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Advances in the Treatment of Chronic Insomnia: A Narrative Review of New Nonpharmacologic and Pharmacologic Therapies

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Abstract: Chronic insomnia disorder, which affects 6–10% of the population, is diagnostically characterized by ongoing difficulties with initiating or maintaining sleep occurring at least three times per week, persisting for at least 3 months, and associated with daytime impairment. While chronic insomnia is often considered a condition primarily related to impaired sleep, the disorder can also adversely affect domains of physical and mental health, quality of life, and daytime function, which highlights the importance of treating the multi-dimensional sleep disorder. Owing to misperceptions about the safety and effectiveness of treatment options, many individuals with insomnia may not seek professional treatment, and alternatively use ineffective home remedies or over-the-counter medications to improve sleep. Some physicians may even believe that insomnia is remediated by simply having the patient “get more sleep”. Unfortunately, treatment of insomnia is not always that simple. The disorder’s complex underlying pathophysiology warrants consideration of different nonpharmacologic and pharmacologic treatment options. Indeed, recent insights gained from research into the pathophysiology of insomnia have facilitated development of newer treatment approaches with more efficacious outcomes. This narrative review provides a summary of the diagnostic criteria and pathophysiology of insomnia and its subtypes. Further, this review emphasizes new and emerging nonpharmacologic and pharmacologic treatments for chronic insomnia, including recent enhancements in approaches to cognitive behavioral therapy for insomnia (CBT-I) and the new dual orexin receptor antagonist (DORA) pharmacologics. These advances in treatment have expanded the treatment options and are likely to result in improved outcomes in patients with chronic insomnia.

Keywords: dual orexin receptor antagonists, cognitive behavioral therapy-insomnia, insomnia subtype, hypnotic

Introduction

Insomnia disorder is described by the American Academy of Sleep Medicine (AASM) International Classification of Sleep Disorders, Third Edition, as having frequent and persistent difficulty initiating or maintaining sleep that results in general sleep dissatisfaction despite adequate opportunity for sleep. The sleep complaint is also accompanied by distress about poor sleep and/or impairment across various domains of functioning (eg, family, social, vocational, academic).^{1,2} Insomnia is classified short-term if it persists less than 3 months and chronic if it persists at least 3 months and occurs at least three times per week.^{1,2} Similar essential features of insomnia are described in the American Psychiatric Association (APA) Diagnostic

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and Statistical Manual of Mental Disorders, Fifth Edition and include dissatisfaction with sleep quantity or quality with complaints of difficulty initiating or maintaining sleep.³ The sleep disturbance must also cause clinically significant distress or impairments in social, occupational, or other important areas of functioning and may occur independently or during the course of another mental disorder or medical condition.³ For many, insomnia becomes a long-term and persistent condition. A recent longitudinal study based on annual survey data demonstrated that 37.5% of participants with insomnia disorder at baseline continued to report insomnia symptoms through 5 years of follow-up.⁴

The International Classification of Sleep Disorders, Third Edition and Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition also describe several secondary insomnias, which arise from co-occurring primary or causative conditions including mental disorders (eg, major depressive disorder), medical conditions (eg, pain), substance use, or another sleep disorder (eg, breathing-related sleep disorder).^{1,3} Despite these insomnia subtypes, it is often difficult to differentiate between them clinically due to substantial symptom overlap between primary and secondary insomnia. Additionally, it is often difficult to assign causation to any single factor or establish the precise nature of the relationship between insomnia and a co-occurring condition.³ Indeed, insomnia frequently persists despite resolution of other conditions and often requires independent treatment.^{5,6} Some studies have shown that cotreatment of insomnia and co-occurring conditions yield more rapid improvement of both conditions compared with independent treatment of only the co-occurring condition, supporting the treatment of insomnia as an independent condition in patients considered to have the “secondary” condition due to a primary medical or mental cause.^{7,8} Other than the different treatments required for distinctive comorbidities, effective treatments for insomnia generally are the same across “primary” or “secondary” insomnia.^{1,2,9,10} It is important to note, however, that for some of the more recent insomnia treatments (eg, dual orexin receptor antagonists [DORAs]), less is known about their effectiveness in patients with insomnia and comorbidities as these newer agents are relatively new and studies of those that have become commercially available have not yet been conducted to evaluate their efficacy specifically in insomnia patients with co-occurring disorders.

In addition to short-term and chronic classifications, insomnia can also be categorized into subtypes

(phenotypes) based on the timing of the sleep difficulty occurrence.^{11–13} The main categories are difficulty falling asleep (sleep-onset insomnia), difficulty staying asleep (sleep-maintenance insomnia), early-morning asleep signalings coupled with an inability to return to sleep (terminal insomnia), and combined insomnia (more than one of these categories).^{13,14} Additionally, insomnia with objective short sleep duration (<6 hours by polysomnography) has also been identified as an important phenotype.¹⁵ Identification of a patient’s specific insomnia phenotype (eg, sleep-onset versus sleep-maintenance insomnia) may help guide treatment.¹⁴ It is critically important to recognize the dynamic nature of insomnia, and that the stability of a patient’s insomnia symptoms may vary over time.¹³ A 4-month longitudinal study of general practice attenders found that only 17–51% of the patients reported the same sleep complaint(s) at follow-up.¹² Similarly, in a large, longitudinal community-based study of individuals with current or lifetime insomnia, approximately 60% retained the same insomnia symptom phenotype after 1 year; 40% had a different phenotype.¹⁴ The demonstration in these studies that many patients have conversion of their insomnia symptoms^{12,14} highlights that ongoing assessment is needed to monitor for potential changes in the presenting insomnia symptoms.

In addition to impairing sleep, insomnia can cause adverse consequences across domains of physical and mental health, quality of life, and daytime function. Certainly, lack of sleep/insomnia is associated with increased risk of premature mortality¹⁶ and linked to serious somatic and psychiatric conditions, including cardiovascular and cerebrovascular disease, diabetes, hypertension, obesity, depression, and post-traumatic stress disorder.^{16–24} Further, insomnia may not necessarily be ameliorated when comorbidities are otherwise successfully managed. A common example of this is persistent sleep difficulties in a person with major depressive disorder despite the substantial relief of mood symptoms with antidepressant medication.²⁵ Insomnia disorder can also have direct adverse effects on mood and behavior, including risk for incident depression and anxiety,²⁶ as well as a strong link with suicidal ideation.²⁷ Treating insomnia can prevent depression in many “at-risk” individuals not depressed at baseline.²⁸

People with chronic insomnia often have more medical problems than those without insomnia.^{29,30} In a large-scale assessment of sleep and health (>9000 elderly individuals), participants with chronic insomnia symptoms and those

reporting rarely or never feeling rested upon asleep signaling were more likely to have respiratory symptoms, physical disabilities, and depressive symptoms; self-reported poorer health; and used more nonprescription medications than those without sleep symptoms.²⁹ Likewise, a retrospective analysis conducted in a community-based population found that adults with insomnia had higher rates of heart disease, high blood pressure, neurologic disease, breathing problems, urinary problems, chronic pain, and gastrointestinal problems.³⁰ Moreover, a retrospective analysis found that more individuals with medical problems reported they had symptoms of chronic insomnia compared to those without medical problems, suggesting considerable comorbidity between insomnia and medical disorders.³⁰

The consequences of insomnia extend even further in that it can also reduce quality of life (QOL), impair neurocognitive functioning,³¹ and pose economic and public health burdens through increased health care utilization, sick leave, and decreased work productivity.^{32,33} An international cross-sectional survey comparing health-related QOL among sufferers of chronic insomnia with good sleepers found that people with insomnia reported significantly reduced health-related QoL as assessed using the 36-Item Short-Form Health Survey.^{34,35} Likewise, in the National Epidemiologic Survey on Alcohol and Related Conditions-III (2012–2013) found that the annual loss of quality-adjusted life-years associated with insomnia was significantly greater than other medical conditions assessed, including arthritis, depression, and hypertension.³⁶

In industrialized nations, chronic insomnia disorder is estimated to occur in 5–10% of the general population, although some studies suggest that the rate is as high as 33% of the adults.^{2,37} Despite the large percentage, a relatively low proportion consult a health care provider about their sleep.^{38–40} The low consultation rate may be due to limited knowledge among the general population about the safety and availability of insomnia treatments that can be offered by clinicians. Self-treatment with over-the-counter sleep aids, as well as alcohol, is not unusual.⁴¹ Owing to this low rate of consultation about insomnia, health care providers may not consistently recognize and diagnose the condition,³⁹ which likely contributes to undertreatment of insomnia.^{13,39,42}

Given the potential negative impact of chronic insomnia on patients, clinicians' knowledge of effective treatment strategies is important. To provide such a resource

for clinicians, the authors developed this narrative review to summarize the pathophysiology of insomnia and new developments in non-pharmacologic and pharmacologic interventions.

Pathophysiology of Insomnia

Several models of insomnia etiology and pathophysiology have been proposed, most of which suggest that both external stressors as well as internal psychologic factors have a role.¹⁸ For example, the Spielman model of insomnia, also known as the “Three Factor” or “Three P” model, comprises three factors: predisposing, precipitating, and perpetuating.⁴³ Predisposing factors are traits that predispose an individual to insomnia such as sleep reactivity,^{44,45} personality traits including the tendency to worry or ruminate, and social factors such as sleep schedule incompatibility between bed partners or social pressures leading to a nonpreferred sleep schedule.⁴⁵ The combination of predisposing factors and precipitating factors (stressors, etc) can lead to the triggering of insomnia.⁴⁴ Chronic insomnia is often maintained by perpetuating factors or behaviors adopted in an attempt to mitigate insomnia symptoms and compensate for sleep deficits, such as going to bed earlier or remaining in bed longer.⁴⁵ These behaviors lead to the dysregulation of sleep homeostasis.⁴⁵ Thus, even after the elimination or improvement in the initial triggering factor, insomnia may persist.⁴⁶

Hyperarousal refers to a state of increased somatic, cognitive, and cortical activation occurring in the central and/or peripheral nervous systems, which often includes both cognitive and emotional processes.⁴⁷ Physiological hyperarousal is associated with short sleep duration in insomnia and activation of both limbs of the stress system (the hypothalamic-pituitary-adrenal axis and the sympathetic system).¹⁸ Consistent with the concept of hyperarousal being associated with stress, many patients with insomnia have increased secretion of adrenocorticotrophic hormone and cortisol compared with healthy individuals.⁴⁶ Although patients with insomnia have overall normal circadian secretory patterns of these hormones, their levels are elevated during the evening and first half of the night, which is consistent with the concept of the bedroom environment being a source of stress and activation in people with insomnia.^{46,48} Patients with insomnia also have higher overall mean sleep metabolic rates (as indicated by overall oxygen use) versus individuals without insomnia.⁴⁹ Similarly, in a functional positron emission tomography study conducted in individuals with and

without insomnia, patients with insomnia had altered glucose metabolism in the brain during sleep and while asleep signaling compared with individuals without insomnia.⁵⁰ This altered metabolism may be related to hyperactivation of arousal mechanisms, which fail to decrease during the wake-to-sleep transition.⁵⁰ This physiological hyperarousal may be related to worry and rumination. Both worry and rumination can also lead to emotional arousal and heightened levels of distress that may activate the stress system, which can contribute to hyperarousal as well as the perpetuation of insomnia.^{51,52} The sleep loss itself may also exacerbate cognitive hyperarousal at night owing to increased wakefulness while lying in bed, which may further exacerbate insomnia and rumination.⁵³

Genetic factors also contribute to the regulation of sleep-wake traits, including sleep duration and timing of sleep.⁴⁷ Current evidence suggests that multiple genes related to brain functioning, arousal regulation, and sleep-wake processes are associated with insomnia.⁴⁷ The first studies conducted to identify genes potentially involved in insomnia examined the role of circadian genes (eg, *CLOCK* and the *Per* genes).⁴⁷ While the overall genetic heritability of insomnia is moderate (30–40%),⁵⁴ only small associations with specific polymorphisms (eg, *Timeless*, *Per2*, and *Per3*) have been identified, suggesting other factors are involved.^{55–58} Indeed, the serotonin transporter-linked polymorphic region (5-HTTLPR) within the serotonin transporter (*SLC6A4*) gene promoter has been implicated as contributing to poor sleep via stress reactivity mechanisms.⁵⁹

Wake/sleep signaling in the brain is driven by two competing sets of brain circuitry: one set of neurotransmitter pathways that promotes sleep and another set that promotes wakefulness.⁶⁰ Transitions between sleep and wake states are dependent on the relative strengths of the two opposing sets of circuits and the end result has been described as akin to a flip-flop switch.⁶⁰ Historically, the most common approach in the pharmacologic treatment of insomnia has been to increase the sleep signal, such as with medications that target the γ -aminobutyric acid (GABA)-A receptor. However, this may not be the best approach physiologically if the insomnia disorder is due to excessive wake signaling occurring at the time when the individual is expected to fall asleep and remain asleep. Decreasing the excessive wake signal has recently become a viable option for medication treatment now that orexin has been identified as a key central promotor of wakefulness.

The orexin neuropeptide signaling system is involved in several physiological functions, particularly sleep and arousal.⁶¹ It is one of the primary systems that maintains wakefulness throughout the day and is involved with the regulation of rapid eye movement (REM) sleep.^{61,62} Two neuropeptides, orexin-A (OX-A) and orexin-B (OX-B), both derived from the common precursor prepro-orexin, activate two postsynaptically localized G protein-coupled receptors, orexin receptor type 1 (OX1R) and orexin receptor type 2 (OX2R).⁶¹ OX1R predominantly interacts with OX-A, whereas OX2R interacts with OX-A and OX-B with similarly high affinity.⁶³ Activation of OX1R and OX2R suppresses the onset of REM sleep and activation of OX2R suppresses non-REM sleep.⁶⁴ If orexin binding to either of its receptors causes arousal (wakefulness), then a substance that acts as an antagonist of OX1R and/or OX2R for an extended period of time can promote sleep by inhibiting the wake-promotion associated with the orexin signaling pathway.^{65,66}

Nonpharmacologic Treatments for Chronic Insomnia

As regards behavioral and psychological treatments for chronic insomnia, clinical practice guidelines from the AASM and the American College of Physicians (ACP) both indicate that standard-of-care should be to at least provide cognitive behavioral therapies for insomnia (CBT-I) as first-line nonpharmacologic treatment.^{9,67} Indeed, CBT-I is the only nonpharmacologic treatment for chronic insomnia that has received a strong recommendation for use by the AASM.⁹ This is likely due in part by the numerous meta-analyses demonstrating robust clinical improvements across numerous sleep-related outcomes using individual, group, internet-based, and self-help CBT-I.⁶⁸

Other nonpharmacologic treatments for the treatment of chronic insomnia have been described in AASM guidelines. Brief therapies for insomnia, stimulus control, sleep restriction therapy, and relaxation therapy, and sleep hygiene (Table 1) are all included as potential treatment options.⁹ However, guidelines acknowledge that usefulness as a treatment for chronic insomnia is often based on a small body of low-quality evidence.⁹ Further, their uses (except for sleep hygiene) are mostly indicated as single-component therapy.

Table I Selected Elements of Good Sleep Hygiene^{155,156}

Element
<ul style="list-style-type: none"> • Keeping a regular sleep/wake schedule • Reducing bedroom noise • Blocking out light • Removing electronic devices from the bedroom • Avoiding daytime napping • Avoiding alcohol, nicotine, and caffeine before sleeping • Avoiding eating dinner late • Regular exercise • Management of stress

CBT-I

CBT-I includes a combination of behavioral interventions: stimulus control therapy to pair the bed with sleep, sleep restriction/compression to increase sleep pressure, relaxation training to reduce hyperarousal, specific cognitive interventions aimed at changing patients' beliefs and attitudes about sleep, and sleep hygiene education.^{69,70} Cognitive strategies (such as cognitive restructuring to identify and address dysfunctional beliefs and unrealistic expectations that can perpetuate insomnia) are used as part of CBT-I to break a cycle that can lead to, maintain, or worsen insomnia.⁷¹ Although cognitive therapy and behavioral therapy alone are effective, patients derive the most benefit when all components of CBT-I are combined with an eight-week course of treatment.^{69,72} It should be noted that CBT-I may be contraindicated in some patients. Sleep loss through sleep restriction in CBT-I may exacerbate comorbidities including seizure disorders, severe obstructive sleep disorder, untreated bipolar disorder, in individuals who are actively suicidal, or in patients with severe parasomnias.^{73–75}

However, not all patients with insomnia disorder may receive sufficient benefit from CBT-I.^{2,10} Indeed, only approximately 30–40% of the patients undergoing CBT-I reach remission.^{76–79} This may be due to the time commitments, the work involved to change sleep habits and schedules, and highly engrained maladaptive beliefs about sleep.^{2,80} Also, an important consideration for CBT-I is that some behavioral treatments may be more appropriate for specific insomnia phenotypes.¹⁴ For example, relaxation may be more useful for sleep onset insomnia, whereas sleep restriction, which increases the pressure for sleep so that sleep inevitably occurs without attention, intention, or effort, may benefit both sleep onset and sleep maintenance insomnia.^{14,81} At times, the typical CBT-I

approach may have limited usefulness because there are too few sessions to address the engrained ways of thinking about and interpreting one's own sleep. This can result in the CBT-I not having a powerful enough effect on the cognitive arousal that occurs at night to provide full remission.

As a caveat, some individuals may have persistent maladaptive beliefs. In an assessment of the effects of CBT-I on sleep-related dysfunctional beliefs, a significant correlation was found between the Athens Insomnia Scale and the Dysfunctional Beliefs and Attitudes About Sleep Scale at baseline and improvements occurred on both scales following CBT-I.⁸² However, the decrease in dysfunctional beliefs and attitudes about sleep was not related to improvements in or decreased severity of insomnia.⁸²

Several barriers prevent CBT-I from being more widely used in clinical practice.⁸⁰ Not all patients are able to gain access to CBT-I because of a lack of availability of providers or cost constraints.^{2,80} In addition, CBT-I requires patients to make a considerable time commitment that they may be unable or unwilling to do. CBT-I also requires a substantial time investment of trained clinicians, which means demand for CBT-I providers often exceeds supply.^{80,83} Both health care practitioners and patients may lack sufficient knowledge about CBT-I and its effectiveness.⁸⁰ Many health care practitioners do not refer their patients for treatment with CBT-I alone, despite CBT-I being a first-line treatment.⁸⁴ A 2015 survey of physicians found that a majority considered medications and other treatment options to be more effective than CBT-I alone.⁸⁴ Thus, more clinician education about CBT-I is necessary and new approaches to its delivery are needed.⁸⁴

A way to increase access to CBT-I is through "stepped care," which is a sequential approach to care management that manages high patient volume via low-intensity treatments initially and progressively moves to more intense treatment based on assessed need.⁸⁵ The initial therapeutic approach should be the least restrictive therapy, readily accessible, the lowest cost, and least inconvenient for patients.⁸⁵ For insomnia treatment, the entry-level treatment would be self-administered CBT-I with more specialized types of CBT-I, such as manualized, small-group CBT-I delivered by nurses, and eventually sleep specialists, including psychologists, at higher levels.⁸⁵

Providing CBT-I via the internet (digital CBT-I) is another possible solution to reduce the time investment and increase accessibility.⁸³ In a randomized controlled trial comparing six guided online CBT-I sessions to six face-to-face CBT-I sessions or wait-listing potential

participants meeting the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition criteria for insomnia, both face-to-face and online interventions had significantly larger treatment effects than the wait-list group.⁸³ The face-to-face treatment yielded a statistically greater treatment effect than the online sessions; however, some improvements were also seen with online CBT-I, suggesting that digital delivery of CBT-I may provide an alternative and/or companion to face-to-face treatment.⁸³ In addition, in a recent meta-analysis of randomized clinical trials comparing digital CBT-I to controls, digital CBT-I significantly reduced insomnia severity and was noninferior to face-to-face delivery.⁸⁶ In fact, digital CBT-I not only improves insomnia but it also has robust and long-lasting effects on improving and preventing depression in patients with insomnia disorder.²⁸

Another new technology useful for facilitating CBT-I is the use of a smartphone application (app) such as CBT-I Coach. CBT-I Coach is a patient-facing app from the US Department of Veterans Affairs, Stanford University's School of Medicine, and the US Department of Defense National Center for Telehealth and Technology designed to enhance CBT-I.⁸⁷ CBT-I Coach is intended for use by patients undergoing CBT-I with a health care professional to act as an educational resource to support, but not replace, the clinician-delivered CBT-I.⁸⁷ The app provides automated sleep diary calculations, sleep education, tools to practice CBT-I skills, and reminders to complete sleep diaries and follow recommendations for time in bed.⁸⁷ These reminders have the potential to reduce treatment dropout and address common adherence issues and, therefore, may improve insomnia outcomes.⁸⁷ Surveys of US Department of Veterans Affairs physicians trained in delivering CBT-I regarding their perceptions of CBT-I Coach 2 years after its launch demonstrated that almost 60% of the clinicians were using the app with their patients and had a favorable view of its utility in improving CBT-I outcomes.⁸⁷

A newer approach to CBT-I therapy itself is to employ a combination of mindfulness-based stress reduction with CBT-I.⁸⁸ This combination approach, which is sometimes called mindfulness-based therapy for insomnia (MBTI),⁸⁹ results in statistically significant and clinically meaningful improvements in multiple nighttime symptoms of insomnia. In addition, significant reductions in presleep arousal, sleep effort, and dysfunctional sleep-related cognitions were observed.⁸⁸ This may be due, in part, to the fact that MBTI was designed to address rumination.⁵² In an

assessment of the long-term effects of the MBTI approach, the benefits of this combined approach on insomnia and symptom severity were generally maintained during the 12-month follow-up.⁹⁰ Use of one or more of these newer approaches to CBT-I, such as digital CBT-I and/or MBTI, may be critical to increase the response of patients to nonpharmacologic treatments for insomnia.

Other new methods of behavioral treatment include CBT-I for specific populations. For example, owing to hormonal, anatomic, and physiological changes, pregnant women tend to experience sleep disturbances and insomnia more frequently than the general population.⁹¹ Since patients and prescribers are likely to have concerns about the use of sleep medication in women who are pregnant or breastfeeding, CBT-I may be a more appropriate and preferred intervention for insomnia during pregnancy and the postpartum period.^{91,92} In a randomized, unmasked, controlled trial comparing CBT-I to control insomnia therapy (modified pseudodesensitization therapy for insomnia) in women with insomnia disorder between 18 and 32 weeks of pregnancy, CBT-I was associated with significantly faster remission of insomnia. In addition, significantly greater improvements in insomnia severity, total wake time, and Edinburgh Postnatal Depression Scale scores versus control therapy ($p < 0.01$ for all) were also observed.⁹³ More women treated with CBT-I attained remission of insomnia than with control therapy with a favorable effect size.^{93,94}

Similarly, the hormonal fluctuations associated with menopause mean that postmenopausal women also experience insomnia at higher rates than the general population.⁹¹ In a clinical trial comparing CBT-I to sleep restriction therapy and sleep hygiene education to treat insomnia in postmenopausal women, CBT-I was associated with greater improvement in Insomnia Severity Index scores, increased improvement in sleep duration, and greater remission rates than sleep restriction therapy or sleep hygiene education.⁹⁵ In addition, both CBT-I and sleep restriction therapy improved fatigue, energy, sleepiness, and work function.⁹⁶ Whereas sleep restriction therapy and sleep hygiene education improved resilience to physical problems, CBT-I was associated with substantial improvements in emotional well-being and resilience to both physical and emotional problems.⁹⁶ CBT-I also reduced depressive symptoms, dysfunctional beliefs about sleep, and presleep somatic hyperarousal in

postmenopausal women more than sleep restriction therapy and sleep hygiene education.⁹⁷

Forehead Temperature Cooling

An alternative nonpharmacologic approach to treating insomnia is to reduce the increased activity and frontal cerebral metabolism that occurs during hyperarousal in patients with insomnia by application of a cooling stimulus to the scalp.⁹⁸ Application of a novel forehead temperature regulating device that can be adjusted to deliver frontal cerebral thermal therapy ranging from 14°C to 16°C (57–61°F) produced improvements in latency to persistent sleep, latency to stage 1 non-REM sleep, latency to stage 2 non-REM sleep, and an increase in the number of minutes of sleep during the first hour of sleep with a trend to reduce latency to stage 3 non-REM sleep. These improvements were observed in men and women with primary insomnia (defined per Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition) without major syndromal mood, anxiety, psychotic, substance use or current sleep disorders other than insomnia.⁹⁸ Similar improvements in insomnia, as well as improvements in anxiety and depressive symptoms, were observed when a forehead cooling device was studied in veterans with chronic insomnia disorder and comorbid medical and psychiatric conditions.⁹⁹ These results suggest that this device could be useful for patients who prefer nonpharmacologic methods of treating insomnia, but are unable to use CBT-I, or as adjunctive therapy for other treatments although the long-term efficacy and safety of this approach needs to be evaluated.^{98,99}

Pharmacologic Treatments for Chronic Insomnia

Treatment Guidelines and Recommendations for Pharmacologic Treatments

Not all patients with chronic insomnia disorder benefit from CBT-I alone or have access to this modality.² Treatment guidelines from both the APA and the ACP recommend health care practitioners use a shared decision-making approach with patients when considering whether to use or add pharmacologic therapy.^{2,67} This approach should include a discussion of the benefits, risks, and costs associated with the use of medications.⁶⁷

The pharmacologic therapies listed in the treatment guidelines from the ACP include those medications approved by the US Food and Drug Administration

(FDA) for treatment of insomnia, such as benzodiazepines (BZDs) and the non-BZD hypnotic “Z-drugs”, the DORAs suvorexant, the melatonin receptor agonist ramelteon, and the first-generation histamine antagonist doxepin, as well as off-label use of other agents.⁶⁷ However, these guidelines note that there was insufficient evidence to determine the efficacy or the benefit:risk ratio of many of these therapies, and therefore the guidelines do not make any specific recommendations for any single medication.⁶⁷

Similarly, the AASM makes suggestions about whether specific pharmacologic therapies should be used for the treatment of sleep onset and/or sleep maintenance insomnia.² Several medications including different BZD receptor agonists and BZDs are recommended for treating both insomnia subtypes.² Therapies recommended specifically for use in sleep onset insomnia include the BZD receptor agonist zaleplon, the BZD triazolam, and the melatonin agonist ramelteon, whereas recommended therapies for sleep maintenance insomnia include suvorexant and doxepin.² However, trazodone, the anticonvulsant tiagabine, and over-the-counter medications such as diphenhydramine, melatonin, L-tryptophan, or valerian are not recommended for treating either type of insomnia.² All of the specific recommendations by the AASM are classified as “weak” because they are based on the degree of confidence in the availability of efficacy data, quality of efficacy data, and other considerations, including potential risks and patient preferences.² The weak classification of these recommendations should not be misinterpreted as meaning that sleep-promoting medications are not efficacious or indicated for insomnia treatment, just that the existing data limit the degree of confidence in these recommendations.²

It is important to note that the most recent ACP and AASM guidelines predate the approval of the DORA lemborexant, which was approved in the United States in December 2019, in Japan in January 2020, and in Canada in November 2020.^{100,101}

In addition, the 2019 American Geriatrics Society Beers Criteria for Potentially Inappropriate Medication Use in Older Adults indicate that older adults should avoid BZDs and non-BZD hypnotic “Z-drugs” because of increased sensitivity to these medications and the increased risk of cognitive impairment, delirium, falls, fractures, and motor vehicle accidents.¹⁰² Older patients should also avoid doxepin doses >6 mg owing to the potential for orthostatic hypotension.¹⁰²

Pharmacologic Agents Used for Treating Insomnia

Historically, pharmacologic agents such as opioids, herbal preparations, barbiturates, alcohol, and pain medications have been used to treat insomnia or to manage sleep disturbances.^{2,38,39} Whereas alcohol can act as a sedative, intake of large amounts of alcohol prior to sleep can cause changes in sleep architecture and disrupted, poor-quality sleep, which can contribute to insomnia.¹⁰³ Many of the other early therapies were effective, but they were associated with next-day residual effects, development of physiological tolerance, and dependence, adverse effects following long-term use, withdrawal effects, and concerns regarding abuse and misuse.^{2,13} In addition, health care practitioners often cite concerns about safety and dependency as key reasons why they hesitate to treat insomnia with medications, particularly BZDs and the non-BZD hypnotics.²

Hypnotics

Clinical trials of hypnotic medications often select participants based on their specific insomnia phenotypes, which could affect the indications and labeling of these agents based on whether they affect sleep onset difficulties, sleep maintenance problems, or both.¹⁴ The AASM treatment guidelines for insomnia also make similar distinctions regarding the use of pharmacologic agents.^{2,14} For example, the BZD receptor agonists zolpidem and zaleplon are often prescribed for patients with sleep onset insomnia because they are fast acting and have relatively short half-lives.^{13,104} In addition, unlike BZDs (which reduce stage 3 and 4 sleep), non-BZD receptor agonists do not consistently alter sleep architecture, although high doses may reduce REM sleep.¹⁰⁵ However, the short half-life of these agents may not be as effective for sleep maintenance problems,¹³ although zolpidem is also available as an extended-release formulation, which has demonstrated efficacy on sleep onset and sleep maintenance outcomes.¹⁰⁶

GABA is the main inhibitory transmitter in the mammalian brain and works through GABA-A and GABA-B receptors.¹⁰⁷ BZDs and non-BZD hypnotics act as positive allosteric modulators on GABA-A receptors, which are widespread throughout the brain, to enhance the action of GABA and cause sedation by prolonging the duration of inhibitory postsynaptic currents.¹⁰⁷ This increase in GABA transmission has an inhibitory effect on norepinephrine transmission through wake-promoting pathways,

which causes sedation and inhibition of wake-promoting regions of the brain, thereby promoting sleep.¹⁰⁸

As discussed, stability of a patient's insomnia symptoms may vary over time.^{12–14} Whereas follow-up and re-assessment of the presenting pattern of insomnia should be conducted regularly,¹⁰⁴ using agents with effects on both sleep initiation and maintenance could address the lack of stability in these temporal insomnia phenotypes. This could also minimize the need for patients to switch medications if their symptoms change over time.

An optimal pharmacologic treatment for insomnia should not only improve sleep maintenance, sleep onset, sleep quality, and daytime functioning, but also be safe and effective for long-term use without next-day residual effects or symptoms of tolerance, rebound, or dependence.¹³ The treatment should also normalize sleep architecture by reducing sleep onset latency (SOL), wake after sleep onset (WASO), awakenings, arousals, and frequency and duration of wake episodes, as well as maintaining normal sleep stage amounts and distribution. Some of the medication therapies mentioned in treatment guidelines may have limited efficacy in treating all phenotypes of insomnia and/or they may be limited by safety and tolerability concerns. For example, whereas specific BZDs are indicated for treating patients with sleep onset insomnia, sleep maintenance insomnia, or both sleep onset and sleep maintenance insomnia, this class of agents can cause next-day sedation and cognitive impairment, and is associated with an increased risk for abuse and dependence.¹³ In addition, in 2019, the FDA added boxed warnings about the possibility of complex sleep behaviors, such as sleepwalking and sleep driving, to prescribing information and patient medication guides for eszopiclone, zaleplon, and zolpidem.¹⁰⁹ Thus, formation of a pharmacologic treatment plan is directed by several factors including perhaps most prominently, symptom pattern (eg, difficulty with sleep onset vs sleep maintenance), as well as treatment efficacy (eg, reduced SOL vs WASO) and side effects.¹⁰

Dual Orexin Receptor Antagonists: A New Class of Pharmacologic Treatment for Insomnia

The DORAs block OX1R and OX2R and promote sleep through a decrease in arousal signaling, which, as has been noted, is a different therapeutic approach for insomnia.^{65,66,110,111} Several DORAs have been evaluated for the treatment of insomnia preclinically and in clinical

trials, with two DORAs currently approved for use (Table 2).^{66,100,101,112} Of note, orexin receptor antagonists do not adversely affect sleep architecture.^{113,114} They have been found to shorten REM latency and increase TST, mainly by increasing the time spent in REM sleep.^{113–115} However the percentage of TST spent in non-REM sleep is left unchanged or possibly lowered.^{113–115} They do not appear to be associated with tolerance, withdrawal, or rebound insomnia if abruptly discontinued.^{116–118} Importantly, the mechanism of action of DORAs suggests that daytime sleepiness would be further exacerbated in patients with narcolepsy (as they already have impaired orexin-mediated wake signaling).^{119–121} Accordingly, DORAs are contraindicated in these patients.

After its initial approval in Japan,¹¹² suvorexant was the first DORA to receive approval in the United States, where it is indicated for the treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance.¹²² Suvorexant has received subsequent approvals in Australia and Canada.^{123,124} The efficacy and safety of suvorexant were evaluated in two randomized double-blind, placebo-controlled, parallel-group Phase 3 clinical trials conducted for 3 months, as well as in one randomized, placebo-controlled, parallel-group phase 3 clinical trial conducted for 1 year.^{116,117} In both the 3-month trials, the higher dose, suvorexant 40/30 mg (40 mg in patients 18–64 years of age and 30 mg in patients ≥65 years of age; not approved), demonstrated superiority versus placebo in improving patient-

reported subjective total sleep time (sTST), subjective time to sleep onset (sTSO), subjective WASO (sWASO) and polysomnography (PSG)-measured wakefulness after persistent sleep onset when assessed at 1 week, 1 month, and 3 months.¹¹⁶ Suvorexant 40/30 mg also demonstrated superiority versus placebo in improving PSG-based latency to onset of persistent sleep (LPS) in both trials when assessed at 1 week and 1 month, but in only one trial when assessed at 3 months.¹¹⁶ The lower dose (suvorexant 20/15 mg; 20 mg in patients 18–64 years of age and 15 mg in patients ≥65 years of age) was superior to placebo on sTST and wakefulness after persistent sleep onset at all study time points, and on sTSO and LPS for most time points.¹¹⁶ In the 1-year trial, suvorexant 40/30 mg significantly improved sTST and sTSO over the first month of treatment versus placebo.¹¹⁷ However, long-term data on approved doses of suvorexant are not available. Significant improvements with suvorexant 40/30 mg versus placebo were also observed for sWASO at 1 month, and for sTST, sTSO, and sWASO at 12 months.¹¹⁷ Additionally, in a four-week, double-blind, placebo-controlled study in 285 patients with mild to moderate Alzheimer's disease, suvorexant (10–20 mg) improved TST as determined by PSG.¹²⁵

Suvorexant was well tolerated in the phase 3 clinical trials with low rates of patients discontinuing because of adverse events or experiencing serious adverse events.^{116,117} Incidences of rebound insomnia, next-

Table 2 Orexin Receptor Antagonists Approved or in Development for Treatment of Insomnia Disorder

Name	Development Status	Doses	Half-Life	Use in Special Populations
Suvorexant (BELSOMRA®) ¹²²	Approved	5 mg, 10 mg, 15 mg, 20 mg	Terminal half-life: approximately 15 hours (range, 10–22 hours)	<ul style="list-style-type: none"> • Not recommended in patients with severe hepatic impairment • Safety and effectiveness have not been established in pediatric patients
Lemborexant (DAYVIGO®) ¹³¹	Approved	5 mg, 10 mg	Effective half-life for lemborexant 5 mg: 17 hours; effective half-life for lemborexant 10 mg: 19 hours	<ul style="list-style-type: none"> • Not recommended in patients with severe hepatic impairment • Safety and effectiveness have not been established in pediatric patients
Daridorexant ¹⁵⁷	Filing in preparation	10 mg, 25 mg, 50 mg ^{145,146}	Elimination half-life: 5.6–8.5 hours ¹⁵⁸	<ul style="list-style-type: none"> • Prescribing information not available
Seltorexant ¹⁴⁹	Phase 3	20 mg	Half-life: 2–3 hours ¹⁴⁹	<ul style="list-style-type: none"> • Under development for use in patients with major depressive disorder and insomnia • Prescribing information not available

morning effects, and withdrawal signs or symptoms were low in the clinical trials.^{116,117} Similar results were reported in a pooled analysis of the 3-month data from the three phase 3 clinical trials.¹²⁶ Overall benefit-to-risk ratio for suvorexant treatment is favorable, as measured by number needed to treat, number needed to harm, and likelihood to be helped or harmed.¹²⁷

Suvorexant was also assessed in patients with mild to moderate obstructive sleep apnea (OSA).¹²⁸ This is of interest because some current insomnia medications, such as BZDs, are associated with respiratory depression, which raises safety concerns, particularly in individuals with compromised respiratory function, such as those with OSA. In this randomized, double-blind, placebo-controlled, crossover study, suvorexant 40 mg (twice the 20-mg maximum approved dose) did not appear to affect respiratory safety during sleep.¹²⁸

In two clinical studies evaluating performance of next-morning driving by using a 1-hour standardized highway driving test in normal traffic conducted 9 hours after dosing in healthy volunteers 23–64 or 65–80 years of age, no clinically meaningful residual effects of suvorexant on driving performance were found versus placebo.^{129,130} However, the authors noted that some individuals experienced somnolence and prematurely stopped their driving tests.^{129,130} Because of concerns related to sleep paralysis, hypnagogic hallucinations, cataplexy, and suicidal ideation, the FDA only approved lower doses of suvorexant (5, 10, 15, or 20 mg).^{112,122} Suvorexant is a schedule IV controlled substance.

In 2019, lemborexant became the second DORA to receive approval in the United States for the treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance in adults.¹³¹ Similar to suvorexant, lemborexant is a schedule IV controlled substance. Lemborexant is also approved in multiple countries, including Japan and Canada, for the treatment of insomnia.¹⁰¹ In a Phase 2, multicenter, randomized, double-blind, placebo-controlled, Bayesian, adaptive, parallel-group study of lemborexant (1, 2.5, 5, 10, 15, or 25 mg) for 15 nights, patients (≥ 18 years of age) receiving lemborexant at doses ≥ 5 mg had significantly greater improvements in sleep efficiency, subjective sleep efficiency, LPS, and subjective SOL versus placebo.¹³² In a randomized, double-blind, parallel-group, placebo-controlled and active-comparator, phase 3 study in females (≥ 55 years of age) and males (≥ 65 years of age) with insomnia disorder, lemborexant (5 mg or 10 mg) demonstrated statistically significantly greater improvements on objective

(PSG-based) measures of sleep onset and sleep maintenance compared with placebo and with zolpidem tartrate extended release (6.25 mg) as assessed at 1 month.¹¹⁸ Additionally, changes from baseline in subjective (sleep diary-based) SOL were greater and statistically significant with lemborexant compared with placebo and with zolpidem as assessed at the end of 1 month.¹¹⁸ Similarly, in a 12-month, randomized, double-blind, parallel-group, phase 3 study, which was placebo-controlled for the first 6 months, patients (≥ 18 years of age) treated with lemborexant (5 mg or 10 mg) had significantly greater decreases from baseline in the primary endpoint of subjective SOL compared with placebo-treated patients as assessed at the end of 6 months.¹³³ Lemborexant also demonstrated significant benefit on sWASO, subjective sleep efficiency, sTST, and quality of sleep compared with placebo at the end of the 6-month placebo-controlled period.¹³³ Taken together, these results indicated lemborexant exhibits efficacy that is sustained long term.

In both phase 3 clinical trials of lemborexant, the rate of serious treatment-emergent adverse events (TEAEs) was low and no deaths occurred; lemborexant was well tolerated, with most TEAEs rated as mild or moderate in severity.^{118,133} Overall, the most prominent adverse event was somnolence. Similarly, in an analysis of the pharmacokinetic, pharmacodynamic, and safety data from three double-blind, placebo-controlled Phase 1 studies, lemborexant was well tolerated with no evidence of clinically relevant next-morning residual sleepiness.¹³⁴ Overall benefit-to-risk ratio for lemborexant treatment is favorable, as measured by number needed to treat, number needed to harm, and likelihood to be helped or harmed.¹³⁵

Lemborexant was assessed in otherwise healthy adult and elderly participants with mild OSA.¹³⁶ In this phase 1, randomized, double-blind, placebo-controlled, two-period crossover study, there were no significant differences on measures of respiratory safety including the apnea-hypopnea index and peripheral oxygen saturation for lemborexant 10 mg versus placebo.¹³⁶

In an analysis of nine clinical studies conducted during the clinical development program of lemborexant, which included assessments of next-morning or across-the-day residual medication effects, lemborexant did not negatively impact next-day functioning in healthy individuals or patients with insomnia.¹³⁷ Lemborexant treatment was associated with significantly greater alertness for up to 6 months versus placebo as determined by next-morning sleep diary ratings.¹³⁷ In addition, whereas zolpidem differed from placebo on multiple measures of the Cognitive

Performance Assessment Battery, power of attention was the only measure that found significantly decreased performance with lemborexant compared with placebo, and only in one of two studies.¹³⁷ Similarly, lemborexant treatment was also not associated with statistically significant or clinically meaningful next-day impairment in a randomized, double-blind, double-dummy, placebo- and active-controlled, four-period, incomplete crossover study conducted in healthy volunteers to determine effects on driving performance during a standardized highway driving test in normal traffic.¹³⁸ However, while there were no stopped drives during the lemborexant conditions, driving ability was impaired in 2 of the 32 participants receiving lemborexant 10 mg, and the product label recommends that patients who take the 10-mg dose should be advised about the possibility of next-morning driving impairment due to individual variation in lemborexant sensitivity; of note, the recommended starting dose of lemborexant is 5 mg.¹³⁹ The effects of lemborexant, zolpidem, and placebo on auditory awakening threshold and postural stability in the middle of the night and upon morning awakening were assessed in healthy females (≥ 55 years of age) and males (≥ 65 years of age).¹⁴⁰ Neither lemborexant nor zolpidem impaired the ability of participants to awaken to auditory signals in the middle of the night (4 hours post-dose).¹⁴⁰ While both lemborexant and zolpidem induced significantly more postural instability than placebo in the middle of the night (4 hours post-dose), lemborexant was associated with significantly less postural instability than zolpidem.¹⁴⁰ In the morning (8 hours post-dose), postural instability was observed with zolpidem compared with placebo, but not for lemborexant compared with placebo.¹⁴⁰ An open-label pilot study (NCT04009577, E2006-A001-312) has been carried out to evaluate prespecified dosing approaches for direct transition from zolpidem to lemborexant.^{141,142} The primary endpoint of the study, which was recently completed, is the proportion of patients with insomnia who successfully transition from intermittent or frequent zolpidem use to lemborexant 5 mg or 10 mg after 2 weeks of treatment.¹⁴² Following the 2-week titration period, 43 out of 53 subjects (81.1%) transitioned to lemborexant.

Daridorexant is a DORA that is in development for the treatment of insomnia; the New Drug Application was submitted in January 2021. Recently, results from two phase 2 trials evaluating the efficacy and safety of daridorexant were published.^{143,144} One trial was conducted to evaluate the dose-response relationship of daily

daridorexant (5, 10, 25, or 50 mg) for 30 days compared with oral placebo or 10 mg zolpidem in adults (≤ 64 years of age) with insomnia disorder.¹⁴³ Daridorexant induced a dose-dependent reduction in WASO and subjective latency to sleep onset with no clinically relevant treatment-related serious adverse events and a low rate of discontinuation due to adverse events.¹⁴³ The second trial was conducted to assess the dose-response of daridorexant (5, 10, 25, and 50 mg) versus placebo in elderly patients with insomnia.¹⁴⁴ Daridorexant-treated patients had statistically significant, dose-dependent improvements in WASO and LPS, with similar rates of TEAEs as those patients treated with placebo.¹⁴⁴

The phase 2 trials supported continued development of daridorexant to phase 3. Positive topline results of the first pivotal trial, which was conducted to evaluate daridorexant 25 and 50 mg in adult and elderly patients with insomnia, were announced in April 2020.¹⁴⁵ Daridorexant treatment improved both objective and subjective sleep parameters and daytime performance over 3 months without evidence of residual effects, rebound insomnia, or withdrawal symptoms after discontinuation.¹⁴⁵ In July 2020, topline results from the second phase 3 study, which examined daridorexant 10 and 25 mg in adult and elderly patients with insomnia were announced.¹⁴⁶ These results were in agreement with the previous findings and demonstrated improvements on objective and subjective sleep measures (sleep onset, sleep maintenance, and sTST) with daridorexant treatment. Additionally, positive effects on daytime functioning were observed, with no reports of morning sleepiness or evidence of rebound or withdrawal symptoms.¹⁴⁶

Almorexant was the first DORA to undergo phase 3 clinical evaluation, but was ultimately discontinued because of safety findings of abnormally elevated liver enzymes.⁶⁶ Other DORAs that had been in clinical development, SB-649868 and filorexant (MK-6096), completed phase 2 trials but have since been discontinued.^{147,148} Seltorexant (JNJ-42847922) is an OX2R antagonist currently in phase 3 clinical development for the treatment of insomnia and major depressive disorder.¹⁴⁹ A phase 2b active- and placebo-controlled study in adult and elderly subjects with insomnia disorder found that seltorexant at 5, 10 and 20 mg significantly improved LPS versus placebo.¹⁵⁰ Greater improvement in LPS was also seen with seltorexant 20 mg compared with zolpidem.¹⁵⁰ Additionally, seltorexant improved LPS and TST, and SE compared with placebo in an exploratory crossover study

in subjects with antidepressant-treated major depressive disorder and who have persistent insomnia.¹⁵¹

Practical Advice for Clinicians Treating Patients with Pharmacologic Therapies

Abrupt changes in treatment with older-generation hypnotics can lead to rebound insomnia with worsened sleep.¹⁵²

This is of practical concern because a common scenario is that of a person with chronic insomnia whose medication treatment has ceased to be effective because of the development of physiological tolerance. A new medication (such as an orexin receptor antagonist) may be prescribed, but the new intervention may fail if the old hypnotic is abruptly discontinued because there is no cross-tolerance between the older medications (such as BZD and non-BZD hypnotics) and orexin receptor antagonists. The patient may misinterpret this failure as due to inefficacy of the new therapy rather than the result of abrupt discontinuation of the prior medication. A gradual tapering off of the old hypnotic may help to avoid rebound insomnia, particularly when the older agent was taken every night for months or years.¹⁵² If patients choose to switch medications, health care practitioners should discuss how to manage this change. A practical approach to managing changes in insomnia medication includes providing patients written information about medication discontinuation, including a discussion of change in the subjective experience they may have with the new medication, using stepped care with a tailored approach to the amount of intervention, and adding CBT-I or behavioral therapies, which may help improve the transition during discontinuation of a hypnotic therapy.^{152,153} Additional research is needed to optimize the process of changing therapies, especially when patients are switching classes of pharmacologic treatments.

Because benzodiazepines can depress respiratory drive, they are generally avoided as hypnotics in patients with OSA. Although the safety of orexin-receptor antagonists has been established in patients with mild-moderate OSA,^{128,136,154} further studies characterizing the use of orexin receptor antagonists in insomnia disorder in people with more severe forms of OSA would also help better inform clinical practice.

In conclusion, several advances in the nonpharmacologic and pharmacologic treatment options for chronic insomnia have occurred recently. The newest delivery enhancements for CBT-I, such as the stepped-care approach, digital delivery of CBT-I, and the inclusion of mindfulness-based stress

reduction as well as the novel approach of forehead cooling, may provide patients with insomnia greater access to and efficacy with nonpharmacologic interventions. In addition, the availability of the new DORA medication class means that more pharmacologic options are available for patients. These new therapies may improve sleep outcomes with fewer TEAEs and less risk of next-morning residual sleepiness or impairments. Additional studies are needed to evaluate the efficacy of combining newly available pharmacologic treatments, such as DORAs, with nonpharmacologic treatments. If patients choose to change classes of therapies from the older pharmacological approaches, health care practitioners need to educate patients to help them manage the transition and avoid rebound insomnia, and thus improve patient satisfaction with their insomnia therapy.

Abbreviations

AASM, American Academy of Sleep Medicine; ACP, American College of Physicians; APA, American Psychiatric Association; BZD, benzodiazepine; CBT-I, cognitive behavioral therapies for insomnia; DORA, dual orexin receptor antagonist; FDA, US Food and Drug Administration; GABA, γ -aminobutyric acid; LPS, latency to onset of persistent sleep; MBTI, mindfulness-based therapy for insomnia; OSA, obstructive sleep apnea; OX-A, orexin-A; OX-B, orexin-B; OX1R, orexin receptor type 1; OX2R, orexin receptor type 2; PSG, polysomnography; QOL, quality of life; REM, rapid eye movement; SOL, sleep onset latency; sTSO, subjective time to sleep onset; sTST, subjective total sleep time; sWASO, subjective wake after sleep onset; TEAE, treatment-emergent adverse event; WASO, wake after sleep onset.

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