

# Clinical research progress of acupuncture combined with repetitive transcranial magnetic therapy in the treatment of primary insomnia

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**Abstract:** *Insomnia, as a common and high incidence disease in modern society, seriously affects the physical and mental health and quality of life of patients. In long-term clinical practice, acupuncture and moxibustion has been proved to be one of the effective treatments for insomnia, with the advantages of fast onset, long-lasting effect, green safety and no side effects. Repetitive transcranial magnetic stimulation (rTMS) is a popular physical therapy method in the treatment of neurological and psychiatric diseases in recent years. It has the advantages of simple operation, significant curative effect and less adverse reactions in the treatment of insomnia, and is widely used in clinic. This paper summarizes the relevant literature of acupuncture combined with repetitive transcranial magnetic stimulation in the treatment of insomnia in recent years, and systematically summarizes the pathological mechanism of insomnia, the mechanism of acupuncture and repetitive transcranial magnetic stimulation and clinical application, in order to provide a better guidance scheme for the clinical treatment of insomnia.*

**Keywords:** *acupuncture therapy; repetitive transcranial magnetic stimulation; primary insomnia; non drug therapy; neurotransmitters*

## 1. Introduction

Insomnia refers to a subjective experience that patients still have difficulty falling asleep or insufficient sleep depth or difficult to maintain sleep when they have sufficient sleep opportunities and comfortable sleep environment, and it seriously affects their study, work and life [1]. With the development of social economy, the change of lifestyle, and the increasing incidence of insomnia in China, the number of adults who meet the diagnostic criteria of insomnia is as high as 10% - 15%, and about 50% of them can last for more than 10 years [2] insomnia often occurs repeatedly, showing a chronic course, and long-term insomnia is a risk factor for a variety of diseases, which can greatly increase the risk of cardiovascular and cerebrovascular diseases, endocrine diseases, tumors and other diseases. Serious insomnia can also lead to reduced work efficiency, reduced attention and alertness, greatly increasing the incidence of accidents among high-risk workers, causing huge economic losses and personal safety threats [3]. According to the 2017 "Chinese adult insomnia diagnosis and treatment guide" [1], the current treatment methods of insomnia include drug treatment, psychotherapy and traditional Chinese medicine treatment. At present, psychotherapy is not popular in China; Although the short-term efficacy of drug treatment is obvious, long-term use is prone to drug resistance, dependence and addiction, which will also cause some damage to memory, and withdrawal reactions are easy to occur after drug withdrawal. As a green therapy of traditional Chinese medicine, acupuncture has outstanding advantages in short-term efficacy, long-term efficacy and safety of insomnia [4]. In recent years, repetitive transcranial magnetic stimulation (rTMS), as an auxiliary physiotherapy in the neuropsychiatric field, has been increasingly applied in the treatment of insomnia [5]. In recent years, a number of clinical randomized controlled trials have confirmed that the combination of acupuncture and rTMS in the treatment of insomnia can significantly improve the curative effect, and its effective rate is better than that of either method alone. This paper summarizes the relevant literature in recent years from the etiology and pathogenesis of insomnia, the mechanism of acupuncture combined with rTMS and its clinical application, in order to provide a new reference for the clinical application of acupuncture combined with rTMS in the treatment of insomnia.

## 2. Etiology and pathogenesis of insomnia

Traditional Chinese medicine classifies primary insomnia into the categories of "insomnia", "no sleep", "eyes do not close", "night does not dusk", etc. From ancient times to the present, taking a broad view of the many opinions of doctors of all generations on the etiology and pathogenesis of insomnia, we can conclude that there are three major categories, namely, the imbalance of yin and Yang, the imbalance of Ying and Wei, and the imbalance of five internal organs.

### 2.1. *Insomnia caused by yin yang imbalance*

Huangdi Neijing is the earliest medical work in China, which believes that the imbalance of yin and Yang is the general pathogenesis of insomnia. The book points out that "when Yang Qi is exhausted, Yin Qi is prosperous, then the eyes are dark; when Yin Qi is exhausted, and Yang Qi is prosperous, then the eyes are dark" is the basis for the normal work and rest law of the human body. Once this law is broken, yin deficiency cannot latent Yang, and Yang Qi floats outside; Or the excess of Yang and Yin can not be absorbed, so that Yang is hyperactive outside, yin and yang are out of touch, and then insomnia occurs [6]. Wangwenqi, a doctor in the Qing Dynasty, further clearly proposed the pathogenesis of Yang deficiency insomnia on the basis of the general pathogenesis of Yang not crossing Yin [7]. He believed that when the human body was deficient in Yang Qi, it was easy to cause deficiency Yang floating, making Yang not entering Yin, thus causing insomnia.

### 2.2. *Insomnia caused by loss of peace between camp and defense*

"Lingshu Kouwen" said: "the Defensive Qi travels in the sun during the day and in the Yin at midnight. The Yin dominates the night, and the night lies. When the Yang Qi is exhausted, the eyes are dark; when the Yin Qi is exhausted and the Yang Qi is prosperous, the eyes are dark." according to this, Luying, a contemporary doctor, proposed that the circadian operation law of the Ying Wei Qi is the hinge of sleep activities [8], indicating that the operation law of the Ying Wei Qi in the human body is directly affected by the circadian rhythm of nature and plays a decisive role in human sleep activities.

### 2.3. *Insomnia caused by five internal organs disorder*

The five zang organs contain five gods, which together play a role in regulating people's spiritual consciousness, thinking and emotion. If the Qi and blood in the five internal organs are adjusted smoothly, the five gods will be restless and unable to sleep if the Qi and blood in the five internal organs are disordered and the Yin and yang are imbalanced [9]. The heart is the master of the five viscera and six viscera. It is mainly responsible for the mind. It has the spirit of the president, and also has the comprehensive will. It plays a role in capturing emotions. If the heart is not full of Qi, the heart blood is scarce, and the heart Yang is not active, it can cause restlessness and insomnia. The liver is in charge of discharging and storing blood. If the liver loses discharging, it can lead to stagnation of liver qi, inversion of liver qi, stagnation of liver Qi turning into fire and insomnia; If the liver blood is insufficient, the blood does not nourish the soul, and the soul is restless, it can cause insomnia, dreaminess, and restlessness at night. The spleen is located in the center and connected with the four internal organs. It is the hub of the Qi machine. If the spleen and stomach qi machine rises and falls out of balance, it can affect the rise and fall of the liver and lung, the intersection of the heart and kidney, and the five internal organs lose harmony, which will lead to insomnia. The lung governs Qi, faces hundreds of meridians, and governs festivals. It has the effect of regulating qi and blood. If the lung qi is weak or stagnant, and the Qi mechanism is not adjusted, the Qi and blood in the five organs will not run smoothly and will not sleep. The kidney is the base of Yang Qi and the source of Yin Qi. If the kidney yang is weak, the latent power is insufficient, and the spirit floats and sleeps; If the kidney Yin is insufficient, there is no way to make Yang, and the Yang does not enter the Yin, then the God will not return to give up and cannot sleep.

## 3. Western medicine's understanding of insomnia

The pathogenesis of insomnia is very complex. In recent years, relevant studies have found that the occurrence of insomnia is closely related to excessive arousal, abnormal activities of sleep related brain regions, neurotransmitter disorders, neuroendocrine immune system disorders and endogenous circadian clock gene abnormalities.

### **3.1. Excessive arousal mechanism**

A study of modern neurobiology has confirmed that excessive arousal from the molecular level to a higher system level plays a key role in the pathophysiology of primary insomnia through a retrospective analysis of studies on autonomic nerve, neuroendocrine, neuroimmunology, electrophysiology and neuroimaging<sup>[10]</sup>.

### **3.2. Mechanism of relevant brain regions**

A large number of studies have confirmed that multiple brain regions and nuclei play important roles in the regulation of sleep wake mechanism. As early as the early 20th century, Von et al.<sup>[11]</sup> found that the brain stem and thalamus contain nuclei that regulate the sleep wake mechanism. Subsequently, relevant scholars continued to conduct in-depth research on it, further confirming that thalamic laminar nucleus, thalamic midline nucleus<sup>[12]</sup>, thalamic paraventricular nucleus<sup>[13]</sup>, etc. play an important role in arousal regulation. The ventrolateral preoptic area, lateral hypothalamic area, amygdala and other nuclei of the hypothalamus play an important role in the process of sleep induction<sup>[14]</sup>. The basal forebrain, as the information transmission center between the arousal promoting reticular ascending activation system and the cortex, has also been confirmed to be involved in the regulation of sleep wake activity<sup>[15]</sup>.

### **3.3. Neurotransmitter mechanisms**

Sleep wake activity is regulated by a variety of central neurotransmitters.  $\gamma$ -Aminobutyric acid  $\gamma$ -Aminobutyric acid (GABA) is an inhibitory sleep promoting neurotransmitter, accounting for about one-third of the reticular formation (RF) of the brain stem. It promotes sleep by inhibiting the nuclei of the arousal promoting brain regions. A large number of clinical studies have found that the GABA level in insomnia patients is generally low, and the inhibitory effect on central nervous system is insufficient, so it is difficult to enter or maintain sleep<sup>[16]</sup>. Acetylcholine (ACh) and norepinephrine (NE) play a role in promoting wakefulness in the sleep wake loop by affecting cortical cells and synaptic physiology and activating cortical regions and limbic system, respectively<sup>[17]</sup>. 5-hydroxytryptamine (5-HT)<sup>[17]</sup> and dopamine (DA)<sup>[18]</sup> are important monoamine neurotransmitters that regulate neuronal activity and synaptic plasticity in the central nervous system. They can have a bidirectional regulatory effect on sleep wake under different targets and levels.

### **3.4. Neuro endocrine immune mechanism**

There are multiple interactive pathways between the nervous endocrine immune system, which can regulate the sleep wake rhythm by regulating the release and expression of hormone levels, neurotransmitters, and immune factors. The hypothalamic pituitary adrenal axis (HPA) is the main central system of the human body to cope with external stimuli. When the human body is subjected to excessive stimuli and pressure, the body is in a state of stress for a long time. HPA is overactivated, cortisol release increases, and the body is hyperexcitable, which leads to insomnia<sup>[19]</sup>. Melatonin (MT) is a metabolite of 5-HT in the pineal gland. It plays an important role in maintaining the circadian rhythm by taking the light stimulation in the external environment as the regulation mode. When the MT level is reduced or the secretion rhythm is disturbed, it is easy to cause insomnia. A study on the effect of Electroacupuncture on hypothalamic cytokines in insomnia rats confirmed that interleukin (IL-1, IL-4, IL-6) and tumor necrosis factor (TNF) also have a certain regulatory effect on the sleep process<sup>[20]</sup>.

## **4. Mechanism of Acupuncture**

The mechanism of acupuncture in the treatment of insomnia in modern medicine has not been very clear. The current main research results show that acupuncture mainly regulates sleep disorders by regulating the nervous system and neurotransmitters<sup>[21]</sup>. Excessive arousal is a major factor in the occurrence of insomnia, and studies have shown that excessive arousal is significantly related to abnormal excitation of the central nervous system and autonomic nerves<sup>[22]</sup>. Kung and his team found in their research on the relationship between the improvement of sleep quality and cardiac autonomic nervous system in postmenopausal women with insomnia by ear acupuncture that while the sleep quality of subjects improved, their cardiac parasympathetic nerve excitability increased, while cardiac

sympathetic nerve activity decreased significantly, indicating that the improvement of sleep by ear acupuncture was significantly related to the regulation of autonomic nerves [23]. Relevant animal experiments also showed that electroacupuncture can effectively reduce the secretion of adrenal cortisol and the expression of glucocorticoid receptors in the hippocampus of rats, so as to regulate the hyperactive HPA axis, so as to relieve excessive tension and improve insomnia [24]. GABA is one of the important neurotransmitters regulating sleep. Wuwenzhong used "Tongdu Tiaoshen" acupuncture to treat insomnia patients. Results the insomnia symptoms of patients in the treatment group were improved to varying degrees, and the serum GABA level of patients in the treatment group was significantly increased, indicating that the improvement of insomnia by acupuncture was significantly related to the increase of central GABA level [25]. 5-HT is an important neurotransmitter in the central nervous system, which can regulate mood, appetite and sleep [26]. Yang et al used "Warming Yang and Supplementing Qi" acupuncture to treat insomnia patients with Yang deficiency, and found that acupuncture can not only improve the sleep quality of patients, but also effectively regulate the level of 5-HT in the brain center, indicating that acupuncture may treat insomnia by regulating the level of 5-HT [27]. Studies have shown that nitric oxide (no) in the central nervous system can promote the production of sleep factors, and relevant scholars have found that acupuncture and moxibustion not only improves the sleep quality of insomnia patients, but also has a certain impact on the level of no in patients, so it shows that acupuncture and moxibustion can improve insomnia by regulating the level of no in human body [28].

## 5. Mechanism of repetitive transcranial magnetic field

Repetitive transcranial magnetic stimulation (rTMS) is a physical method of noninvasive and painless extracerebral stimulation invented by British scholar Barker et al. [29] in 1985. It uses the time-varying magnetic field generated by the coil to generate an induced current in the patient's cerebral cortex, and generates an action potential by changing the neurons in the cerebral cortex in the stimulation area, thus regulating the metabolism and neuroelectric activity of the human brain center. Relevant studies have found that [30], the excitability of local cerebral cortex can change with the stimulation frequency of rTMS. High frequency rTMS can improve the excitability of cerebral cortical neurons, and low frequency rTMS can inhibit the excitability of cerebral cortical neurons. Therefore, many scholars and clinicians applied low-frequency rTMS to the treatment of insomnia and received considerable curative effect. A large number of clinical studies have found that low-frequency rTMS can induce and deepen the sleep depth and sleep time of insomnia patients [31], promote the recovery of cognitive function [32], and also have a considerable improvement effect on anxiety, depression and other adverse emotions [33]. These effects were confirmed to be related to the regulation of local brain metabolic function and neurotransmitter levels by R TMS, and the influence of melatonin secretion [34].

## 6. Clinical efficacy

Acupuncture combined with rTMS has a good clinical effect on primary insomnia. Kou Xuelian et al. [35] used acupuncture, rTMS, and acupuncture combined with rTMS to treat 180 patients with insomnia in three groups, and studied the clinical correlation of their prognosis, and used PSQI scale as the clinical efficacy evaluation index. The results showed that the effective rate of acupuncture combined with rTMS group was 89.47%, significantly higher than 66.67% of acupuncture group and 74.14% of rTMS group, and the observation results showed that it had significant effects on sleep quality, sleep time, sleep time, sleep efficiency Daytime function and other aspects improved significantly. Zhang Yangpu [36] used Tongren Tiaodu acupuncture combined with rTMS and sham rTMS to treat 100 patients in the observation group and 95 patients in the control group respectively on the basis of the conventional treatment of insomnia, for a total of 4 weeks. Before and after treatment, PSQI scale score, ISI scale score, sleep log, polysomnography monitoring and other indicators were used to evaluate the curative effect. The results showed that after 4 weeks of treatment, the total effective rate was 95% in the observation group and 89.5% in the control group, suggesting that Tongren Tiaodu acupuncture combined with rTMS can help improve the sleep quality, sleep mode and sleep structure of insomnia patients. Gao Ruirui et al. [37] randomly divided 200 patients with primary insomnia into the control group and the observation group with 100 cases in each group. The control group was treated with oral estazolam tablets, and the observation group was treated with Tiaodu Shugan Anshen acupuncture combined with ultra-low frequency transcranial magnetic stimulation. The PSQI score changes, daily awakening times, clinical efficacy, serum 5-hydroxytryptophan (5-HT) and dopamine (DA) levels before and after treatment were compared between the two groups, and the side effects were observed. The results showed that the curative effect of the observation group was better

than that of the control group. Tiaodu Shugan Anshen acupuncture combined with ultra-low frequency transcranial magnetic stimulation can safely and effectively improve the sleep of patients, and can better improve the serum 5-HT and DA levels of patients. Zhang Shengnan [38] used "dajiejing" acupuncture combined with low-frequency repetitive transcranial magnetic stimulation to observe and compare the TCM syndrome score, PSQI score and amino acid neurotransmitters Glu and GABA levels between the control group (n=42) and the observation group (n=43). It was concluded that "dajiejing" acupuncture combined with low-frequency repetitive transcranial magnetic stimulation in the treatment of insomnia can effectively improve insomnia symptoms and sleep quality of patients. Liu Jiafeng et al. [39] randomly divided 80 insomnia patients into treatment group (n=40) and control group (n=40). The treatment group was treated with acupuncture combined with ultra-low frequency transcranial magnetic stimulation, and the control group was treated with oral estazolam tablets. The results showed that acupuncture combined with ultra-low frequency transcranial magnetic stimulation could effectively improve the negative emotions and sleep quality of patients, and its long-term maintenance effect was better than drug treatment. Bo Danhua et al. [40] randomly divided 46 patients with insomnia into treatment group and control group. The control group was only treated with low-frequency repetitive transcranial magnetic stimulation, and the treatment group was treated with acupuncture on the basis of the control group. 10 days was a course of treatment, a total of 3 courses of treatment; The PSQI scores before and after treatment were evaluated. The results showed that both groups could improve insomnia, and the curative effect of acupuncture combined with rTMS was better than that of rTMS alone.

## 7. Conclusion

Sleep is the basis for ensuring the normal operation of various physiological functions of the human body and advanced functions of the brain, but the incidence of insomnia in modern society is increasing year by year, which not only greatly reduces people's quality of life, but also seriously threatens people's health [41]. At present, the clinical treatment of primary insomnia is mainly drug treatment and behavioral cognitive intervention treatment [42], but due to the many adverse reactions of drug treatment, patients' compliance is poor; There is a lack of therapists who have received professional training in behavioral cognitive intervention therapy in clinic, so now there is an urgent need for a safe and effective insomnia treatment method with no side effects and lasting curative effect. Therefore, it is of great significance to find a new method to treat primary insomnia. A large number of clinical studies and animal experiments have shown that [43,44], acupuncture can improve the sleep quality of insomnia patients by regulating the levels of sleep related neurotransmitters and hormones, improving mental health, etc., and the effect is long-lasting without obvious adverse reactions. R TMS is another therapy that can effectively help insomnia patients improve their sleep. R TMS can correct patients' sleep disorders by reducing the abnormal excitability of the cerebral cortex in the stimulation area, regulating neurotransmitters in the stimulation area, improving cerebral blood flow and metabolism, promoting the expression of brain-derived neurotrophic factor and stimulating brain slow wave activity [45]. Relevant studies have confirmed that the combination of acupuncture and rTMS can effectively improve the sleep quality of insomnia patients, and its curative effect is better than that of any therapy alone, showing significant synergy. However, there are still many deficiencies in the existing studies. For example, subjective scales are often used for efficacy evaluation, and there are few objective evaluation indicators. PSG, multiple sleep latency measurement (MSLT), actigraphy, electroencephalography (EEG), fMRI and other tests can be used as objective evaluation methods for sleep. Future studies can combine these objective detection methods to reflect the efficacy of acupuncture combined with rTMS in the treatment of insomnia through objective data, to avoid the influence of subjective factors on curative effect to the greatest extent. The setting of stimulation parameters of rTMS instrument related treatment largely determines the effect of treating insomnia, but there are great differences in the setting of stimulation parameters in many previous clinical trials of rTMS for insomnia. Therefore, in the follow-up study, more objective data, large sample study and multi center randomized double-blind control study are needed to optimize the stimulation parameters. There are also many methods of acupuncture in the treatment of insomnia. The author believes that large sample clinical randomized controlled trials comparing different acupuncture methods combined with rTMS in the treatment of insomnia can be further carried out in the later stage, and a set of best schemes for the treatment of insomnia convenient for clinical promotion can be summarized.

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