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# Managing Insomnia: A Review of Pharmacological and Non-Pharmacological Approaches

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## ABSTRACT

**Introduction and Aim:**
Insomnia is one of the most common sleep disorders, affecting about 10% of the population. It poses a significant public health concern due to its association with increased risk of depression, hypertension, obesity, diabetes, substance abuse, and suicide. Given its impact on health and quality of life, effective treatment is essential. This review aims to present pharmacological and non-pharmacological treatment methods for insomnia with proven scientific efficacy.

**Materials and Methods:**
A literature review was conducted using PubMed and Google Scholar, focusing on studies published between 2000 and 2024. Keywords related to pharmacological and non-pharmacological treatments of insomnia were used, and the most relevant articles were selected.

**Brief Description of the State of Knowledge:**
Cognitive behavioral therapy for insomnia (CBT-I) is considered the first-line treatment. It provides short-term efficacy comparable to pharmacotherapy, with longer-lasting benefits and fewer side effects. Pharmacological treatments should be used when CBT-I is unavailable or insufficient. Benzodiazepines and non-benzodiazepine hypnotics may be effective short term but carry significant risks, especially in older adults. Newer agents, such as melatonin receptor agonists, low-dose doxepin, and orexin receptor antagonists, offer additional options with improved safety profiles.

**Conclusions:**
Effective management of insomnia requires an individualized approach. CBT-I remains the preferred option, with pharmacotherapy considered when necessary. Proper treatment improves patient well-being and reduces the broader social and economic consequences of untreated insomnia.

**Keywords:** insomnia; pharmacological treatment of insomnia; non-pharmacological treatment of insomnia; cognitive behavioral therapy for insomnia; hypnotic medications;

## Introduction

Sleep is one of the basic biological needs of the human body. On average, each of us spends between 20 and 40 percent of the day sleeping. Adequate quantity and quality of sleep is essential for the proper functioning of the body. Sleep disorders, in terms of sleep duration and quality, can lead to serious health consequences. [1]
Insomnia is one of the most common sleep disorders, its prevalence is estimated at 10% in the general population and is considered a serious public health problem. [2,3] It is characterized by difficulty falling asleep, staying asleep, or early morning awakenings occurring despite sufficient opportunity for sleep, resulting in significant impairment in daily functioning. [3,4,5]. Insomnia very often coexists with other medical and psychiatric conditions. The relationship between these disorders is often bidirectional. Insomnia can be both a consequence of other medical conditions and a risk factor for their development. [3] It is a known risk factor for depression - people suffering from insomnia are almost three times more likely to develop depression compared to people without sleep problems. [6] It is also associated with an increased risk of other conditions, such as anxiety disorder, hypertension, obesity, diabetes, myocardial infarction, cardiovascular diseases, and headaches. Insomnia also increases the risk of suicide and substance abuse. [4,7] Despite the high prevalence of this condition, the exact mechanisms underlying insomnia are still unknown. [3] Given the significant negative impact of insomnia on health and quality of life, effective and appropriate treatment of this condition is essential. This review aims to present both pharmacological and non-pharmacological methods of treating insomnia that have proven scientific effectiveness.

## Materials and Methods

An extensive literature review was conducted using PubMed and Google Scholar, focusing on studies published between 2000 and 2024. Keywords related to pharmacological and non-pharmacological treatment of insomnia were used to guide the search, including: “insomnia,” “treatment of insomnia,” “non-pharmacological treatment,” “pharmacological treatment,” “insomnia medications,” “hypnotic medications,” and “cognitive behavioral therapy for insomnia.” Studies were evaluated based on their relevance, methodological quality, and scientific significance. Only articles published in English were included in the review.

## Insomnia disorder - current state of knowledge:

### Diagnosis

Insomnia is characterized by a persistent dissatisfaction with sleep quality or duration, often manifesting as difficulty falling asleep, staying asleep, frequent or prolonged awakenings at night, or waking up too early and being unable to fall back asleep. [3,4] These difficulties persist

despite having sufficient opportunities for sleep in a safe, dark environment and are linked to significant daytime impairment. Commonly reported daytime issues include fatigue, decreased energy level, low mood or irritability, and diminished cognitive abilities, such as impaired attention, concentration, and memory. [2-4] Chronic insomnia, according to the third edition of the International Classification of Sleep Disorders (ICSD-3), or persistent insomnia, according to the DSM-5, is diagnosed when sleep disturbances occur at least three nights per week and persist for more than three months. Short-term insomnia (ICSD-3) or episodic insomnia (DSM-5) can be diagnosed when the symptoms last less than three months. [4] In Europe, the ICD classification system is primarily used. While ICD-10 distinguished between "organic" and "non-organic" insomnia, this distinction was removed in ICD-11 due to a lack of supporting evidence. The updated version adopts the categories of "chronic insomnia" and "short-term insomnia". The diagnostic criteria for insomnia disorder in DSM-5, ICSD-3, and ICD-11 are largely consistent now. The only notable difference is that ICD-11 describes the frequency of sleep disturbances as occurring "several times per week", whereas DSM-5 and ICSD-3 specify a minimum of three nights per week. [5] If sleep problems can be fully explained by the presence of another mental or medical condition, including other sleep disorders, a diagnosis of insomnia should not be made. However, if the insomnia symptoms are severe enough to require separate clinical attention, regardless of whether they were triggered by another disorder or occur alongside it, insomnia should be recognized as a distinct comorbid condition. [2]

**Epidemiology**

The prevalence of insomnia varies between countries. However, on average, in both the European and American populations, it affects approximately 10% of the population. [7,8] Insomnia is more common in females than in males, with a prevalence of 60% compared to 40%, and its occurrence tends to increase with age. [7] Studies indicate that up to 65% of people aged 65 and older experience insomnia symptoms. [9] For many patients, insomnia tends to be a chronic condition, with 74% reporting symptoms persisting for at least one year. It is more likely to persist in individuals with more severe symptoms at baseline, as well as in women and older adults [10]
Individuals with underlying health conditions, particularly respiratory diseases, heart failure, and chronic pain-related conditions such as cancer, are at a higher risk of experiencing insomnia. Also, patients with neurological disorders, including Alzheimer's disease and Parkinson's disease, are more prone to sleep disturbances. [9] Insomnia is strongly associated with mental health disorders, most commonly depression, anxiety, and post-traumatic stress disorder. Most individuals with major depression report having insomnia. [6]

**Treatment**

Insomnia can be managed through both pharmacological and non-pharmacological approaches. It is important to consider coexisting conditions that may contribute to sleep disturbances. Proper management of these underlying conditions is crucial for effectively addressing insomnia. [9,11]

**Non-Pharmacological treatment:**

## Sleep hygiene

Providing initial education on healthy sleep habits is an important first step in the treatment of insomnia. [11] Poor sleep hygiene can cause sleep fragmentation, disturbance of normal circadian rhythms, and overstimulation. [9] Sleep hygiene involves the optimization of behavioral and environmental factors that can improve sleep quality. [12]
Behaviors that contribute to maintaining good sleep hygiene [9,12,13,14]:
- Go to bed and wake up at consistent times.
- Avoid daytime naps.
- Avoid caffeine, alcohol, and nicotine before bedtime.
- Sleep in a dark and quiet bedroom.
- Maintain an optimal temperature in the bedroom.
- Avoid using a computer, phone, or watching TV before bedtime.
- Avoid looking at the clock while trying to fall asleep.
- Engage in regular physical activity, but avoid intense exercise a few hours before sleep.
- Avoid stressful situations before sleep and try to maintain a relaxation period before bedtime.
- Sleep in a comfortable bed.

However, studies have shown that using sleep hygiene as a standalone treatment for insomnia does not show sufficient results. Therefore, it should not be used as the sole approach to treating insomnia but rather as part of a multifaceted treatment strategy for this condition. [15]

## Cognitive-behavioral therapy

The guidelines on insomnia published in recent years recommend cognitive-behavioral therapy for insomnia (CBT-I) as the first-line treatment for managing the condition. [5, 7]
Cognitive-behavioral therapy for insomnia (CBT-I) is just as effective as pharmacological treatments in the short term, but it offers longer-lasting benefits even after the therapy has ended. [16] Moreover, in contrast to medications typically prescribed for insomnia, CBT-I carries minimal risk of side effects. [16,17] It combines cognitive therapy, behavioral techniques like sleep restriction and stimulus control, with educational strategies including sleep hygiene and relaxation training. [2,5,17] The therapy is conducted by mental health professionals and typically consists of 4 to 8 sessions. [18]

## CBT-I strategy components:

### 1) Stimulus control:

Associating the bed and bedroom with being awake causes the bed to become a conditioned stimulus for arousal, which prevents proper sleep. [2] These behavioral guidelines are designed to reinforce the connection between the bed and sleep while preventing the patient from associating the bed with stimulating activities. [17] Patients are advised to leave the bed if they are unable to sleep, go to bed only when feeling sleepy, and limit the use of the bed strictly to sleep and sexual activity. Other activities such as studying, reading, or watching television should not be performed in bed. It is also recommended to wake up at the same time every day of the week, leave the bed within 15 minutes of waking up, and refrain from daytime napping. [3,17,18]

### 2) Sleep restriction

A common factor contributing to the development of insomnia is the tendency to spend

excessive time in bed, which can result in conditioned arousal and fragmented sleep. [5] Sleep restriction is a behavioral therapy that aims to enhance sleep drive by limiting the time spent in bed (referred to as the sleep window) to the patient's actual sleep duration. [3,17] The sleep window is individually determined for each patient based on sleep diaries maintained throughout the treatment [18] and should not be set below 5 hours. [2] Records from sleep diaries help calculate average sleep efficiency, which represents the percentage of actual sleep time in relation to total time spent in bed. The minimum target for sleep efficiency is set at 85%. [5,16] Once a sufficiently high sleep efficiency is achieved, the sleep window can be gradually extended until the patient reaches optimal sleep satisfaction. [3,18]

**3) Relaxation**

Relaxation techniques equip patients with effective tools to reduce arousal both before bedtime and during nighttime awakenings. [2] These techniques aim to decrease autonomic activation, muscle tension, and cognitive arousal. Common methods include progressive muscle relaxation, breathing exercises, autogenic training, guided imagery, meditation, and mindfulness. [3, 5, 17, 18]

**4) Cognitive therapy**

Cognitive therapy is a psychotherapeutic approach aimed at identifying and changing faulty beliefs about sleep, as well as negative thought patterns linked to excessive worry, intrusive thoughts, and the emotional distress that disrupts sleep. It focuses on employing various techniques to help patients challenge their ingrained negative beliefs about sleep and its perceived impact on daily functioning, contributing to the reduction of heightened emotions and counterproductive efforts to fall asleep. Additionally, it supports individuals in adjusting to unrealistic sleep expectations and alleviating anxiety related to missing out on sleep. This therapy is especially beneficial in reducing anxiety, regulating emotions, and interrupting the persistent patterns that contribute to insomnia. [3, 7, 17,18]

**Results of CBT-I**

CBT-I is an evidence-based treatment that effectively improves sleep parameters. Many studies and meta-analyses have proven the efficacy of CBT-I in treating insomnia. [16-22] In a meta-analysis by van Straten et al. [16], which included 87 randomized controlled trials investigating at least one component of cognitive behavioral therapy for insomnia (CBT-I), 118 treatment conditions (3724 patients) were compared to non-treated controls (2579 patients). Treatment effectiveness, measured using Hedges' *g*, demonstrated a large impact on the Insomnia Severity Index ($g$ = 0.98), sleep efficiency ($g$ = 0.71), the Pittsburgh Sleep Quality Index ($g$ = 0.65), wake after sleep onset ($g$ = 0.63), and sleep onset latency ($g$ = 0.57). A small to moderate effect was found for the number of awakenings ($g$ = 0.29) and sleep quality ($g$ = 0.40). The smallest effect was observed for total sleep duration ($g$ = 0.16). Studies have demonstrated sustained benefits, with improvements lasting up to 12 months post-treatment, although a gradual decline in effectiveness is observed over time. A meta-analysis by Van der Zweerde et al. [19] examined the long-term effects across 29 randomized controlled trials, comparing CBT-I with non-active control groups. The analyses showed that CBT-I is effective at 3-, 6-, and 12-months compared

to non-active controls. Improvement in sleep measured Hedges' *g*, for the Insomnia Severity Index: 0.64 (3 m), 0.40 (6 m) and 0.25 (12 m); for sleep onset latency: 0.38 (3 m), 0.29 (6 m) and 0.40 (12 m); and for sleep efficiency: 0.51 (3 m), 0.32 (6 m) and 0.35 (12 m).
Compared to pharmacological treatments, CBT-I is at least as effective [22] and provides longer-lasting benefits with fewer side effects. [16,17,19] The therapy has been shown to be beneficial across diverse populations, including individuals with comorbid psychiatric and medical conditions. [21] Additionally, CBT-I is available in various delivery formats, such as individual, group, and online interventions, making it accessible to a broader range of patients. [17,19, 20] Despite its proven efficacy, a major challenge in healthcare systems is the limited availability of in-person CBT-I, which significantly restricts patient access to treatment. [5] A promising solution lies in digital interventions, which research suggests can be as effective as traditional face-to-face therapy. [20] Expanding access to online CBT-I could facilitate treatment by clinical guidelines. Overall, CBT-I is widely recognized as the first-line treatment for chronic insomnia due to its long-term effectiveness, accessibility through various delivery methods, and minimal risk of adverse effects compared to pharmacological interventions. [16-22]

**Pharmacological treatment**

Pharmacological treatment for insomnia can be used in patients who do not respond to non-pharmacological therapy or whose symptoms are severe. [23,24] The choice of medication should be individually adjusted to the patient's symptoms and should take into account any coexisting conditions. For example, in patients with coexisting anxiety or depressive disorders, sedative antidepressants such as mirtazapine or trazodone may be beneficial. [11] The majority of hypnotic medications are authorized for short-term use only, may have serious side effects, and can lead to addiction. [25,26] Medications used in the treatment of insomnia can be classified into those approved by the U.S. Food and Drug Administration (FDA) for this condition and those used off-label. [4] Not all of the FDA-approved drugs for insomnia are approved by the European Medicines Agency (EMA) and therefore available in Europe. [5] This paper will provide an overview of pharmacological classes used in the treatment of insomnia, incorporating the updated 2023 recommendations from the European Insomnia Guidelines. [5]

**FDA-approved drugs for insomnia disorder [3,5]:**
- Benzodiazepines (triazolam, flurazepam, temazepam, quazepam, estazolam)
- Non-benzodiazepine hypnotics (zolpidem, zaleplon, eszopiclone)
- Melatonin receptor agonists (ramelteon) - not available in Europe
- Selective histamine H1 receptor antagonists (doxepin)
- Dual orexin receptor antagonists (suvorexant, lemborexant, daridorexant) - only daridorexant has been approved in Europe

**Drugs used off-label [3,5]:**
- Other benzodiazepines
- Melatonin (fast release - available OTC, prolonged release - approved by the EMA for insomnia treatment in patients >55 years of age in Europe)
- Sedative antidepressants
- Atypical antipsychotics
- Antihistamines

## 1) Benzodiazepines

Benzodiazepines are a group of drugs that act as depressants on the central nervous system (CNS). They are lipophilic and are characterized by rapid penetration across the blood-brain barrier. [26] They act via positive allosteric modulation of the gamma-aminobutyric acid (GABA) type A receptor. GABA is an inhibitory neurotransmitter in the CNS and has a reducing effect on the excitability of neurons. Benzodiazepines bind to a specific site on the GABA-A receptor complex known as the benzodiazepine binding site. This causes a change in the conformation of the proteins that build the receptor and, as a consequence, an increase in the inhibitory effect of the GABA neurotransmitter upon binding to the receptor. The GABA-A receptor consists of various subunits, each with many isoforms. [25-27] Isoforms determine the effects of benzodiazepines on the CNS. Benzodiazepines exhibit high affinity for a wide variety of receptor subunits and bind to both type I and type II receptors. [25] The enhancement of GABA's effect results in the sedative, anxiolytic, anticonvulsant, and muscle-relaxant properties of benzodiazepines. [25]

Benzodiazepines are prescribed for a variety of conditions. Their sedative properties make them effective in treating anxiety disorders and halting panic attacks, while their anticonvulsant properties make them useful for stopping seizures. [26] Due to their sedative effects, benzodiazepines are also used to treat insomnia as they help reduce sleep onset latency and sleep duration. In a meta-analysis conducted by Holbrook et al. [27], which reviewed 45 randomized controlled trials involving 2,672 patients, benzodiazepines were compared with placebo or other active treatments. The findings showed that, in comparison to placebo, benzodiazepines significantly increased total sleep duration by 61.8 minutes (95% confidence interval [CI]: 37.4 to 86.2) and reduced sleep latency by an average of 4.2 minutes, though this result was not statistically significant. Patient-reported outcomes indicated a more notable reduction in sleep latency, with an estimated decrease of 14.3 minutes in those treated with benzodiazepines (95% CI: 10.6 to 18.0). Adverse effects such as daytime drowsiness, dizziness, and light-headedness were more commonly reported in the benzodiazepine group. Studies also reported cognitive side effects, including memory impairment.

Despite the similar effects among all benzodiazepines, only five - triazolam, flurazepam, temazepam, quazepam, and estazolam - have received FDA approval for the pharmacological treatment of insomnia.[9, 25] Drugs from this group differ in the onset of action, duration of effects, and metabolic pathways. When prescribing benzodiazepines, special attention should be given to patients with liver or kidney impairments, as well as older adults, as these factors can lead to drug accumulation in the body, increasing the risk of adverse effects. [26,28]

Adverse effects are common with the use of benzodiazepines, as shown in a meta-analysis by Holbrook et al. [27]. These include negative effects on cognitive functioning, such as memory impairment, including anterograde amnesia, impaired motor coordination, and an increased risk of falls, particularly in the elderly [28]. Other adverse effects may involve dizziness, reduced ability to operate vehicles, and a higher risk of accidents, especially with long-acting benzodiazepines [5, 26–30]. A particularly dangerous adverse effect of benzodiazepines is respiratory depression, which is most likely to occur in patients with pre-existing breathing disorders such as sleep apnea syndrome and chronic pulmonary disease, the presence of these conditions is a contraindication to the use of benzodiazepines. [9, 30] Benzodiazepines have a high potential for addiction and, therefore, can be abused. [26, 30] Chronic use of benzodiazepines disrupts the quality of sleep by reducing the duration of deep sleep. Additionally, even after a few weeks of therapy, rebound insomnia and increased anxiety may

occur. [28] Regular and prolonged use of benzodiazepines leads to the development of tolerance and both psychological and physical dependence. Benzodiazepine withdrawal symptoms are similar to those of alcohol withdrawal and can be life-threatening [26] According to a meta-analysis by Barker et al. [29], negative effects on cognitive functions may last even up to 6 months after withdrawal from long-term benzodiazepine use.
Given the risks associated with prolonged benzodiazepine use, including the risk of dependence, their administration is not recommended for more than 2-4 weeks. [30] The 2023 European Insomnia Guideline also does not recommend the use of these medications beyond 4 weeks. [5]

**2) Non-benzodiazepine hypnotics**

Non-benzodiazepine hypnotics, also known as „Z-drugs," are the most frequently prescribed medications for insomnia. [28]
Their mechanism of action, similarly to benzodiazepines, involves binding to the GABA-A receptor, but they do so more selectively than benzodiazepines, binding mainly to type I receptors. As a result, they act mainly as sedatives rather than anxiolytics. Due to more selective binding to the GABA-A receptor, Z-drugs cause fewer side effects compared to benzodiazepines. [25]
Non-benzodiazepine hypnotics are only approved for the indication of insomnia.
As a result of their effects, sleep latency is shortened, and sleep quality is enhanced, though the overall duration of sleep may not be significantly increased. [32] A meta-analysis of data submitted to the Food and Drug Administration [33] from 13 studies containing 65 separate drug-placebo comparisons and including 4378 participants found that Z-drugs reduced sleep latency by an average of 22 minutes compared to the placebo group. Compared to benzodiazepines, Z-drugs have a faster onset of action and a shorter half-life (1-7h), which results in fewer residual effects the next day, such as impaired motor skills or memory disturbances. [32]
The FDA currently approves three non-benzodiazepine drugs for treatment of insomnia:
- Zolpidem - reduces sleep latency, increases total sleep duration, is also available in extended-release formulations, lower than standard doses of this medication are recommended for women due to delayed drug elimination [32]
- Zaleplon - a very short-acting drug, reduces sleep latency, can be used for nighttime awakenings, but is not suitable for treating difficulties in maintaining sleep. [32]
- Zopiclone (the active enantiomer is eszopiclone) - effective in both sleep induction and maintenance; has the longest duration of action, which contributes to an increased risk of residual effects. [32]
Adverse effects of non-benzodiazepine hypnotics include sedation, memory impairment, disorientation, nightmares, amnesia, headaches, dizziness, hallucinations, falls, an increased risk of fractures (especially in older adults), impaired ability to operate vehicles resulting in motor vehicle accidents, parasomnias, gastrointestinal disturbances, overdose, tolerance, and addiction. [28, 31, 32, 34] Due to more adverse side effects in the elderly, lower doses are recommended in this age group. [32] At higher doses, Z-drugs may produce euphoric, anxiolytic, and stimulating effects, which contribute to their potential for abuse. [28] Cases of addiction, misuse, and severe adverse effects are increasingly being reported, particularly with zolpidem. Therefore, caution is advised when using these medications, especially in older adults and patients with mental health disorders. [32] The use of Z-drugs should generally be limited to a maximum of four weeks. Although eszopiclone and extended-release zolpidem (zolpidem

ER) have been studied for longer durations, up to six months for zolpidem ER [35] and up to twelve months for eszopiclone [36],

their prolonged administration requires great caution. When considering use beyond four weeks, the potential benefits and risks should be carefully evaluated and discussed individually with each patient. [5]
Given the serious side effects and risk of addiction, the 2023 update to The European Insomnia Guideline does not support the use of non-benzodiazepine hypnotics in the long-term treatment of insomnia beyond 4 weeks. [5]

**3) Melatonin receptor agonists**

Melatonin is a hormone produced and secreted by the pineal gland during the night. Exposure to light inhibits its production. Melatonin's primary function is to regulate circadian rhythms, it is crucial for falling asleep and maintaining sleep. Reduced production of this hormone may contribute to the onset of insomnia. Endogenous melatonin levels decrease with age, which may lead to sleep difficulties in older adults. It binds to melatonin receptors, MT1 and MT2, located in the hypothalamic suprachiasmatic nuclei (SCN). Melatonin is effectively used to treat sleep disorders caused by disruptions in the biological clock, such as jet lag, sleep issues in shift workers, and delayed sleep phase syndrome. [37, 38] It has a high safety profile with mild side effects, can be used long-term, and does not lead to addiction. [2] Melatonin is available as an OTC drug in Europe and the US. [4,5] The meta-analysis by Choi et al. [39], which reviewed 24 randomized controlled trials, assessed the efficacy of melatonin compared to placebo or other hypnotic agents in enhancing sleep quality and duration in patients with chronic insomnia. For non-comorbid insomnia, melatonin significantly improved sleep onset latency and total sleep time only in children and adolescents. In adults, melatonin did not show any significant effects on sleep onset latency, total sleep time, or sleep efficiency. For comorbid insomnia, melatonin reduced sleep onset latency across all age groups, although only one study was conducted in adults. Based on these results, melatonin may be effective in children and adolescents, but its efficacy in adults remains unproven. Melatonin's effectiveness in treating sleep disorders is limited due to its short half-life of 20-40 minutes. As a result, prolonged-release melatonin and melatonin receptor agonists with longer half-lives have been developed. [40]

**- Prolonged-release melatonin**
The development of prolonged-release melatonin (PRM) was dictated by the rapid absorption and short half-life of melatonin, as well as documented decline in melatonin production with age and the associated deterioration in sleep quality. Due to the sustained release of PRM in the gastrointestinal tract, this drug mimics the natural patterns of melatonin secretion in the human body. The peak concentration of melatonin in plasma occurs 2.6 hours after administration, the concentration is maintained for the next 3.5 hours and then slowly decreases, maintaining effective serum concentrations of melatonin throughout the night. [41]
Wade et al. [42] conducted a placebo-controlled trial of 2 mg prolonged-release melatonin, including 354 primary care patients. The main outcome was measured by responder analysis; the responder was a patient who improved 10 mm or more on the QOS (quality of sleep) and BFW (behavioral integrity the following morning) domains of the Leeds Sleep Evaluation Questionnaire. This analysis revealed clinically meaningful improvements in sleep quality and morning alertness with extended-release melatonin compared to placebo, as confirmed by

responder analysis (26% vs. 15%; $p = 0.014$) as well as on each of these parameters separately. A significant enhancement in sleep quality was observed, as measured by the Pittsburgh Sleep Quality Index (PSQI) ($p = 0.036$). Sleep latency was also significantly reduced, with a decrease of 24.3 minutes for the treatment group compared to 12.9 minutes for placebo, a result comparable to that of widely used sleep medications ($p = 0.028$). Additionally, patients experienced a significant enhancement in quality of life ($p = 0.034$), as measured by the WHO-5 questionnaire. Prolonged-release melatonin exhibited a favorable safety profile, with no significant differences in safety-related measures observed between the treatment and placebo groups.
The efficacy and safety of 2 mg prolonged-release melatonin were demonstrated in a 6- to 12-month double-blind, placebo-controlled study by Lemoine et al. [43], involving patients aged 20 to 80 with primary insomnia. The discontinuation of the drug after 12 months did not lead to adverse effects, rebound insomnia, withdrawal symptoms, or suppression of endogenous melatonin production. Prolonged-release melatonin also improves sleep quality in patients with schizophrenia and major depressive disorders. [41] It has been approved by the European Medicines Evaluation Agency for insomnia treatment in patients over 55 years of age in Europe. [5]

**- Ramelteon**

The synthetic melatonin receptor agonist - Ramelteon was approved by the FDA in 2005 for the treatment of insomnia characterized by difficulty in sleep onset. [41] Currently, it is not available in Europe. [5]
Ramelteon is a highly selective agonist of the melatonin MT1 and MT2 receptors, exhibiting an affinity 3 to 16 times stronger than that of melatonin to these receptors. [38] It has negligible binding affinity for other receptors, including MT3, dopaminergic, and GABAergic receptors. [44]
In a meta-analysis by Kuriyama et al. [45] involving 5812 patients with insomnia or insomnia symptoms. Ramelteon has been shown to reduce sleep latency (weighted mean difference [WMD], - 4.30 min [95% CI, 7.01 to 1.58]) and improve sleep quality (standardized mean differences [SDM], 0.074 [95% CI, 0.13 to 0.02]) compared to placebo. No effect on total sleep time was observed. The only significant adverse effect observed was somnolence. Based on these findings, ramelteon improves some sleep parameters in patients with insomnia, but its clinical impact appears to be small. It is characterized by a high safety profile, no risk of dependence, and a benign profile of adverse effects. [45] Notably, ramelteon does not cause motor or cognitive impairment, even when administered at doses up to 20 times the recommended therapeutic dose. [44]

According to the European Insomnia Guideline 2023, due to insufficient evidence and, therefore, lack of proven efficacy of fast-release melatonin and ramelteon, these drugs are not recommended for the treatment of insomnia, except in cases where circadian factors are involved. Given the evidence in several studies, the prolonged-release melatonin can be considered in patients ≥ 55 years of age with insomnia in both short and long-term (beyond 4 weeks) administration. [5]

**4) Dual orexin receptor antagonists**

In 2014, the FDA approved the first of a new group of sleep medications, suvorexant. It is a dual orexin receptor antagonist. This group also includes lemborexant and daridorexant. [46]

Orexins are excitatory neurotransmitters secreted by the hypothalamus that stimulate the state of wakefulness. Dual orexin receptor antagonists (DORAs) work by blocking the signals responsible for arousing wakefulness rather than directly inducing sleep like benzodiazepines or nonbenzodiazepine GABA receptor agonists. [47] They cross the blood-brain barrier and act as antagonists of both orexin receptor 1 (OX1R) and orexin receptor 2 (OX2R), exhibiting comparable affinity for each. By blocking the binding of the wake-promoting neuropeptides orexin-A and orexin-B to these receptors, DORAs diminish the brain's wake drive. [46] Of this group, only daridorexant has been approved by the European Medicines Agency (EMA, 2022/2023). It is approved for the treatment of insomnia in adults lasting at least three months and has a considerable impact on daytime functioning. [5]A meta-analysis of 4 randomized clinical trials by Jiang et al. [48] included 2271 patients diagnosed with insomnia disorder who were administered daridorexant (5mg/10mg/25mg/50mg) or placebo. It showed that daridorexant at doses of 25 mg and 50 mg significantly improved insomnia-related outcomes compared to placebo. At the 1-month follow-up, 50 mg demonstrated strong short-term efficacy with notable reductions in wake time after sleep onset (WASO) (SMD = –0.62), sleep latency (LPS) (SMD = –0.36), and daytime sleepiness (SMD = –0.37), along with an increase in total sleep time (TST) (SMD = 0.45), all with $p < 0.001$. These improvements were sustained at 3 months, with 50 mg continuing to show superior effects over 25 mg in all parameters. At month 3, WASO and LPS were reduced (SMD = –0.53 for both), sTST increased (SMD = 0.35), and daytime functioning improved (measured by Insomnia Daytime Symptoms and Impacts Questionnaire, SMD = –0.31). The 25 mg dose also showed significant, though less pronounced, benefits across the same measures. Improvements were observed as early as days 1–2 of treatment, with 50 mg dose providing the most consistent results. The most commonly reported side effects were nasopharyngitis, fatigue, and headache. Daridorexant was well tolerated at all doses investigated.

To evaluate the long-term safety and tolerability of daridorexant, Kunz et al. [49] conducted a double-blind study, where patients were administered daridorexant (10 mg/25 mg/50 mg) or placebo. The 40-week treatment period was followed by a 7-day placebo run-out. It showed improvements in sleep parameters and daytime functioning, with the greatest effects observed at the 50 mg dose. Daridorexant significantly increased self-reported sleep time and improved daytime functioning, with the strongest effects at week 12 (total sleep time [TST] increased by 20.4 minutes [95% CI: 4.2, 36.5] and maintained through week 36 (TST increased by 17,8 minutes [95% CI: –0,4 to 35,9]). It also improved all Insomnia Daytime Symptoms and Impacts Questionnaire scores compared to placebo. The adverse effects were similar across all groups and included, most commonly, nasopharyngitis. The other adverse effects, including falls, headache, and somnolence, were reported in < 3% of patients, and dizziness and fatigue in < 2% of patients in any group. Daridorexant during the course of 12 months was safe, well tolerated, and did not cause next-day sleepiness, tolerance, rebound insomnia, dependence, or withdrawal symptoms at any of the studied doses. The findings of this study support the use of daridorexant for long-term treatment of insomnia.

Following the European Insomnia Guideline, an update 2023 [5], orexin receptor antagonists can be used for periods of up to 3 months. In certain cases, treatment may be prolonged for up to one year, but the advantages and disadvantages of such therapy should be discussed with each patient individually.

### 5) Histamine receptor antagonists

Doxepin is a sedating tricyclic drug that, in low doses, 3 and 6 mg, is approved by the FDA for treating insomnia associated with difficulty with sleep maintenance. Doxepin works by blocking histamine H1, cholinergic, and alpha-1-noradrenergic receptors. It also prevents the reuptake of noradrenaline and serotonin. Low doses of doxepin selectively block H1 receptors but have a minimal affinity for adrenergic and serotonin receptors. The effect on other doxepin receptors is revealed at higher doses, which are used in the treatment of depression. [25] Doses above 75 mg are used for this indication. [50] For adult insomnia treatment, a 6 mg dose is administered 30 minutes before bedtime. In older adults (≥65 years), treatment typically begins with a 3 mg dose, which may be increased to 6 mg if the initial dose proves insufficient. [51]
It is believed that inhibiting the histamine H1 receptor during a phase of the circadian rhythm when both histamine activity and alertness naturally decline may help promote and maintain sleep. [51]
A meta-analysis by Yeung et al. [50], where nine randomized placebo-controlled trials were analyzed, found that low-dose doxepin had a small to medium effect size against placebo for sleep maintenance and sleep duration but not for sleep initiation. No significant next-day residual effect was observed with low-dose doxepin. The most common side effects were headache, somnolence, and dry mouth. In another study, a 12-week randomized, double-blind, placebo-controlled trial conducted by Krystal et al. [52] that involved elderly patients with chronic primary insomnia, doxepin at a 3 mg dose produced significant improvements over placebo on the first night in several sleep parameters: wake time after sleep onset (WASO, $p < 0.0001$), total sleep time (TST, $p < 0.0001$), overall sleep efficiency (SE, $p < 0.0001$), SE in the last quarter of the night ($p < 0.0001$), and SE during the eighth hour of sleep ($p < 0.0001$). These benefits were maintained through night 85, with continued significance observed for WASO, TST, overall SE, and SE in the final quarter of the night. Doxepin 1 mg also showed notable improvements across the same measures. Overall, the therapeutic effect of doxepin was most pronounced during the final part of the night and was not associated with next-day residual effects, memory impairment, complex sleep behaviors, anticholinergic side effects, weight gain, or increased appetite. No signs of dependence were observed during the course of the trial. The findings of these studies indicate that low-dose doxepin has no potential for abuse, is associated with a benign side effect profile, and does not produce next-day residual effects. It can be used in patients with sleep maintenance problems, especially those who report early morning awakenings, which is often the case with elderly people experiencing insomnia. Unfortunately, the 3 and 6 mg doses are only available in the original „Silenor" formulation available in the United States. In Europe, the lowest available dose of doxepin is 10 mg [47]
In Europe, doxepin is not approved for the treatment of insomnia without comorbid depression. However, according to the 2023 European Insomnia Guidelines [5], based on available scientific evidence, it may be used off-label for short-term treatment of insomnia (up to 4 weeks). Long-term use should be considered individually for each patient.

**5) Sedative antidepressants**

Sedative antidepressants, which include agomelatine, amitriptyline, doxepin, mianserin, mirtazapine, trazodone, and trimipramine, are frequently used medications for insomnia associated with comorbid conditions as well as in primary insomnia. [5] In patients with coexisting anxiety or depressive disorders, sedative antidepressants can be an appropriate form of treatment. [10] However, in Europe, none of these medications are officially approved for the treatment of insomnia as a stand-alone condition without coexisting depression. [5] Apart from doxepin, none have received FDA approval for the treatment of insomnia disorder either.

[4] Sedating antidepressants are generally prescribed at lower doses for the off-label treatment of insomnia than for managing depression. [53]
A meta-analysis by Everitt et al. [53] on the use of antidepressants for insomnia in adults found that short-term treatment with low-dose doxepin or trazodone may lead to a significant but small improvement in sleep quality compared to placebo. The effects of doxepin on sleep parameters have been thoroughly discussed earlier in this paper.
Trazodone is an antagonist at 5-HT1A, 5-HT2, and alpha-1 adrenergic receptors and also acts as a weak inhibitor of serotonin reuptake. The meta-analysis involving 370 participants showed a moderate improvement in self-reported sleep outcomes with trazodone compared to placebo (SMD -0.34, 95% CI -0.66 to -0.02). However, trazodone was also associated with a higher incidence of adverse effects, including morning grogginess, dry mouth, and increased thirst.
The safety and tolerability of antidepressants for insomnia remain unclear, largely due to insufficient data on adverse events.
According to the European Insomnia Guideline 2023 [5], low-dose antidepressants may be used for short-term treatment of insomnia, however, contraindications and potential side effects have to be carefully evaluated. While long-term use is generally not recommended due to limited supporting evidence and the risk of adverse effects, it may be considered in select cases.

**6) Antihistamines**

First-generation antihistamines have sedative properties, but research on their effectiveness in treating sleep disorders is very limited. These medications can lead to side effects such as dry eyes, dry mouth, constipation, urinary retention, and confusion, with older adults being more vulnerable. Additionally, tolerance to the sedative effect of first-generation antihistamines develops rapidly, typically between the third and fourth day of use, which limits their effectiveness in the treatment of insomnia. [55]
Because of insufficient evidence, antihistaminics are not recommended by the European Insomnia Guidelines for insomnia treatment, either short or long term. [5,54]

**7) Atypical antipsychotics**

Sedating atypical antipsychotics, particularly quetiapine, have been used off-label for the treatment of insomnia. However, a meta-analysis by Thompson et al. found that quetiapine does not produce significant improvements in sleep parameters compared to placebo in individuals with primary insomnia. Moreover, atypical antipsychotics are associated with a range of adverse effects, including metabolic disturbances, weight gain, dry mouth, and dizziness.[56]
High-quality evidence on the efficacy and safety of atypical antipsychotics for the treatment of insomnia is currently lacking.
Due to limited evidence and their potential side effects, antipsychotics are not recommended for the treatment of insomnia without comorbidities in either the short or long term by the European Insomnia Guidelines. [5,54]

**Conclusions**

Sleep is one of the most essential physiological needs, and insomnia, given its high prevalence in the population, significantly affects both health and quality of life. Early recognition and timely intervention are, therefore, crucial. Insomnia is a well-established risk factor for numerous mental and physical health conditions, including depression, obesity, hypertension,

and cardiovascular diseases. Due to its substantial impact on daily functioning and overall well-being, effective diagnosis and treatment are vital.

This paper provides an evidence-based overview of insomnia treatment options. Non-pharmacological interventions, particularly cognitive behavioral therapy for insomnia (CBT-I), play a central role in the management of insomnia. Numerous studies have demonstrated that CBT-I is at least as effective as pharmacological treatments in the short-term, while also providing more durable long-term benefits and a significantly lower risk of adverse effects. Given its proven efficacy and safety profile, CBT-I should be considered a first-line treatment in clinical practice. Patients should be informed about its advantages and actively encouraged to engage in behavioral strategies to improve sleep quality.

When pharmacological treatment is necessary, a range of effective options is available. Treatment choice should be individualized based on the patient's primary sleep complaints (e.g., difficulty falling asleep vs. early awakenings), age, and comorbidities. It is important to remember that, in addition to commonly prescribed benzodiazepines and non-benzodiazepine hypnotics, there are other medications with proven efficacy and significantly better safety profiles. When using pharmacological treatments in clinical practice, it is essential to carefully evaluate the potential benefits and risks associated with the use of a given medication. While benzodiazepines and non-benzodiazepine hypnotics can be effective short term, their use carries risks such as dependence, cognitive impairment, and adverse side effects, especially in older or medically vulnerable patients. These medications should be avoided for long-term use, and healthcare providers must remain vigilant for signs of misuse or drug-seeking behavior.

Overall, insomnia treatment is critical not only for improving individual patients' quality of life but also from a broader social and economic perspective, as insomnia significantly impacts daytime performance and productivity.

**Disclosure**

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