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2026 Volume 11, Issue 3
Advances in Precision Medicine
ISSN: 2424-9106 (Online)
ISSN: 2424-8592 (Print)

Research Progress of Transcutaneous Auricular Vagus Nerve Stimulation in the Treatment of Depression

Heng Li[1], **Chao Wang**[2]*
[1]Chengdu University of Traditional Chinese Medicine, Chengdu 610075, Sichuan, China
[2]Sichuan Provincial Hospital of Integrated Traditional Chinese and Western Medicine, Chengdu 610041, Sichuan, China

Author to whom correspondence should be addressed.

Abstract: Depression is one of the most prevalent and severe mental disorders worldwide, with its epidemiological burden increasing significantly. Existing treatment modalities are associated with issues such as prolonged treatment duration, drug tolerance, and poor adherence. Transcutaneous auricular vagus nerve stimulation (taVNS) is a safe, low-cost, and non-invasive physical therapy developed from vagus nerve stimulation techniques. This review primarily elucidates the regulatory effects of transcutaneous auricular vagus nerve stimulation on depression and its applications in the treatment of depression.

Keywords: taVNS; Depression; Research progress

Online publication: March 26, 2026

1. Introduction

The epidemiological status and social burden of depression

Depression is a common chronic mental disorder characterized by persistent low mood, loss of interest, and cognitive impairment [1]. According to the World Health Organization (WHO) report, over 300 million patients worldwide have been affected, with a lifetime prevalence rate of 6.8% in China. It is projected that by 2030, it will become the second-largest disease burden after cardiovascular diseases [2]. According to the Global Burden of Disease (GBD) study data, in China, the number of depression cases increased from 34.4 million to 53.1 million between 1990 and 2021, a rise of 54%; the overall prevalence was approximately 2.9%, with women (3.5%) higher than men (2.2%), and the prevalence was even higher among the elderly aged 55 and above (6.5%). The detection rate of anxiety with depressive symptoms in adolescents also showed an upward trend, which was further exacerbated during the pandemic [3,4]. This disease not only leads to a decline in patients' quality of life but also imposes a significant socioeconomic burden, including healthcare expenditures, productivity losses, and increased suicide risk, making it a major global public health challenge.

1.1. Existing treatment modalities (pharmacological, psychological, and physical therapy) and their limitations

The first-line treatment of depression includes pharmacotherapy, psychotherapy, physical therapy, etc.

Pharmacotherapy is the most commonly used intervention for depression, with frequently employed medications including selective serotonin reuptake inhibitors (SSRIs, such as fluoxetine and sertraline), serotonin-norepinephrine reuptake inhibitors (SNRIs, such as venlafaxine), tricyclic antidepressants (TCAs), and newer agents like bupropion. These drugs exert their effects by modulating monoamine neurotransmitters. The STAR*D study (Sequenced Treatment Alternatives to Relieve Depression) demonstrated that only approximately 30% of patients achieve remission after the first phase of antidepressant treatment, with the remission rate further declining to around 25% in the second phase. After four cumulative phases, the total remission rate remains at approximately 67%, with the probability of remission progressively decreasing after each dose change or dose escalation. Multiple meta-analyses have further confirmed that about 30% of major depressive disorder (MDD) patients fail to achieve clinical remission after receiving adequate doses and durations (at least 8 weeks) of two or more antidepressant medications [5,6]. Additionally, pharmacotherapy is associated with significant adverse effects and adherence issues. Long-term use may also lead to drug resistance, cognitive impairment, and increased risk of metabolic syndrome.

Psychotherapy is one of the core non-pharmacological interventions recommended in the depression guidelines, primarily including Cognitive Behavioral Therapy (CBT), Interpersonal Therapy (IPT), and Mindfulness-Based Cognitive Therapy (MBCT). Cognitive Behavioral Therapy (CBT), through techniques such as identifying and correcting negative cognitive biases and behavioral activation, has been demonstrated by numerous randomized controlled trials (RCTs) to significantly improve depressive symptoms [7–9]. A systematic review [10] has shown that CBT can improve depressive symptoms by more than 50%, especially in patients with mild-to-moderate MDD or drug intolerance. Its short-term efficacy is comparable to that of pharmacotherapy, while its long-term advantage in preventing relapse is particularly evident. However, psychotherapy faces multiple barriers in its practical promotion. First is the severe shortage of professionals: the number of psychological counselors/therapists worldwide and in China is far from meeting the demand [11], resulting in waiting times of several months or even longer. The second issue is patient compliance [12,13]: While CBT emphasizes homework (e.g., cognitive records, behavioral experiments), multiple studies indicate a completion rate of only 40%–60%. Key barriers include time conflicts, lack of motivation, difficulty in task execution during severe symptoms, and misconceptions about the treatment process.

Physical therapy has developed rapidly in recent years, mainly including repetitive transcranial magnetic stimulation (rTMS). rTMS, which stimulates the left dorsolateral prefrontal cortex (DLPFC) through non-invasive magnetic fields, has been approved by the FDA and China's NMPA for the treatment of TRD and MDD. Relevant studies have shown [14,15] that standard high-frequency rTMS (10Hz) or intermittent theta burst stimulation (iTBS) can elicit responses in approximately 50% of patients and achieve remission in 30%, particularly effective for drug-resistant cases with mild side effects (primarily headache and scalp discomfort).

1.2. Origin and development of Vagus Nerve Stimulation (VNS)

Vagus nerve stimulation (VNS) was first used for epilepsy treatment in the 1880s. In 1997, the U.S. FDA approved implantable VNS (iVNS) for refractory epilepsy, and in 2005, its application was expanded to adjunctive therapy for chronic or recurrent depression. iVNS involves surgical implantation of electrodes to stimulate the main trunk of the cervical vagus nerve, which can improve activity in brain regions related to mood regulation. However, issues such as surgical trauma, infection risks, and high costs have limited its widespread adoption.

1.3. Advantages and research significance of transcutaneous Vagus Nerve Stimulation (taVNS)

taVNS (transcutaneous electrical vagus nerve stimulation) delivers electrical stimulation to the auricular branch of the vagus nerve (ABVN) via the skin of the ear, offering non-invasive, portable, low-cost, and minimal side-effect advantages, enabling home-based self-management. Compared to iVNS (intracranial vagus nerve stimulation), taVNS demonstrates similar efficacy with enhanced safety and has been studied in various conditions, including epilepsy, depression, and migraine [16].

2. Theoretical basis of transcutaneous Vagus Nerve Stimulation

2.1. Theoretical basis of Traditional Chinese Medicine

2.1.1. The connection between auricular points and visceral meridians

The "Yin-Yang Eleven Meridian Moxibustion Classic" unearthed from the Western Han Dynasty tomb at Mawangdui in Changsha first documented the "ear meridian," which is associated with the upper limbs, eyes, cheeks, and throat. This represents the earliest discussion on the relationship between the ear and meridians. The "Yellow Emperor's Inner Canon" further systematically elaborated on the connection between the ear and the body's internal organs and meridians. The "Ling Shu: Oral Questions" explicitly states: "The ear is the convergence point of the Zong meridians," indicating that all twelve meridians directly or indirectly pass through the ear, making it the convergence point of the body's meridians. The "Ling Shu: Pathogenic Factors, Visceral Diseases, and Manifestations" also mentions: "The twelve meridians and 365 collaterals, whose blood and Qi all ascend to the face and traverse the orifices... their collateral Qi travels to the ear to enable hearing." This demonstrates the close connection between the ear and all meridians.

In the theory of ear-organ correspondence, the "Suwen·Jingui Zhenyan Lun" states: "The southern red color connects to the heart, which opens to the ear." Although the heart normally opens to the tongue, the tongue is not a natural orifice, so the "orifice is associated with the ear." This theory established the foundation for the connection between the ear and heart in the treatment of emotional disorders. Meanwhile, the theory that the kidneys open to the ear has been emphasized by medical practitioners throughout history. The "Comprehensive Medical Treatise of Ancient and Modern Times" quotes Chao Yuanfang: "The kidney is the meridian of the foot-Shaoyin, and its essence and Qi connect to the ear." The Qing Dynasty's "Essential Techniques of Correct Massage" further proposed that the back of the ear corresponds to the five zang organs, linking the anatomical position of the auricle to the functions of the five zang organs, thereby forming a systematic theory of ear acupoints and zang-fu relationships.

2.1.2. Syndrome of heat

Depression falls under the category of "Yuzheng" (Stagnation Syndrome) in Traditional Chinese Medicine (TCM). Its pathogenesis primarily involves emotional distress and Qi stagnation, with affected organs including the heart, liver, and spleen. The "Compendium of Acupuncture and Moxibustion" records: "When the mind is preoccupied, the spirit has a destination, and the righteous Qi stagnates, leading to Qi accumulation," elucidating the pathogenic characteristics of Qi stagnation caused by emotional internal injury.

Acupoints closely associated with emotional disorders in auricular therapy include Shenmen (MA-TF1), Xin (CV1), and Jiaoyang (LI1), whose functional localization largely overlaps with the distribution of the vagus nerve in the auricular region. Historically, Auricular Shenmen (MA-TF1) has been recognized as a pivotal point for calming the mind and regulating emotions, commonly employed in clinical practice to stabilize mood and alleviate stress. Modern research confirms that stimulating Auricular Shenmen can modulate autonomic nervous system function, thereby improving emotional disturbances. The Xin point (CV1) is grounded in the theoretical concepts of "the heart storing spirit" and "the heart governing clarity," which helps alleviate depressive states by regulating mental focus.

2.1.3. The relationship between auricular acupoints Shenmen, Xin, Jiaoyang and other points and emotional disorders

Based on the Traditional Chinese Medicine (TCM) theories of "the ear as the convergence of ancestral meridians" and "treating ear disorders with brain-based therapies," modern researchers have combined traditional auricular stimulation techniques with vagus nerve stimulation technology to develop transcutaneous auricular vagus nerve stimulation (taVNS) therapy. Professor Rong Peijing's team [17] systematically elucidated the theoretical connotation of' brain-ear therapy, 'pointing out that auricular acupoints, as regions on the body surface where the vagus nerve is distributed, can activate the' ear-vagus nerve-islet nucleus-brain network' pathway through electrical stimulation, thereby regulating neurological disorders such as depression. Acupuncture at the auricular points can achieve therapeutic effects such as nourishing the heart and calming the mind, as well as promoting Qi circulation and relieving stagnation by unblocking meridians and harmonizing the yin-yang balance of the viscera.

2.2. Fundamentals of modern medicine

2.1. Anatomical distribution and function of the vagus nerve

The vagus nerve (the Xth cranial nerve) is the longest cranial nerve in the body, containing approximately 80% of the afferent fibers. It originates from the dorsal nucleus and ambiguus nucleus of the medulla oblongata and is widely distributed to thoracic and abdominal organs. Its primary functions include regulating heart rate, gastrointestinal motility, immune and inflammatory responses, and emotional homeostasis. The afferent fibers mainly project to the nucleus tractus solitarii (NTS), which then forms extensive connections with brainstem nuclei such as the locus coeruleus (LC) and dorsal raphe nucleus (DRN), as well as the limbic system (amygdala, hippocampus, prefrontal cortex), thereby achieving integrated regulation of autonomic function, inflammation, and emotion [16].

2.2. Distribution characteristics of the auricular branch of the vagus nerve in the auricular region

Anatomical studies demonstrate that the auricular branch of the vagus nerve (ABVN) is primarily distributed in the cymba conchae (100% exclusively innervated by ABVN), the cavity conchae (approximately 45%), the tragus (approximately 45%), and the anterior wall of the external auditory canal. Regions such as the auricle are mainly innervated by the great auricular nerve or the lesser occipital nerve, with no distribution of ABVN. This distribution pattern provides precise superficial stimulation targets for taVNS [18].

2.3. Regulatory pathways of taVNS on the central nervous system

Studies have shown that taVNS stimulation of the anterior ventral nucleus (ABVN) relays signals through the nucleus tractus solitarii (NTS) to the locus coeruleus (LC) (which releases norepinephrine) and dorsal raphe nucleus (DRN) (which releases serotonin), thereby modulating depression-related brain regions such as the prefrontal cortex, cingulate cortex, and hippocampus [19–23]. Simultaneously activates the cholinergic anti-inflammatory pathway (α7 nicotinic acetylcholine receptor) and inhibits peripheral and central inflammatory factors (e.g., TNF-α, IL-6). fMRI studies have confirmed that taVNS enhances internal connectivity within the DMN, reduces abnormal connections between the DMN and the insula, and upregulates BDNF expression, thereby promoting neural plasticity.

3. Advances in mechanism research

In recent years, mechanistic studies have been conducted from multiple dimensions, including neuroimaging, molecular biology, and animal models. In terms of neuroimaging [19,24–28], resting-state fMRI demonstrated that taVNS could reduce functional connectivity (FC) between the posterior cingulate cortex and the middle frontal gyrus, which was significantly associated with improved HAMD scores. Another study confirmed that taVNS modulates the topological structure of visual networks, reducing feature path lengths and enhancing degree centrality. Studies on the gut microbiota-brain-gut axis demonstrate that transcranial vagus nerve stimulation (taVNS) can improve gut microbiota diversity in depression model mice, reduce lipopolysaccharide (LPS) translocation, and regulate short-chain fatty acid levels. Electrophysiological studies further confirm that taVNS enhances γ-aminobutyric acid (GABA)ergic inhibition, thereby balancing excitatory-inhibitory dysregulation. These findings indicate that taVNS exerts antidepressant effects through multi-target and multipathway synergistic mechanisms. However, further exploration is required regarding parameter optimization (frequency 20–30 Hz, pulse width 200–500 μs, current 0.5–2 mA) and individual variability.

4. Clinical application and efficacy studies

Multiple randomized controlled trials (RCTs) and meta-analyses have confirmed the clinical efficacy of transcutaneous electrical nerve stimulation (taVNS).In 2013, Hein et al. [29] first demonstrated in a randomized controlled trial (RCT) that 2-week transcranial electrical stimulation (taVNS) significantly reduced the Beck Depression Inventory (BDI) scores. Rong et al. [30] carried out a large-scale study in China in 2016 (91 cases in the real stimulation group), and HAMD-24 scores decreased significantly after 12 weeks of treatment compared with the sham stimulation group, and the improvement continued to the follow-up period. The 2023 meta-analysis by Tan et al. [31] included 12 randomized controlled trials (RCTs) (n = 838) and demonstrated that transcranial vagus nerve stimulation (taVNS) significantly increased the response rate compared to sham stimulation (RR = 12.30) and showed a large effect size in HAMD score reduction (Hedges' g = -1.47). Compared with antidepressant medications (ATDs), taVNS exhibited equivalent or higher response rates (RR = 1.22) with small to moderate HAMD score reduction effects. When combined with ATDs, taVNS demonstrated superior HAMD improvement (g = -0.95). Subgroup analysis revealed significant benefits in patients with mild to moderate depression and post-stroke depression. Other studies [32–34], such as open-label trials for treatment-resistant depression, demonstrated that approximately 40%–60% of patients achieved response criteria after 8 weeks of transcranial electrical nerve stimulation (taVNS), with some patients maintaining efficacy for 3–6 months.In general, taVNS is indicated for patients with drug intolerance or treatment-resistant depression (TRD), with a treatment duration of 4 to 12 weeks and a daily session of 20 to 30 minutes.

5. Safety and adverse effects

The 2022 systematic review by Kim et al. [35] included 177 studies (6,322 cases), reporting an extremely low overall incidence of adverse events (AEs) with transcutaneous vagus nerve stimulation (taVNS) (12.84 per 100,000 stimulation person-minutes-day). The most common AEs were earache, headache, tingling, and skin erythema, all of which were mild, transient, and self-limiting. There was no significant difference in the risk of adverse events (AE) between the true stimulation group and the sham stimulation group or control group (risk difference RD = 0.013). No severe AEs (such as cardiac events or epileptic seizures) were directly associated with taVNS, with only 2 potentially relevant events failing to meet the causal determination criteria. Occasional dizziness and nausea were occasionally observed during clinical trials and resolved after discontinuation. Compared to iVNS or ECT, taVNS demonstrated significantly higher safety, making it suitable for long-term use.

6. Conclusion

Transcutaneous auricular vagus nerve stimulation (taVNS), as an emerging technology in the field of neuromodulation, integrates traditional Chinese medicine (TCM) auricular acupoint theory with modern vagus nerve stimulation techniques, offering significant advantages of being non-invasive, safe, convenient, and cost-effective. Current evidence indicates that taVNS can effectively ameliorate mood symptoms in patients with depression, demonstrating efficacy comparable to antidepressant medications while maintaining good safety profiles, particularly suitable for patients with drug intolerance or treatment-resistant depression. Its mechanisms of action involve multiple pathways, including monoamine neurotransmitter regulation, HPA axis modulation, promotion of neural plasticity, suppression of neuroinflammation, and brain network remodeling. Although current research faces limitations such as insufficient parameter standardization and a lack of long-term evidence, with the advancement of large-scale clinical studies and deeper mechanistic investigations, taVNS is poised to become a crucial component in the comprehensive prevention and treatment system for depression, providing novel strategies to alleviate the global burden of depression.

Disclosure statement

The author declares no conflict of interest.

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