapy.
- If no effect, consider adding additional nonpharmacologic modalities.
- If still no improvement, reconsider diagnosis.
  - » Reevaluate, especially for occult comorbid disorders.
- If still no improvement, combine CBT with evidence-based pharmacology.
- If still no improvement, introduce alternative therapies (eg, valerian, melatonin).

The ACP does not recommend specific pharmacotherapy, but rather that clinicians use a shared decision-making approach when determining whether to add pharmacotherapy in adults with chronic insomnia disorder in whom cognitive behavioral therapy for insomnia (CBTI) alone was unsuccessful.[2]

The AASM recommends the following pharmacotherapies[1]:

- For sleep maintenance insomnia: suvorexant, eszopiclone, zolpidem, temazepam, doxepin
- For sleep onset insomnia: eszopiclone, zaleplon, zolpidem, triazolam, temazepam, ramelteon

The AASM recommends against using trazodone, tiagabine, diphenhydramine, melatonin, tryptophan, or valerian for either sleep-onset or sleep-maintenance insomnia.[1]

The AHRQ does not make recommendations but notes the following from a systematic review of 169 randomized controlled trials and 12 observational studies[3]:

- In the general adult population:
  - » Eszopiclone improves global outcomes, SOL, and total sleep time (TST) as well as reduces WASO.
  - » Zolpidem improves global outcomes, sleep latency, TST, and sleep quality; it may reduce WASO.
  - » Zaleplon improves sleep quality but likely has no effect on TST.
  - » Suvorexant improves global outcomes, sleep latency, and TST as well as reduces WASO.
  - » Ramelteon improves global outcomes and sleep quality but likely has no effect on other sleep outcomes.
  - » Doxepin may improve some global outcomes. Other antidepressants noted in the AHRQ review (trazodone, amitriptylline, and mirtazapine) are not approved for the treatment of insomnia.
- In the older adult (≥55 years) population:
  - » Eszopiclone may improve some outcomes.
  - » Zolpidem and ramelteon may improve SOL.
  - » Doxepin improves TST and may improve other sleep and global outcomes.

Current Treatment Options

Treatment Goals

The goals of treatment are to improve sleep quality and related poor daytime functioning while reducing distress and anxiety related to sleep fragmentation.[2,8] Patients should be reevaluated at least every 6 months. Management is highly personalized, and treatments may need to be switched and/or combined. Successive treatment failures may suggest an unrecognized underlying comorbidity.

Pharmacologic Interventions

Nonpharmacologic interventions may help many individuals with insomnia, but many people will not overcome their insomnia without assistance from medications. Withdrawal from CBTI is as high as 40% before midtreatment.[9] Over-the-counter (OTC) medications are not recommended by the AASM due to lack of efficacy and safety data.[1] The choice of prescription medication should be based on treatment goals and patient-specific characteristics.

Measures of Sleep Function/Dysfunction

Specific outcomes for sleep research generally include measures of WASO, sleep latency, number of awakenings, TST, and sleep efficiency.[8] People with insomnia have average sleep latency and WASO greater than 30 minutes, sleep efficiency less than 85%, and/or TST shorter than 6.5 hours.[8] Psychological measures of sleep include patient-reported outcomes and psychological assessment scales that describe sleep-related psychological distress, daytime function, quality of life, and sleep quality.

OTC Medications

A patient's first attempt to control insomnia often involves the use of OTC medications. Alcohol is commonly used but its effects are of short duration, and it can adversely affect sleep quality.[10] The use of alcohol can disrupt sleep homeostasis and carries the potential for abuse and dependency.[11] Persons with alcohol use disorder may experience profound insomnia as a result of chronic, excessive alcohol consumption.

The most common antihistamines in OTC products are diphenhydramine and doxylamine.[12] With antihistamines, the possibility exists for next-day sedating effects and some individuals develop paradoxical reactions such as agitation and anxiety. Antihistamines are associated with dry mouth, blurred vision, increased heart rate, difficulty urinating, memory problems, and confusion. According to the American Geriatrics Society Beers Criteria, antihistamines should be avoided in elderly patients due to the increased risk of cognitive impairment, falls, and motor vehicle accidents.[1,13] Diphenhydramine inhibits cytochrome P450 2D6 (CYP2D6), which can cause drug interactions with a diverse collection of medications.[14]

Many herbal preparations and supplements for insomnia are available on the market, although most lack sufficient evidence demonstrating a sleep benefit.[15] Herbal preparations carry a risk of possible unknown drug interactions as well as of contamination from nonstandardized production and quality control, which may result in variable concentrations of active ingredients among brands and lots.[16,17] Valerian is a common herbal sleep aid for chronic insomnia.[18] Its effects are gradual, and abrupt discontinuation is associated with withdrawal symptoms similar to those caused by benzodiazepines.[19] Melatonin is produced in the pineal gland in response to circadian signaling.[20] The rise in melatonin level facilitates sleep onset, and study results have shown a small effect on sleep latency but not on other sleep measures.[21,22]

Prescription Medications

The medications that are available specifically for treatment of insomnia target receptors that contribute to the regulation of the sleep and wake cycle: γ-aminobutyric acid (GABA-A), melatonin, histamine, and orexin/hypocretin receptors.[9,12,23] With the exceptions of doxepin and ramelteon, most approved medications for insomnia are Schedule IV controlled substances, owing to the potential for abuse.

Many people with insomnia experience it for extended periods of time, often for more than 1 year. In studies of up to 12 months in length in elderly patients, doxepin, eszopiclone, ramelteon, suvorexant, zaleplon, and zolpidem retained their efficacy without tolerance, abuse, withdrawal effects, or any new AEs developing.[24]

GABA-A AGONISTS

The GABA-A receptor is a chloride ion channel widespread in the central nervous system (CNS). When activated, GABA-A allows passage of chloride ions into the cell, resulting in hyperpolarization and decreased likelihood of action potential transmission. Facilitation of GABA-A results in sedative, anxiolytic, muscle-relaxant, and hypnotic effects.

Benzodiazepines are GABA-A agonists indicated for people with difficulty with sleep onset, difficulty with sleep onset and sleep maintenance, or middle-of-the-night awakenings with difficulty returning to sleep. Benzodiazepines are associated with rapid development of tolerance as well as risk of abuse or dependency, cognitive impairment, and rebound insomnia after discontinuation.[25] Tolerance can lead to dose escalation, and use of benzodiazepines for as little as 3 to 4 weeks is associated with withdrawal symptoms if stopped abruptly. This drug class is not recommended for use in elderly patients as listed by Beers Criteria.[18,26] In spite of this, benzodiazepines are used frequently in older patients, and up to one-third of elderly patients who take benzodiazepines use them on a long-term basis.[18] Long-term use is associated with ataxia, sedation, greater risk of falls and fractures, cognitive decline, and dependency. An increased risk of sedation, respiratory depression, coma, and death is associated with combined use of benzodiazepines and opioids.[27]

Nonbenzodiazepine GABA-A agonists ("Z-drugs" or "nonbenzodiazepines") are effective for people with sleep-onset and sleep-maintenance difficulties, and they are among the drugs most commonly prescribed for insomnia. Eszopiclone is useful in managing insomnia with comorbid depression or generalized anxiety disorder. However, nonbenzodiazepines are not considered to be "safer" than benzodiazepines as both have a risk of tolerance, daytime somnolence, anterograde amnesia, slowness of mental processes and body movements, and, when combined with other sedative drugs (eg, opioids), overdose.[28] Complex behaviors, such as sleep driving, sleep eating, and sleep walking, have been reported by persons using nonbenzodiazepines. Nonbenzodiazepines have adverse effects similar to benzodiazepines (eg, falls, fractures, delirium) and as a result are also included in the Beers Criteria list of drugs that should be avoided in elderly patients.[18,26] Nonbenzodiazepine use in elderly patients offers minimal improvement in sleep latency and duration and is associated with increased hospitalization as well as emergency department visits.

SEDATING ANTIDEPRESSANTS

Histamine in the CNS potently promotes wakefulness. Doxepin, at doses of 25 mg to 300 mg, is a tricyclic antidepressant with serotonin and norepinephrine reuptake inhibition as well as antihistamine and anticholinergic activity. At low doses (3-6 mg), it is a pure H_1 receptor antagonist. Doxepin should not be coadministered with monoamine oxidase inhibitors.[29,30]

Trazodone does not carry an indication for insomnia but has been used in patients with primary or secondary insomnia at

doses of 50 mg to 100 mg. It is a serotonin antagonist and reuptake inhibitor that also has moderate antihistamine and low anticholinergic activity. In a systematic review, trazodone was effective in decreasing sleep latency and increasing sleep duration and quality of sleep. The most common adverse effects of trazodone were drowsiness, headache, and orthostatic hypotension. Postural hypotension is a concern, particularly in elderly patients who are at risk of falls and injury.[29,31]

MELATONIN RECEPTOR AGONIST

Ramelteon is a melatonin receptor agonist, targeting melatonin receptors 1 and 2 preferentially over receptor 3. Melatonin acts in the hypothalamus, causing sedation, and regulates sleep-wake cycles. Ramelteon marginally reduces sleep latency but does not increase TST. Melatonin receptor agonists carry a low risk of dependency and would be appropriate in patients with substance use disorders.[5] High-fat meals can delay absorption, and the potential for drug interactions is moderately high.

Orexin Receptor Antagonists

The orexin/hypocretin receptor is central to the regulation of sleep-wake cycles, arousal, and appetite.[32] A medication that acts as an antagonist to the orexin receptor could induce sleepiness and sustain longer periods of sleep, which could be helpful for the treatment of insomnia.[33]

SUVOREXANT

Suvorexant is a dual-orexin receptor antagonist (DORA) that was approved in 2014 for the treatment of insomnia. Suvorexant suppresses the wake drive by blocking both the orexin-1 and orexin-2 receptors. Compared with another DORA, almorexant, suvorexant demonstrated a more balanced sleep architecture profile due to its promotion of both rapid eye movement (REM) and non-REM sleep, whereas almorexant primarily increases REM sleep. Suvorexant has been shown to increase time spent in each stage of sleep and to increase TST.[33]

Suvorexant was studied in 3 clinical trials in patients with insomnia characterized by difficulties with sleep onset and sleep maintenance. In study 1 and study 2, suvorexant was superior to placebo for sleep latency, assessed objectively by polysomnography and subjectively by patient estimation. Suvorexant was also superior to placebo for sleep maintenance, assessed objectively by polysomnography and subjectively as patient-estimated TST.

In a 1-month crossover study (study 3), adults (aged 18-64 years) were treated with placebo and suvorexant. Suvorexant 10 mg and 20 mg were superior to placebo for sleep latency and sleep maintenance, assessed objectively by polysomnography. Higher doses of suvorexant were found to have similar efficacy to lower doses but were associated with significantly higher incidence of AEs.

In clinical trials, the most common AE (reported in ≥5% of patients treated with suvorexant and at least twice the placebo rate) in patients with insomnia treated with suvorexant 15 mg or 20 mg was somnolence (suvorexant 7% vs placebo 3%). The AE profile in elderly patients was generally consistent with that in nonelderly patients. The discontinuation rate due to AEs for patients treated with suvorexant 15 mg or 20 mg was 3% compared with 5% for placebo.

Individuals with narcolepsy lack most or all orexin receptors in the hypothalamus and should not receive suvorexant. Before increasing the dose, it should be considered that obese patients and women have reduced clearance compared with leaner people and men.[34]

LEMBOREXANT

Lemborexant is a DORA that was approved in late December 2019 for the treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance in adults.[35,36] Lemborexant has a half-life of approximately 17 to 19 hours; it decreases wakefulness and promotes non-REM sleep with no effect on REM sleep.[33] Lemborexant was studied in the SUNRISE 1 and SUNRISE 2 trials.[37] In the SUNRISE studies, lemborexant significantly improved objective and subjective measures of sleep onset and sleep maintenance compared with placebo. These were 1-month and 6-month, placebo-controlled trials, respectively, with the primary end point of sleep latency and secondary end points of sleep efficiency and WASO. Comparator arms were 10 mg and 5 mg lemborexant versus placebo. Both trials achieved their primary end point.

The most common AE (reported in ≥5% of patients treated with lemborexant and at least twice the rate of placebo) in both SUNRISE 1 and SUNRISE 2 was somnolence (lemborexant 10 mg, 10%; lemborexant 5 mg, 7%; placebo, 1%).[38] Treatment discontinuation was highest in the 10-mg lemborexant group compared with the other groups (8.3%, 4.1%, and 3.8%, respectively).[39] No respiratory concerns were noted in the trials. Patients with mild OSA did not experience worsening sleep apnea, as measured by changes in apnea-hypopnea index or peripheral oxygen saturation.[40]

Other Orexin Inhibitors in Phase 3 Clinical Trials

DARIDOREXANT (NEMOREXANT)

Daridorexant (nemorexant) is a DORA with a half-life of approximately 6 hours. Phase 2 study results have shown a dose-dependent effect on reducing WASO and latency to sleep onset. The most common AEs reported were headache, somnolence, diarrhea, and fatigue.[41,42]

SELTOREXANT

Unlike other orexin inhibitors that antagonize both orexin-1 and orexin-2 receptors, seltorexant is a selective orexin-2 receptor antagonist. This unique mechanism of action may offer hypnotic effects while preserving normal sleep architecture and reduced risk for cataplexy. Seltorexin has a half-life of 2 to 3 hours.[43] In its phase 2

clinical trials, seltorexant was shown to improve sleep induction and prolong sleep duration. It is also being studied for the treatment of hyperarousal-related insomnia in patients with depression. The most common AEs reported were headache, dizziness, and somnolence.[44-46]

Pharmacologic Treatment Failure

A specific insomnia medication will not be effective for everyone, so a personalized approach to management is needed.[4,8] Comorbid conditions should be suspected in patients who repeatedly have limited or only transient improvements with medication and CBT. Polypharmacy is a significant concern, particularly in elderly patients. In the ambulatory setting, approximately one-third to two-thirds of elderly patients use 5 or more daily prescription medications, in addition to about half using OTC medications and dietary supplements.[47] In the nursing home setting, up to 40% of residents are using 9 or more daily medications. Polypharmacy is associated with increased healthcare costs and increased risk of AEs (eg, drug interactions, falls, cognitive impairment). Pharmacists can be instrumental in reducing polypharmacy.[48]

Pharmacotherapy for Specific Populations

As people age, sleep timing advances (ie, earlier bedtimes and rise times), and falling asleep becomes more difficult.[18,24] Elderly people may have a disrupted sleep architecture, with less REM sleep and more stage I and stage II non-REM sleep. They frequently have comorbidities and reduced cognitive function. Older adults often have insomnia, and many medications are not suitable for use in this population. CBT is the first choice of treatment but may require longer periods of time to have an effect. Medication choice should be tailored to the patient's needs[18,24]:

- Patients with sleep-onset disturbance may have better results with a hypnotic that has a short half-life.
- Patients with sleep-maintenance difficulties may benefit more from a hypnotic with a longer half-life but should avoid hypnotics with a very long half-life to reduce the occurrence of next-day sedation.
- Comorbidities (medical, psychological), drug interactions, and polypharmacy will need careful attention.
- Caution should be used when initiating complex medication regimens, and downward adjustments should be considered.[8,12]

Conclusions

Chronic insomnia is a prevalent and difficult-to-treat condition.[1] Difficulty falling asleep or maintaining sleep leads to daytime struggles, such as fatigue, mood disturbances, and decreased ability and desire to work or socialize. Women and elderly patients are at particular risk of chronic insomnia. Treatment should be tailored to the individual needs of the patient, and patients may need to switch medications to find the one that alleviates their symptoms best. Guidelines are discordant and vague, which is likely a reflection of the individual nature of insomnia and the difficulty of developing a one-size-fits-all algorithm.[1-3,8] ■

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Funding source: This activity is supported by an educational grant from Eisai.

Author disclosure: Dr Liu has no relevant financial relationships with commercial interests to disclose.

Authorship information: Substantial contributions to the intellectual content including concept and design, analysis and interpretation of data, drafting of the manuscript, and critical revision of the manuscript for important intellectual content.

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Medical writing and editorial support provided by: David Modrak, PhD, and Patrick Stone.

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REPORT

Economic Burden and Managed Care Considerations for the Treatment of Insomnia

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Introduction

Insomnia is defined by the American Academy of Sleep Medicine (AASM) Clinical Practice Guidelines as a complaint of sleep associated with daytime consequences that are not attributable to environmental circumstances or inadequate opportunity to sleep.[1] When evaluating the economic burden of insomnia, it is important to consider both direct costs (eg, office visits, medication costs, testing) as well as indirect costs, which result in lost resources (eg, absenteeism, presenteeism, work- and non–work-related accidents).[1] Estimating healthcare costs of untreated insomnia has been both difficult and varying due to contributing comorbid conditions, limited studies that differentiate primary versus comorbid insomnia, the significant percentage of patients who self-medicate, and difficulty in accurately quantifying indirect costs.[2]

Direct and Indirect Costs of Insomnia

The direct costs of patients with untreated insomnia have been shown to be significantly higher when compared with those of patients without insomnia. One retrospective study aimed to better understand the direct healthcare costs of insomnia by analyzing claims from a large health plan. Anderson and colleagues found that a diagnosis of insomnia was associated with 26% higher costs at baseline and 46% higher costs at 12 months after diagnosis. When comorbidities were recognized, the insomnia cohort had 80% higher costs, on average, than the matched control cohort. The insomnia cohort experienced greater general health decline as measured by increases in Charlson Comorbidity Index scores, as well as by greater proportion of patients with mental health diagnoses and use of psychiatric medications, which were drivers in the increase in overall cost.[3]

A recent study evaluated the economic consequences of untreated insomnia using a sample of claims data obtained from the CMS Chronic Conditions Data Warehouse (CCW); it included all-cause inpatient and outpatient visits, emergency department (ED) visits, nursing home stays, prescription medication use, and all-cause costs. The study found that patients with insomnia had higher rates of healthcare resource utilization (HRU) in all points of service locations

ABSTRACT

Insomnia is a common sleep disorder in adults that can have many negative health impacts. The aggregate total of direct and indirect insomnia healthcare costs has been estimated to be as high as $100 billion US dollars per year. In addition to the societal cost burden, insomnia also negatively affects patients' quality of life (QOL), including social and occupational functioning or productivity as well as impaired cognition or mood. Insomnia may also exacerbate and increase morbidity and complications from psychological disorders, such as depression, as well as have serious consequences, such as increased risk of suicide. Comorbidities, medications, and/or psychosocial contributors may negatively influence QOL. Many medications for the treatment of insomnia have adverse effect (AE) profiles that increase the risk of falls and related injuries, cognitive impairment, and motor vehicle accidents. These AEs place additional burden on the already vulnerable older adult population and those with comorbidities. Managed care organizations must evaluate clinical considerations, including safety profiles and the negative impact of disease on patients' QOL, to develop strategies for cost-effective treatment plans for patients with insomnia and to ensure appropriate use of these medications.

***Am J Manag Care*. 2020;26:S91-S96**

For author information and disclosures, see end of text.

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evaluated, with HRU being highest for inpatient care (rate ratio [RR], 1.61; 95% CI, 1.59-1.64) and lowest for prescription fills (RR, 1.17; 95% CI, 1.16-1.17).[4] Similarly, when compared with controls, patients with insomnia demonstrated $63,607 (95% CI, $60,532-$66,685) higher all-cause costs, which were driven primarily by inpatient care ($60,900; 95% CI, $56,609-$65,191).[4] Further, Wickwire et al estimated that total costs of untreated insomnia may be as high as $100 billion US dollars per year, with a majority of costs being indirect. These indirect costs include not only inpatient admissions, but also ED visits, days hospitalized, and outpatient provider visits.[5]

As insomnia is associated with daytime sleepiness, fatigue, psychomotor deficits, and mood dysregulation, it may be expected to have negative impacts on US workers. Studies have demonstrated the impact of insomnia on impaired workplace functioning, including absenteeism due to sickness, injuries, and disability.[6] Insomnia is a risk factor for workplace accidents and increased risk of associated falls and injuries, such as hip fractures.[7] The American Insomnia Survey of 4991 respondents revealed that the average costs of insomnia-related accidents and errors are $32,062; these costs were significantly higher than those of other accidents and errors not associated with insomnia ($21,914). Simulations associated insomnia with an estimated 7.2% of all costly workplace accidents and errors, and with 23.7% of the total costs of overall incidents. Annualized US population projected estimates of 274,000 insomnia-related workplace accidents and errors had a combined value of $31.1 billion.[6]

Insomnia has been shown to have substantial burdens on the US workforce. After evaluating a sample of more than 7000 employed health plan subscribers via the Brief Insomnia Questionnaire, Kessler and colleagues found that the prevalence of insomnia was more than 23%, with an annualized individual-level association of insomnia with presenteeism equivalent to 11.3 days of lost work performance, accounting for $2280 of individual-level lost capital. When generalizing to the US workforce, this approximates to an annualized population-level estimate of more than 252 days and $63.2 billion per year in lost productivity resulting from insomnia.[8] In a study that evaluated the results of a US National Health and Wellness survey, patients with anxiety who experienced insomnia characterized by nighttime awakenings reported 3.0 more provider visits in the past 12 months compared with those without chronic insomnia, 15.8% greater work impairment (among full-time employed), and 20.4% greater activity impairment (P <.001 for all). Patients with depression who experienced insomnia characterized by nighttime awakenings reported 2.4 more provider visits, 13.2% greater work impairment, and 18.2% greater activity impairment (P <.001 for all).[9]

Healthcare costs may also be higher in those with more severe insomnia. A retrospective study linking health claims data with a telephone survey of health plan members sought to compare the association between insomnia severity (using the Insomnia Severity Index) and healthcare productivity and cost. It found that, compared with the group without insomnia, mean total healthcare costs were 75% higher in the group with moderate to severe insomnia ($1323 vs $757; P <.05) and mean lost productivity costs were 33% greater for the subthreshold insomnia group ($1352 vs $1013; P <.001). Healthcare cost trend drivers were chronic medical and psychiatric comorbidities. Similarly, lost productivity costs were 72% greater in the moderate to severe insomnia group compared with the group without insomnia ($1739 vs $1013; P <.001).[10]

Effect on Quality of Life

The societal burden of insomnia is not limited to economic impacts. It also has profound effects on quality of life (QOL). Insomnia is more prevalent in psychiatrically and medically ill patients and is associated with numerous negative health outcomes.[1]

An estimated 85% to 90% of chronic insomnia is attributed to comorbidities, which may have a substantial impact on QOL.[11] Insomnia occurs prior to and represents a risk factor for new-onset depression, and it has been suggested that treatment of insomnia may improve depression.[12] Many patients with depression attribute their inability to obtain an adequate amount of nighttime sleep to low daytime functioning (including poor concentration and memory), decreased reaction time and coordination, fatigue, mood disturbance, and anxiety.[11] Decreased sleep levels may contribute to impulsivity and may increase unplanned suicidal behaviors, and therefore should be considered as a potential therapeutic target.[13] Patients with chronic obstructive pulmonary disease who had insomnia were found to have a poorer QOL.[14] Military members returning from combat with posttraumatic stress disorder report insomnia as their most common symptom.[15] Insomnia is a common symptom of patients with cancer and is associated with increased depression, pain, and tiredness.[16] Insomnia has also been associated with increased risk for incident hypertension.[17] When developing an insomnia treatment plan, it is important to consider treatment of comorbidities that may be exacerbating insomnia symptoms as well as potential benefits of possibly improving comorbidities in order to improve overall QOL.

Limited studies have assessed specific treatment plans and measurement of effect on QOL. Both behavioral and pharmacologic interventions may be considered in a treatment plan.[1] The American College of Physicians as well as the AASM recommend the use of cognitive behavior therapy for insomnia (CBTI) as first-line treatment for insomnia.[18] CBTI generally consists of 4 to 7 therapy sessions and has been found to be as effective as medication treatment in the short term.[1,18] The majority of available studies evaluating pharmacotherapy treatments on QOL—including zolpidem, zopiclone, and eszopiclone—have demonstrated positive impact on patients' perceptions of QOL.[5]

Using the Medical Outcomes Study 8-item Short-Form Survey (SF-8), Bolge and colleagues found that patients with anxiety and

depression as well as insomnia had impaired QOL. Responses from the US National Health and Wellness survey revealed that patients with depression and chronic insomnia had SF-8 physical component summary scores that were 5.2 points lower and SF-8 mental component summary scores that were 7.0 points lower than those of patients without insomnia. SF-8 physical component summary scores were 5.9 points lower and SF-8 mental component summary scores were 7.9 points lower for patients with anxiety and chronic insomnia than for those without insomnia (P <.001 for all).[9]

Considerations for Vulnerable Populations

Older adults have an increased risk of insomnia due to comorbid medical conditions.[1,7] It is important to consider the adverse effect (AE) profiles of insomnia treatments and associated risks for this patient population when evaluating whether treatment is appropriate and making appropriate recommendations for pharmacotherapy.

The American Geriatrics Society Beers Criteria recommend against benzodiazepine use in older adults due to known increased risk of cognitive impairment, delirium, falls, fractures, and motor vehicle accidents.[19] The criteria also recommend avoiding use of nonbenzodiazepine GABA-A receptor agonist hypnotics (such as eszopiclone, zolpidem, and zaleplon) as they have AEs similar to those of benzodiazepines and are also associated with increased ED visits and hospitalizations with minimal improvement of sleep latency and duration.[19]

The treatment of choice for older adults, rather than pharmacologic therapy, is CBTI. However, for patients who require pharmacologic therapy, careful attention must be given with regard to dose and drug, as older adults may experience slower drug metabolism. This can result in older patients being vulnerable to AEs, particularly related to age-related deficits, such as gait instability, sedation, and cognitive dysfunction. In addition to increased risk of AEs, the literature has also documented possible links of hypnotics to infection, depression, and overall mortality risks that are most frequently observed in the older adult population.[1] Older patients—who commonly experience declining renal function—are also at increased risk of prolonged drug exposure to hypnotics due to reduced metabolism and/or excretion. The risks of hypnotics increase when used in patients with comorbidities, such as Alzheimer disease; when used at dose levels higher than those recommended; or when combined with other psychoactive medications.[1] Clinicians should be cautious and warn patients of risks of hypnotics regarding sedation, especially with agents with longer half-lives or intended long-term use, such as extended-release zolpidem, eszopiclone, and temazepam.[1] Due to the risks of hypnotic agents and the potential of drug–drug interactions for patients with comorbidities whose current medication profile includes medications that may be sedating or increase the risk of AE occurrence, it is important to weigh medication safety profiles when evaluating initial insomnia treatment for vulnerable patient populations.

Cost-Effectiveness of Insomnia Treatment

Evaluating the cost-effectiveness of medications is a primary focus when making appropriate recommendations for treatment of insomnia. A large number of study designs have aimed to compare the cost-effectiveness of insomnia treatments using quality-adjusted life-years (QALYs). This measure is meant to determine both survival and QOL by incorporating a utility score of health-related QOL (HRQOL), such as the Medical Outcomes Study 36-item Short-Form (SF-36), which is often used in insomnia cost-effectiveness studies. If the QALY is 1, that suggests 1 year of perfect health, with 0 representing death. The ratio of $50,000 to $150,000 per QALY gained by using an intervention has been a commonly accepted threshold for cost-effectiveness in the United States. Varying models have been used to measure QALY in relation to direct and indirect costs, including absenteeism, presenteeism, and fall-related costs.[5]

The first study to evaluate cost-effectiveness of insomnia pharmacotherapy treatment examined the cost-effectiveness of 6-month duration nightly eszopiclone. The study used previously published data and claims information from a payer database with more than 5 million enrollees. The study incorporated both direct costs from the payer perspective, including prescription costs, dispensing fees, and 1 physician visit, in addition to indirect costs, such as days-out-of-role (including worker compensation and disability) and presenteeism costs (using averages from previously published data). Patients receiving eszopiclone were 2.5 times more likely than those receiving placebo to have remitted from insomnia (95% CI, approximately 1.75-3.60).[20] The total 6-month cost of insomnia due to lost productivity time, including absenteeism and presenteeism, was found to be $1091 per person (or $182 per person per month). Presenteeism occurs when an employee does not miss work, but is unable to work to their full productivity. Many patients with insomnia report impairment in next-day functioning and alertness. Absenteeism occurs when an employee is unable to work due to issues associated with the disease state, which has an effect on overall productivity.[20] Treatment with eszopiclone was associated with a total cost of $497.15 per person over 6 months (including physician visit, drug costs, and time taken for physician visit). However, when incorporating total savings from indirect and direct costs of treatment, the net cost of eszopiclone therapy was $67.83 per person over 6 months. The incremental cost, including direct and indirect costs, per QALY gained was $9930 relative to placebo.[20] The study found 6-month treatment with eszopiclone for adults to be cost-effective when accounting for indirect costs.

Another study evaluated the use of many insomnia medications on reduction of healthcare costs from the payer perspective

using a medical claims database of more than 55 million covered lives. Healthcare costs included physician visits, hospitalizations, ED visits, and prescription drugs (excluding insomnia medications). The unadjusted mean reduction in per-person total health costs for pharmacotherapy treatment of insomnia was $1100.[20,21] The medications that showed the greatest impact on per person per year (PPPY) cost savings when using total sleep time as the primary value of efficacy were low-dose trazodone at $1022 PPPY (95% CI, −$1151 to −$894), zolpidem at $1158 PPPY (95% CI, −$1281 to −$1036), and zolpidem extended-release at $2573 PPPY (95% CI, −$3681 to −$1465).[21] Of note, ramelteon was predicted to increase costs by $763 PPPY (95% CI, −$641 to $2125).[21] The study did not evaluate indirect costs or impact on QOL.

The most encompassing evaluation of pharmacotherapy cost-effectiveness included efficacy data from a previous study on eszopiclone and costs data from a claims database. HRQOL was measured using the SF-36. Direct healthcare costs included medication use, physician visits, the wholesale price of eszopiclone, and dispensing fees. Indirect costs, such as days-out-of-role, were measured using absences, disability, and worker compensation. Presenteeism was included and measured using the Work Limited Questionnaire. Although treatment with eszopiclone resulted in a net cost increase of $67, eszopiclone showed a net gain of 0.0137 QALYs over placebo.[22] Treatment with eszopiclone increased HRQOL with incremental cost per QALY of less than $5000.[22] When absenteeism and presenteeism costs were excluded, the cost-effectiveness ratio increased to $33,000 per QALY gained, which is below the common threshold of $50,000 used to determine cost-effectiveness.[22]

A more recent 2019 study evaluated the economic aspects of insomnia and insomnia medication treatment among a nationally representative sample of older adult Medicare beneficiaries using claims from the CMS CCW between 2006 and 2013. The study evaluated HRU and costs in the year following insomnia diagnosis. No significant differences in pre- and postdiagnosis costs were found between individuals who received insomnia medication treatment and those who were untreated.[4] However, this study did not account for impact on QOL or potential indirect costs, possibly due to being limited to the Medicare population and likely minimal impact on the US workforce.

Application of Clinical Practice Guidelines and Managed Care Considerations

The 2017 AASM guideline recommends CBTI as first-line treatment for insomnia.[1,23] Nonpharmacologic treatment with CBTI is effective for adults, as demonstrated in many studies.[23] When pharmacologic intervention is recommended, the AASM recommends all pharmacotherapy treatment with a "WEAK" recommendation rating. The "WEAK" rating denotes less of a degree of certainty that the recommendation should apply to all patients both in outcomes and appropriateness, but it does not necessarily denote ineffectiveness of the treatment option. The AASM states that the recommendations were downgraded due to the lack of quality data in the literature regarding efficacy, treatment-emergent AEs, and outcomes.[1] Managed care decision makers must consider the safety and potential harm associated with pharmacologic use, especially in the vulnerable patient populations previously mentioned.

The **Table**[24-35] shows currently available insomnia medications. Given the varying differences in cost among insomnia agents and recommendations outlined by the AASM, managed care organizations may want to take additional measures to ensure appropriate use of high-cost insomnia medications for those patients most likely to benefit from therapy. Additional measures may also be considered for patients, such as older adults, who are most likely to experience negative effects due to the AE profile of these agents. HRU management programs or clinical pathway protocols should guide providers to begin with CBTI for all patients. If pharmacologic therapy is warranted, dosing and drug choice selection should be guided by age, comorbidities, and potential fall risk or next-day sedation. In addition, therapy should not be continued indefinitely, and patients should be reevaluated often to ensure that the benefit of the pharmacologic therapy is not outweighing any potential risk from the medication.

Step Therapies, Age Screening, and Quantity Limits

Step therapies require utilizing a clinically effective prescription prior to trying a medication with less evidence of clinical effectiveness or higher cost.[36] Step therapies may be considered for moderate- to high-cost agents to ensure that cost-effective or safer alternatives are being used before initiating agents that are even more costly or associated with greater risks. Step therapies may also incorporate the consideration of age, for older adults, to ensure that safer alternatives are used first. Step therapies do not require a high payer burden, as they do not require manual review and are incorporated into the electronic claims adjudication system. However, step therapies may still delay treatment if a provider is unaware of the step therapy requirements. Best practices recommend that payers provide rejection messages with an included list of required step 1 agents at point of sale at the pharmacy to decrease delay to treatment. This may result in primary medication nonadherence, in which a patient never receives treatment for insomnia, despite obtaining a prescription from their provider.

Age screening edits are an important tool for managed care professionals to utilize to help ensure appropriate use of insomnia medications with minimal patient disruption. Particularly in patients older than 65 years, the Beers criteria recommend against the use of benzodiazepines due to increased risks, and they recommend a short maximum duration (less than 90 days) for the newer-generation nonbenzodiazepine GABA-A receptor agonists.

TABLE. Commonly Prescribed Insomnia Agents[24-35]

Medication	DEA Controlled Substance Schedule	Generic Availability	FDA-Approved *Only* for Short-Term Use in Insomnia
Triazolam 0.125 mg, 0.25 mg	IV	Yes	Yes
Temazepam 7.5 mg, 15 mg, 22.5 mg, 30 mg	IV	Yes	Yes
Suvorexant 5 mg, 10 mg, 15 mg, 20 mg	IV	No	No
Ramelteon 8 mg	-	Yes	No
Eszopiclone 1 mg, 2 mg, 3 mg	IV	Yes	No
Zaleplon 5 mg, 10 mg	IV	No	Yes
Zolpidem 5 mg, 10 mg	IV	Yes	Yes
Zolpidem CR 6.5 mg, 12.5 mg	IV	Yes	No
Zolpidem sublingual 1.75 mg, 3.5 mg	IV	Yes	Yes
Zolpidem mist	IV	No	Yes
Doxepin 3 mg, 6 mg	-	No	No
Trazodone[a] 50 mg, 100 mg	-	Yes	N/A

CR indicates extended release; N/A, not applicable.
[a]Reflects off-label use.

Limiting the quantity of medication prescribed in a given timeframe may be considered to ensure that agents that are approved for short-term use are not being used for longer periods without proper physician evaluation. Quantity limits may also ensure appropriate dosing, especially for medications with recommended starting dosages for older adults and maximum daily doses.

Prior Authorizations

Prior authorizations may be considered for the highest-cost agents to ensure appropriate use. Despite the costs for payers that are associated with providing the clinical support and resources to review prior authorizations, the delay in treatment therapy for patients, and the administration burden for prescribers, managed care organizations may want to review additional documentation from patients' prescribers to ensure that these agents are being reserved for those who are most likely to benefit from therapy.[37] Managed care organizations developing coverage criteria may consider the following general requirements, then present them for approval to the organization's Pharmacy and Therapeutics Committee:

- Diagnosis of chronic insomnia lasting at least 3 months
- Potential underlying causes of insomnia have been addressed
- Patient has tried and failed sleep hygiene practices or CBTI
- Lower-cost alternatives were already tried and failed *OR* specific patient factors explain why cost-effective alternatives are not appropriate
- Patient is being evaluated by a provider every 6 to 12 months to attest that benefit of treatment continues to outweigh risk and that patient is benefiting from therapy

Conclusions

Insomnia is prevalent among adults, results in high HRU costs, and negatively impacts patients' QOL. Untreated insomnia is associated with higher healthcare costs, largely attributed to indirect costs that include absenteeism, presenteeism, and work-related accidents and errors. The severity of insomnia has been shown to have a direct correlation to healthcare costs. The AASM recommends CBTI and sleep hygiene practices as first-line treatment for insomnia. Additionally, the AASM provides "WEAK" strength of recommendations for the use of all pharmacologic treatments for insomnia, mostly due to lack of quality data in the peer-reviewed literature. The Beers Criteria recommend avoiding hypnotic medications for insomnia in the elderly population due to potential AEs, including cognitive impairment, delirium, falls, fractures, and motor vehicle accidents. These agents are sedating and pose increased risk for vulnerable patient populations who are at increased fall risk and have an increased sensitivity to AE profiles. The benefits of treating insomnia, such as improved QOL, must be weighed against potential risks of these agents. Managed care decision makers may want to implement HRU strategies to ensure safe, appropriate, cost-effective use for patients. ■

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Funding source: This activity is supported by an educational grant from Eisai.

Author disclosure: Dr Taddei-Allen has the following relevant financial relationship with a commercial interest to disclose:

Advisory Board Member – Novo Nordisk

Authorship information: Substantial contributions to the intellectual content including concept and design, analysis and interpretation of data,

drafting of the manuscript, and critical revision of the manuscript for intellectual content.

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Medical writing and editorial support provided by: Jenna Wood, PharmD.

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POSTTEST

A Managed Care Review on Insomnia: Treatment Guidelines, Emerging Therapies, and the Need for Safe, Effective Options

Release date: March 11, 2020
Expiration date: March 11, 2021

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Sample of Online Posttest

Choose the best answer for each of the following:

1. Insomnia has been shown to worsen some medical and psychiatric disorders, including:

A. Depression, anxiety, and traumatic brain injury (TBI)
B. Depression, osteoarthritis, and TBI
C. Depression, asthma, and anxiety
D. TBI, anxiety, and obsessive-compulsive disorder

2. Which nondrug treatment is recommended in the first-line setting to treat chronic insomnia?

A. Sleep hygiene education
B. Mindfulness meditation
C. Cognitive behavioral therapy for insomnia (CBTI)
D. Relaxation training

3. Which sleep aid is associated with withdrawal symptoms upon abrupt discontinuation of treatment?

A. Doxylamine
B. Diphenhydramine
C. Melatonin
D. Valerian

4. AL is a 34-year-old man with a history of substance use disorder. He has difficulty falling asleep but sleeps through the night. Although he has tried to improve his sleep hygiene, he continues to have difficulty falling asleep. In addition to CBTI, which agent would you recommend for him?

A. Ramelteon
B. Suvorexant
C. Temazepam
D. Zolpidem

5. NR is a 50-year-old woman with mild obstructive sleep apnea and obesity. She started using a continuous positive airway pressure device, but she continues to have difficulty falling asleep and maintaining sleep. What option is most appropriate for sleep onset and sleep maintenance?

A. Lemborexant
B. Ramelteon
C. Triazolam
D. Zaleplon

6. What is considered an indirect cost of untreated insomnia?

A. Dispensing fees
B. Physician visits
C. Medication average wholesale price
D. Missed days from work

7. What first-line treatment does the American Academy of Sleep Medicine recommend for patients diagnosed with insomnia?

A. Short-acting benzodiazepines
B. Benzodiazepine receptor agonists
C. CBTI
D. Melatonin-receptor agonists

8. Which agent is not recommended to be used for more than 90 days in the elderly population, according to the Beers Criteria?

A. Doxepin 3 mg
B. Trazodone
C. Melatonin
D. Zolpidem

9. Which statement is true regarding newer-generation benzodiazepine receptor agonists?

A. Benzodiazepine receptor agonists are safe for use in older adults and are approved for long-term use.

B. Benzodiazepine receptor agonists should be used for the shortest duration possible, particularly in older patients due to their risk of adverse effects, including confusion, delirium, and risk of falls.

C. The Beers Criteria recommend benzodiazepine receptor agonists for long-term use by older adults.

D. Benzodiazepine receptor agonists have not been shown to improve quality of life.

10. You are designing pharmacy benefits for a health plan and want to incorporate utilization strategies to ensure safe and appropriate use of sleep therapy agents, as you noticed this therapeutic class is increasing in number of claims every quarter. What would be the most appropriate strategy for utilization management?

A. No utilization management is needed, as many options are available as low-cost generics.

B. Approve use of zaleplon for long-term insomnia only.

C. Limit quantity of zolpidem IR 10 mg to 90 tablets/30 days for patients older than 65 years.

D. Require prior authorization for use of benzodiazepines and nonbenzodiazepine GABA-A receptor agonist hypnotics in adults older than 65 years.

NOTES

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