International Journal of Innovative Technologies in Social Science

e-ISSN: 2544-9435

Scholarly Publisher
RS Global Sp. z O.O.
ISNI: 0000 0004 8495 2390

Dolna 17, Warsaw,
Poland 00-773
+48 226 0 227 03
editorial_office@rsglobal.pl

ARTICLE TITLE	CURRENT REVIEW OF TREATMENTS FOR INSOMNIA: EFFECTIVENESS, EFFICACY AND ADVANCES
DOI	https://doi.org/10.31435/ijitss.4(48).2025.4536
RECEIVED	15 November 2025
ACCEPTED	26 December 2025
PUBLISHED	30 December 2025
LICENSE	The article is licensed under a **Creative Commons Attribution 4.0 International License.**

CURRENT REVIEW OF TREATMENTS FOR INSOMNIA: EFFECTIVENESS, EFFICACY AND ADVANCES

Adrianna Kaczmarek *(Corresponding Author, Email: adrianna.kaczmarek99@gmail.com)*
10th Military Research Hospital and Polyclinic, Independent Public Healthcare Centre in Bydgoszcz, Bydgoszcz, Poland
ORCID ID: 0009-0005-6490-0483

Franciszek Szweda
Władysław Biegański Regional Specialist Hospital in Grudziądz, Grudziądz, Poland
ORCID ID: 0009-0001-1251-1380

Tomasz Poczwardowski
Jan Biziel University Hospital No. 2, Bydgoszcz, Poland
ORCID ID: 0009-0000-2056-1073

Katarzyna Anna Kowalska
Norbert Barlicki Memorial Teaching Hospital No. 1 of the Medical University of Łódź, Łódź, Poland
ORCID ID: 0009-0000-8444-1505

Jakub Tomasz Latos
Medical University of Łódź, Łódź, Poland
ORCID ID: 0009-0001-1262-0173

Marcin Chwalczuk
116th Military Hospital in Opole, Opole, Poland
ORCID ID: 0009-0007-1357-6788

Olivia Grygorcewicz
Medical University of Łódź, Łódź, Poland
ORCID ID: 0009-0005-0983-7661

Marta Koneczna
Medical University of Łódź, Łódź, Poland
ORCID ID: 0009-0006-7373-6539

Karolina Alicja Krystyniak
Norbert Barlicki Memorial Teaching Hospital No. 1 of the Medical University of Łódź, Łódź, Poland
ORCID ID: 0009-0003-1880-7232

Kinga Augustyniak
Independent Public Health Care Institution in Turek, Turek, Poland
ORCID ID: 0009-0000-7631-3685

ABSTRACT

This narrative review aimed to synthetically evaluate the current efficacy of pharmacological and non-pharmacological methods for treating chronic insomnia, to identify their risk profiles, and to determine the future prospects and chances for the development of modern therapeutic strategies.

Methods: A literature analysis was conducted, encompassing key clinical trials and systematic reviews concerning Cognitive Behavioral Therapy for Insomnia (CBT-I), hypnotics (BDZs, NBDZAs, DORAs), and innovative treatment modalities (neuromodulation, novel molecules, diet, stimulants, physical avtivity).

Key findings: The analysis demonstrated that CBT-I invariably remains the first-line therapy and gold standard, showing durable efficacy in improving objective and subjective sleep parameters (latency, total sleep time, quality) while minimizing the risk of dependence, in contrast to pharmacotherapy. Pharmacological methods, due to their lower safety profile, are considered second-line therapy. A significant advance in this area is the introduction of Dual Orexin Receptor Antagonists (DORAs), such as daridorexant, which is safe and well-tolerated in long-term treatment, filling a gap left by older hypnotics. Active development of innovative techniques (e.g., NIBS, VeNS) was also noted, but their implementation is hindered by a lack of protocol standardization and insufficient clinical evidence.

Conclusions: CBT-I is the optimal strategy for insomnia management. However, further research on its long-term efficacy is essential. Future studies should focus on implementing sequential therapies and developing DORAs and neuromodulation techniques for personalized treatment. Regardless of the intervention, comprehensive sleep hygiene is crucial for maintaining remission.

KEYWORDS

Insomnia, Insomnia Treatment, CBT-I, Brain Stimulation, DORAs

CITATION

Adrianna Kaczmarek, Franciszek Szweda, Tomasz Poczwardowski, Katarzyna Anna Kowalska, Jakub Tomasz Latos, Marcin Chwalczuk, Olivia Grygorcewicz, Marta Koneczna, Karolina Alicja Krystyniak, Kinga Augustyniak (2025) Current Review of Treatments for Insomnia: Effectiveness, Efficacy and Advances. *International Journal of Innovative Technologies in Social Science*. 4(48). doi: 10.31435/ijitss.4(48).2025.4536

Introduction

Insomnia is the most common sleep disorder and the second most frequent mental disorder, immediately after anxiety disorders [1]. Insomnia represents a significant clinical concern, exhibiting high prevalence rates, reported in up to half of all primary care patients. This condition may manifest independently (as primary insomnia) or concomitantly with underlying medical illnesses or psychiatric disorders. Furthermore, untreated insomnia is recognized as a contributing risk factor to both the onset and the worsening (exacerbation) of these co-occurring health issues [2]. Diagnostic criteria encompass difficulties with sleep initiation, nocturnal awakenings or waking up too early, or poor, non-restorative sleep quality [3]. Furthermore, the disorder impairs daytime functioning and well-being [3]. The temporal criterion specifies that the disturbance occurs for at least 3 days in a week, when symptoms are present for less than three months (short term insomnia), or when they persist for three months or longer (chronic insomnia) [3]. The prevalence of chronic insomnia is estimated at approximately 10% in Western industrialized populations, with a higher prevalence observed among females compared to males [4].

Chronic insomnia is fundamentally a manifestation of global neuronal and somatic hyperarousal, stemming from persistent dysregulation within the sleep- and wake-promoting systems. The pathophysiology encompasses impaired inhibition across key cerebral circuits [5]:

- Ascending Reticular Activating System (ARAS): enhanced activity of the ARAS is observed within the brainstem, including its cholinergic and monoaminergic branches. This leads to abnormally high cortical activation and is directly implicated in the inability to both initiate and maintain sleep.
- "Flip-Flop Switch" Mechanism Dysfunction (VLPO): There is an impairment of reciprocal inhibition between the arousal-promoting systems (ARAS) and the VLPO (ventrolateral preoptic nucleus) in the

hypothalamus, which promotes sleep via GABA and galanin. This failure results in unstable sleep/wake boundaries and the persistence of heightened vigilance.

- Thalamus and Prefrontal Cortex: Impaired deactivation of the thalamic reticular nuclei is noted (leading to sensory hyper-responsiveness), alongside aberrant activation of the prefrontal cortex, serving as a correlate for the failure of cognitive deactivation and persistent rumination.
- Neuroendocrine Axis: The presence of HPA axis dysfunction (Hypothalamic-Pituitary-Adrenal axis) is evidenced by elevated nocturnal concentrations of cortisol and ACTH, correlating with accelerated sympathetic nervous system activity and the maintenance of a physiological state of readiness.

It should be noted that the involvement of the HPA axis is an observation restricted to a subset of patients, and certain mechanisms, such as the role of the basal ganglia, remain hypothetical, necessitating caution in their interpretation as universal correlates of insomnia. Studies [6],[7] indicate that patients with primary insomnia exhibit increased EEG activity, specifically high-frequency beta and gamma oscillations, at sleep onset and throughout the NREM sleep phase. This suggests that these patients maintain active information processing during sleep, which also correlates with a negative subjective perception of sleep quality.

It is also emphasized that biological mechanisms interact with cognitive, behavioral, and emotional factors in the perpetuation of insomnia [5].

Insomnia represents a clinically significant problem due to its impact on the daily functioning of affected individuals. Concurrently, it is often a neglected issue, frequently treated symptomatically without delving into its underlying etiologies. This paper aims to review the current literature concerning the treatment of insomnia and the directions for future research in this area.

Materials and methods

This paper presents a narrative review of the scientific literature, aimed at presenting and summarizing the current literature regarding both pharmacological and non-pharmacological therapeutic methods for the treatment of chronic insomnia, focusing on their efficacy, safety, and advancements.

The literature search was systematically conducted in the following electronic bibliographic databases and trial registries: PubMed/MEDLINE, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), and PsycINFO.

To maximize search comprehensiveness and minimize the risk of bias, the search was supplemented by including the SpringerLink platform and performing a hand-search of the reference lists from key identified articles and previous systematic reviews.

The search was limited to publications from the last 10 years to ensure maximal data currency.

The search was strictly focused on scientific works concerning therapeutic interventions for insomnia, specifically addressing the following thematic domains:

1. The efficacy of pharmacological interventions (e.g., hypnotics, new generation drugs, antidepressants) in the treatment of primary and chronic insomnia.
2. The effectiveness of non-pharmacological methods, with particular emphasis on Cognitive-Behavioral Therapy for Insomnia (CBT-I) and other behavioral interventions (e.g., stimulus control, sleep hygiene, relaxation therapies).
3. The comparison and safety assessment of various insomnia treatment strategies.
4. Advancements and future research directions in insomnia treatment, including new drug classes (e.g., orexin receptor antagonists) and therapeutic technologies.

Articles were included if they met the following criteria:

1. Study Type: Randomized Controlled Trials (RCTs) and established systematic reviews with meta-analyses assessing the efficacy or safety of insomnia treatments.
2. Population: Adult patients diagnosed with primary or chronic insomnia according to established diagnostic criteria (e.g., DSM-5 or ICD-11).
3. Intervention: Any intervention aimed at treating insomnia, including sleep medications, psychotherapies (CBT-I), behavioral interventions, and other non-pharmacological methods.
4. Language: Publications in English or Polish.

The review included randomized controlled trials, prospective studies, observational studies, as well as previous narrative and systematic reviews.

The review rigorously excluded the following publication types to maintain data quality: comments, letters to the editor, case reports, conference abstracts, and study protocols (without published results).

The selection process was independently performed by two reviewers in two stages. First, titles and abstracts were screened against the inclusion criteria. Second, the full texts of the tentatively included articles were retrieved and assessed for final eligibility. Any disagreements between the two reviewers were resolved through discussion and consensus or, if necessary, consultation with a third reviewer.

The study results were grouped thematically, which allowed for the separate discussion of the efficacy of specific therapeutic modalities, their safety profile, and the latest developments in the field of insomnia treatment.

The adopted narrative methodology allowed for the flexible inclusion of studies with diverse research designs and various assessment instruments. This adaptability is particularly relevant for a topic with such a broad spectrum of interventions as pharmacological and non-pharmacological treatment methods for insomnia.

In this review, the primary objective was the qualitative interpretation and substantive synthesis of the available evidence, rather than the conduct of a quantitative meta-analysis. For this reason, statistical analysis procedures and formal assessment of systematic bias risk were not performer.

Data were extracted independently using a standardized form, capturing the following details: authors, publication year, country of origin, study design (RCT/Meta-analysis), participant characteristics (sample size, age, diagnosis criteria), intervention type and dosage/duration, observation period, and key objective (e.g., PSG, Total Sleep Time (TST) and Sleep Efficiency (SE) and subjective (e.g., ISI, sleep diaries, QoL scores, QoS, sNAW, Sleep Latency (SL), subjective Total Sleep Time (sTST), Latency to Persistent Sleep (LPS), Wake Time After Sleep Onset (WASO).

Results

I. CBT-I

Cognitive Behavioral Therapy (CBT), and specifically its specialized variant designed for the treatment of insomnia (CBT-I), is recommended as the first-line treatment for this condition in adults of any age (including patients with comorbidities) [8], [9],[10],[11], [16] and the standarized protocol has been developed [9]. A primary advantage of employing CBT-I over pharmacological agents is its demonstrable superiority in maintaining long-term efficacy, given that evidence supporting sleep medications is typically limited to short-term outcomes [8]. Furthermore, while CBT-I may be associated with side effects, these are generally less severe than the significant risks linked to hypnotics, such as the potential for drug dependence, overuse, accidents, or the exacerbation of comorbid chronic pain. Beyond sleep improvement, CBT-I has the added benefit of mitigating symptoms of depression and anxiety and enhancing patients' sleep-related quality of life [8]. According to Chan NY et al. [12] CBT-I is the most extensively studied non-pharmacological approach for insomnia management, supported by strong evidence across various populations. CBT-I has demonstrated efficacy in achieving significant sleep improvements across diverse age ranges and clinical groups. This includes populations where insomnia is comorbid with psychiatric or medical problems. Furthermore, these substantial sleep benefits are produced by different formats of CBT-I delivery. Promising evidence suggests that CBT-I also yields concomitant improvement in functional outcomes. Specifically, this therapeutic method is effective in the context of mitigating symptoms of depression, anxiety, and pain. This dual effect indicates that CBT-I functions as an effective adjunctive treatment for patients dealing with psychiatric and medical comorbidities. Miller CB et al. [13] also provide valuable implications about CBT-I efficacy in different insomnia subtypes based on polisomnography (PSG). This retrospective cohort study confirms that CBT is an effective intervention across different polysomnographically defined insomnia subtypes, specifically demonstrating a clinically significant reduction in ISI scores for both normal sleep duration (I-NSD) and short sleep duration (I-SSD) insomnia subgroups. Critically, patients with I-NSD showed a significantly higher response rate to CBT compared to those with I-SSD (70% vs. 37%), suggesting that CBT may be particularly potent for the I-NSD subtype. These findings underscore the importance of utilizing PSG-based subtyping to personalize insomnia treatment algorithms and maximize long-term therapeutic success. According to this study [13] Cognitive Behavioral Therapy (CBT), delivered either in a digital or face-to-face format demonstrated high acceptability among participants with insomnia disorders and among the participants who completed the follow-up assessment, CBT was found to be effective for the reduction in the Insomnia Severity Index (ISI), which confirms the efficacy of this therapy.

Furthermore, Morin et al. [14] analysed the difference between digital CBT-I (dCBT-I) and face-to-face CBT-I (FtfCBT-I). The current study established that comparing to medication alone, first-step treatment with dCBT-I or combined treatment resulted in significantly larger effects on reducing insomnia severity than only pharmacological treatment. Furthermore, the dCBT-I constitutes an effective treatment modality for patients

experiencing chronic insomnia within primary care settings. Accroding to Forma et al. [19] review it can also be more effective compared to FtFCBT-I, sleep medications or placebo. A distinct advantage observed was the potential for treatment intensification to FtFCBT-I for individuals who did not achieve initial remission.

Rajabi Majd N et al. [15] also confirm these findings in their 2-arm single-blind parallel-group RCT. Outcomes were assessed at baseline and 1 month, 3 months, and 6 months postintervention. Sleep hygiene was improved in the CBT-I group compared with the PE group as well as severity of insomnia and sleep quality.

Moreover, Forma et al. [18] in their meta-analysis established that the prescription digital therapeutic (PDT) delivery of CBT-I offered the highest statistical probability of effectiveness for chronic insomnia, superior to both placebo and face-to-face CBT-I. This conclusion is based on significant reductions in the mean ISI score and higher rates of ISI-defined remittance. This efficacy highlights PDT's potential to significantly enhance patient access to established CBT-I guidelines. However, defining the most effective and cost-effective long-term interventions requires further research with extended follow-up periods.

When analyzing the long-term effect of CBT-I in the treatment of insomnia, the study conducted by Jernelöv et al. [20] deserves attention. This study aimed to investigate whether improvement was stable at one-year and ten-year follow-up after the completion of CBT-I. Based on the three-arm CBT-I long-term effects RCT, participants initially received an insomnia self-help manual. They were then randomly assigned to one of three groups: a group receiving therapist support (TST), a group without support, or a wait-list group receiving no support after a delay. The six-week intervention involved 133 participants diagnosed with insomnia. At the one-year and ten-year follow-up marks, participants underwent assessment using both self-ratings and interviews. The improvement achieved was statistically significant and maintained well throughout the follow-up period. Specifically, the severity of insomnia remained low, and two-thirds of the participants no longer met the diagnostic criteria for insomnia. This finding extends previous conclusions regarding CBT, confirming its position as the treatment of choice for insomnia.

Despite the efficacy of CBT-I Alimoradi et al. [8] assessed the effects of cognitive behavioral therapy for insomnia (CBT-I) on quality of life. The authors analysed 24 studies including 1977 patients. In the studies analyzed by the authors utilized various measures to assess quality of life, such as QLQ-C30, QLQ-C33, and SF-36 and based on those multiple studies they concluded that CBT-I confirmed a significant, moderate overall effect in improving the quality of life. The effect size of CBT-I on QoL was found to be stronger in patients with primary insomnia compared to individuals with insomnia comorbid with another major disorder. The study's results are primarily generalizable to general health-related QoL, as this was the most common type of measure assessed in the included studies.

In summary, CBT-I remains the first-line treatment for insomnia due to its minimal adverse effects and its efficacy in reducing the severity of insomnia symptoms, particularly among patients with comorbid disorders. However, further research is still warranted owing to challenges in conducting long-term follow-up and the moderate impact observed on patients' overall QoL and its general effectiveness in long-term follow-up.

II. Pharmacological treatment

In case CBT-I proves insufficiently effective, pharmacological intervention is warranted.

Pharmacological Options for Insomnia Treatment [16]:

For the short-term treatment of insomnia, typically defined as a period of up to four weeks, the use of several substance classes is recommended. These include: benzodiazepines, benzodiazepine receptor agonists (often referred to as 'Z-drugs'), daridorexant, and low-dose sedative antidepressants. Although these medications are primarily favored for short-term use, long-term treatment may be considered in individual cases, necessitating a precise assessment of the potential benefits versus risks.

There are also options for extended use. Orexin receptor antagonists may be employed for a duration of up to three months, and in certain clinical circumstances, even longer. A specific recommendation pertains to prolonged-release melatonin, which can be utilized for up to three months, but is restricted to patients aged 55 years and older.

It must be emphasized that certain drug classes are not recommended for the treatment of insomnia. This includes: antihistamines, antipsychotics, immediate-release melatonin, ramelteon, and phytotherapeutics (herbal remedies). Their use for this indication is not advised.

According to study conducted by Buscemi et al. [17] benzodiazepines (BDZs) and non-benzodiazepine hypnotics (non-BDZs) are effective treatments for chronic insomnia, although their use is associated with a risk of harm such as somnolence, headache, dizziness, nausea. Furthermore, there is some evidence indicating that antidepressant drugs (ADPs) are effective in the management of chronic insomnia but also carry some risk of adverse effects (similar to BDZ-s and non-BDZs). In addition, indirect comparisons suggest that non-

benzodiazepine agents (non-BDZs) are safer than benzodiazepines (BDZs). The utility of these review findings may be more relevant for the short-term treatment of chronic insomnia, as only two trials assessed long-term efficacy. Further research is required to investigate the long-term efficacy and safety of these agents for chronic insomnia.

However, Everitt et al. [17] in Cochrane Review has reviewed 23 RCTs with 2806 patients and they suggested that published clinical trials do not provide evidence to support the long-term use of antidepressants in the management of primary insomnia. Regarding short-term therapy, there is insufficient evidence to confidently suggest a benefit from the use of low-dose tricyclic antidepressants (TCAs), trazodone, selective serotonin reuptake inhibitors (SSRIs), or amitriptyline. Further high-quality research is required to reliably assess the long-term efficacy and safety of these interventions.

About the daridorexant (or orexin receptor antagonist), Kunz et al. [21] leaded the extended study that encompassed a forty-week treatment phase, which was followed by a thirty-day safety observation period. This safety follow-up included a seven-day, single-blind, gradual placebo run-down phase. Patients who successfully completed the preceding twelve-week trial and had been receiving oral daridorexant at doses of 10 mg, 25 mg, or 50 mg continued on the identical regimen in a double-blind manner for an additional forty weeks, resulting in a cumulative treatment period of fifty-two weeks. Conversely, participants initially randomized to receive twelve weeks of placebo were re-randomized (1:1). Consequently, they received, under double-blind conditions, either daridorexant at a 25 mg dose or placebo for forty subsequent weeks.

Analysis of the study results indicates that daridorexant, across all tested dosages and administered for a duration of up to one year, is generally safe and well-tolerated by patients afflicted with sleep disorders. Furthermore, daridorexant when administered at the 50 mg dose extended patients' total sleep time and ameliorated both nocturnal and daytime symptoms of insomnia, while simultaneously demonstrating no evidence of tolerance development or dependence. This comprehensive evidence justifies the utilization of the 50 mg daridorexant dose for the long-term management of chronic insomnia in adult populations. These data still require confirmation in clinical practice, given that, at the time of this writing, daridorexant has not yet been introduced to the market in most European countries. Therefore, caution is warranted [16].

Furthermore, a systematic review and meta-analysis conducted by Marupuru et al. [22] evaluated the current evidence regarding the use of melatonin and a melatonin receptor agonist (ramelteon) in older adults, defined as individuals over 50 years, for the treatment of chronic insomnia. Specifically, the review assessed the effects on Total Sleep Time (TST), Sleep Latency (SL), Sleep Efficiency (SE), and subjective sleep quality. The study confirms evidence of moderate efficacy for melatonin and the melatonin receptor agonist (ramelteon) in extending TST and reducing SL. Given the well-established safety concerns associated with conventional hypnotics, such as benzodiazepines and non-benzodiazepine benzodiazepine receptor agonists, melatonin and/or ramelteon may represent safe and effective therapeutic options for older patients suffering from insomnia. The conclusion regarding the moderate efficacy of ramelteon contradicts European guidelines, which do not recommend the use of ramelteon for the treatment of insomnia. Further research in this area may be necessary to either definitively exclude or confirm its efficacy in the future. It must be noted that European guidelines are based on the most reliable scientific evidence and therefore serve as the primary direction for disease management. Nonetheless, this represents a certainly interesting area requiring further analysis.

According to The Eurpoean Insomnia Guideline [16] melperone and pipamperone are the sole medications listing insomnia as an indication for use. However, randomized controlled trials (RCTs) confirming the efficacy of these substances for both short- and long-term treatment are lacking. Consequently, the use of these drugs, as well as quetiapine, is not recommended. Similarly, antihistamines are also not recommended due to a lack of confirmed efficacy, the risk of developing tolerance, and studies reporting an increased risk of mortality [16],[23].

In summary, pharmacological treatment is used when CBT-I methods fail. They are used in short-term treatment, however research on long-term treatment is conducted. The most common drugs are non-BDZs and BDZs but due to many side effects other options such as daridorexant are being analysed.

III. New advancements

Despite the availability of therapeutic options CBT-I remains ineffective in approximately one-third of cases, while currently available pharmacological agents often present with uncertain safety and efficacy profiles [24]. According to this fact, researchers continue to seek novel insomnia treatments that offer efficacy across the broadest possible patient population. The following analysis examines several modern techniques and pharmacological agents used in insomnia management, along with an assessment of their efficacy and future perspectives.

Transcranial electrical stimulation (tES) involves the non-invasive modulation of cortical activity via the application of weak electrical currents through electrodes placed on the scalp. It modifies the spontaneous activity of cortical neurons by altering their excitability [24].

Non-invasive vagus nerve stimulation (nVNS) targets the peripheral branch of the vagus nerve by applying electrical stimulation to the tragus or the auricle of the ear [24].

Cranial cooling techniques are predicated on the hypothesis that reducing the skull's temperature slows brain metabolism, which, in turn, prevents sleep fragmentation and diminishes the perception of wakefulness in patients with insomnia [24].

- Brain stimulation techniques

Modern science offers clinicians tools for the increasingly effective modulation of brain activity using contemporary stimulation techniques, such as non-invasive brain stimulation (NIBS), including rTMS and tES. Recent report [24] suggest that brain stimulation may improve both subjective and objective sleep parameters. However, the influence of the placebo effect remains a critical consideration, as well-controlled studies often indicate that stimulation devices exhibit a similarly potent and lasting effect. Currently, no brain stimulation protocol has been established that yields documented, significant therapeutic benefits for insomnia treatment. The clinical application of these methods is hindered by gaps in the knowledge concerning sleep physiology and the pathophysiology of insomnia. Optimizing stimulation protocols will necessitate a precise understanding of how the cerebral cortex regulates sleep and which patterns of cortical activity are disrupted in patients with insomnia.

Non-invasive vagus nerve stimulation (VeNS) is an emerging technique that applies electrical stimulation to the peripheral branch of the vagus nerve (via the tragus or auricle of the ear). In a double-blind randomized clinical trial, Cheung et al. [25] demonstrated that VeNS can serve as an adjunctive treatment for primary insomnia. They observed a significant reduction in insomnia severity and an improvement in quality of life in the active VeNS group compared to the placebo group.

As for frontal thermal therapy Roth et al. [26], in their prospective randomized controlled trial, demonstrated that a two-day course of frontal thermal brain therapy led to improved polysomnography (PSG) outcomes regarding sleep onset ability in patients with insomnia, and exhibited a mild safety profile.

While the modulation of sleep through brain stimulation is theoretically possible, its clinical efficacy still requires verification. Conversely, preliminary results for VeNS and frontal cooling are encouraging, suggesting that VeNS studies should form the basis for future multicenter comparative trials.

Future research should focus on optimizing stimulation protocols and gaining a better understanding of the pathophysiology of insomnia. This knowledge is crucial so that targeting the cerebral cortex (e.g., using tES or rTMS) can yield clinically significant therapeutic benefits, potentially also through the improvement of daytime functioning as an alternative or supplementary strategy.

- GABA

According to its mechanism of action, the activation of GABA (gamma-aminobutyric acid) receptors exerts an inhibitory and relaxing effect on the central nervous system. In humans, two main types of these receptors have been identified: the fast-acting ionotropic GABAA receptors (GABAAR and the slow-acting metabotropic GABAB receptors (GABABR) [27].

GABAAR activation is associated with sedative-hypnotic, anxiolytic, antidepressant, anticonvulsant, and analgesic effects. GABAARs constitute the primary type of GABA receptors in the brain and are ligand-gated pentameric chloride ion channels. The typical pentamer structure consists of two alpha, two beta, and one gamma subunits, although delta and epsilon subunits may substitute the gamma subunit, and the sigma subunit may replace the beta subunit. The activation of these receptors permits the influx of chloride ions into the cell, leading to neuronal membrane hyperpolarization. This effect exerts an inhibitory influence on neurotransmission, thereby alleviating neuronal hyperexcitability. Furthermore, the stimulation of GABAergic neurons promotes the induction of NREM sleep while simultaneously inhibiting REM sleep [27].

A review of studies [27] on the oral administration of natural or biosynthetic GABA to insomniac individuals suggests that a dose of 100 to 300 mg of biosynthetic GABA is sufficient to achieve a therapeutic effect. Oral GABA supplementation demonstrated improvement in sleep onset, sleep maintenance, morning sleepiness, and fatigue recovery in insomniac individuals, thus facilitating natural sleep induction. However, at least one week of GABA use is required to achieve the full effect. This suggests the necessity of long-term therapy to obtain sustained improvement in insomnia.

Despite the established role of GABA, significant research gaps persist across several key areas. Specifically, there is a lack of clinical trials evaluating existing GABAergic agents. Furthermore, continued

research into the molecular mechanisms of GABA is necessary, including the exploration of its relationship with NF-kappa-B signaling, melatonin's circadian rhythms, and the GABAB receptor, as current knowledge regarding the latter remains limited.

Looking ahead, conducting a greater number of clinical trials is crucial to assess the safety of currently used GABA analogs. Additionally, epidemiological studies are essential for monitoring and confirming the clinical significance of GABA analogs in the treatment of insomnia.

- TS-142 (vornorexant)

TS-142 is a novel dual orexin receptor antagonist (DORA) targeting both the OX1 and OX2 receptors, characterized by rapid absorption and a short plasma half-life pharmacokinetic profile. While the efficacy and safety of TS-142 are not yet fully elucidated, research is ongoing in this area.

Uchiyama et al. [28] conducted a multicenter, randomized, double-blind study involving 24 patients aged 20 to 64 years with diagnosed insomnia. Participants were administered 5 mg, 10 mg, or 30 mg of TS-142 or the corresponding placebo. PSG was used to assess objective parameters, including TST, sleep ffficiency (SE), and the number of awakenings. Patients also maintained sleep diaries for the subjective evaluation of Quality of Sleep (QoS), subjective Number of Awakenings (sNAW), Sleep Latency (SL), and subjective Total Sleep Time (sTST), among other variables. The results were as follows: all doses of TS-142 significantly reduced Latency to Persistent Sleep (LPS) as measured by PSG compared with placebo (a clinically significant effect). A dose-related trend was not observed for LPS. Furthermore, TS-142 at all doses significantly increased Total Sleep Time (TST) and Sleep Efficiency (SE) as measured by PSG. A dose-related trend was observed for the reduction in Wake Time After Sleep Onset (WASO) as measured by PSG.

Regarding adverse events, all adverse events were mild or moderate.

In conclusion, a single oral administration of TS-142 to insomnia patients showed clinically significant improvement in both objective and subjective evaluations of sleep. A single dose of TS-142 was well tolerated. Although the frequency of adverse events increased with dose, the low incidence of next-day residual effects when used within the therapeutic dose range is promising. Furthermore, these data may support the idea that next-day residual effects can be avoided by treating with orexin receptor antagonists, such as TS-142, that have a short half-life.

However, this study had several limitations, notably the relatively small number of patients who completed the study, and the exclusion of elderly patients. Moreover, as this was a single-dose study, the sustained efficacy in repeated dosing of TS-142 needs to be evaluated. Therefore, additional larger studies will be needed to fully evaluate the efficacy, safety, and risk of adverse events in a broader patient population and with long-term use.

- Nutrition, stimulants, sleep hygiene, physical activity

A growing number of studies and scientific evidence suggest that physical activity, sleep hygiene, and nutrition can influence sleep quality. Sejbuk et al. [29] analyzed the effect of these factors on sleep quality in their narrative review:

Dietary Factors and Sleep Architecture

Sleep quality is significantly influenced by macronutrient intake and quality.

- Macronutrients and Tryptophan: The balance and quality of macronutrients are important. Both insufficient protein intake (below 16% of total energy) and excessive intake (above 19% of total energy) may disturb sleep. This is because tryptophan, an amino acid found in proteins, is a precursor to serotonin and melatonin, both of which are crucial for sleep regulation.
- Carbohydrates and Fiber: Diets rich in carbohydrates with a high Glycemic Index (GI) and refined sugars are linked to an increased risk of insomnia and a higher number of awakenings. Conversely, a higher intake of dietary fiber promotes deeper and more restorative sleep.
- Fats: A diet abundant in Saturated Fatty Acids (SFA) is associated with poorer sleep quality. In contrast, consumption of fatty fish and omega-3 fatty acids may positively influence sleep regulation.
- Micronutrients: Vitamin D and gamma-aminobutyric acid (GABA) may potentially improve sleep parameters.

Psychoactive Substances and Sleep Disruption

The consumption of psychoactive substances and stimulants before bedtime represents a fundamental error in sleep hygiene that can disrupt sleep continuity and structure.

- Caffeine: Caffeine acts as an adenosine receptor antagonist, leading to arousal. Caffeine consumption (even up to 6 hours before sleep) leads to a significant deterioration of sleep quality, shortening of total sleep time, and an increased feeling of daytime tiredness.

- Alcohol: Initially, alcohol may reduce sleep latency, but subsequently leads to sleep fragmentation and disruption of REM and NREM phases. Furthermore, alcohol can exacerbate snoring and increase the risk of Obstructive Sleep Apnea.
- Nicotine: Exhibits stimulant effects and is associated with increased difficulty in sleep maintenance, sleep apnea, and lower subjective sleep quality.
- Cannabis: Although short-term use may have hypnotic effects, long-term use leads to tolerance and worsened sleep efficiency, and withdrawal symptoms may exacerbate sleep disorders.

Physical activity

Engaging in moderate to intense physical activity is correlated with improved sleep quality, including greater depth and shorter sleep latency.

- While daytime exercise generally supports sleep, intense exercise late in the evening may delay melatonin secretion and increase physiological arousal, potentially interfering with sleep initiation [29],[30].
- Regular exercise can alleviate symptoms of OSA, partly through weight loss and a positive impact on the upper respiratory tract.

It is vital to keep physical activity as it improves quality of sleep and reduces sleep latency but it i salso helpful in curing sleeping disorders and insomnia [30].

While lifestyle undoubtedly impacts both the quality and quantity of sleep, further large-scale studies in patient populations are still necessary to unequivocally confirm these relationships.

Conclusions

The findings of this analysis indicate that Cognitive Behavioral Therapy for Insomnia (CBT-I) invariably remains the gold standard treatment, demonstrating proven efficacy in improving sleep parameters (quality, duration, and latency), even in cases of comorbid insomnia. However, further research is crucial to investigate its long-term effectiveness and impact on overall quality of life.

Pharmacological methods should be considered a second-line therapy when CBT-I proves ineffective. This approach is necessitated by their lower safety profile, limited potential for long-term treatment, and risk of adverse effects. While Non-Benzodiazepine Receptor Agonists (NBDZAs) are considered safer than Benzodiazepines (BDZs), unequivocal data regarding their long-term use remains scarce. Newer options, such as daridorexant (an orexin receptor antagonist), are promising for chronic therapy, yet their availability is still limited.

Ongoing efforts are directed toward identifying innovative therapeutic techniques, including brain stimulation and novel molecules (e.g., TS-142, GABA agonists), which may represent future treatment options. Nevertheless, there is currently a lack of sufficient, unequivocal clinical evidence to confirm their safety and efficacy. Irrespective of the treatment method, comprehensive sleep hygiene—based on physical activity, appropriate diet, and balanced management of nervous system stimulants—is of paramount importance in the prevention and maintenance of insomnia remission.

Discussion

This narrative review aimed to synthetically evaluate the current efficacy of pharmacological and non-pharmacological methods for treating chronic insomnia and to identify the directions in which contemporary science is moving. The main finding, consistent with international clinical guidelines, is that CBT-I invariably remains the first-line therapy and gold standard in the management of this conditio [8],[9],[10],[11],[16].

The proven efficacy of CBT-I, observed in both objective (latency, total sleep time) and subjective (sleep quality, daytime functioning) parameters, is well-established. In contrast to pharmacotherapy, which has a purely symptomatic and inhibitory effect, CBT-I directly targets the cognitive and physiological components of hyperarousal [8]. This results in more durable effects and eliminates the risk of dependence or tolerance, representing a key advantage [12]. However, further long-term studies are necessary to unequivocally document the impact of CBT-I on patients' overall quality of life in a multi-year perspective [8], its effectiveness across different insomnia subtypes [13], and to evaluate which CBT-I delivery model is the most efficacious [14], [19]. This necessity stems from the fact that few studies to date have assessed long-term follow-up after CBT-I application, meaning the persistence of the therapy's effects is not fully understood.

Pharmacological methods, due to their lower durability of effects and higher risk profile (including the risk of dependence, overdose, and residual daytime sleepiness), should be treated as second-line therapy. A significant advance in pharmacotherapy is the introduction of Dual Orexin Receptor Antagonists (DORAs). In contrast to traditional benzodiazepine receptor agonists (BDZs and NBDZAs), which induce sleep through

global inhibition, DORAs act more physiologically by blocking the neurotransmitter pathway responsible for maintaining wakefulness—orexin [16]. Clinical trial results, including the extended phase, have shown that daridorexant is safe and well-tolerated for up to one year, without leading to the development of tolerance or dependence. Importantly, it demonstrates efficacy in alleviating both nighttime and daytime symptoms of insomnia, which is of key clinical relevance. This profile justifies the use of daridorexant as a promising option for the long-term treatment of chronic insomnia in adults, addressing a significant gap that older hypnotics could not fill. Simultaneously, its still low availability across most EU member states remains a clinical limitation [21].

What is most interesting and significant in the present review is the active pursuit of innovative, non-pharmacological treatment methods, such as brain stimulation techniques (e.g., VeNS, NIBS) and frontal thermal therapy. These approaches are theoretically promising because they enable the targeted modulation of neuronal activity, which aligns with the trend toward personalized therapy. Techniques like Non-Invasive Brain Stimulation (NIBS), including transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), offer the possibility of regulating cortical excitability. This concept is particularly appealing in the context of the cerebral hyperarousal observed in insomnia patients. Conversely, methods such as vagus nerve stimulation (VeNS) or frontal thermal therapy aim to reduce the general level of physiological arousal. Despite their theoretical appeal, the practical application of these techniques is currently hampered by the lack of sufficient and unequivocal clinical trials confirming their efficacy beyond a strong placebo effect. There is a lack of consensus regarding optimal treatment protocols (frequency, intensity, stimulation site), and the heterogeneity of the studied populations and a lack of methodological standardization impede their integration into clinical routine. A thorough understanding of the specific mechanisms of action of these interventions on the neuronal networks responsible for sleep and wakefulness is necessary [24], [25], [26].

Concurrently, intensive work is underway on novel molecules that have the potential to expand the portfolio of available pharmacological options, offering a better safety profile than existing hypnotics.

Research on TS-142 and a new generation of GABA agonists (with modified pharmacokinetic and pharmacodynamic profiles) suggests that in the future, we may gain access to medications that are more targeted and less burdensome for the patient, minimizing the risk of residual sedation and rebound insomnia. Their efficacy in initial studies is promising for the long-term clinical perspective. However, analyses of the molecular mechanisms of GABA action, establishing the precise role of the GABAB receptor, and their influence on sleep stages are still being conducted. These discoveries could, in time, bring a significant improvement to pharmacological options for treating insomnia [27]. In trials, TS-142 demonstrates efficacy and good tolerability upon single administration, making it a certainly important area for further research into its mechanism of action [28].

Irrespective of the complexity of the pathophysiological mechanisms of insomnia and the advancement of treatment methods, this review confirms the critical importance of lifestyle factors in maintaining sleep health. Elements of sleep hygiene, such as maintaining a consistent circadian rhythm, optimizing the sleep environment, and managing alerting factors, constitute the foundation of prevention and are an integral component of CBT-I [29], [30]. It is necessary that in the process of insomnia treatment—regardless of the application of CBT-I or pharmacotherapy—emphasis is placed on comprehensive patient education regarding these elements. Proper sleep hygiene is a key prognostic factor for the long-term maintenance of symptom remission and it is vital for the effectiveness of other insomnia treatment methods.

Author's Contributions:
Conceptualization: Adrianna Kaczmarek
Methodology: Franciszek Szweda, Adrianna Kaczmarek
Software: Tomasz Poczwardowski, Adrianna Kaczmarek
Check: Katarzyna Anna Kowalska, Adrianna Kaczmarek
Validation / Check: Jakub Tomasz Latos, Adrianna Kaczmarek
Formal Analysis: Marcin Chwalczuk, Adrianna Kaczmarek
Investigation: Oliwia Grygorcewicz, Adrianna Kaczmarek
Resources: Marta Koneczna, Adrianna Kaczmarek
Data curation: Karolina Alicja Krystyniak, Adrianna Kaczmarek
Writing – rough preparation: Kinga Augustyniak, Adrianna Kaczmarek
Writing – Review and Editing: Tomasz Poczwardowski, Adrianna Kaczmarek
Supervision / Project Administration: Franciszek Szweda, Adrianna Kaczmarek

All authors have read and agreed to the published version of the manuscript.

Funding Statement: The author received no external funding for this work.

Data Availability Statement: All supporting data are available within the cited peer-reviewed literature.

Acknowledgments: The author acknowledges the contribution of investigators and data curators whose high-quality research underpins the advances reviewed herein.

Conflict of Interest Statement: The author declares no conflict of interest.

Declaration of the use of generative AI and AI-assisted technologies in the writing process: In preparing this work, the authors used Gmini AI Pro for the purpose of improving language and readability. After using this tool, the authors have reviewed and edited the content as needed and accept full responsibility for the substantive content of the publication.

REFERENCES

1. Van Someren, E. J. W. (2021). Brain mechanisms of insomnia: New perspectives on causes and consequences. *Physiological Reviews, 101*(3), 995–1046. https://doi.org/10.1152/physrev.00046.2019
2. Perlis, M. L., Posner, D., Riemann, D., Bastien, C. H., Teel, J., & Thase, M. (2022). Insomnia. *The Lancet, 400*(10357), 1047–1060. https://doi.org/10.1016/S0140-6736(22)00879-0
3. Sateia, M. J. (2014). International classification of sleep disorders—Third edition: Highlights and modifications. *Chest, 146*(5), 1387–1394. https://doi.org/10.1378/chest.14-0970
4. Baglioni, C., Regen, W., Teghen, A., Spiegelhalder, K., Feige, B., Nissen, C., & Riemann, D. (2014). Sleep changes in the disorder of insomnia: A meta-analysis of polysomnographic studies. *Sleep Medicine Reviews, 18*(3), 195–213. https://doi.org/10.1016/j.smrv.2013.04.001
5. Perlis, M., Pigeon, W., Gehrman, P., Findley, J., & Drummond, S. (2009). Neurobiological mechanisms in chronic insomnia. *Sleep Medicine Clinics, 4*(4), 549–558. https://doi.org/10.1016/j.jsmc.2009.07.002
6. Freedman, R. R. (1986). EEG power spectra in sleep-onset insomnia. *Electroencephalography and Clinical Neurophysiology, 63*(5), 408–413. https://doi.org/10.1016/0013-4694(86)90122-7
7. Krystal, A. D., Edinger, J. D., Wohlgemuth, W. K., & Marsh, G. R. (2002). NREM sleep EEG frequency spectral correlates of sleep complaints in primary insomnia subtypes. *Sleep, 25*(6), 630–640.
8. Alimoradi, Z., Jafari, E., Broström, A., Ohayon, M. M., Lin, C.-Y., Griffiths, M. D., Blom, K., Jernelöv, S., Kaldo, V., & Pakpour, A. H. (2022). Effects of cognitive behavioral therapy for insomnia (CBT-I) on quality of life: A systematic review and meta-analysis. *Sleep Medicine Reviews, 64*, Article 101646. https://doi.org/10.1016/j.smrv.2022.101646
9. Riemann, D., Baglioni, C., Bassetti, C., Bjorvatn, B., Dolenc Groselj, L., Ellis, J. G., Espie, C. A., Garcia-Borreguero, D., Gjerstad, M., Gonçalves, M., Hertenstein, E., Jansson-Fröjmark, M., Jennum, P. J., Leger, D., Nissen, C., Parrino, L., Paunio, T., Pevernagie, D., Verbraecken, J., Weeß, H.-G., Wichniak, A., Zavalko, I., Arnardottir, E. S., Deleanu, O.-C., Strazisar, B., Zoetmulder, M., & Spiegelhalder, K. (2017). European guideline for the diagnosis and treatment of insomnia. *Journal of Sleep Research, 26*, 675–700. https://doi.org/10.1111/jsr.12594
10. Wilson, S., Anderson, K., Baldwin, D., Dijk, D.-J., Espie, A., Espie, C., Gringras, P., Krystal, A., Nutt, D., Selsick, H., & Sharpley, A. (2019). British Association for Psychopharmacology consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders: An update. *Journal of Psychopharmacology, 33*(8), 923–947. https://doi.org/10.1177/0269881119855343
11. Qaseem, A., Kansagara, D., Forciea, M. A., Cooke, M., & Denberg, T. D. (2016). Management of chronic insomnia disorder in adults: A clinical practice guideline from the American College of Physicians. *Annals of Internal Medicine, 165*(2), 125–133. https://doi.org/10.7326/M15-2175

12. Chan, N. Y., Chan, J. W. Y., Li, S. X., & Wing, Y. K. (2021). Non-pharmacological approaches for management of insomnia. *Neurotherapeutics, 18*(1), 32–43. https://doi.org/10.1007/s13311-021-01029-2
13. Miller, C. B., Espie, C. A., Bartlett, D. J., Marshall, N. S., Gordon, C. J., & Grunstein, R. R. (2018). Acceptability, tolerability, and potential efficacy of cognitive behavioural therapy for insomnia disorder subtypes defined by polysomnography: A retrospective cohort study. *Scientific Reports, 8*(1), Article 6664. https://doi.org/10.1038/s41598-018-25033-3
14. Morin, C. M., Chen, S. J., Lemieux, K., Ivers, H., Cheung, J. M. Y., Lamy, M., & Ritterband, L. (2025). Stepped care for insomnia in primary care using digital and face-to-face cognitive behavioral therapies: A pragmatic nonrandomized clinical trial. *Sleep Medicine, 132*, Article 106551. https://doi.org/10.1016/j.sleep.2025.106551
15. Rajabi Majd, N., Broström, A., Ulander, M., Lin, C.-Y., Griffiths, M. D., Imani, V., Ahorsu, D. K., Ohayon, M. M., & Pakpour, A. H. (2020). Efficacy of a theory-based cognitive behavioral technique app-based intervention for patients with insomnia: Randomized controlled trial. *Journal of Medical Internet Research, 22*(4), e15841. https://doi.org/10.2196/15841
16. Riemann, D., Espie, C. A., Altena, E., Arnardottir, E. S., Baglioni, C., Bassetti, C. L. A., Bastien, C., Berzina, N., Bjorvatn, B., Dikeos, D., Dolenc Groselj, L., Ellis, J. G., Garcia-Borreguero, D., Geoffroy, P. A., Gjerstad, M., Gonçalves, M., Hertenstein, E., Hoedlmoser, K., Holzinger, B., Jansson-Fröjmark, M., Järnefelt, H., Jernelöv, S., Jennum, P. J., Khachatryan, S., Krone, L., Kyle, S. D., Lancee, J., Leger, D., Marques, D. R., Nissen, C., Palagini, L., Paunio, T., Perogamvros, L., Pevernagie, D., Schabus, M., Shochat, T., Szentkiralyi, A., Van Someren, E., van Straten, A., Verbraecken, J., Wichniak, A., & Spiegelhalder, K. (2023). The European insomnia guideline: An update on the diagnosis and treatment of insomnia 2023. *Journal of Sleep Research, 32*(6), e14035. https://doi.org/10.1111/jsr.14035
17. Buscemi, N., Vandermeer, B., Friesen, C., Bialy, L., Tubman, M., Ospina, M., Klassen, T. P., & Witmans, M. (2007). The efficacy and safety of drug treatments for chronic insomnia in adults: A meta-analysis of randomized controlled trials. *Journal of General Internal Medicine, 22*(9), 1335–1350. https://doi.org/10.1007/s11606-007-0251-z
18. Everitt, H., Baldwin, D. S., Stuart, B., Lipinska, G., Mayers, A., Malizia, A. L., Manson, C. C. F., & Wilson, S. (2018). Antidepressants for insomnia in adults. *Cochrane Database of Systematic Reviews*, 2018(5), Article CD010753. https://doi.org/10.1002/14651858.CD010753.pub2
19. Forma, F., Pratiwadi, R., El-Moustaid, F., Smith, N., Thorndike, F., & Velez, F. (2022). Network meta-analysis comparing the effectiveness of a prescription digital therapeutic for chronic insomnia to medications and face-to-face cognitive behavioral therapy in adults. *Current Medical Research and Opinion, 38*(10), 1727–1738. https://doi.org/10.1080/03007995.2022.2108616
20. Jernelöv, S., Blom, K., Hentati Isacsson, N., Bjurner, P., Rosén, A., Kraepelien, M., Forsell, E., & Kaldo, V. (2022). Very long-term outcome of cognitive behavioral therapy for insomnia: One- and ten-year follow-up of a randomized controlled trial. *Cognitive Behaviour Therapy, 51*(1), 72–88. https://doi.org/10.1080/16506073.2021.2009019
21. Kunz, D., Dauvilliers, Y., Benes, H., García-Borreguero, D., Plazzi, G., Seboek Kinter, D., Coloma, P., Rausch, M., Sassi-Sayadi, M., & Thein, S. (2023). Long-term safety and tolerability of daridorexant in patients with insomnia disorder. *CNS Drugs, 37*(1), 93–106. https://doi.org/10.1007/s40263-022-00980-8
22. Marupuru, S., Arku, D., Campbell, A. M., Slack, M. K., & Lee, J. K. (2022). Use of melatonin and/or ramelteon for the treatment of insomnia in older adults: A systematic review and meta-analysis. *Journal of Clinical Medicine, 11*(17), Article 5138. https://doi.org/10.3390/jcm11175138
23. Oyekan, P. J., Gorton, H. C., & Copeland, C. S. (2021). Antihistamine-related deaths in England: Are the high safety profiles of antihistamines leading to their unsafe use? *British Journal of Clinical Pharmacology, 87*(10), 3978–3987. https://doi.org/10.1111/bcp.14819
24. Krone, L. B., Fehér, K. D., Rivero, T., & Omlin, X. (2023). Brain stimulation techniques as novel treatment options for insomnia: A systematic review. *Journal of Sleep Research, 32*(6), e13927. https://doi.org/10.1111/jsr.13927
25. Cheung, T., Lam, J. Y. T., Fong, K. H., Cheng, C. P., Xiang, Y.-T., & Li, T. M. H. (2025). Efficacy of electrical vestibular stimulation (VeNS) on adults with insomnia: A double-blind, randomized, sham-controlled trial. *Dialogues in Clinical Neuroscience, 27*(1), 236–248. https://doi.org/10.1080/19585969.2025.2526547
26. Roth, T., Mayleben, D., Feldman, N., Lankford, A., Grant, T., & Nofzinger, E. (2018). A novel forehead temperature-regulating device for insomnia: A randomized clinical trial. *Sleep, 41*(5), zsy045. https://doi.org/10.1093/sleep/zsy045
27. Zhu, W., Huang, L., Cheng, H., Li, N., Zhang, B., Dai, W., Wu, X., Zhang, D., Feng, W., Li, S., & Xu, H. (2024). GABA and its receptors' mechanisms in the treatment of insomnia. *Heliyon, 10*(23), e40665. https://doi.org/10.1016/j.heliyon.2024.e40665
28. Uchiyama, M., Kambe, D., Imadera, Y., Kajiyama, Y., Ogo, H., & Uchimura, N. (2022). Effects of TS-142, a novel dual orexin receptor antagonist, on sleep in patients with insomnia: A randomized, double-blind, placebo-controlled phase 2 study. *Psychopharmacology, 239*(7), 2143–2154. https://doi.org/10.1007/s00213-022-06089-6
29. Sejbuk, M., Mirończuk-Chodakowska, I., & Witkowska, A. M. (2022). Sleep quality: A narrative review on nutrition, stimulants, and physical activity as important factors. *Nutrients, 14*(9), Article 1912. https://doi.org/10.3390/nu14091912
30. Alnawwar, M. A., Alraddadi, M. I., Algethmi, R. A., Salem, G. A., Salem, M. A., & Alharbi, A. A. (2023). The effect of physical activity on sleep quality and sleep disorder: A systematic review. *Cureus, 15*(8), e43595. https://doi.org/10.7759/cureus.43595