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Insomnia Neurobiology and Therapy

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Abstract

Insomnia is highly prevalent in clinical practice and can present independently or alongside other medical and mental health disorders. Insomnia is a risk factor for the development and exacerbation of medical and mental health conditions. Behavioral and pharmacological treatments for insomnia are available. In this article, we review important mechanisms associated with insomnia including the hyperarousal model of insomnia and the neurobiology of insomnia. We then review the treatment approaches and management strategies for insomnia including cognitive behavioral therapy for insomnia, transcranial magnetic stimulation, pharmacologic treatment, and adjunctive treatments for insomnia.

Keywords
- insomnia
- cognitive behavioral therapy
- sleep
- hyperarousal

Insomnia occurs in up to a third of the adult population worldwide.[1] Chronic insomnia (CI) is defined by the International Classification of Sleep Disorders, third edition (ICSD-3) as a persistent difficulty with sleep initiation or maintenance, which occurs despite adequate opportunity and circumstances for sleep, accompanied by significant discomfort and/or diurnal functional impairment in different areas of life. The sleep difficulty must occur at least three times a week over a minimum period of 3 months to be considered chronic. The perception of poor sleep quality is associated with daytime symptoms including daytime sleepiness, fatigue, somatic symptoms (e.g., head or body aches), mood disturbance, compromised cognitive or occupational function, concerns about sleep, or dissatisfaction with sleep. As such, insomnia is considered a 24-hour condition due to the disturbed sleep at night and associated distress or impaired functioning during the day.

Longitudinal studies have shown individuals with CI show a heightened risk for development of acute myocardial infarction,[2] and short sleep duration has been linked to cardiovascular disease when assessed subjectively[3] and objectively (i.e., polysomnography).[4] Additionally, insomnia arises frequently in neurological and mental health disorders. Insomnia ranges in prevalence from 25 to 60% of patients with multiple sclerosis, Alzheimer's disease, traumatic brain injury, epilepsy, or stroke.[5] A meta-analysis showed people with insomnia have a 2-fold increased risk to develop depression as compared with people without insomnia[6] and sleep disturbance is considered a core symptom of mood disturbance. Insomnia is regarded as an independent risk factor for sick leave, work disability, and reduced work performance.[7]

CI carries substantial economic burden including direct costs related to treatment which have been estimated at $13.9 billion annually in the United States.[8] When indirect costs are factored in (e.g., lost productivity, insomnia-related accidents, increased medical problems), the annual costs exceed $100 billion.[8] Individuals with insomnia demonstrate increased rates of health care utilization, which contributes to increased insomnia-related health care costs. When compared with good sleepers, individuals with insomnia have more visits to general clinicians as well as specialists, twice as many hospitalizations and use more medication than good sleepers.[9,10] The health and economic costs underscore the importance of understanding insomnia from a neurobiological perspective and identification of effective treatments.

In this review, we discuss the basics of physiological and psychological arousal and the associated neurobiology of CI. We also review current treatment modalities of CI.

Evolution of Chronic Insomnia

An American Historian and Academic focused on the history of human sleep, Dr. Roger Ekirch's widely accepted theory of

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segmented sleep, with two distinct phases separated by a period of wakefulness, may provide valuable insights into the neurobiology of sleep maintenance insomnia by reframing our understanding of "normal" sleep patterns and how modern advancements and expectations might conflict with human neurobiology.[11] A period of wakefulness between first and second sleep in preindustrial societies was considered natural and productive, not pathological. Sleep was divided into two distinct periods (first, 8–11 pm, and second sleep, 2 am to sunrise), separated by 1 to 2 hours of quiet wakefulness in the middle of the night. Activities during this time included prayer, reflection, chores, or even social interactions. Conversely, today's sleeper strives for uninterrupted sleep. Wakefulness during the night, which may align with this historical pattern of segmented sleep, is now often diagnosed as insomnia, poor sleep, or restless sleep.

There are two types of CI: delayed initial sleep latency and sleep maintenance insomnia (where a person wakes up in the middle of the night and can't get back to sleep for a couple of hours). However, if there is not an identified underlying undiagnosed or untreated medical disorder (e.g., sleep apnea or pain) causing awakening, it could simply be due to reemergence of an innate tendency. The diagnosis of CI requires daytime symptoms that are not secondary to a medical or environmental issue.

CI is the most common sleep disorder seen in sleep clinics by far, and prevalence increased by 32% during the COVID-19 pandemic[12] leading to creation of a dedicated name (COVID-somnia).[13] Factors that contribute to CI include poor sleep practices such as the use of electronics at bedtime, inconsistent sleep–wake schedules, and inadequate light exposure. The rise of virtual or remote work has exacerbated these issues by disrupting natural light exposure, which is essential for regulating circadian rhythms. Additionally, excessive screen time, particularly exposure to blue light, suppresses melatonin production, making it harder to fall asleep. Stress, anxiety, and the lack of clear boundaries between work and rest in home settings further feed into the cycle of CI, creating a feedback loop that disrupts both sleep quality and overall health. In an age dominated by politics, current events, and social media, many people feel increasingly isolated. Social media often exacerbates loneliness as individuals compare themselves to heavily filtered and curated images that rarely reflect the whole story. Dr. Vivek Murthy, the U.S. Surgeon General and author of *Together: The Healing Power of Human Connection in a Sometimes Lonely World*, highlights loneliness as a profound public health crisis, linking it to increased risks of anxiety, depression, and heart disease, all of which can contribute or exacerbate CI.[14] Lastly, consumer devices, now widely available and frequently used, have been linked to the emergence of orthosomnia which is a type of insomnia increasingly observed in sleep centers that stems from anxiety about achieving "perfect sleep" as tracked by wearable technology. Interestingly, nomophobia, defined as the fear of being without access to a mobile phone, is also gaining recognition as an emerging psychological condition and societal phenomenon, further highlighting the pervasive impact of technology on mental health and sleep, particularly worsening insomnia.[15]

Physiological and Psychological Arousal in Insomnia

Sleep is a naturally unfolding process that emerges when the homeostatic sleep pressure, which refers to the buildup of a "sleep drive," is strong and aligns with the endogenous circadian rhythm, and the mind is quiet. When sleep is normal, the downregulation of arousal is effortless and automatic.[16] Essentially, individuals who sleep well tend to not try to sleep. They simply go to sleep. In contrast, people with insomnia often try to sleep, which leads to increase in physiological, cognitive, and emotional arousal during the time allotted for sleep. Insomnia is considered a sleep disorder, and its pathophysiology suggests hyperarousal during sleep and wakefulness.[17]

A prominent model of insomnia, hyperarousal theory has gained attention as an integrative approach to the pathophysiology of insomnia assuming an interplay between psychological and physiological factors in the etiology and perpetuation of CI. Essentially, insomnia emerges from dysfunctional learning processes by which cognitive processing of the ongoing, past, or future sleep disturbance leads to aversive reactions toward sleep and sleep-related stimuli. Thus, sleep disturbance increases, which strengthens the aversive reaction leading to a conditioned response and permanent state of increased arousal.[17] The conditioned response perpetuates insomnia as it is further exacerbated by a person's tendency to compensate for poor sleep.

From a physiological perspective, increased arousal in patients with insomnia has been associated with increased cortisol secretion.[18] There is evidence that individuals with insomnia have a more active sympathetic nervous system than healthy controls. People with insomnia have greater sympathetic hyperactivity than controls. This is evidenced by greater low and high frequency spectral power of heart rate[19,20] and higher basal metabolic rates during the day and night[21] in individuals with insomnia as compared with individuals without insomnia. There is also evidence that individuals with insomnia have greater activation in brain regions involved in the regulation of sleep and their sleep electroencephalographic patterns include more activity in frequency bands characteristic of wakefulness.[22–24] Disruptions in circadian rhythms and sleep homeostasis also contributes to insomnia.[25]

Neuroimaging studies, although somewhat inconsistent, show growing evidence that primary limbic structures might contribute to dysregulated affect and arousal in insomnia and play a crucial role in maintaining processes like dysfunctional learning and enhanced recall of negative experiences.[26] This may serve as a negative feedback loop in which the physiological and psychological arousal in insomnia patients essentially feeds on itself creating more difficulty in achieving quality sleep.

From a behavioral perspective, the hyperarousal therapy posits that CI occurs in association with predisposing and precipitating factors, and chronically in association with perpetuating factors.[27] This perspective is extended by that stating conditioned arousal may act as a perpetuating

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factor. Specifically, the bed and the sleep environment become a stimulus for arousal instead of "sleepiness." It is further hypothesized cortical arousal occurs as a result of classical conditioning and promotes abnormal levels of sensory and information processing, and of long-term memory formation. These phenomena are linked to sleep continuity disturbances characterized as insomnia.[17]

Neurobiology of Insomnia

Studies suggest that there is a hereditary component to insomnia, as it appears to "run in families."[28] However, it remains unclear whether this is due to genetic factors or shared environmental influences and behaviors. Insomnia has been linked to genetic polymorphisms associated with psychiatric disorders, including genes involved in serotonin transport (5-HTTLPR) and metabolism (MAO-A). It may also be influenced by genes regulating circadian rhythms, such as PER2, PER3, CLOCK, BMAL1, and PGC-1a.[29–35] Additionally, while carriers of the Apoε4 allele show a higher likelihood of insomnia, some studies show that individuals carrying the Met allele (especially Met/Met homozygotes) of the catechol-O-methyltransferase (COMT) Val158Met polymorphism may exhibit heightened cognitive arousal and increased stress reactivity, which can predispose them to insomnia. This polymorphism modulates dopamine degradation in the prefrontal cortex, influencing arousal regulation. Additionally, COMT genotype may impact sleep architecture, with Met allele carriers displaying lighter sleep and greater sleep fragmentation in some studies.[36,37]

CI is increasingly recognized as a 24/7 disorder and one of hyperarousal, marked by a persistent state of heightened physiological and psychological activation. This hyperarousal extends beyond the nighttime symptoms of difficulty falling or staying asleep, manifesting as a trait-like condition that affects individuals both during sleep and wakefulness. Consistent with the hyperarousal theory, alterations in the default mode network (DMN) have been observed (►**Fig. 1**). These alterations may manifest as hyperconnectivity, resulting in heightened self-referential processing and the processing of irrelevant stimuli. This leads to rumination even prior to sleep onset on a 24-hour basis.[38]

It has been previously shown that individuals with CI exhibit an increased capacity for neuroplasticity during the day, particularly in response to use-dependent plasticity (UDP) observed during motor training tasks. UDP refers to the brain's ability to adapt and reorganize neural connections in response to repetitive activity.[39] This enhanced neuroplasticity in CI is likely linked to increased glutamatergic intracortical activity, a marker of heightened excitability within the brain's cortical circuits. This suggests a state of heightened neuroplasticity in CI, which may represent a form of maladaptive plasticity. The observed heightened plasticity also aligns with the hyperarousal state of CI. Hyperarousal may amplify the brain's responsiveness to stimuli, potentially contributing to these changes in plasticity.

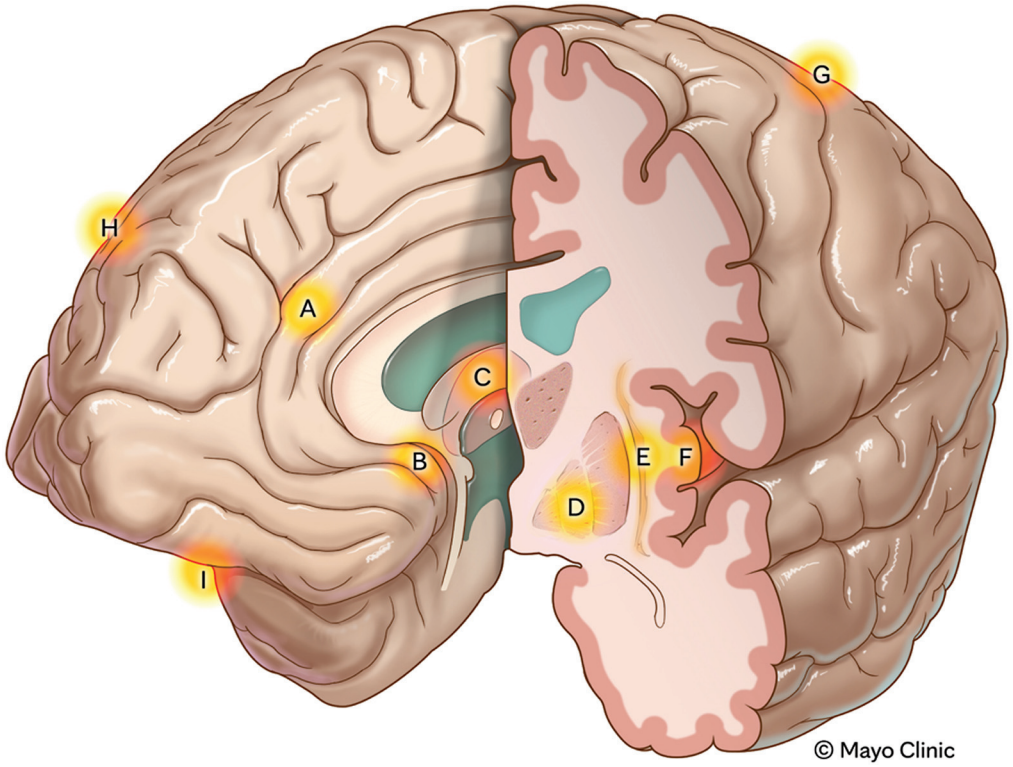

Fig. 1 Insomnia: Cortical and subcortical imaging correlates. Many of these structures are components of the default mode network (DMN) including the mPFC, posterior cingulate cortex (not shown), precuneus, and inferior parietal cortex (not labeled). A, anterior cingulate cortex (ACC); B, subgenual ACC; C, thalamus; D, basal ganglia; E, claustrum; F, insula; G, precuneus (not fully shown); H, medial prefrontal cortex (mPFC); I, orbitofrontal cortex.

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CI is also associated with higher levels of cerebral metabolism during both sleep and wakefulness.[40] This contrasts with the normal drop in brain metabolism that facilitates restful sleep and promotes energy conservation. Elevated metabolism in key regions, including the prefrontal cortex and limbic system, perpetuates a state of overactivation and emotional reactivity. The metabolic rate may be elevated in a subset of individuals with insomnia, particularly those who exhibit short sleep duration. This finding underscores the potential heterogeneity within the insomnia population, suggesting that specific physiological markers, such as heightened metabolism, may characterize distinct subtypes. Similarly, 24-hour hypothalamic–pituitary–adrenal axis (HPA) axis activation appears to be most pronounced in short-sleeping individuals with CI.[41] This supports the conceptualization of insomnia as a disorder of hyperarousal rather than merely a disorder of sleep loss.

Unlike sleep deprivation, which is often (though not always) associated with decreased or unchanged cortisol levels, CI is consistently linked to sustained activation of the HPA axis, resulting in elevated evening and overall cortisol levels. This suggests that CI is characterized by persistent physiological hyperarousal, distinguishing it from the typically transient effects of short-term sleep deprivation.

Insomnia is characterized by fragmented and restless sleep, which disrupts critical neurobiological processes that occur during specific sleep stages. Sleep instability refers to the inherent fragility of a sleep stage, characterized by frequent transitions between stages, brief arousals, or interruptions that fragment otherwise continuous sleep. These micro-level disruptions are not fully captured by global metrics such as sleep efficiency or time spent in each stage. In individuals with insomnia, increased sleep instability reflects the influence of hyperarousal mechanisms beyond just reduced total sleep time—for example, through prolonged wake after sleep onset (WASO).[17,42] While sleep fragmentation focuses on observable interruptions in sleep, sleep instability emphasizes the underlying weakness or susceptibility of the sleep state to disruption.[43,44] Restless REM sleep specifically highlights REM sleep changes associated with insomnia, including its fragmentation and instability.

Although individuals with CI often report having no sleep at all, sometimes for several days, there is generally sleep happening, but it is less restorative due to fragmentation and instability in sleep architecture. The use of polysomnography (PSG) to identify clinically relevant subgroups of patients with insomnia shows promise, but remains a topic of debate and is not used in clinical practice to diagnose or evaluate insomnia. However, ambulatory EEG devices may be used in clinical practice to more objectively evaluate insomnia.[45] Frequent nocturnal awakenings and lower sleep efficiency (percentage of time asleep while in bed) are the most robust indicators of insomnia on PSG.[46] Insomnia sufferers spend less total time in sleep, particularly in deeper sleep (N3) and REM sleep, compared with individuals with normal sleep. People with insomnia experience arousals during all sleep stages, but they are particularly disruptive to REM sleep, which is already reduced in duration.[47–50] People with insomnia also show an increased propensity to transition from N3 to lighter sleep stages. This instability makes it harder for them to sustain deep sleep. Interestingly, when they do reach N3 sleep, it closely resembles that of good sleepers, without significant instability or disruptions.

Advanced EEG analysis has revealed that even during N3, individuals with insomnia show evidence of superficial sleep activity riding on top of deep sleep.[50] This suggests that their deep sleep may not be as restorative or consolidated as it appears. The most consistent finding is increased power in the β frequency range during sleep in those with insomnia, which reflects cortical oscillations linked to wakefulness, alertness, and information processing. This heightened β activity during sleep is not limited to specific cortical regions, but is globally distributed across the brain, as indicated by both scalp-level topography and source estimates. Additionally, individuals with insomnia exhibit increased α band activity, particularly in sensory–motor areas, further highlighting disruptions in sleep regulation. These alterations in EEG patterns correspond to increased cortical excitability and heightened sensitivity to sensory stimuli, including auditory inputs. Research suggests that individuals with insomnia may be more sensitive to sounds, have heightened anticipation, a lower threshold for responding to stimuli, increased brain excitability, and difficulty filtering out sensory input. They may also show stronger brain responses to irrelevant sounds, struggle to tune them out over time, and continue to perceive them as new or emotionally significant, putting them in a futile cycle of disrupted sleep.[51–54]

Altogether, these findings highlight that insomnia is not simply a matter of insufficient sleep, but rather a qualitative issue with the stability and restorative quality of sleep. The disruptions, particularly in REM sleep and deep N3 sleep, are central to the condition. This instability contributes to the non-restorative sleep often reported by individuals with insomnia, even if their sleep architecture seems superficially normal in certain aspects.

A key focus in the neurobiology of insomnia is the dysfunction of REM sleep, a stage essential for emotional regulation and synaptic plasticity.[55] During sound REM sleep, the locus coeruleus (LC) responsible for releasing noradrenaline (NA) is silenced, creating a unique "time-out" for the brain. This NA-free state supports delicate processes like synaptic potentiation and depotentiation, allowing for emotional recovery and memory integration. In individuals with insomnia, insufficient LC silencing may disrupt synaptic plasticity, impairing the brain's ability to adapt to emotional stress and process emotional memories effectively. Over time, this can result in amygdala activation (emotional reactivity) and prevent proper engagement of prefrontal circuits, which are critical for rational emotional regulation. This maladaptive pattern may worsen emotional distress, creating a vicious cycle that sustains insomnia.

The importance of NA-free REM sleep for overnight emotion regulation provides insight that insomnia may not simply be a sleep disorder, but rather a condition tied to impaired overnight emotional memory regulation, stemming from a presymptomatic vulnerability to restless sleep.[56] This vulnerability may also contribute to the

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development of anxiety disorders, depression, and posttraumatic stress disorder (PTSD), as these conditions share overlapping genetic and other risk factors, and often co-occur. The key distinction among these disorders may lie in the specific type of emotional distress (e.g., fear, anxiety, stress, or sadness) that fails to resolve overnight due to disrupted REM sleep. People with insomnia show EEG signatures of sleep with disrupted and fragmented sleep, with frequent arousals (brief awakenings) and stage shifts (transitions to lighter sleep stages).

While this review highlights some important aspects of the neurobiology of insomnia from a more clinical aspect, a comprehensive and insightful paper that dives deep into the neurobiology of insomnia and supportive research, offering an integrated model that synthesizes genetic, developmental, neuroimaging, physiological, and subjective findings can be found elsewhere in the literature.[56]

Treatment Approaches to Insomnia

"Somnomics," the study of sleep's relationship to health with a precision medicine approach, as described by Porosnicu et al is a useful framework which allows us to understand the impact of sleep on mood, cognition, well-being, physiology, and homeostasis from a personalized medicine perspective.[57] CI can be a challenging disorder to treat as the intervention that works for one individual may not work for the next individual. Personalized sleep medicine takes a collaborative approach with the patient, which allows us to consider each patient's unique needs and values as it relates to CI.[57] The unique needs and values of each patient, "personomics" framework, and our understanding of insomnia from a hyperarousal and neurobiological perspective and overall health in relation to sleep (i.e., somnomics) can thus inform our treatment recommendations.[58] Additionally, as patient preferences grow toward alternative, nonpharmacologic therapies, complementary and alternative treatments for insomnia, it will be increasingly important for clinicians to approach treatment from a "personomics" framework "in the quest of personalized medicine to provide high-value care."[59]

The treatment options for CI include cognitive behavioral therapy for insomnia (CBT-I), prescribed and over-the-counter medications, complementary treatments, and transcranial magnetic stimulation (TMS).[1] All insomnia-related guidelines published in the past 5 years agree that CBT-I should be the first-line treatment for insomnia, based on the accumulated scientific evidence from the literature. Hypnotics are recommended for short-term use and only if CBT-I is not available or ineffective, although not all insurance companies cover CBT-I despite it being the gold standard. The primary goal of CI treatment is to improve the quality and quantity of sleep, and to improve daytime functioning.

Cognitive Behavioral Therapy for Insomnia

CBT-I is the most widely researched non-pharmacological treatment for insomnia and has a large and consistent body of literature providing strong empirical support for the efficacy of the treatment. CBT-I has been found to have durable outcomes and clinical effects that persist after treatment discontinuation for periods measured up to 2 years.[60,61] The short-term effects of CBT-I over 6 to 8 weeks are comparable with or superior to those of hypnotic medications.[62] Evidence from clinical trials and meta-analysis showed improvement in insomnia symptom severity (effect size, 0.98; 95% confidence interval, 0.82–1.15), sleep onset latency (effect size 0.57; 95% confidence interval, 0.50 to 0.65), and time awake after sleep onset (effect size, 0.63; 95% confidence interval, 0.53 to 0.730). Additionally, improved sleep continuity (i.e., sleep onset, wake after sleep onset) was associated with improved sleep efficiency (the ratio of time asleep to time spent in bed; effect size, 0.71; 95% confidence interval, 0.61 to 82).[4,63,64] Overall, 60 to 70% of patients have a clinical response to CBT-I, which is defined as a reduction of 7 points on the Insomnia Severity Index (ISI). The weight of evidence supporting CBT-I has led to the American College of Physicians and several other professional societies to recommend that CBT-I be the first line of therapy for insomnia.[65–68]

CBT-I is a multicomponent therapy that usually consists of four core treatments: stimulus control, sleep restriction, sleep hygiene, and cognitive therapy. To a large extent, CBT-I helps individuals abandon efforts to control sleep and return to reliance upon the involuntary sleep process.[69] This helps to decrease sleep effort, and the cognitive, emotional, and physiological arousal associated with insomnia, which is counterproductive for sleep.

Specifically, the behavioral interventions of CBT-I are generally stimulus control and sleep restriction or sleep compression (►**Table 1**). Stimulus control limits the amount

Table 1 Summary of combined stimulus control and sleep restriction guidelines

1. Wake up at the same time every day, regardless of how much you slept, and get out of bed within 10–15 minutes.
2. Go to bed when you are sleepy, but not before your goal bedtime. If you do not feel sleepy at this time, wait until you feel sleepy.
3. If you can't sleep, stop trying. Get up and do something calming and return to bed only when you are sleepy again. When you lie in bed awake trying to sleep, wanting and hoping to go back to sleep, you are training yourself to be awake in bed.
4. Use the bed only for sleeping. Do not read, eat, watch TV, etc., in bed. Sex is an exception. The most important activity to eliminate from the bed is the activity of "trying to sleep," because it inevitably interferes with the natural sleep processes.
5. Avoid daytime napping unless you believe sleepiness compromises your safety.

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of time spent in bed awake with the goal of having the patient associate the sleep environment with sleep as opposed to other stimuli (e.g., frustration, trying to sleep, hyperarousal). The proposed mechanism of action for stimulus control is thought to be the reestablishment of the bed and bedroom as a discriminative stimulus for sleepiness and sleep, and thus the extinction of insomnia. Stimulus control instructions reverse conditioned arousal by strengthening the bed as a cue for sleep. Additionally, stimulus control likely increases homeostatic sleep drive which helps with the next night of sleep. Sleep restriction is a process which focuses on sleep quality first and then gradually on increasing sleep quantity. Sleep restriction can help individuals consolidate sleep and decrease unwanted wakefulness by reducing their time in bed to be equal to the average amount of time the patient reports sleeping.

The cognitive component of CBT-I is utilized to help individuals understand how some of their thoughts and beliefs about sleep contribute to their insomnia. The goal is to establish alternative, more helpful, and often more accurate thoughts and beliefs about sleep. The cognitive model of insomnia suggests people with insomnia demonstrate attention bias toward sleep-related threat cues, such as deficits in their daytime performance.[70] As such, the psychological arousal associated with sleep-specific conditions (e.g., worrying about sleep) or thoughts and emotions that are not related to sleep (e.g., fear, anxiety, excitement) can be addressed with cognitive interventions which reduce arousal and help facilitate changes in behaviors that are incongruent with sleep.

Transcranial Magnetic Stimulation for Insomnia

Transcranial magnetic stimulation (TMS) is a relatively new treatment method for a variety of neuropsychiatric conditions. The procedure generates magnetic fields to create an electrical current to depolarize neurons and modulate neuronal activity in localized cortical regions a few centimeters below the scalp.[71] TMS has been shown to have potential benefits in multiple conditions including major depressive disorder, obsessive compulsive disorder, and anxiety. Several studies have reported that repetitive TMS for various conditions improved subjective measures of sleep quality.[72,73] It has been suggested that repetitive TMS may have a positive effect on sleep outside of its application to neuropsychiatric conditions (i.e., major depressive disorder).[74]

Although the exact mechanism by which repetitive TMS may influence sleep has not been fully explained, it is believed that repetitive TMS engages neuronal plasticity to modulate compensatory brain processes and alter cortical states through the dorsolateral prefrontal cortex.[71,75] This is important, as insomnia has been linked to brain dysfunction, particularly in the dorsolateral prefrontal cortex area.[76] Several studies have assessed the efficacy of repetitive TMS in treating chronic insomnia and reported significant improvements in insomnia symptoms in active repetitive TMS groups.[77–79]

Pharmacologic Treatment

Pharmacologic treatments for insomnia management are considered second line to nonpharmacological strategies due to weak evidence supporting efficacy. However, pharmacological treatment plays a role in the management of insomnia in the short term or refractory insomnia.

The most widely prescribed classes of medications for insomnia are benzodiazepines (e.g., temazepam) and benzodiazepine receptor agonists (e.g., zolpidem). These medications bind to the benzodiazepine-receptor binding site of GABA receptor, increasing intrinsic activity of the inhibitory outputs to all the major cell groups in the brainstem and hypothalamus that promote arousal.[80] Meta-analyses of randomized controlled trials have concluded benzodiazepine and benzodiazepine-receptor agonist are safe and effective short-term treatments for acute insomnia.[81,82] Benzodiazepines are nonselective in the binding to benzodiazepine receptors and have longer half-lives which contribute to prolonged sedation, adverse events, and an increased risk of tolerance and dependence.

An alternative pharmacological route is the use of sedative antidepressants (e.g., amitriptyline, trazodone) or antihistamines (e.g., doxepin). A major advantage is that, unlike benzodiazepines, these drugs do not cause addiction. However, these medications can be associated with side-effects including rebound insomnia after withdrawal and heart rhythm disturbances which may require additional medical monitoring.

Dual orexin receptor antagonists (DORAs) are the newest class of medications to be FDA-approved for insomnia.[83,84] There are three FDA-approved DORAs for insomnia: suvorexant, lemborexant, and daridorexant. DORAs work by blocking orexin from binding to its receptor, which prevents arousal and wakefulness pathways to the brain.[76] This class of medications can reduce sleep-onset latency and help maintain sleep.

Other Therapeutic and Adjunctive Treatments for Insomnia

For patients who have not responded to CBT-I or are unable to access CBT-I due to limited availability, there are other nonpharmacologic treatment options (►**Table 2**). Digital CBT-I programs can also be considered (e.g., internet sites and smartphone apps), and these have become increasingly popular in the treatment of CI. The current European Insomnia Guidelines for the treatment of insomnia include movement therapy, yoga, and tai chai as possible therapeutic measures.[85] We will specifically discuss mind–body therapies (mindfulness meditation and exercise) herein.

Mindfulness

Mindfulness-based therapies have been adapted to treat insomnia. A meta-analysis of six randomized clinical trials determined that mindfulness-based strategies can be effective in treating sleep disturbances when compared with control groups.[86] Mindfulness-based strategies have been shown to reduce total wake time and sleep-onset latency with increased sleep quality and sleep efficiency.[86,87] Specifically, mindfulness-based therapy for insomnia (MBTI) is a meditation-based program which targets both the arousal component of insomnia and nocturnal wakefulness.[88] MBTI is thought to improve sleep and daytime functioning by reducing hyperarousal. In contrast to CBT-I, MBTI aims to

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Table 2 Summary of adjunctive treatments for chronic insomnia

Approach	Description
Mindfulness-based therapy for insomnia	Meditation-based program which integrates behavioral techniques for insomnia by reducing hyperarousal
Digital CBT-I programs (internet sites and smartphone apps)	SHUTi (a six-module internet-delivered treatment based on CBT-I) Go! To Sleep[86] (6-week CBT-I-based online program) CBT-I Coach
Acceptance and commitment therapy (ACT) administered with CBT-I	Third wave therapy which uses mindfulness and acceptance as key approaches to the treatment of insomnia. ACT-based interventions for insomnia are combined with evidenced-based behavioral components such as sleep restriction and stimulus control.[87]
Use of bright light	Exposure to bright light by either sunlight or light therapy box, which impacts the endogenous sleep–wake cycle as the perception of light delays the brain's melatonin production.
Melatonin supplements	Research has not proven that melatonin is an effective treatment for insomnia but may be used to help anchor the circadian rhythm.
Weighted blanket	May reduce sympathetic arousal which can help to increase calmness and be sleep-promoting.
Modius sleep	Recently FDA-cleared, head-worn device that treats chronic insomnia through non-invasive electrical stimulus of the vestibular nerve.[88]

shift metacognitions to reduce sleep-related arousal at night through meditation practice.[88]

Exercise

Exercise is one of the most beneficial interventions for well-being and health, including sleep quality. A recent meta-analysis reported exercise interventions for insomnia have a positive effect on subjective sleep parameters.[89] Exercise interventions may influence mechanisms of hyperarousal and interrupt the maintenance of insomnia. Additionally, exercise may be used to combat fatigue and sleepiness associated with insomnia or as treatment for insomnia (i.e., during sleep restriction training).[90–92]

Conclusion

Insomnia is increasingly prevalent and contributes to public health concerns including mental health disorders, stroke, and coronary artery disease. The pathophysiology of insomnia involves hyperarousal during non-REM sleep and disruption in circadian rhythm and homeostatic sleep drive. This review discussed the basics of physiological and psychological arousal, the neurobiology of CI, and treatment modalities. Increasing awareness of neurobiological aspects of CI is fundamentally important. Potential treatments include psychotherapy techniques (e.g., CBT-I), pharmacological interventions, non-invasive brain stimulation techniques (e.g., TMS), and adjunctive interventions, but the goal should be to select and implement personalized treatment based on the individual neurobiological, psychological, and clinical characteristics of each patient.

Conflict of Interest
None declared.

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References

1 Perlis ML, Pigeon WR, Grandner MA, et al. Why treat insomnia? J Prim Care Community Health 2021;12:21501327211014084
2 Laugsand LE, Vatten LJ, Platou C, Janszky I. Insomnia and the risk of acute myocardial infarction: a population study. Circulation 2011;124(19):2073–2081
3 Edinger JD, Arnedt JT, Bertisch SM, et al. Behavioral and psychological treatments for chronic insomnia disorder in adults: an American Academy of Sleep Medicine clinical practice guideline. J Clin Sleep Med 2021;17(02):255–262
4 Fernandez-Mendoza J, Vgontzas AN, Liao D, et al. Insomnia with objective short sleep duration and incident hypertension: the Penn State Cohort. Hypertension 2012;60(04):929–935
5 Mayer G, Jennum P, Riemann D, Dauvilliers Y. Insomnia in central neurologic diseases—occurrence and management. Sleep Med Rev 2011;15(06):369–378
6 Baglioni C, Battagliese G, Feige B, et al. Insomnia as a predictor of depression: a meta-analytic evaluation of longitudinal epidemiological studies. J Affect Disord 2011;135(1-3):10–19
7 Kucharczyk ER, Morgan K, Hall AP. The occupational impact of sleep quality and insomnia symptoms. Sleep Med Rev 2012;16 (06):547–559
8 Martin SA, Aikens JE, Chervin RD. Toward cost-effectiveness analysis in the diagnosis and treatment of insomnia. Sleep Med Rev 2004;8(01):63–72
9 Léger D, Guilleminault C, Bader G, Lévy E, Paillard M. Medical and socio-professional impact of insomnia. Sleep 2002;25(06):625–629
10 Roy AN, Smith M. Prevalence and cost of insomnia in a state Medicaid fee-for-service population based on diagnostic codes and prescription utilization. Sleep Med 2010;11(05):462–469
11 Ekirch AR. Segmented sleep in preindustrial societies. Sleep 2016; 39(03):715–716

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12 Moreno CRC, Conway SG, Assis M, et al. COVID-19 pandemic is associated with increased sleep disturbances and mental health symptoms but not help-seeking: a cross-sectional nation-wide study. Sleep Sci 2022;15(01):1–7
13 Hurley D. Sleep Neurologists Call It "COVID-Somnia"—Increased Sleep Disturbances Linked to the Pandemic. Accessed June 6, 2025 at: https://journals.lww.com/neurotodayonline/fulltext/2020/07090/sleep_neurologists_call_it.1.aspx
14 Murthy VH. Together: The Healing Power of Human Connection in a Sometimes Lonely World. Harper; 2020
15 Jahrami H, Trabelsi K, Vitiello MV, BaHammam AS. The tale of orthosomnia: I am so good at sleeping that I can do it with my eyes closed and my fitness tracker on me. Nat Sci Sleep 2023;15:13–15
16 Espie CA. Insomnia: conceptual issues in the development, persistence, and treatment of sleep disorder in adults. Annu Rev Psychol 2002;53:215–243
17 Riemann D, Spiegelhalder K, Feige B, et al. The hyperarousal model of insomnia: a review of the concept and its evidence. Sleep Med Rev 2010;14(01):19–31
18 Zhang J, Lam SP, Li SX, et al. A community-based study on the association between insomnia and hypothalamic-pituitary-adrenal axis: sex and pubertal influences. J Clin Endocrinol Metab 2014;99(06):2277–2287
19 Bonnet MH, Arand DL. Heart rate variability in insomniacs and matched normal sleepers. Psychosom Med 1998;60(05):610–615
20 Lushington K, Dawson D, Lack L. Core body temperature is elevated during constant wakefulness in elderly poor sleepers. Sleep 2000;23(04):504–510
21 Bonnet MH, Arand DL. 24-Hour metabolic rate in insomniacs and matched normal sleepers. Sleep 1995;18(07):581–588
22 Nofzinger EA, Buysse DJ, Germain A, Price JC, Miewald JM, Kupfer DJ. Functional neuroimaging evidence for hyperarousal in insomnia. Am J Psychiatry 2004;161(11):2126–2128
23 Freedman RR, Sattler HL. Physiological and psychological factors in sleep-onset insomnia. J Abnorm Psychol 1982;91(05):380–389
24 Perlis ML, Merica H, Smith MT, Giles DE. Beta EEG activity and insomnia. Sleep Med Rev 2001;5(05):363–374
25 Kutscher S, Juang C. Insomnia. Continuum (Minneap Minn) 2023; 29(04):1167–1187
26 Wassing R, Schalkwijk F, Lakbila-Kamal O, et al. Haunted by the past: old emotions remain salient in insomnia disorder. Brain 2019;142(06):1783–1796
27 Spielman AJ, Caruso LS, Glovinsky PB. A behavioral perspective on insomnia treatment. Psychiatr Clin North Am 1987;10(04):541–553
28 Lind MJ, Gehrman PR. Genetic pathways to insomnia. Brain Sci 2016;6(04):64
29 Bouvette-Turcot A-A, Pluess M, Bernier A, et al; MAVAN research team. Effects of genotype and sleep on temperament. Pediatrics 2015;136(04):e914–e921
30 Brummett BH, Krystal AD, Ashley-Koch A, et al. Sleep quality varies as a function of 5-HTTLPR genotype and stress. Psychosom Med 2007;69(07):621–624
31 Brummett BH, Krystal AD, Siegler IC, et al. Associations of a regulatory polymorphism of monoamine oxidase-A gene promoter (MAOA-uVNTR) with symptoms of depression and sleep quality. Psychosom Med 2007;69(05):396–401
32 Li J, Huang C, Lan Y, Wang Y. A cross-sectional study on the relationships among the polymorphism of period2 gene, work stress, and insomnia. Sleep Breath 2015;19(04):1399–1406
33 Brower KJ, Wojnar M, Sliwerska E, Armitage R, Burmeister M. PER3 polymorphism and insomnia severity in alcohol dependence. Sleep 2012;35(04):571–577
34 Ziv-Gal A, Flaws JA, Mahoney MM, Miller SR, Zacur HA, Gallicchio L. Genetic polymorphisms in the aryl hydrocarbon receptor-signaling pathway and sleep disturbances in middle-aged women. Sleep Med 2013;14(09):883–887
35 Wang CC, Lung FW. The role of PGC-1 and Apoε4 in insomnia. Psychiatr Genet 2012;22(02):82–87
36 Goel N, Banks S, Mignot E, Dinges DF. Dopaminergic polymorphisms associated with sleep and circadian phenotypes. Sleep 2011;34(05):513–520
37 Holzman JB, Bridgett DJ, Green MJ. Personality and catechol-O-methyltransferase (COMT) genotype interact to predict insomnia symptoms. Pers Individ Dif 2018;120:250–256
38 Killgore WDS, Jankowski S, Henderson-Arredondo K, et al. Functional connectivity of the default mode network predicts subsequent polysomnographically measured sleep in people with symptoms of insomnia. Neuroreport 2023;34(14):734–740
39 Salas RE, Galea JM, Gamaldo AA, et al. Increased use-dependent plasticity in chronic insomnia. Sleep 2014;37(03):535–544
40 Nofzinger EA, Buysse DJ, Germain A, Price JC, Miewald JM. Kupfer DJ. Functional neuroimaging evidence for hyperarousal in insomnia. Am. J Psychiatry 2004;161(11):2126–2128
41 Pejovic S, Vgontzas AN. Neurobiological disturbances in insomnia: clinical utility of objective measures of sleep. In: Sateia JM, Buysse D, eds. Insomnia. Boca Raton, FL: CRC Press; 2010: 65–76
42 Johns Hopkins University. Accessed June 6, 2025 at: https://doi-org.proxy1.library.jhu.edu/10.1111/jsr.14032
43 Carskadon MA, Brown ED, Dement WC. Sleep fragmentation in the elderly: relationship to daytime sleep tendency. Neurobiol Aging 1982;3(04):321–327
44 Stepanski E, Lamphere J, Badia P, Zorick F, Roth T. Sleep fragmentation and daytime sleepiness. Sleep 1984;7(01):18–26
45 Finan PH. Richards JM, Gamaldo CE, et al. Validation of a wireless, self-application, ambulatory electroencephalographic sleep monitoring device in healthy volunteers. J Clin Sleep Med 2016; 12(11):1443–1451
46 Baglioni C, Regen W, Teghen A, et al. Sleep changes in the disorder of insomnia: a meta-analysis of polysomnographic studies. Sleep Med Rev 2014;18(03):195–213
47 Feige B, Al-Shajlawi A, Nissen C, et al. Does REM sleep contribute to subjective wake time in primary insomnia? A comparison of polysomnographic and subjective sleep in 100 patients. J Sleep Res 2008;17(02):180–190
48 Riemann D, Spiegelhalder K, Nissen C, Hirscher V, Baglioni C, Feige B. REM sleep instability—a new pathway for insomnia? Pharmacopsychiatry 2012;45(05):167–176
49 Parrino L, Milioli G, De Paolis F, Grassi A, Terzano MG. Paradoxical insomnia: the role of CAP and arousals in sleep misperception. Sleep Med 2009;10(10):1139–1145
50 Christensen JAE, Wassing R, Wei Y, et al. Data-driven analysis of EEG reveals concomitant superficial sleep during deep sleep in insomnia disorder. Front Neurosci 2019;13:598
51 Feige B, Baglioni C, Spiegelhalder K, Hirscher V, Nissen C, Riemann D. The microstructure of sleep in primary insomnia: an overview and extension. Int J Psychophysiol 2013;89(02):171–180
52 Blanken TF, Benjamins JS, Borsboom D, et al. Insomnia disorder subtypes derived from life history and traits of affect and personality. Lancet Psychiatry 2019;6(02):151–163
53 Terzano MG, Parrino L, Smerieri A. [Neurophysiological basis of insomnia: role of cyclic alternating patterns]. Rev Neurol (Paris) 2001;157(11 Pt 2):S62–S66
54 Van Someren EJW. Brain mechanisms of insomnia: new perspectives on causes and consequences. Physiol Rev 2021;101(03): 995–1046
55 Swift KM, Gross BA, Frazer MA, et al. Abnormal locus cooeruleus sleep activity alters sleep signatures of memory consolidation and impairs place cell stability and spatial memory. Curr Biol 2018;28(22):3599–3609.e4
56 Van Someren EJW. Brain mechanisms of insomnia: new perspectives on causes and consequences. Physiol Rev 2021;101(03):995–1046
57 Porosnicu Rodriguez KA, Salas RME, Schneider L. Insomnia: personalized diagnosis and treatment options. Neurol Clin 2023;41(01): 1–19

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58 Ziegelstein RC. Personomics: the missing link in the evolution from precision medicine to personalized medicine. J Pers Med 2017;7(04):11
59 Perez MN, Salas RME. Insomnia. Continuum (Minneap Minn) 2020;26(04):1003–1015
60 Beaulieu-Bonneau S, Ivers H, Guay B, Morin CM. Long-term maintenance of therapeutic gains associated with cognitive-behavioral therapy for insomnia delivered alone or combined with zolpidem. Sleep 2017;40(03):zsx002
61 Castronovo V, Galbiati A, Sforza M, et al. Long-term clinical effect of group cognitive behavioral therapy for insomnia: a case series study. Sleep Med 2018;47:54–59
62 Mitchell MD, Gehrman P, Perlis M, Umscheid CA. Comparative effectiveness of cognitive behavioral therapy for insomnia: a systematic review. BMC Fam Pract 2012;13:40
63 van Straten A, van der Zweerde T, Kleiboer A, Cuijpers P, Morin CM, Lancee J. Cognitive and behavioral therapies in the treatment of insomnia: a meta-analysis. Sleep Med Rev 2018;38:3–16
64 Brasure M, Fuchs E, MacDonald R, et al. Psychological and behavioral interventions for managing insomnia disorder: an evidence report for a clinical practice guideline by the American College of Physicians. Ann Intern Med 2016;165(02): 113–124
65 Qaseem A, Kansagara D, Forciea MA, Cooke M, Denberg TDClinical Guidelines Committee of the American College of Physicians. Management of chronic insomnia disorder in adults: a clinical practice guideline from the American College of Physicians. Ann Intern Med 2016;165(02):125–133
66 Sateia MJ, Buysse DJ, Krystal AD, Neubauer DN, Heald JL. Clinical practice guideline for the pharmacologic treatment of chronic insomnia in adults: an American Academy of Sleep Medicine clinical practice guideline. J Clin Sleep Med 2017;13(02):307–349
67 Wilson S, Anderson K, Baldwin D, et al. British Association for Psychopharmacology consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders: an update. J Psychopharmacol 2019;33(08):923–947
68 Mansfield D, Grima NA, Bei B. Insomnia management. Aust J Gen Pract 2019;48(04):198–202
69 Espie CA, Broomfield NM, MacMahon KM, Macphee LM, Taylor LM. The attention-intention-effort pathway in the development of psychophysiologic insomnia: a theoretical review. Sleep Med Rev 2006;10(04):215–245
70 Harvey AG. A cognitive model of insomnia. Behav Res Ther 2002; 40(08):869–893
71 Valero-Cabré A, Amengual JL, Stengel C, Pascual-Leone A, Coubard OA. Transcranial magnetic stimulation in basic and clinical neuroscience: a comprehensive review of fundamental principles and novel insights. Neurosci Biobehav Rev 2017;83:381–404
72 van Dijk KD, Møst EI, Van Someren EJ, Berendse HW, van der Werf YD. Beneficial effect of transcranial magnetic stimulation on sleep in Parkinson's disease. Mov Disord 2009;24(06):878–884
73 Sánchez-Escandón O, Arana-Lechuga Y, Terán-Pérez G, et al. Effect of low-frequency repetitive transcranial magnetic stimulation on sleep pattern and quality of life in patients with focal epilepsy. Sleep Med 2016;20:37–40
74 Gao X, Wang L, Liu X, Yan T. The effect of repetitive transcranial magnetic stimulation on sleep: a meta-analysis. Sleep Med Rev 2020;49:101225
75 Berlim MT, Van den Eynde F, Jeff Daskalakis Z. Clinically meaningful efficacy and acceptability of low-frequency repetitive transcranial magnetic stimulation (rTMS) for treating primary major depression: a meta-analysis of randomized, double-blind and sham-controlled trials. Neuropsychopharmacology 2013;38 (04):543–551
76 Cheng Y, Xue T, Dong F, et al. Abnormal functional connectivity of the salience network in insomnia. Brain Imaging Behav 2022;16 (02):930–938
77 Jiang CG, Zhang T, Yue FG, Yi ML, Gao D. Efficacy of repetitive transcranial magnetic stimulation in the treatment of patients with chronic primary insomnia. Cell Biochem Biophys 2013;67 (01):169–173
78 Jiang B, He D, Guo Z, Mu Q, Zhang L. Efficacy and placebo response of repetitive transcranial magnetic stimulation for primary insomnia. Sleep Med 2019;63:9–13
79 Song P, Lin H, Li S, et al. Repetitive transcranial magnetic stimulation (rTMS) modulates time-varying electroencephalography (EEG) network in primary insomnia patients: a TMS-EEG study. Sleep Med 2019;56:157–163
80 Kryger MH, Roth T, Dement WC. Principles and Practice of Sleep Medicine. 5th ed. Elsevier/Saunders; 2011:xlii, 1723 p
81 Smith MT, Perlis ML, Park A, et al. Comparative meta-analysis of pharmacotherapy and behavior therapy for persistent insomnia. Am J Psychiatry 2002;159(01):5–11
82 Nowell PD, Mazumdar S, Buysse DJ, Dew MA, Reynolds CF III, Kupfer DJ. Benzodiazepines and zolpidem for chronic insomnia: a meta-analysis of treatment efficacy. JAMA 1997;278(24): 2170–2177
83 Michelson D, Snyder E, Paradis E, et al. Safety and efficacy of suvorexant during 1-year treatment of insomnia with subsequent abrupt treatment discontinuation: a phase 3 randomised, double-blind, placebo-controlled trial. Lancet Neurol 2014;13(05): 461–471
84 Riemann D, Spiegelhalder K. Orexin receptor antagonists: a new treatment for insomnia? Lancet Neurol 2014;13(05):441–443
85 Riemann D, Espie CA, Altena E, et al. The European Insomnia Guideline: an update on the diagnosis and treatment of insomnia 2023. J Sleep Res 2023;32(06):e14035
86 Gong H, Ni CX, Liu YZ, et al. Mindfulness meditation for insomnia: a meta-analysis of randomized controlled trials. J Psychosom Res 2016;89:1–6
87 Rusch HL, Rosario M, Levison LM, et al. The effect of mindfulness meditation on sleep quality: a systematic review and meta-analysis of randomized controlled trials. Ann N Y Acad Sci 2019;1445(01):5–16
88 Ong J, Sholtes D. A mindfulness-based approach to the treatment of insomnia. J Clin Psychol 2010;66(11):1175–1184
89 Riedel A, Benz F, Deibert P, et al. The effect of physical exercise interventions on insomnia: a systematic review and meta-analysis. Sleep Med Rev 2024;76:101948
90 Bernstein AM, Allexandre D, Bena J, et al. "Go! to sleep": a Web-based therapy for insomnia. Telemed J E Health 2017;23(07): 590–599
91 Saldaña KS, McGowan SK, Martin JL. Acceptance and commitment therapy as an adjunct or alternative treatment to cognitive behavioral therapy for insomnia. Sleep Med Clin 2023;18(01): 73–83
92 Curry G, Cheung T, Zhang SD, et al. Repeated electrical vestibular nerve stimulation (VeNS) reduces severity in moderate to severe insomnia; a randomised, sham-controlled trial; the modius sleep study. Brain Stimul 2024;17(04):782–793

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