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Anesthetic Therapy for Chronic Insomnia

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Abstract

Chronic insomnia is a common sleep disorder that significantly impacts patients' quality of daily life as well as physical and mental health. This paper examines the potential utility of anesthetic sleep therapy for chronic insomnia, and, under certain circumstances, provides a comparative analysis of the strengths and limitations of this approach versus conventional insomnia therapies. This paper aims to highlight current developmental challenges in anesthetic sleep therapy for chronic insomnia, provide clinical practitioners with recommendations regarding the application of anesthetic sleep therapy in chronic insomnia management, and prospects for future advancements.

Keywords

Chronic Insomnia, Anesthesia, Sleep Disorders, Propofol

1. Introduction

The International Classification of Sleep Disorders, Third Edition (ICSD-3), defines chronic insomnia as a sleep disorder characterized by insomnia occurring at least three times per week, lasting for more than three months, and accompanied by impaired daytime function. The prevalence of chronic insomnia is 2% - 10%, accounting for approximately 15% of insomnia patients, and it has gradually become a clinical disease that cannot be ignored [1]. Chronic insomnia can lead to symptoms such as irritability, anxiety, difficulty concentrating, and physical and mental fatigue through its impact on daytime function, and in severe cases, it can even affect the patient's mental health. Multiple studies have also shown a close relationship between chronic insomnia and depression [2]. Furthermore, chronic insomnia is a risk factor for other chronic diseases [3].

Although Cognitive Behavioral Therapy for Insomnia (CBT-I) is currently recommended as the first-line treatment of choice, its widespread use in clinical prac-

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tice is limited due to a shortage of mental health professionals trained in behavioral sleep medicine, as well as low treatment adherence and completion rates [4]. Traditional sedative medications (such as benzodiazepines) can improve symptoms in the short term but are controversial due to associated dependence, tolerance, cognitive impairment, and other systemic side effects [5]. Against this backdrop, anesthetic sleep therapy has emerged as one of the most groundbreaking strategies for treating chronic insomnia in recent years, leveraging its unique advantages of "rapidly reshaping the homeostatic sleep structure" and being "safer, with less dependence".

Table 1. Clinical protocols for anesthetic sleep therapy.

Treatment Method	Mechanism of Action	Clinical Application Effects	Recommended Treatment Protocol	Adverse Reactions and Incidence Rates
Propofol	1. Enhances GABA-mediated channel activation 2. Increases c-fos expression in the VLPO sleep center 3. Reduces neurons in arousal systems	1. Improves postoperative sleep quality 2. Treats refractory chronic insomnia	Anesthesia-induced sleep balance technique: 1) Effect-site concentration: 3.0 μg/L 2) Duration: 2 hours/day 3) Course: 3 days	1. Stuttered breathing: 67% 2. Increased airway secretions: 8% 3. Hypotension and bradypnea exceeding 20% from baseline: 29% 4. Morning drowsiness (next day): 8% 5. Mild nausea and lightheadedness: 8%
Dexmedetomidine	1. α2-adrenergic receptor agonist 2. Induces c-fos expression in PO galanin neurons 3. Increases NREM sleep delta power 4. Attenuates neuronal apoptosis	1. Improves sleep quality in chronic insomnia patients 2. Improves cognitive function 3. Maintains natural sleep state 4. Minimal respiratory depression	1. Anesthesia-induced sleep balance technique: a) Initial dose: 0.5 - 1 μg/kg/h for 10 min b) Maintenance dose: 0.2 -0.7 μg/kg/h c) Course: 3 - 7 days 2. Patient-controlled sleep: a) Basal rate: 0.4 μg/h b) Bolus dose: 10 μg 3. Intranasal spray: a) Dose: 1 - 2 μg/kg	1. Anesthesia-induced sleep balance technique: Blood pressure decreased by 10.4%, and heart rate decreased by 15.3% 2. Patient-controlled sleep and intranasal spray: no significant adverse reactions
Esketamine	1. NMDA receptor antagonist 2. Increases NREM sleep slow-wave activity 3. Alters BDNF expression 4. Promotes glutamate release	1. Improves sleep disorders 2. Rapid and sustained antidepressant effect 3. Especially suitable for insomnia patients with comorbid depression	Combined with dexmedetomidine regimen: 1) Dex initial: 1 μg/kg, for 10 min 2) Dex maintenance: 0.2 -1.5 μg/kg/h 3) Esketamine: 0.5 mg/kg 4) Duration: 2 hours/day 5) Course: 4 days	1. Oral dryness: 32.5% 2. Nausea: 5%

Continued

Tramadol	1. Weak μ-opioid receptor agonist 2. Inhibits 5-HT/NA reuptake 3. Prolongs REM sleep latency	1. Shortens REM sleep duration 2. Prolongs slow-wave sleep time 3. Potentially beneficial for depressed patients	1. Experimental regimen: a) Dose: 100 mg/dose 2. PCIA: 7.5 mg/kg Background infusion: 2.0 mL/h PCIA dose: 1ml Lockout time: 15 minutes	1. Bradycardia: 21% 2. Tachycardia: 42% 3. Hypotension: 51%
Stellate Ganglion Block	1. Blocks sympathetic nerve conduction. 2. Reduces hippocampal inflammatory factors. 3. Increases melatonin levels. 4. Regulates the autonomic nervous system	1. Alleviates sleep disorders 2. Treats various painful and non-painful diseases	Local anesthetic block regimen: 1) Preferred drug: Ropivacaine 2) Recommended concentration: 0.375% 3) Single dose: 4 – 5 ml 4) Optimal dose: 4 ml (0.375%)	Recurrent laryngeal nerve block: 28%

Note: GABA: γ-aminobutyric acid, VLPO: ventrolateral preoptic nucleus, NREM: non-rapid eye movement, NMDA: N-methyl-D-aspartate receptor, BDNF: brain-derived neurotrophic factor, Dex: Dexmedetomidine, 5-HT: serotonin, NA: norepinephrine

This study will explore the application advantages of anesthetic sleep therapy for chronic insomnia, summarize currently feasible clinical treatment methods and specific protocols (Table 1), analyze the practical constraints hindering its development and the inherent limitations of the therapy itself, aiming to systematically evaluate the efficacy, safety, and clinical prospects of anesthetic induction sleep therapy for chronic insomnia.

2. Advantages of Anesthetic Sleep Therapy

2.1. Improving Sleep Homeostatic Structure

Traditional drugs primarily rely on sedative effects to treat chronic insomnia by reducing sleep onset latency and increasing total sleep time. However, these drugs often fail to effectively reshape the pathological sleep structure, making it difficult to gradually cure chronic insomnia from the root cause; conversely, they may disrupt the patient's sleep microstructure. Among them, benzodiazepines can increase stage 2 of non-rapid eye movement (NREM) sleep and decrease the duration of NREM stage 3 (N3), as well as reduce the time spent in rapid eye movement (REM) sleep during the night [5]-[7]. The increase in NREM stage 2 (N2) and decrease in REM may subjectively improve the patient's perception of sleep, but objectively fail to correct the sleep structure effectively, which may lead to suboptimal treatment outcomes ultimately.

In contrast, anesthetic hypnotic drugs can efficiently improve sleep by partially acting on endogenous sleep-wake pathways or influencing circadian rhythms to alter sleep phases. For example, propofol and dexmedetomidine may work through mechanisms closer to natural sleep [8], reducing REM, increasing the total dura-

tion and percentage of NREM, and regulating the duration of various NREM stages [9]. Specifically, they increase the duration and percentage of N2 and N3, improve sleep structure, and help patients with chronic insomnia return to normal sleep [10] [11]. Studies have proven that correspondingly increasing NREM, correcting the distribution and duration of various sleep stages, and reshaping the homeostatic sleep structure are beneficial for the body's sleep recovery and health, forming one of the theoretical bases for currently improving and treating patients with chronic insomnia [9] (**Table 2**).

Table 2. Impact of general anesthetics on sleep architecture.

Drug Category	NREM			REM
	N1	N2	N3	
Propofol	↓	–	↑	↓
EsKetamine	–	–	↑	–/↓
Benzodiazepines	↑	↑	↓	–/↓
Dexmedetomidine	↑/–/↓	↑/–	↑/–	–/↓
Opioids	↑/–	↑/–	–/↓	–/↓

Note: ↑: Increase; –: No effect; ↓: Decrease; NREM: non-rapid eye movement sleep; N1: NREM stage 1; N2: NREM stage 2; N3: NREM stage 3, REM: rapid eye movement.

2.2. Breaking the Dilemma of Dependence, Tolerance, and Adverse Effects

Pharmacological treatment for chronic insomnia is usually not the first-line choice, likely due to issues of tolerance and dependence [12] [13], as well as adverse effects such as impaired cognitive function [12]. The mainstream drugs for clinically treating chronic insomnia are benzodiazepine sedatives. The improvement effects of these drugs in short-term treatment are widely recognized by expert consensus and treatment guidelines. However, after long-term treatment with such drugs, patients with chronic insomnia find it difficult to fall asleep without them and develop tolerance. Particularly for some elderly patients, these therapeutic drugs can negatively affect physical stability and cognitive function, potentially leading to fatal events [14]. Furthermore, many chronic insomnia patients experience side effects of drug addiction after traditional drug treatment, with benzodiazepine addiction already causing a significant number of accidental overdose deaths in the United States [15], a severe side effect that outweighs the benefits. In contrast, non-benzodiazepine anesthetic drugs, especially when using dexmedetomidine's mechanism close to normal sleep for treating chronic insomnia, are more gentle.

Additionally, anesthetic drugs have applications in treating related drug addictions [16]. Studies have shown that in neonatal intensive care units, anesthetic drugs are already used to reduce benzodiazepine dosage as an alternative sedative treatment [17]. It is evident that for chronic insomnia patients addicted to seda-

tives, anesthetic drug treatment can not only achieve the basic effect of treating chronic insomnia but also help patients break free from the control of traditional drug adverse effects. This characteristic adds clinical value to the use of anesthetic drugs for chronic insomnia. For example, stellate ganglion block (SGB), a commonly used anesthetic treatment method, lacks dependence and addiction potential. When performed correctly by a skilled physician, the incidence of adverse reactions is low, making it a common anesthetic option to help chronic insomnia patients escape the dilemma of traditional drug treatment.

Whether considered from the perspective of long-term chronic insomnia treatment or as an alternative therapy following dependence on traditional drug treatment, anesthetic sleep therapy for chronic insomnia is a feasible solution to break the current pharmacological treatment dilemma.

2.3. Broader Medical Foundation

The 2024 "Canadian Consensus for the Management of Chronic Insomnia" emphasizes that CBT-I is the first-line therapy of choice for chronic insomnia. CBT-I effectively improves sleep quality by reshaping patients' sleep-related cognitions and behavioral patterns, with lasting effects and the potential to correct sleep problems fundamentally. However, a severe shortage of specialized healthcare professionals in CBT-I and lack of related awareness in primary hospitals are important reasons for the slow promotion of CBT-I [18]. Training relevant professionals and establishing specialized diagnosis and treatment departments is a long-term and expensive challenge. In comparison, there is a broad and mature foundation of anesthesiologists globally [19], possessing the potential to practice as clinical providers of anesthetic sleep therapy. Referring to the development path of pain medicine, establishing anesthetic sleep therapy clinics, incorporating sleep medicine treatment into anesthesiology residency training programs, and promoting dual certification in related specialties [20] can inject new vitality into the field of chronic insomnia treatment. Integrating existing anesthesiology resources in this way can not only expand career development directions for anesthesiologists but also provide more diverse and professional treatment options for insomnia patients, efficiently promoting the innovation and advancement of insomnia treatment technologies.

3. Anesthetic Sleep Therapy Drugs and Clinical Treatment Methods

3.1. Propofol

Propofol primarily exerts its sedative or anesthetic effects by enhancing γ-aminobutyric acid (GABA)-mediated channel activation and prolonging the postsynaptic inhibitory current. High-dose propofol significantly increases c-fos expression in the ventrolateral preoptic nucleus (VLPO) sleep center and reduces the number of c-fos immunoreactive neurons in arousal-related systems, including the tuberomammillary nucleus (TMN) and perifornical nucleus (PeF), thereby increasing

slow-wave sleep (SWS) [21].

Previous studies have shown that propofol improves postoperative sleep quality, particularly reducing sleep latency and improving daytime dysfunction related to sleep quality on the first postoperative night [22]. Other studies have used propofol for the treatment of refractory primary chronic insomnia, conducting subjective and objective assessments of patients' sleep status. The results showed immediate improvement in sleep status after treatment, with effects lasting up to 6 months. Meanwhile, no serious adverse events occurred during medication and within 6 months after treatment ended [23].

Currently, the main method of propofol treatment for insomnia is the anesthesia-induced sleep balance technique, which involves prolonged micro-infusion of propofol via a pump to reduce excessive cortical arousal levels and improve sleep. According to current clinical experimental research, for patients with sleep disorders, the recommended effect-site concentration for intravenous propofol infusion is 3.0 μg/L, with a daily treatment duration of 2 hours and a treatment course of 3 days, which can be adjusted based on individual circumstances [24].

3.2. Dexmedetomidine

Dexmedetomidine is a highly selective α_2-adrenergic receptor agonist with sedative-hypnotic, analgesic, sympatholytic, anti-anxiety, delirium-reducing, anti-inflammatory, and organ-protective effects, hence its widespread use for sedation in perioperative and ICU patients. Mouse experiments indicate that dexmedetomidine induces c-fos expression in PO galanin neurons, thereby consolidating NREM sleep and modulating sleep structure [25]. Compared to other drugs, dexmedetomidine has unique advantages: it activates endogenous sleep-promoting pathways, allowing patients to maintain a natural sleep state, be awakened by external stimuli or speech, and has minimal respiratory depression while stabilizing cardiopulmonary status [26]. Animal studies show that dexmedetomidine can attenuate neuronal apoptosis, improve neurodegenerative damage, and protect nerves [27], thereby improving sleep. Furthermore, dexmedetomidine increases delta power in the EEG spectrum during NREM sleep; delta activity during NREM sleep is not only a marker of NREM sleep but also reflects sleep depth [28].

Currently, methods for clinical insomnia treatment with dexmedetomidine are diverse, including anesthesia-induced sleep balance technique, patient-controlled sleep, and intranasal spray therapy. Among these, there are relatively more clinical studies on the anesthesia-induced sleep balance technique, providing more references for treatment methods. Ye Weibiao *et al.* [29] administered continuous micro-pump infusion of dexmedetomidine to patients with chronic primary insomnia, with an initial dose of 1 μg/kg/h pumped for 10 minutes, followed by a maintenance dose of 0.2 - 0.7 μg/kg/h, continued for 8 hours each night, for a course of 7 days. The results showed that this therapy was safe and reliable within one course and could improve the sleep quality of patients with chronic primary insomnia early on. Dai Zhen *et al.* [30] gave elderly patients with refractory in-

somnia an initial dose of 0.5 - 1.0 μg/kg/h, pumped for 10 minutes, then changed to a maintenance dose of 0.2 - 0.7 μg/kg/h, continued for 1 hour each night, for a course of 3 days. The results showed that dexmedetomidine used in the sleep balance technique for refractory insomnia could improve sleep quality and cognitive function in these patients.

Patient-controlled sleep (PCSL) devices allow patients to self-administer by pressing a button when they wake up at night. This facility, similar to a patient-controlled analgesia pump, enables patients to pump a safe and appropriate dose of dexmedetomidine intravenously by pressing a button when experiencing sleep disturbances at night, achieving sleep induction. According to relevant research, the recommended basal rate for dexmedetomidine patient-controlled sleep is 0.4 μg/h, with a bolus dose of 10 μg, a lockout interval of 10 minutes, and a loading dose of 25% of the sleep dose [31].

Intranasal spray therapy is also a newer treatment method, primarily used to improve postoperative sleep disturbances. According to relevant studies, the usage method is nasal spray at 21:00 at night, with a single dose of 1 - 2 μg/kg [32] [33]. Compared to the previous two methods, the nasal spray is more convenient and easier to operate, does not require ward management, and patients can use it at home before sleep as prescribed. However, it is relatively expensive and has not been widely used clinically.

3.3. Esketamine

Esketamine is an N-methyl-D-aspartate receptor (NMDAR) antagonist. It inhibits its NMDA receptor-mediated glutamate entry into the GABAergic system, causing changes in excitability in the cortex and limbic system, leading to loss of consciousness, thereby exerting sedative, analgesic, anesthetic, and antidepressant effects. In sleep studies, ketamine selectively increased electroencephalogram (EEG) slow wave activity (SWA) during non-rapid eye movement (NREM) sleep and altered the expression of central brain-derived neurotrophic factor (BDNF) [34]; esketamine may have similar effects on sleep structure. Furthermore, under esketamine anesthesia, patients lose conscious response to external sensory input but retain most reflexes or involuntary body movements, exhibiting a "dissociative anesthesia" state, the mechanism of which can be partly attributed to esketamine promoting glutamate release in different regions [35] [36]. Many chronic insomnia patients have varying degrees of depressive manifestations due to daytime functional impairment [37]. Relevant studies have proven that esketamine infusion can not only improve sleep disorders in insomnia patients [38] [39] but also exert rapid and sustained antidepressant effects in depressed patients. Therefore, esketamine has unique advantages for chronic insomnia patients comorbid with depression.

The current insomnia treatment with esketamine mainly involves combination with dexmedetomidine for treating chronic insomnia patients with comorbid depression. The primary method used is the anesthesia-induced sleep balance tech-

nique. Relevant studies indicate micro-pump injection of dexmedetomidine with an initial dose of 1 μg/kg, pumped for 10 min, then changed to a maintenance dose of 0.2 - 1.5 μg/kg/h, while simultaneously pumping esketamine 0.5 mg/kg, daily for 2 hours, for a course of 4 days [40].

3.4. Tramadol

Tramadol is a widely used centrally acting opioid analgesic for treating acute and chronic pain. As a weak agonist of the μ-opioid receptor, tramadol inhibits serotonin (5-HT) and noradrenaline (NA) reuptake. Most reuptake inhibitors and monoamine oxidase inhibitors increase REM sleep latency and suppress REM sleep duration, suggesting that tramadol might have beneficial effects in treating sleep disorders in patients, especially those with depression [41].

Some clinical experiments have shown that 100 mg tramadol significantly reduced the duration of REM sleep on the night of use, and on subsequent nights, the duration of stage 2 (N2) sleep was significantly shortened, while the duration of slow-wave sleep was significantly prolonged [42]. However, this experiment had a small number of subjects, and the mechanism of action is unclear, providing limited clinical guidance for tramadol in treating sleep disorders. This therapy remains an exploratory and adjunctive approach, principally indicated for postoperative sleep disturbances. Clinical studies have also shown that tramadol can be added to the PCIA pump to improve sleep quality on postoperative days 1, 2, and 3. A total dose of 7.5 mg/kg is added to the PCIA pump, with a background infusion rate of 2.0 mL/h, a PCIA bolus dose of 1 mL, and a lockout interval of 15 minutes [43].

3.5. Stellate Ganglion Block

The stellate ganglion is an autonomic ganglion formed by the fusion of the inferior cervical sympathetic ganglion and the first thoracic sympathetic ganglion, the latter accounting for about 80%. It is located in front of the neck of the first rib and contains neurons providing sympathetic innervation to the head and neck. SGB involves injecting local anesthetic around the stellate ganglion to block the preganglionic and postganglionic fibers of the sympathetic nervous system, thereby regulating the human autonomic nervous system, circulatory system, endocrine system, and immune system, achieving the purpose of treating various painful and non-painful diseases [44]. Existing animal research shows that SGB alleviates sleep disorders mainly by reducing pathological damage in the hippocampus, decreasing hippocampal inflammatory factors and Caspase-3 expression, while increasing melatonin levels [45].

The local anesthetics used clinically for SGB are mainly ropivacaine, lidocaine, and bupivacaine, with ropivacaine being the most widely used. Regarding dosage, 0.375% ropivacaine is typically used in a single dose of 4 - 5 ml [46]-[48]. Some studies suggest that 4 ml of 0.375% ropivacaine is the optimal dose balancing efficacy in improving sleep quality in insomnia patients and safety [46]. 0.2% ropi-

vacaine is typically used in a single dose of 5 ml [49]-[51]. Some studies have used higher concentrations and doses of ropivacaine, for example, 0.5% ropivacaine with a single block dose of 5 - 7 ml [44].

4. Limitations and Challenges

4.1. Limitations of the Studies

Although anesthetic therapy for chronic insomnia shows promising prospects, there are still corresponding research gaps. While some basic research exploring the theoretical foundation exists[21] [26]-[28], there is a considerable lack of high-quality, double-blind, multi-center clinical controlled trials, which leaves clinical practice lacking authoritative treatment protocols and recommended dosages for anesthetic treatment of chronic insomnia. Most existing studies also focus on the treatment of postoperative sleep disturbances, with a relative lack of targeted insomnia treatment research. Comparative data regarding the long-term safety of chronic insomnia treatments are still quite scarce. Simultaneously, anesthetic drug therapy could be combined with other treatment modalities like transcranial magnetic stimulation to form comprehensive treatment plans, the efficacy and feasibility of which are also worthy of research and discussion. If CBT-I is feasible, combining it with anesthetic therapy could provide a novel treatment strategy.

4.2. Clinical Application Challenges

Anesthetic sleep therapy for chronic insomnia also has some limitations. The use and management of anesthetic drugs are stricter compared to traditional drugs, and their effects on respiratory and circulatory depression are significant [52], requiring anesthesiologists to use them strictly according to clinical guidelines. Therefore, currently, anesthetic sleep therapy, compared to traditional drug therapy, has lower portability and safety for patient self-administration at home, and is more inclined towards treatment under medical supervision. Furthermore, SGB is an invasive procedure requiring skilled and experienced anesthesiologists to perform; otherwise, improper operation can lead to nerve damage, high epidural block, and other serious complications [53] [54].

Therefore, we recommend the following patients as suitable candidates for anesthetic sleep therapy: those with chronic insomnia who have shown an inadequate response to or intolerance of CBT-I or conventional sedative medications; patients with refractory, intractable insomnia, particularly those with long-term benzodiazepine dependence complicated by tolerance, dependence, or cognitive impairment; individuals with comorbid depression or anxiety in whom traditional antidepressant therapy has been suboptimal; and patients at high risk for perioperative sleep disturbances due to surgical environment, pain, or stress, for whom anesthetic therapy may also serve as an adjunctive treatment. In addition, special caution should be exercised in patients with severe cardiovascular diseases (e.g., uncontrolled hypotension, severe bradycardia, sick sinus syndrome, severe heart failure); patients with respiratory insufficiency (e.g., severe obstructive sleep

apnea); patients with severe hepatic or renal dysfunction; and pregnant or lactating patients.

5. Summary and Outlook

This paper briefly discussed the advantages of anesthetic therapy for chronic insomnia over current drug treatments in reshaping the homeostatic sleep structure, its role as an alternative therapy to improve dependence and adverse effects associated with traditional drugs, introduced some drugs and protocols for anesthetic therapy of chronic insomnia in recent years, and summarized the limitations and challenges in the development of anesthetic sleep therapy for chronic insomnia. It is believed that with sufficient clinical research and application, anesthetic therapy will make significant progress in the field of chronic insomnia, opening a new window for patients suffering from chronic insomnia.

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Final Notes

Ethics committee approval was not required, and the Helsinki Declaration was not relevant to this study, and the same was true for the informed consent.

This post does not contain any studies involving humans or animals.

Author Contributions

Conceptualization, Wanxin Wei and Wei Xu; methodology, Wanxin Wei; validation, Rui Xia, Wanxin Wei, and Wei Xu; investigation, Juan Du; data curation, Li TANG and Juan Du; writing—original draft preparation, Wanxin Wei; writing—review and editing, Wei Xu; supervision, Rui Xia; funding acquisition, Wei Xu and Li Tang. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare that there are no competing interests.

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