Official Title: Transcutaneous Auricular Vagus Nerve Stimulation for Social Anxiety Disorder A Randomized Clinical Trial

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Study Protocol

1. Research Background

Anxiety disorders are a group of conditions characterized by symptoms such as excessive worry, fear of social interactions or public speaking, unexpected or induced panic attacks, anticipatory anxiety, and avoidance behaviors. In China, anxiety disorders exhibit the highest prevalence among all mental disorders, with a 12month prevalence rate of 5.0% and a lifetime prevalence rate of 7.6%, imposing a substantial burden on public health. Among these, social anxiety disorder (SAD) manifests as intense fear or anxiety in social situations, driven by concerns about negative evaluation of one's behavior or performance, leading to persistent avoidance of social interactions. In China, SAD has a lifetime prevalence of 0.6%, presenting with a chronic or episodic course that impairs multiple functional domains—particularly interpersonal relationships and social experiences. SAD is frequently comorbid with other mental disorders, resulting in severe social dysfunction, including increased dropout rates, occupational impairment, and reduced socioeconomic status, significantly diminishing patients' quality of life. Identifying reliable neurobiological biomarkers may facilitate earlier and more precise diagnosis and treatment of SAD, thereby improving patient prognosis and quality of life.

Firstline treatments for SAD include psychotherapy such as cognitive behavioral therapy (CBT) and pharmacotherapy with selective serotonin reuptake inhibitors (SSRIs) or serotoninnorepinephrine reuptake inhibitors (SNRIs). Although these therapies have demonstrated efficacy, approximately onethird of patients exhibit no significant therapeutic response. CBT may not be suitable for individuals with limited cognitive capacity, while anxiolytic and antidepressant medications can induce adverse effects, including dizziness, fatigue, drowsiness, nausea, and potential dependence (Leichsenring F. N Engl J Med. 2017).

Vagus nerve stimulation (VNS) has been employed in the treatment of psychiatric disorders, particularly treatmentresistant depression and posttraumatic stress disorder (George MS. Neuropsychopharmacology. 2010; Lespérance P. Int J Mol Sci. 2024; Gurel NZ. Brain Stimul. 2020). However, the necessity of surgical intervention, perioperative risks, and potential adverse effects limit its clinical application. In recent years, transcutaneous auricular vagus nerve stimulation (taVNS) has been objectively evaluated for its efficacy in treating major depressive disorder (Tu Y. Brain Stimul. 2018), primary insomnia (Wu Y. Brain Sci. 2022), epilepsy (Lampros M. Seizure. 2021), irritable bowel syndrome (Shi X. JCI Insight. 2021), and mild cognitive impairment (Murphy AJ. Neurotherapeutics. 2023). As a noninvasive procedure, taVNS significantly reduces surgical risks and exhibits minimal side effects. Compared to conventional pharmacotherapy and CBT, taVNS offers inherent advantages, including safety, costeffectiveness, convenience, and high patient tolerability (Redgrave J. Brain Stimul. 2018). A 2025 evaluatorparticipantblinded, randomized shamcontrolled study further confirmed the efficacy of taVNS in alleviating symptoms of generalized anxiety disorder (Lai J. Heliyon. 2025). However, no evidence currently supports the

clinical effectiveness of taVNS in treating mildtomoderate SAD.

Here is the professionally translated and polished version of your biomedical research protocol in English, adhering strictly to academic writing standards in the field:

1. Study Objectives
Primary Objective

To evaluate the preliminary clinical efficacy of transcutaneous auricular vagus nerve stimulation (taVNS) in treating social anxiety disorder (SAD) and the feasibility of the study protocol.
Secondary Objective
To assess patient compliance and safety profiles of taVNS intervention.

2. Study Design and Methods
Study Design
Type: Sham randomized controlled, doubleblind clinical trial
Allocation: Participants will be randomized into either the intervention group (highcurrent taVNS) or the shamcontrol group (lowcurrent taVNS)
Randomization: Microsoft Excel was used to generate random computer-generated sequences for 1:1 simple random grouping.
Blinding:
Blinded: Blinding was implemented among patients, assessors, and data analysts (assessors were unaware of the specific group assignments; patients were unaware whether they received a sham intervention; data analysts performed statistical analyses solely based on the A-and B-labels).
Duration: 1 year (commencing upon ethics approval, concluding July 2026)

Inclusion Criteria
Participants must meet all of the following:
1. DSM5 diagnostic criteria for SAD
2. Liebowitz Social Anxiety Scale (LSAS) score of 30 or higher and a Social Phobia Inventory score greater than 30
3. Aged 18–70 years
4. Willing to provide written informed consent

Exclusion Criteria
Participants will be excluded for any of the following:
1. Lifetime diagnoses of bipolar disorder, schizophrenia, or obsessivecompulsive disorder
2. Comorbid cognitive impairments that may interfere with assessments
3. Significant suicidal ideation/behavior within 6 months
4. taVNS treatment within the past month
5. Contraindications to taVNS (e.g., active ear infections, dermatological lesions, auricular hypersensitivity)
6. Implanted pacemakers/neurostimulators OR severe neurological/renal/cardiovascular/hepatic comorbidities

7. Concurrent psychotherapy
8.psychotropic medications/alcohol use
9. Inability to complete psychological evaluations
10. Lack of informed consent capacity
11. Pregnancy or lactation

Intervention Measures
Intervention Group:
Patients in both groups were subjected to electrical stimulation at the bilateral cymba conchae (Kidney acupoint, CO10) and cavum conchae (Heart acupoint, CO15), regions rich in transcutaneous auricular vagus nerve stimulation (taVNS) distribution (Faraji N. Neurosci Biobehav Rev. 2024). The taVNS group received stimulation with the following parameters: 20 Hz frequency, pulse width <1 ms, current intensity <5 mA (adjusted to patient tolerance), administered twice daily for 30 min per session over 8 weeks (total of 112 sessions). Participants who completed >80% of the treatment sessions ($\geqslant$90 sessions) were considered perprotocol cases. A followup was conducted at 1 month postintervention (Rong P. J Affect Disord. 2016; Li S. Neuromodulation. 2022; Lai J. Heliyon. 2025).

Sham Intervention Group:
Identical stimulation parameters were applied, but the current intensity was set at 0.1 mA.
Primary and Secondary Outcome Measures
Primary Outcome Measure:
Change in Liebowitz Social Anxiety Scale (LSAS) scores (baseline, weeks 2, 4, 8, and 12).
Secondary Outcome Measures:
Hamilton Anxiety Scale (HAMA) scores (baseline, weeks 2, 4, 8, and 12).
Hamilton Depression Scale (HAMD) scores (baseline, weeks 2, 4, 8, and 12).
Social Interaction Anxiety Scale (SIAS)(baseline, weeks 2, 4, 8, and 12).
Social Adaptation Self-evaluation Scale (SAS)(baseline, weeks 2, 4, 8, and 12).
Brief Fear of Negative Evaluation (BFNE)(baseline, weeks 2, 4, 8, and 12).
Pittsburgh Sleep Quality Index (PSQI)(baseline, weeks 4, 8, and 12).
Intervention adherence (completed sessions/rate) (baseline, weeks 2, 4, and 8).
Adverse event records (e.g., excessive anxiety, panic attacks) (baseline, weeks 2, 4, and 8).
heart rate variability (HRV) (baseline and weeks 8).
blood concentrations of IL-6, IL-10, CRP, and cortisol (baseline and weeks 8).
Sample Size Estimation
Pilot Study Sample Size Design:
This exploratory study adopted a parallel design with reference to similar domestic and international pilot studies. Participants were randomized at a 1:1 allocation ratio into two groups: an intervention group (n=20) and a sham intervention group (n=20). Considering an estimated 20% dropout rate in clinical trials and randomization requirements, the total sample size was expanded to 25 cases per group (intervention and control), yielding a final sample of 50 participants.

Statistical Analysis
The primary efficacy analysis was conducted according to the intention-to-treat (ITT) principle,

with all randomized participants included in the analysis according to their initially assigned groups. Per-protocol (PP) analysis was performed as a sensitivity analysis to assess the robustness of the study findings.

Continuous variables are presented as mean ± standard deviation or median (interquartile range) depending on their distributional characteristics; categorical variables are expressed as frequencies and percentages. Appropriate parametric or nonparametric statistical methods were selected based on data type and distribution.

The primary efficacy outcome was the change from baseline to week 8 in the total score on the Liebowitz Social Anxiety Scale (LSAS). For continuous outcome measures with multiple follow-up time points, longitudinal analyses were conducted using linear mixed-effects models (LMM), with group, time, and group × time interaction included in the model, and adjustment for baseline values and other covariates as appropriate. Adjusted between-group differences and 95% confidence intervals are reported.

For missing data, the linear mixed-effects model used all available observations for estimation, without imputation of missing values by the last observation carried forward (LOCF) method. Sensitivity analyses were performed using multiple imputation (MI) and PP analysis, and additional sensitivity analyses under different missing data assumptions were conducted for the primary outcome to evaluate the robustness of the results.

For categorical outcomes such as treatment response rates, remission rates, and adverse events, between-group comparisons were performed using the χ^2 test or Fisher's exact test as appropriate. For exploratory outcomes related to autonomic function and inflammatory/stress markers, appropriate statistical methods were selected based on data distribution, with data transformation and multiple comparison correction applied as needed.

All statistical tests were two-sided, and a P value <0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics software.

1. Sample Size Calculation

As an exploratory study, the sample size was determined with reference to similar domestic and international pilot studies. A parallel design was adopted, randomizing participants at a 1:1 ratio into an intervention group (n=20) and a sham intervention group (n=20). Accounting for an estimated 20% dropout rate and randomization requirements, the total sample size was expanded to 25 cases per group (intervention and control), totaling 50 participants.

2. Data Management and Confidentiality

Data collection for this study will be conducted in the Department of Psychiatry outpatient clinic at the Second Affiliated Hospital of Zhejiang University, and all participant screening and data recording procedures will be completed within this hospital. All treatments will be administered either by the patients themselves or with the assistance of their family members. To ensure data accuracy and traceability, all data will be entered into Excel spreadsheets, followed by verification against original records by a second researcher; subsequently, the data will be organized and imported into SPSS for analysis. All records pertaining to participant identities will be kept strictly confidential, and such data will not be disclosed to external parties unless permitted by applicable laws and/or regulations.

1. Informed Consent

(1) Patients, particularly hospitalized patients with severe illnesses or psychiatric disorders: For those lacking decisionmaking capacity, informed consent shall be obtained from their legal guardians.

(2) Illiterate individuals

(3) Prisoners, pregnant women, individuals with intellectual disabilities, and other potentially economically or educationally disadvantaged groups

(4) Children: Written informed consent must be obtained from their legal guardians. If the child is capable of providing assent, their agreement must also be obtained.

(5) Students, institutional employees, etc.: Participation in research conducted by their supervisors must not involve undue inducement or coercion.

(6) Special considerations for obtaining informed consent from patients with psychiatric/cognitive impairments:

Prior to study initiation, it must be confirmed that the inclusion of such patients is necessary and that cognitively intact subjects cannot be substituted.

Psychiatrists shall assess the selfawareness capacity of patients with psychiatric disorders based on mental status evaluations, document conclusions, and sign accordingly.

Physicians from relevant clinical departments (e.g., neurology, neurosurgery, neurocritical care) shall evaluate the consciousness status of subjects with other disorders of consciousness.

If the psychiatric patient retains full selfawareness capacity, the subject shall sign and date the consent form.

If partial selfawareness capacity is present, both the subject and their legal guardian shall sign and date the form.

If the patient lacks selfawareness capacity, the legal guardian shall sign and date the form.

2. Adverse Event Reporting

All adverse events (AEs): Appropriate measures shall be taken promptly, and events shall be documented in the case report form (CRF).

Serious adverse events (SAEs):

Immediate measures shall be implemented, and events shall be recorded in the CRF.

The investigator shall determine whether to discontinue or reduce the dosage of the investigational drug.

The SAE shall be reported immediately to the Institutional Review Board (IRB), the clinical trial institution, and the sponsor.

The event must also be reported to the national and provincial Food and Drug Administration within 24 hours. SAEs shall be logged into the Hospital Internal Network NonPunitive Reporting System for Adverse Events and Near Misses.

Informed Consent Form for Human Research (PI Signature)

Zhejiang University School of Medicine Second Affiliated Hospital

Dear Patient,

You are invited to participate in a clinical study titled "Transcutaneous Auricular Vagus Nerve Stimulation for the Treatment of Social Anxiety Disorder." Before deciding whether to participate, please carefully review the following information, which outlines the purpose of the study, its procedures and duration, as well as the potential benefits, risks, and inconveniences associated with participation.

Study Introduction

1. Background and Objectives

Social anxiety disorder (SAD) is an anxiety disorder characterized by social fear and avoidance, significantly impairing patients' social functioning. Currently, there is no highly effective treatment for SAD, as pharmacological and psychological therapies exhibit limited efficacy. Therefore, exploring novel therapeutic approaches for SAD is imperative.

Vagus nerve stimulation (VNS) has been utilized in the treatment of psychiatric disorders, particularly treatmentresistant depression (TRD) and posttraumatic stress disorder (PTSD). However, its clinical application is restricted due to the need for surgical intervention, perioperative risks, and potential adverse effects. In recent years, the efficacy of transcutaneous auricular vagus nerve stimulation (taVNS) in treating major depressive disorder (MDD), primary insomnia, epilepsy, and mild cognitive impairment has been objectively evaluated. As a noninvasive procedure, taVNS significantly reduces surgical risks and demonstrates an extremely low incidence of side effects, with its safety and tolerability wellestablished in prior studies.

A 2025 evaluatorparticipant blinded, randomized shamcontrolled trial conclusively demonstrated the efficacy of taVNS in alleviating symptoms in patients with generalized anxiety disorder (GAD). However, no evidence currently supports the clinical effectiveness of taVNS in treating SAD. This pilot randomized controlled trial (RCT) aims to investigate the clinical applicability and feasibility of taVNS in patients with SAD, providing preliminary data and implementation guidelines for subsequent largescale clinical trials. Additionally, longterm followup will be conducted to monitor disease progression in participants.

II. Specific Procedures and Workflow

This study adopted a randomized controlled trial (RCT) design. Upon enrollment, participants were randomly allocated (via lottery or computergenerated assignment) to either the intervention group or the sham intervention group. The randomization process ensured equal probability of assignment, with each participant having a 50% chance of being placed in either group. This approach was implemented to maintain scientific rigor and fairness in the study. Each participant was assigned a unique identification number, and medical records were securely stored in locked filing cabinets accessible only to authorized research personnel.

Study Duration: June 2025

Followup Assessments: Evaluations were conducted at baseline (week 0) and at weeks 2, 4, 8, and 12 postintervention. The assessments included the Liebowitz Social Anxiety Scale (LSAS), Hamilton

Anxiety Rating Scale (HAMA), Hamilton Depression Rating Scale (HAMD), Social Interaction Anxiety Scale (SIAS), Social Adaptation Self-evaluation Scale (SAS), Brief Fear of Negative Evaluation (BFNE) and Pittsburgh Sleep Quality Index (PSQI) and heart rate variability (HRV) and peripheral blood concentrations.

3. Study Procedures for Participants

If you agree to participate in this study, a detailed discussion will be conducted with you or your family members to explain the study protocol. You will be requested to provide relevant medical information, including disease progression, family history, previous medical consultations, and copies of prior diagnostic test results.

In this study, you will be subjected to transcutaneous auricular vagus nerve stimulation (taVNS), a noninvasive neuromodulation technique. This method involves the delivery of mild electrical pulses via electrodes affixed to specific regions of the ear to stimulate the auricular branch of the vagus nerve (ABVN) for research purposes.

The electrodes will be placed on the anterior medial conchal cartilage regions of your ear, primarily targeting the cymba conchae (located superior to the external auditory canal) and the cavum conchae (situated inferior to the external auditory meatus). These areas are known to be innervated by the ABVN and are thus suitable for effective stimulation. The electrode patches are surfaceadhesive and do not penetrate the skin.

During stimulation, you may experience mild tingling, vibration, or numbness, which is generally welltolerated. If discomfort occurs, you may inform the researchers at any time. Additionally, you will be required to maintain a daily mood and treatment diary, documenting the exact treatment time, date, emotional state, and any treatmentrelated or transient adverse effects, such as headache, dizziness, tinnitus, hearing impairment, or cutaneous toxicity.

4. Potential Benefits of Participation in This Study

The intervention employed in this study may significantly alleviate your negative emotions, reduce social stress, mitigate somatic symptoms, and improve symptoms of social anxiety disorder (SAD). However, it may not provide direct health benefits to you personally. Nevertheless, your participation will contribute to a deeper understanding of SAD, potentially aiding in the development of future treatments and benefiting other patients.

5. Potential Adverse Reactions, Risks, and Risk Mitigation Measures

During transcutaneous auricular vagus nerve stimulation (taVNS), mild side effects such as dizziness or ear itching may occur, which are considered normal. These symptoms typically do not require intervention if tolerable. However, if severe dizziness, tinnitus, or other significant discomfort arises, the treatment will be discontinued immediately.

No harm is anticipated from the communication and interactions conducted throughout the study. All collected information will be kept strictly confidential.

6. Research-Related Costs and Participant Compensation

The costs associated with blood sample collection and biomarker testing in this study will be covered by the laboratory of Principal Investigator Han Xu, and no related fees will be charged to participants. Given the potential inconvenience caused by additional blood sample collection

during the study, participants will receive a total compensation of 200 RMB, which includes nutritional allowances related to the additional blood draws. In addition, snacks, candies, and other food items will be provided at the study site to ensure appropriate nutritional supplementation for participants.

7. Fee Structure

All assessments in this study, including the Liebowitz Social Anxiety Scale (LSAS), Hamilton Anxiety Rating Scale (HAMA), Hamilton Depression Rating Scale (HAMD), Social Interaction Anxiety Scale (SIAS), Social Adaptation Self-evaluation Scale (SAS), Brief Fear of Negative Evaluation (BFNE) and Pittsburgh Sleep Quality Index (PSQI) and heart rate variability (HRV) and peripheral blood concentrations, will be provided free of charge. No fees will be incurred for any procedures throughout the study.

8. Compensation for Participation and Injury Coverage

If you sustain any researchrelated injury, you will receive prompt medical treatment at no cost. Should the injury or adverse effects occur without fault on the part of the study physician, standard medical care will be provided in accordance with routine clinical practice.

9. Alternative Options

Participation in this study is entirely voluntary. You retain the right to decline participation without providing justification and will not face any disadvantage or loss of entitled benefits. Your decision to participate or withdraw will not affect your current or future access to standard diagnosis and treatment at this institution. No suitable alternative to participation is available within the scope of this study.

10. Confidentiality of Personal Information

Your medical records (including research documentation and laboratory reports) will be securely stored at the hospital in compliance with institutional regulations. Access to your records will be restricted to the research team, ethics committee, regulatory monitors, auditors, and relevant governmental authorities. Unauthorized personnel will not be permitted to review your records. Any published results will ensure anonymity, with no personally identifiable information disclosed. Every effort will be made to safeguard the privacy of your medical data within legal and ethical boundaries.

11. Termination of Participation in the Study

Participation in this study is entirely voluntary. You may refuse to participate or withdraw from the study at any time without providing a reason, and this will not affect your relationship with the physician or compromise your medical care or other benefits. Additionally, your participation in this study may be terminated for the following reasons:

1. Non-compliance with the study physician's instructions.
2. Occurrence of a serious condition requiring medical intervention.
3. The study physician determines that discontinuation is in the best interest of your health and welfare.

12. Ethics Committee

This study was reported to the Institutional Review Board (IRB) of the Second Affiliated Hospital, Zhejiang University School of Medicine. After comprehensive review and risk assessment for participants, approval was obtained. For any ethical or rightsrelated concerns during the study, please contact the IRB of the Second Affiliated Hospital, Zhejiang University School of Medicine.

Contact Information:

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Informed Consent Form for Research Participation

I confirm that I have read and understood the informed consent document for this study. I voluntarily agree to be subjected to the treatment protocols described herein and consent to the use of my medical data for publication in this research.

Participant Signature:

Contact Information:

Date:

Legal Representative (if applicable):

Relationship to Participant:

Contact Information:

Date:

Witness (if applicable):

Contact Information:

Date:

I confirm that I have explained the details of this study to the participant, including their rights, potential benefits, and risks, and have provided them with a signed copy of this informed consent form.

Investigator Signature:

Contact Information (Mobile):

Date: