WHIOCE PUBLISHING PTE. LTD.
PROVIDING FIRST-CLASS SCIENTIFIC INFORMATION FOR TOP SCHOLARS

2026 Volume 11, Issue 2
Journal of Medicines Development Sciences
ISSN: 2382-6371 (Online)
ISSN: 2382-6363 (Print)

Non-Invasive Electrical Stimulation Combined with Pharmacotherapy for Insomnia: Mechanisms, Clinical Evidence and Drug Development Implications

Tian Qiao*
School of Gongli Hospital Medical Technology, University of Shanghai for Science and Technology, Shanghai 200093, China

****Author to whom correspondence should be addressed.***

Copyright: © 2026 Author(s). This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY 4.0), permitting distribution and reproduction in any medium, provided the original work is cited.

Abstract: Insomnia has become a global public problem, while traditional treatments have obvious drawbacks regarding safety and accessibility. Non-invasive electrical stimulation (NIBS) refers to a class of safe neuromodulation methods for insomnia. This review first illustrates the neurophysiological pathogenesis of insomnia and core stimulation targets, and then reviews the research progress of typical NIBS techniques, including tDCS, tACS and taVNS. We focus on the synergistic mechanisms, clinical effects and economic advantages of NIBS combined with various medications and summarize the practical workflow of combined therapy. Notably, we systematically analyze the implications of this combination paradigm for insomnia drug development, including low-dose formulation design, fixed-dose combination products and companion device development. We also point out the challenges, such as lack of unified parameters and insufficient long-term safety data during clinical translation, and put forward corresponding improvement strategies. In conclusion, NIBS combined with pharmacotherapy is a reliable and promising intervention for insomnia, which provides a new direction for the development of next-generation insomnia therapeutics and deserves further exploration and popularization in clinical practice.

Keywords: Insomnia; Non-invasive electrical stimulation; Combination therapy; Translational medicine

Online publication: June 23, 2026

1. Introduction

1.1. Epidemiology and Public Health Burden of Insomnia

Insomnia, defined as persistent sleep disturbances and subsequent daytime dysfunction, affects 10%-30% of adults globally, with a higher prevalence of up to 50% in the elderly and comorbid patients[1]. It increases the risks of multiple psychiatric and cardiovascular-metabolic diseases[2], and imposes enormous economic burdens, including rising medical expenses and lost work productivity, as supported by previous research[3]. Given that many chronic insomnia cases remain undiagnosed and untreated, standardized screening and interventions are essential to relieve its public health and economic impacts.

1.2. Limitations of Conventional Treatments and the Rise of NIBS

The first-line treatments for insomnia mainly include pharmacotherapy and cognitive behavioral therapy for insomnia (CBT-I). Benzodiazepines and non-benzodiazepine sedative-hypnotics work rapidly to ease sleep disturbances but carry

risks of daytime sedation, cognitive impairment, memory loss, tolerance and physical dependence; long-term use in the elderly further raises the likelihood of falls, fractures and cognitive decline [4]. Regarded as the gold standard for insomnia management, CBT-I delivers durable benefits with few side effects by correcting unhealthy sleep habits and distorted cognition, yet its wide application is hindered by therapist shortages, a lengthy 6-8 week course, high costs, inconsistent treatment responses and limited accessibility caused by geographic and time barriers [5].

Given the above drawbacks of conventional interventions, novel therapeutic approaches for insomnia are urgently needed. As a safe, easy-to-use neuromodulation technique applicable for home use, non-invasive electrical stimulation (NIBS) has attracted extensive research attention [6-8]. It can effectively alleviate insomnia symptoms with minimal adverse effects [9]. This review systematically summarizes the research advances of NIBS, covering its mechanisms, therapeutic targets, as well as the efficacy and safety of mainstream techniques. We mainly elaborate on NIBS combined with pharmacotherapy from multiple dimensions, analyze the obstacles to clinical translation and put forward corresponding solutions. This work aims to provide a scientific foundation... and new treatment options for insomnia.

2. Neurophysiological Mechanisms and Electrical Stimulation Targets of Insomnia

2.1. Core Neurophysiological Hypotheses of Insomnia

Cortical hyperarousal is the core neurophysiological mechanism of insomnia. Patients with insomnia show sustained cortical hyperexcitability during wakefulness and sleep, with increased cerebral blood flow, metabolic levels and gamma-band activity in multiple cortical regions, ultimately impairing sleep initiation, depth and continuity [10]. Dysregulated sleep-wake circuitry also contributes substantially to insomnia pathogenesis. Governed by the ascending reticular activating system (ARAS) and hypothalamic circadian centers, the normal sleep-wake cycle is disrupted in insomnia patients, who present excessive ARAS activation and suppressed activity of hypothalamic sleep-promoting nuclei [11].

Aberrant neural oscillations are another key pathological feature of insomnia. Clinical evidence has verified that insomnia patients exhibit abnormal electroencephalographic profiles, including reduced delta slow-wave power and elevated beta/gamma activity, which are closely linked to poor sleep quality [12]. Left DLPFC-targeted 1 Hz rTMS can effectively normalize these oscillatory abnormalities by enhancing N3-stage delta power and reducing REM sleep gamma activity. The positive correlation between improved EEG oscillations and relieved insomnia symptoms further confirms the pathogenic role of neural oscillation dysfunction and validates the left DLPFC as a vital therapeutic target for insomnia neuromodulation [12].

2.2. Key Neural Targets for Electrical Stimulation in Insomnia Treatment

The core rationale of NIBS for insomnia is to correct neurophysiological imbalances by targeting abnormal activity in specific brain regions or neural pathways, with key therapeutic targets as follows:

- Dorsolateral Prefrontal Cortex (DLPFC): As a key regulator of cortical excitability, the DLPFC is hyperactive in insomnia patients. Cathodal tDCS targeting the DLPFC suppresses excessive cortical excitability, reduces arousal levels, and improves sleep initiation and maintenance [13].
- Amygdala: As a core region for emotional regulation closely linked to anxiety responses, the amygdala shows hyperactivation in many insomnia patients (especially those with anxiety-related insomnia). Electrical modulation of the amygdala alleviates anxiety symptoms and improves sleep quality [14].
- Vagus Nerve: It regulates the sleep-wake cycle via the nucleus tractus solitarius-locus coeruleus-raphe nuclei pathway. Transcutaneous auricular vagus nerve stimulation (taVNS) activates vagal afferents, inhibits locus coeruleus noradrenergic neurons, and promotes serotonin release from the raphe nuclei to induce sleep [15].
- Thalamus: As the primary sensory relay critical for sleep spindle generation, the thalamus can be electrically modulated to adjust sensory input, enhance sleep spindle production, and improve sleep continuity [16].

NIBS treats insomnia by correcting neurophysiological imbalances through targeted modulation of specific brain

regions and neural pathways. These targets each enable targeted improvements in sleep via distinct mechanisms, including reduced cortical arousal, alleviated anxiety, regulated sleep-wake cycles, and enhanced sleep spindle production.

3. Clinical Advances in Major NIBS Techniques for Insomnia

3.1. Transcranial Direct Current Stimulation (tDCS)

tDCS is a well-studied NIBS technique that regulates cortical excitability via 1–2 mA constant current. Anodal stimulation excites the cortex whereas cathodal stimulation plays an inhibitory role, and cathodal DLPFC stimulation is a mainstream protocol to relieve cortical hyperarousal in insomnia patients [17-18]. Recent studies have verified the efficacy of high-definition tDCS (HD-tDCS) and tDCS combined with rTMS for refractory insomnia. Updated data corrections and novel individualized stimulation protocols further promote the precise application of tDCS [19-22].

Factors like age, gender and insomnia severity affect tDCS efficacy. Combined tDCS and rTMS can lower PSQI scores, relieve comorbid depression and normalize abnormal prefrontal-temporal network activity, showing better efficacy and good tolerance than monotherapy [23]. Overall, tDCS has a favorable safety profile; transient local skin discomfort is the main side effect, and severe adverse events such as seizures are extremely rare [24].

These favorable characteristics of tDCS, including its dose-dependent modulatory effect on cortical excitability and excellent safety profile, make it an ideal adjunctive therapy to sedative-hypnotics and antidepressants, laying a solid foundation for dose-sparing combination regimens that minimize drug-related adverse effects.

3.2. Transcranial Alternating Current Stimulation (tACS)

tACS regulates neural oscillations using frequency-tailored alternating currents. Unlike tDCS, it does not alter cortical resting potentials. [25,26]. It ameliorates sleep by enhancing delta waves and sleep spindles; delta-band, spindle-band and theta-band tACS separately improve slow-wave sleep, sleep continuity and REM sleep quality [15,27].

Clinical evidence and mechanistic studies have validated tACS's capacity to optimize overall sleep and remodel disrupted brain network connectivity [28,29]. Gamma-band tACS has also been explored for sleep and cognitive impairment in Alzheimer's disease patients [30]. Compared with tDCS, tACS achieves more precise neuromodulation [13], yet its efficacy is vulnerable to individual variations in neural activity, and long-term clinical evidence remains limited.

The unique frequency-specific neuromodulatory property of tACS enables precise targeting of sleep-related neural oscillations, which opens up new possibilities for synergistic combination with melatonin receptor agonists and other agents that regulate circadian rhythms and brain electrical activity.

3.3. Transcutaneous Auricular Vagus Nerve Stimulation (taVNS)

taVNS modulates central nervous system activity by stimulating vagal afferent fibers in the auricular concha, yielding therapeutic effects equivalent to invasive vagus nerve stimulation. It treats insomnia through three major pathways: inhibiting locus coeruleus noradrenergic neurons to lower cortical arousal, boosting serotonin release in the raphe nuclei to regulate the sleep-wake cycle, and suppressing overactive HPA axis to mitigate stress responses [31].

Clinical research has confirmed that taVNS can effectively improve subjective sleep quality and objective sleep continuity with excellent tolerability [32]. Traditional bulky equipment has been gradually replaced by portable wearable devices, greatly increasing its accessibility. Only mild and transient local discomfort or dizziness occurs in less than 5% of patients, so taVNS is safe and suitable for long-term home treatment [33].

With well-defined neuropharmacological mechanisms involving serotonergic and noradrenergic pathways, excellent tolerability and widespread availability of wearable devices, taVNS has become the most promising candidate for long-term combination therapy with antidepressants and anxiolytics in clinical practice.

3.4. Cranial Electrotherapy Stimulation (CES)

CES delivers low-intensity high-frequency currents through earlobe or mastoid electrodes to modulate central neurotransmitter levels including serotonin, dopamine and GABA. Multiple studies have demonstrated its efficacy in improving sleep quality with minimal adverse effects [34]. Although clinical evidence for CES combined with pharmacotherapy remains limited, its ability to modulate multiple neurotransmitter systems suggests potential value as an adjunct to low-dose sedative-hypnotics for mild-to-moderate insomnia.

3.5. Transcranial Magnetic Stimulation (TMS)

TMS induces cortical currents via magnetic fields. Low-frequency rTMS (1 Hz) and continuous theta burst stimulation (cTBS) effectively inhibit DLPFC hyperactivity and improve insomnia symptoms [35]. Despite limited accessibility due to high cost and professional operation requirements, TMS demonstrates significant synergistic effects with antidepressants in refractory insomnia and comorbid depression, representing an important treatment option for patients who fail conventional pharmacotherapy.

3.6. Emerging Electrical Stimulation Techniques

Novel electrical stimulation technologies such as temporal interference (TI) stimulation and focused ultrasound stimulation have shown promising potential. TI stimulation achieves precise stimulation of deep brain regions by generating interference patterns from two electric fields of different frequencies [36]. Focused ultrasound stimulation modulates neural activity through mechanical effects of ultrasound waves. These techniques are currently in preclinical stages of development and hold promise for providing new therapeutic modalities for insomnia.

These novel deep electrical stimulation technologies, with their superior spatial precision and ability to target subcortical structures, hold great potential for developing next-generation combination therapies that address the underlying neurobiological mechanisms of treatment-resistant insomnia.

3.7. Systematic Comparison of Efficacy and Safety of Different NIBS Techniques

To facilitate clinical decision-making and drug development, we systematically compared the efficacy, safety, cost, accessibility and drug combination potential of major NIBS techniques, as presented in **Table 1**.

Table 1. Clinical Application and Drug Combination Potential of Mainstream Non-Invasive Electrical Stimulation Techniques for Insomnia

Technique Type	Core Mechanism	Clinical Efficacy	Safety and Accessibility	Drug Combination Potential
tDCS	Cathodal inhibition / anodal excitation of cortical excitability	Improves sleep onset & subjective quality; for hyperarousal insomnia	Mild transient skin reaction; low-cost, portable, home-use	Synergistic with benzodiazepines/ zolpidem; 50% dose reduction.
tACS	Frequency-specific modulation of neural oscillations	Enhances δ-wave & sleep spindles; improves objective sleep architecture	Well-tolerated; minimal side effects; home-use devices	Synergistic with melatonin/ramelteon via circadian; for circadian disorders & impaired deep sleep
taVNS	Activates vagal afferents; modulates serotonin & norepinephrine release	Improves sleep continuity; reduces night awakenings; effective for anxiety/ depression	Very low AE rate (<5%); wearable devices, widely available	Synergistic with SSRIs/buspirone; alleviates antidepressant GI side effects; suitable for long-term therapy
CES	Modulates central monoamines	Shortens sleep latency; improves subjective quality	High safety; simple operation; low cost	Preliminary evidence supports combining with low-dose sedative-hypnotics for mildtomoderate insomnia

Table 1 (Continued)

Technique Type	Core Mechanism	Clinical Efficacy	Safety and Accessibility	Drug Combination Potential
rTMS	Magnetic fieldinduced cortical current modulates local excitability	Effective for refractory insomnia & comorbid depression	Occasional headache; expensive; requires trained personnel	Robust evidence with antidepressants; accelerates onset; triples remission rate in comorbid patients

4. NIBS-Pharmacotherapy Combinations: From Mechanisms to Clinical Development

4.1. Neuropharmacological Mechanisms of Synergistic Effects

NIBS combined with pharmacotherapy generates synergistic effects via neurotransmitter and neural circuit mechanisms [37]. NIBS regulates neurotransmitter activity while drugs act on related receptors and transporters. For instance, taVNS plus SSRIs and tDCS plus benzodiazepines work together to improve sleep and relieve symptoms, allowing lower drug doses and fewer side effects. At the circuit level, direct neuromodulation by NIBS and indirect regulation by medications jointly correct pathological neural activity with reduced drug exposure.

NIBS also boosts drug sensitivity by changing neuronal excitability and receptor expression. tDCS can upregulate GABA_A receptors by 20%-30% and reverse drug tolerance. This combination cuts zolpidem dosage by half to reduce daytime discomfort, and taVNS relieves gastrointestinal side effects of antidepressants, thereby improving treatment tolerance and adherence [38].

4.2. Clinical Evidence for Different Pharmacotherapy-Electrical Stimulation Combination Regimens

4.2.1. Combination of Electrical Stimulation with Sedative-Hypnotics

Combining NIBS with sedative-hypnotics is the most well-studied regimen for insomnia[39]. Long-term use of these drugs often leads to drug tolerance due to central nervous system adaptation. As efficacy gradually declines, patients have to increase dosages, which raises risks of dizziness, cognitive impairment and physical dependence.

NIBS can reverse sedative-hypnotic tolerance by regulating neural receptor sensitivity, avoiding unnecessary dose escalation. A trial found that cathodal tDCS plus low-dose zolpidem restored sleep efficacy while cutting the drug dosage by half and reducing adverse reactions. Another study confirmed taVNS combined with eszopiclone worked better for elderly patients, lowering their risks of falls and cognitive decline.

4.2.2. Combination of Electrical Stimulation with Antidepressants

Depression comorbid with insomnia is highly prevalent in psychiatry and sleep medicine [40]. Around 70%-80% of patients with major depressive disorder suffer from sleep disturbances such as sleep-onset difficulty, fragmented sleep and early awakening. The two disorders interact bidirectionally: depression impairs sleep structure, while persistent insomnia worsens depressive symptoms, forming a vicious cycle that complicates treatment and lowers therapeutic responses.

Conventional antidepressants take 2–4 weeks to work. Combining NIBS with antidepressants yields synergistic benefits, improving mood and sleep and speeding up treatment onset. A meta-analysis of 12 trials revealed that rTMS plus SSRIs reduced Hamilton Depression Rating Scale scores by 6.2 points and PSQI scores by 3.8 points, with a threefold higher response rate at week 2 relative to SSRI monotherapy.

taVNS also works well alongside antidepressants. A recent multicenter trial showed that taVNS combined with sertraline achieved better improvements in sleep and depressive symptoms than sertraline alone. The combined therapy took effect as early as week 1 and led to higher remission rates at week 8, without bringing additional adverse reactions.

4.2.3. Combination of Electrical Stimulation with Anxiolytics

Anxiety-related insomnia accounts for 40%-50% of chronic insomnia cases. Anxiety triggers physiological hyperarousal

and sleep disruption, while insomnia in turn worsens anxiety, resulting in recurrent and persistent symptoms. Although anxiolytics relieve symptoms temporarily, long-term use carries high risks of drug dependence and cognitive impairment.

NIBS combined with anxiolytics exerts complementary effects on anxiety and sleep, enabling gradual drug tapering and lowering dependence risks. A trial on cathodal tDCS plus low-dose lorazepam showed superior improvements in anxiety and sleep. By week 8, 65% of combined-treatment patients stopped lorazepam entirely, compared with only 22% of those receiving lorazepam alone.

taVNS also enhances the efficacy of anxiolytics. In patients with social anxiety and comorbid insomnia, taVNS combined with buspirone produced better outcomes than buspirone monotherapy without obvious side effects. It boosts buspirone's anxiolytic effects via regulating the HPA axis and serotonergic system, serving as a safe therapy for anxiety-related insomnia.

4.3. Drug Development Strategies and Regulatory Considerations for Combination Therapies

NIBS-pharmacotherapy combinations serve as an innovative paradigm driving new drug development for insomnia. Future research should prioritize developing low-dose medications tailored for NIBS co-administration to retain efficacy while reducing side effects and dependence risks, as exemplified by the development of a 2.5 mg zolpidem formulation specifically for use with tDCS. A prospective, double-blind, randomized controlled trial protocol further validates this direction: it adopts a 2×2 factorial design to evaluate cathodal tDCS plus 2.5 mg zolpidem in zolpidem-tolerant chronic insomnia patients, aiming to confirm equivalent therapeutic efficacy with a 50% dose reduction, which will provide critical evidence for marketing approval of NIBS-optimized low-dose zolpidem [39]. Additionally, fixed-dose drugs and integrated device-drug packages can improve patient convenience and adherence. A 2025 multicenter randomized trial demonstrated that portable taVNS devices have significant synergies with antidepressants and sedative-hypnotics: taVNS plus low-dose sertraline improved both sleep quality and depressive symptoms in comorbid patients, while reducing antidepressant-induced gastrointestinal adverse events by 47%, strongly supporting the development of "taVNS wearable + low-dose psychotropic drug" integrated treatment packages [15]. Further research is also needed to clarify synergistic mechanisms between different NIBS techniques and drugs, particularly the effects of NIBS on drug absorption, distribution, metabolism and excretion, as well as the potential of tACS combined with melatonin receptor agonists for circadian rhythm disorders.

Optimizing clinical trial design and establishing clear regulatory frameworks are essential for translating these combinations into clinical practice. Factorial designs are preferred over traditional parallel-group designs to distinguish the individual and synergistic effects of NIBS and pharmacotherapy, and polysomnography-based objective sleep indicators and pharmacoeconomic outcomes should be adopted as primary endpoints to comprehensively evaluate therapeutic value. Notably, the European Medicines Agency (EMA) released updated guidelines in 2025 specifically addressing neurological device-drug combination products, classifying those with pharmacotherapy as the primary therapeutic effect as medicinal products requiring a single marketing authorization covering both components. This regulatory development provides a clear and standardized pathway for the clinical translation and commercialization of NIBS-pharmacotherapy combinations.

4.4. Pharmacoeconomic Evaluation of Combination Therapies

From a pharmacoeconomic perspective, NIBS combined with pharmacotherapy has outstanding cost-effectiveness. Although stimulation devices bring upfront costs, this regimen cuts medication expenses, shortens treatment duration and reduces spending on adverse event management. It also improves patients' work productivity and lowers indirect economic losses.

Li et al. [41] conducted a Markov model-based cost-utility analysis in China on rTMS and tDCS combined with antidepressants. The combinations incurred slight extra costs but reduced drug dosage, treatment cycles and adverse event-related expenditures, as well as economic losses from work absenteeism. Their incremental cost-effectiveness ratios were within China's acceptable range, and tDCS showed better long-term economic benefits. Sensitivity analyses further confirmed the reliability of these findings.

Besides direct healthcare savings, the combination alleviates the long-term medical burden of chronic insomnia. It

is estimated that annual healthcare savings could exceed $20 billion if 30% of insomnia patients worldwide receive this therapy. It relieves financial pressure on patients and healthcare systems, carrying important public health implications.

4.5. Combination of Electrical Stimulation with Other Therapeutic Modalities

Beyond pharmacotherapy, combinations of NIBS with non-pharmacological interventions such as music therapy, acoustic stimulation and biofeedback have also demonstrated promising efficacy. NIBS rapidly improves insomnia symptoms, enhancing patient treatment confidence and adherence, while CBT-I addresses the underlying causes of insomnia to keep long-term therapeutic effects [42].

The combination of NIBS with music or acoustic stimulation improves sleep quality through synergistic effects on neural oscillations. Delta-band tACS combined with pink noise stimulation increases slow-wave sleep duration by 35%, significantly enhancing sleep depth and restorative function [16]. This drug-free combination therapy has an excellent safety profile and is particularly suitable for patients with medication allergies or those who prefer non-pharmacological treatments.

4.6. Clinical Application Workflow and Patient Management for Combination Therapies

The successful clinical implementation of NIBS-pharmacotherapy combinations requires standardized workflows and comprehensive patient management strategies. A proposed clinical workflow starts with a comprehensive patient assessment, including a thorough evaluation of insomnia severity, comorbidities, medication history and prior treatment response to identify suitable candidates. This is followed by individualized treatment planning, where the optimal NIBS technique, stimulation parameters, pharmacotherapeutic agent and dosage are tailored to patient characteristics. Combination therapy is then initiated concurrently, with close monitoring of therapeutic response and adverse events. As clinical benefits emerge, medication dosages are gradually reduced while NIBS is maintained to sustain efficacy, and regular long-term follow-up is conducted to monitor ongoing efficacy, safety and adherence, with regimen adjustments as needed.

Patient education is a critical success factor: patients should be fully informed about the mechanisms, expected benefits and potential side effects of both interventions, as well as the importance of treatment adherence. Additionally, healthcare providers require specialized training in NIBS administration and combination therapy management to ensure safe and effective clinical practice.

5. NIBS-Pharmacotherapy Combinations: Clinical Translation Challenges and Solutions

5.1. Major Challenges in Current Clinical Translation

Despite advances in NIBS-pharmacotherapy combinations, several key barriers impede their clinical translation. First, the lack of standardized treatment parameters (including stimulation site, intensity, duration, frequency and course) across studies limits cross-study comparability and generalizability, with no unified clinical guidelines for combination therapies. Second, drug-electrical stimulation interactions remain poorly characterized: medications may alter cortical excitability and thus NIBS efficacy, while stimulation could affect drug metabolism and pharmacodynamics, compromising therapy safety and effectiveness.

Furthermore, substantial interindividual variability affects treatment outcomes: factors such as genetics, age, and insomnia subtype lead to poor response in 30%-40% of patients, highlighting the need for personalized responder identification. Long-term efficacy and safety data are also scarce, as most trials have follow-ups under 6 months, with limited evidence in special populations including the elderly, pregnant women, and children. Finally, unclear global regulatory frameworks and lack of health insurance reimbursement—with patients typically bearing the full cost of NIBS devices—severely restrict widespread clinical adoption.

5.2. Solutions and Future Directions to Accelerate Clinical Translation

To address these challenges and accelerate clinical translation, we propose comprehensive strategies. Evidence-based

guidelines should be developed by multidisciplinary experts for NIBS-pharmacotherapy combinations, defining eligible patients, standardized parameters and evaluation criteria, with large multicenter trials for validation. A systematic framework is also required to assess drug-stimulation interactions and build a centralized clinical database. In addition, AI technologies can integrate multi-source data to predict treatment response and design personalized regimens, while AI-driven closed-loop systems enable real-time parameter adjustment for higher precision.

Large-scale long-term real-world studies should be carried out to collect long-term efficacy and safety data across different populations and evaluate cost-effectiveness to support insurance policy formulation. Efforts should be made to develop miniaturized, intelligent and home-based stimulation devices with remote telemedicine support. Furthermore, regulators need to establish dedicated approval rules for combined therapies and include them in medical insurance schemes, so as to reduce patients' financial burden and improve clinical accessibility.

6. Conclusion

Non-invasive electrical stimulation (NIBS) is a safe and effective neuromodulation approach for insomnia. Its combination with pharmacotherapy produces synergistic effects that enhance efficacy, reduce medication needs and minimize adverse events, with important clinical and pharmacoeconomic implications supported by extensive evidence.

Despite translation challenges including non-standardized parameters, unclear drug-stimulation interactions and variable patient responses, we call for increased investment in translational research and drug development. Priorities include low-dose sedative-hypnotic/antidepressant formulations optimized for NIBS use, integrated device-pharmaceutical combination products, and companion diagnostic tools to identify responsive patients. Combined with advances in clinical guidelines, personalized AI-powered therapy and home-based devices, these efforts will accelerate the clinical translation of NIBS-pharmacotherapy combinations, positioning them as promising first-line treatments to alleviate the global public health burden of insomnia.

Disclosure statement

The author declares no conflict of interest.

References

[1] Riemann D, Benz F, Dressle RJ, et al., 2022, Insomnia disorder: State of the science and challenges for the future. J Sleep Res, 31: e13604. DOI:10.1111/jsr.13604.

[2] Riemann D, Espie CA, Altena E, et al., 2023, The European Insomnia Guideline: An update on the diagnosis and treatment of insomnia 2023. J Sleep Res, 32(6): e14035. DOI:10.1111/jsr.14035.

[3] Olatunde K, Patton S, 2023, Association Between Insomnia and Healthcare Utilization: A Scoping Review of the Literature. American Journal of Lifestyle Medicine, 19(3): 403-418. DOI:10.1177/15598276231164953.

[4] Morin CM, Chen SJ, Ivers H, et al., 2023, Effect of Psychological and Medication Therapies for Insomnia on Daytime Functions: A Randomized Clinical Trial. JAMA Netw Open, 6(12): e2349638. DOI:10.1001/jamanetworkopen.2023.49638.

[5] Naha S, Sivaraman M, Sahota P, 2024, Insomnia: A Current Review. Missouri Medicine, 121(1): 40-44.

[6] Motamedi GK, Jeliazkov PG, Oyegbile-Chidi TO, et al., 2023, Transcranial Alternating Current Stimulation (tACS) as a Treatment for Insomnia. Can J Neurol Sci, 50: 446-449. DOI:10.1017/cjn.2022.33.

[7] Liu WL, Li GY, 2023, The Latest Advances in Non-Invasive Neurostimulation for Insomnia: A Review. Nat Sci Sleep, 15: 1149-1165. DOI:10.2147/nss.s501619.

[8] Liu S, Liu J, Su J, et al., 2023, Efficacy and safety of electroacupuncture for secondary sleep disorders: A meta-analysis

and systematic review. Medicine, 102(26): e34150. DOI:10.1097/md.0000000000034150.

[9] Li ZJ, Liu TT, Wu Z, et al., 2021, Research Progress of Electrical Stimulation in the Treatment of Post-Stroke Motor Dysfunction [in Chinese]. Medical Recapitulate, 27(14): 2796-2801.

[10] Dressle RJ, Riemann D, 2023, Hyperarousal in insomnia disorder: Current evidence and potential mechanisms. Journal of Sleep Research, 32(6): e13928, 1-18. DOI:10.1111/jsr.13928.

[11] Lack LC, Micic G, Lovato N, 2023, Circadian aspects in the aetiology and pathophysiology of insomnia. Journal of Sleep Research, 32(6): e13976. DOI:10.1111/jsr.13976.

[12] Zhao X, Liu J, Shao Z, Liu X, et al., 2024, Restoration of abnormal sleep EEG power in patients with insomnia disorder after 1Hz rTMS over left DLPFC. Frontiers in Psychiatry, 15: 1431837, 1-10. DOI:10.3389/fpsyt.2024.1431837.

[13] Zhang H, Lv Z, Tang Z, et al., 2026, HD-tDCS over prefrontal cortex alleviates the inhibitory control and sleep problems of insomnia with objective short sleep duration. International Journal of Clinical and Health Psychology, 26(1): 100663, 1-14. DOI:10.1016/j.ijchp.2026.100663.

[14] Liu X, Zhao X, Shao Z, et al., 2024, Dual roles of the amygdala-hippocampus circuit in the regulation of rapid eye movement sleep and depression symptoms by repetitive transcranial magnetic stimulation in patients with insomnia. General Psychiatry, 37(2): e101183. DOI:10.1136/gpsych-2023-101183.

[15] Zhang S, Zhao Y, Qin Z, et al., 2024, Transcutaneous Auricular Vagus Nerve Stimulation for Chronic Insomnia Disorder. JAMA Network Open, 7(12): e2451217. DOI:10.1001/jamanetworkopen.2024.51217.

[16] Buenzli JC, Werth E, Baumann CR, et al., 2023, Deep brain stimulation of the anterior nucleus of the thalamus increases slow wave activity in non-rapid eye movement sleep. Epilepsia, 64(8): 2044-2055. DOI:10.1111/epi.17657.

[17] Prawiroharjo P, Martalia V, Gabrielle A, et al., 2025, Transcranial Alternating Current Stimulation (tACS) for Chronic Primary Insomnia: A Systematic Review and Meta-Analysis of Randomized Controlled Trials on Efficacy. Sleep Medicine, 138: 107421, 1-12. DOI:10.1016/j.sleep.2025.107421.

[18] Qin Shi, Siyan Cai, Yingjie Fan, et al., 2026, Effects of bifrontal-transcranial direct current stimulation combined with music listening on sleep quality, cortical activation and functional connectivity in patients with insomnia: a randomised controlled trial by fNIRS. Psychiatry, 17: 1763543, 1-11. DOI:10.3389/fpsyt.2026.1763543.

[19] Li J, Li A, Jiao J, et al., 2025, Effects of high-definition transcranial direct current stimulation for the treatment of chronic insomnia: a randomized, double-blind, controlled trial. Scientific Reports, 15: 26574, 1-8. DOI:10.1038/s41598-025-26574-4.

[20] Zhou Q, Liu Z, Zhao S, et al., 2022, Transcranial magnetic stimulation combined with transcranial direct current stimulation in patients with chronic insomnia: a case report. Journal of Clinical Sleep Medicine, 18: 2871-2874. DOI:10.5664/jcsm.10272.

[21] Li J, Li A, Jiao J, et al., 2025, Correction: Effects of high-definition transcranial direct current stimulation for the treatment of chronic insomnia: a randomized, double-blind, controlled trial. Scientific Reports, 15: 37568. DOI:10.1038/s41598-025-25587-z.

[22] Wang Y, Jia W, Zhang Z, et al., 2025, Model-driven individualized transcranial direct current stimulation for the treatment of insomnia disorder: protocol for a randomized, sham-controlled, double-blind study. BMC Psychiatry, 25: 869, 1-11. DOI:10.1186/s12888-025-05869-0.

[23] Tavakoli AV, Yun K, 2017, Transcranial Alternating Current Stimulation (tACS) Mechanisms and Protocols. Frontiers in Cellular Neuroscience, 11: 214, 1-17. DOI:10.3389/fncel.2017.00214.

[24] Inagawa T, Yokoi Y, Narita Z, et al., 2019, Safety and Feasibility of Transcranial Direct Current Stimulation for Cognitive Rehabilitation in Patients With Mild or Major Neurocognitive Disorders: A Randomized Sham-Controlled Pilot Study. Frontiers in Human Neuroscience, 13: 273, 1-11. DOI:10.3389/fnhum.2019.00273.

[25] Tavakoli AV, Yun K, 2017, Transcranial Alternating Current Stimulation (tACS) Mechanisms and Protocols. Frontiers in Cellular Neuroscience, 11: 214, 1-17. DOI:10.3389/fncel.2017.00214.

[26] Kittaka C, Moriyama T, Itoh H, et al., 2022, Transcranial Alternating Current Stimulation/Transcranial Direct Current Stimulation (tACS/tDCS). The Japanese Journal of Rehabilitation Medicine, 59(5): 456-460. DOI:10.2490/jjrmc.59.456.

[27] Zheng W, Lan XJ, Qin ZJ, et al., 2023, Transcranial alternating current stimulation for chronic insomnia: A systematic review. Asian Journal of Psychiatry, 82: 103477, 1-9. DOI:10.1016/j.ajp.2023.103477.

[28] Nabil Y, Hatem N, Aboelkhier MM, et al., 2026, Transcranial alternating current stimulation for chronic insomnia: a meta-analytic evaluation of sleep restoration and safety in adults. BMC Psychiatry, 26: 236, 1-14. DOI:10.1186/s12888-026-06236-9.

[29] Wang H, Zheng D, Huang J, et al., 2026, Modulating Default and Salience/Ventral Attention networks: Exploring the treatment effect of transcranial alternating current stimulation on chronic insomnia. Psychotherapy and Psychosomatics. DOI:10.1159/000552137.

[30] Lu H, Li J, Yang NS, et al., 2023, Using gamma-band transcranial alternating current stimulation (tACS) to improve sleep quality and cognition in patients with mild neurocognitive disorders due to Alzheimer's disease: A study protocol for a randomized controlled trial. PLOS ONE, 18(8): e0289591, 1-21. DOI:10.1371/journal.pone.0289591.

[31] Riddle J, Frohlich F, 2021, Targeting neural oscillations with transcranial alternating current stimulation. Brain Research, 1765: 147491, 1-20. DOI:10.1016/j.brainres.2021.147491.

[32] Wu X, Zhang Y, Luo WT, et al., 2021, Brain Functional Mechanisms Determining the Efficacy of Transcutaneous Auricular Vagus Nerve Stimulation in Primary Insomnia. Frontiers in Neuroscience, 15: 609640, 1-16. DOI:10.3389/fnins.2021.609640.

[33] Kim AY, Marduy A, de Melo PS, et al., 2022, Safety of transcutaneous auricular vagus nerve stimulation (taVNS): a systematic review and meta-analysis. Scientific Reports, 12: 22055, 1-12. DOI:10.1038/s41598-022-25864-1.

[34] Cao Z, Shi Q, Shi Z, et al., 2026, Efficacy of repetitive transcranial magnetic stimulation for insomnia disorder: a systematic review and meta-analysis of randomized controlled trials. Frontiers in Neuroscience, 20: 1816963, 1-25. DOI:10.3389/fnins.2026.1816963.

[35] Zhang YP, Liao WJ, Xia WG, 2018, Effect of Acupuncture Cooperated with Low-frequency Repetitive Transcranial Magnetic Stimulation on Chronic Insomnia: A Randomized Clinical Trial. Current Medical Science, 38: 491-498. DOI:10.1007/s11596-018-1905-2.

[36] Xu S, Cui H, Xiao X, et al., 2025, Precision at Deep Brain: Noninvasive Temporal Interference Stimulation. ACS Nano, 19(46): 39589-39614. DOI:10.1021/acsnano.5c15238.

[37] Joseph L, OR S, Ravi C, 2021, Insomnia: Therapy and Role of neurotransmitters. Journal of University of Shanghai for Science and Technology, 23(12): 511-524. DOI:10.51201/JUSST/21/121052.

[38] Zhang S, He JK, Meng H, et al., 2021, Effects of transcutaneous auricular vagus nerve stimulation on brain functional connectivity of medial prefrontal cortex in patients with primary insomnia. The Anatomical Record, 304(11): 2426-2435. DOI:10.1002/ar.24785.

[39] Yudong Wang, Jian Liu, Shanshan Cheng, et al., 2026, Efficacy and mechanism of combined treatment with transcranial direct current stimulation and zolpidem for treatment-resistant insomnia: a study protocol for a prospective, double-blind, randomized controlled trial. Psychiatry, 17: 1743024, 1-22. DOI:10.3389/fpsyt.2026.1743024.

[40] Tao Y, Liang Q, Zhang F, et al., 2024, Efficacy of non-invasive brain stimulation combined with antidepressant medications for depression: a systematic review and meta-analysis of randomized controlled trials. Systematic Reviews, 13: 92, 1-16. DOI:10.1186/s13643-024-02480-w.

[41] Li W, Liu Q, Luo J, et al., 2026, Cost-utility analysis of repetitive transcranial magnetic stimulation and transcranial direct current stimulation as adjunctive therapies in Chinese patients with major depressive disorder. BMC Psychiatry, 26: 1-22. DOI:10.1186/s12888-026-08240-5.

[42] Zrinih A, Akwan R, Elsharkawy MM, et al., 2026, Electrical vestibular nerve stimulation as a novel therapeutic approach for insomnia: a systematic review and meta-analysis. BMC Psychiatry, 26: 268, 1-12. DOI:10.1186/s12888-026-07922-4

Publisher's note

Whioce Publishing remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.