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Efficacy and safety of auricular acupressure on reduction of estazolam in patients with insomnia: a study protocol for a three-arm, blinded randomized controlled trial

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Abstract

Background Drug-dependent insomnia refers to insomnia patients taking sedatives and sleeping pills regularly for a long period. Auricular acupressure (AA) has attracted growing attention as a complementary treatment for insomnia. Nevertheless, there is a lack of rigorous studies evaluating AA specifically for estazolam-dependent insomnia. Our proposed trial aims to assess the therapeutic effect of AA on estazolam-dependent insomnia.

Methods This study is a randomized, single-blinded, three-arm controlled trial. No less than 108 participants will be randomized into one of three groups: AA group, sham auricular acupressure (SAA) group, and conventional dosage reduction group. All treatments will be administered for 4 weeks, with a follow-up period of 1 month. The primary clinical outcomes will be estazolam dosing and reduction rates, serum gamma-aminobutyric acid (GABA) and cortisol (CORT) levels. Secondary outcomes will concern the Pittsburgh sleep quality index (PSQI) and Benzodiazepine Withdrawal Symptom Questionnaire (BWSQ). Both intention-to-treat and per-protocol analyses will be performed, with the significance level determined as 5%.

Discussion The study results will provide evidence on the efficacy and safety of AA in managing estazolam-dependent insomnia by analyzing its immediate effect, time-effect relationship, and reduction of estazolam use.

Trial Registration Clinicaltrials.gov (identification number: NCT06258226; Registered 5 February 2024, https://clinicaltrials.gov/ct2/show/NCT06258226).

Keywords Auricular acupressure, Estazolam, Insomnia, Drug-dependent, Estazolam-dependent insomnia, Randomized controlled trial

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Background

Insomnia is a disorder characterized by trouble getting to sleep, staying asleep, or waking up too early, and impairment of daytime functioning [1]. In recent years, with the accelerated pace of life, increased competition in the workplace, social problems and family conflicts, the incidence of insomnia is rising year by year, and it has become one of the most common sleep disorders. Data show that nearly 10.64% of people who have difficulty controlling themselves choose to rely on sleeping pills to alleviate symptoms and assist in falling asleep. Over 25% of adults globally have similar symptoms, and 10% of individuals match the diagnostic criteria for insomnia [2]. Insomnia is like an "invisible epidemic" spreading in the population.

Long-term insomnia is often accompanied by symptoms such as decreased concentration, lack of energy, dizziness and headache, resulting in physical and mental torture, seriously affecting the quality of life of patients and easily leading to depression, anxiety and other diseases [3]. Benzodiazepines (BZDs) are commonly used in clinical practice because of their rapid effects and easy access. Intermediate-acting drugs such as estazolam and alprazolam account for 86.2% of the total use of BZDs [4], especially estazolam tablets, which are most commonly used in private practice because of easy access. Some studies have shown that estazolam is prescribed in community outpatient clinics in up to 2.64% of prescriptions. However, due to the population's lack of knowledge of estazolam, patients and even some doctors applying estazolam do not meet the norms, which ultimately leads to drug abuse and the accumulation of toxic substances in the body.

Sleeping drug-dependent insomnia refers to insomnia patients taking sedative sleeping pills regularly for long periods, resulting in both physiological and psychological dependence. The hasty discontinuation of the drug not only aggravates the patient's insomnia symptoms, but also often triggers withdrawal reactions, such as irritability, anxiety, and even a series of neurosomatic symptoms, which seriously affect daily study, work, and life [5]. BZDs have a significant inhibitory effect on the central nerve system, and long-term use may produce adverse symptoms such as easy falling, decrease in memory and judgment, drowsiness, and slow reaction time [6]. According to foreign surveys, the probability of cognitive abnormalities, negative psychomotor seizure symptoms and daytime malaise is 4.8 times, 2.6 times and 3.8 times higher than usual after taking tranquilizers [7].

Western medical treatment mainly consists of planned withdrawal, psychotherapy, drug substitution, etc. The diagnostic and therapeutic programs are not perfect and the efficacy is not satisfactory. Many patients are unable to tolerate the severe side effects caused by the withdrawal reaction, leading to treatment failure. Therefore, it is urgent to explore a simple, convenient and efficient therapy.

For thousands of years, China and other Asian nations have employed auricular acupressure (AA) to treat a wide range of illnesses, including sleep disorders. AA is a non-pharmacological treatment that includes applying pressure to several ear sites on their surface. AA treatment can increase the effectiveness of sleep [8–11]. It has been suggested that AA regulates the autonomic nervous system through the auriculovagal afferent pathway [12] to account for its ability to enhance sleep quality. Acupressure stimulation and vagal control are connected through the auricular branch of the vagus nerve. AA may initiate vagal modulation and rectify sympathetic nerve hyperactivity, both of which are important factors in estazolam-dependent insomnia. Consequently, for those with insomnia who are reliant on estazolam, AA may be useful in enhancing the quality of their sleep. However, the effectiveness and safety of AA in treating estazolam-dependent insomnia are not well supported by the available data. Most experimental research conclusions are predicated on the assumption that study participants are not dependent on sleeping pills, that taking sleeping pills during treatment is a rejection criterion, that they are excluded from the study, or that they are receiving joint treatment with a stable dose of sleeping pills. Numerous clinical practices have demonstrated that AA is more effective and safe than conventional medications [13, 14]. This form of insomnia has steadily gained attention in recent years because of the rise in patients with estazolam dependency, indicating that AA plays a role in drug-dependent insomnia. This is a significant issue that requires study.

In the present study, for patients with estazolam-dependent insomnia, estazolam dosing, estazolam reduction rate, gamma-aminobutyric acid (GABA), cortisol (CORT), Pittsburgh sleep quality index (PSQI), Benzodiazepine Withdrawal Symptom Questionnaire (BWSQ) will be used as evaluating indicators, the conventional drug reduction method and sham auricular acupressure (SAA) as controls, to verify the clinical efficacy of AA in the treatment of estazolam-dependent insomnia, and to expand the clinical ideas for helping dependent patients to discontinue the medication and alleviate withdrawal reactions.

Taken together, this trial aims to: (1) verify that AA is effective in lowering the dosage of estazolam, increasing the rate of dosage reduction, lowering the incidence of withdrawal syndrome, and lowering the recurrence rate of insomnia by comparing it with SAA; and (2) investigate any potential mechanisms that may underlie AA's ability to improve insomnia.

Materials and methods

Study design

A randomized, single-blinded, controlled trial is how this research is set up. A 1:1:1 random assignment will be used to place qualified individuals in the AA, SAA, or conventional dose reduction groups. The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guideline [15] is followed in the reporting of this protocol (Additional file 1). Table 1 presents the trial's overall schedule, and Fig. 1 displays the study's flow diagram.

Participants

Posters on hospital websites as well as the outpatient clinics at Wenzhou Central Hospital will be used to find potentially suitable volunteers with estazolam-dependent insomnia. The protocol will be thoroughly explained to each participant before their signature on the informed consent form. Patients will be able to leave the study at any time, and personal information will only be utilized for studies related to medicine.

Diagnostic criteria

The following diagnostic standards from the Chinese Classification and Diagnostic Criteria for Mental Disorders, Third Edition (CCMD-3) will be used to describe insomnia [16], as follows: [1] Sleep disorder symptoms, which may be accompanied by other symptoms secondary to insomnia, such as dreaminess, early awakening, and difficulty maintaining sleep [2]. Indications of a sleep disturbance that has persisted for more than a month, at least three times a week [3]. Sleep disorder may affect daytime functioning, with tiredness, fatigue, poor concentration and forgetfulness, which seriously affects daily life, work and study [4]. Any possible organic factors will be excluded.

The diagnostic criteria for drug-dependent insomnia will be based on the World Health Organization's International Classification of Diseases, version 10 (ICD-10).

The diagnosis consists of at least the first 3 of the following criteria: [1] Insomnia as the main complaint [2]. Daily use of hypnotic drugs for three weeks or more [3]. Discontinuation of the hypnotic medication results in more severe sleep disturbance than before taking the medication [4]. Abnormal symptoms and negative emotions such as nausea, headache and anxiety may occur during discontinuation of the drug [5]. Exclude sleep disorders triggered by other factors.

Inclusion criteria

(1) Fulfill criteria for insomnia diagnosis;
(2) Fulfill criteria for hypnotic drug-dependent insomnia diagnosis;
(3) Regularly taking estazolam tablets for more than 2 months, and need to stop the medication;

Table 1 Schedule of enrolment, interventions, and assessment

Study Period	Enrolment	Intervention period						Follow-Up period
	Before Treatment (D1)	Immediately After First Treatment (D1)	After 7 d Treatment (D7)	After 14 d Treatment (D14)	After 21 d Treatment (D21)	After 28 d Treatment (D28)	At 1 d after the last study treatment(D29)	1 month after completion of treatment (D58)
Eligibility screening	×							
Sign informed consent	×							
Baseline information collection	×							
Randomization	×							
Intervention								
AA		×						
SAA		×						
Routine drug reduction								
Outcomes								
Estazolam dosing			×	×	×	×		×
Estazolam reduction rates						×		×
GABA			×				×	
CORT			×				×	
PSQI			×			×		×
BWSQ			×			×		×

Abbreviations; ×, required; GABA, gamma-aminobutyric acid; CORT, cortisol; PSQI, Pittsburgh sleep quality index; BWSQ, Benzodiazepine Withdrawal Symptom Questionnaire

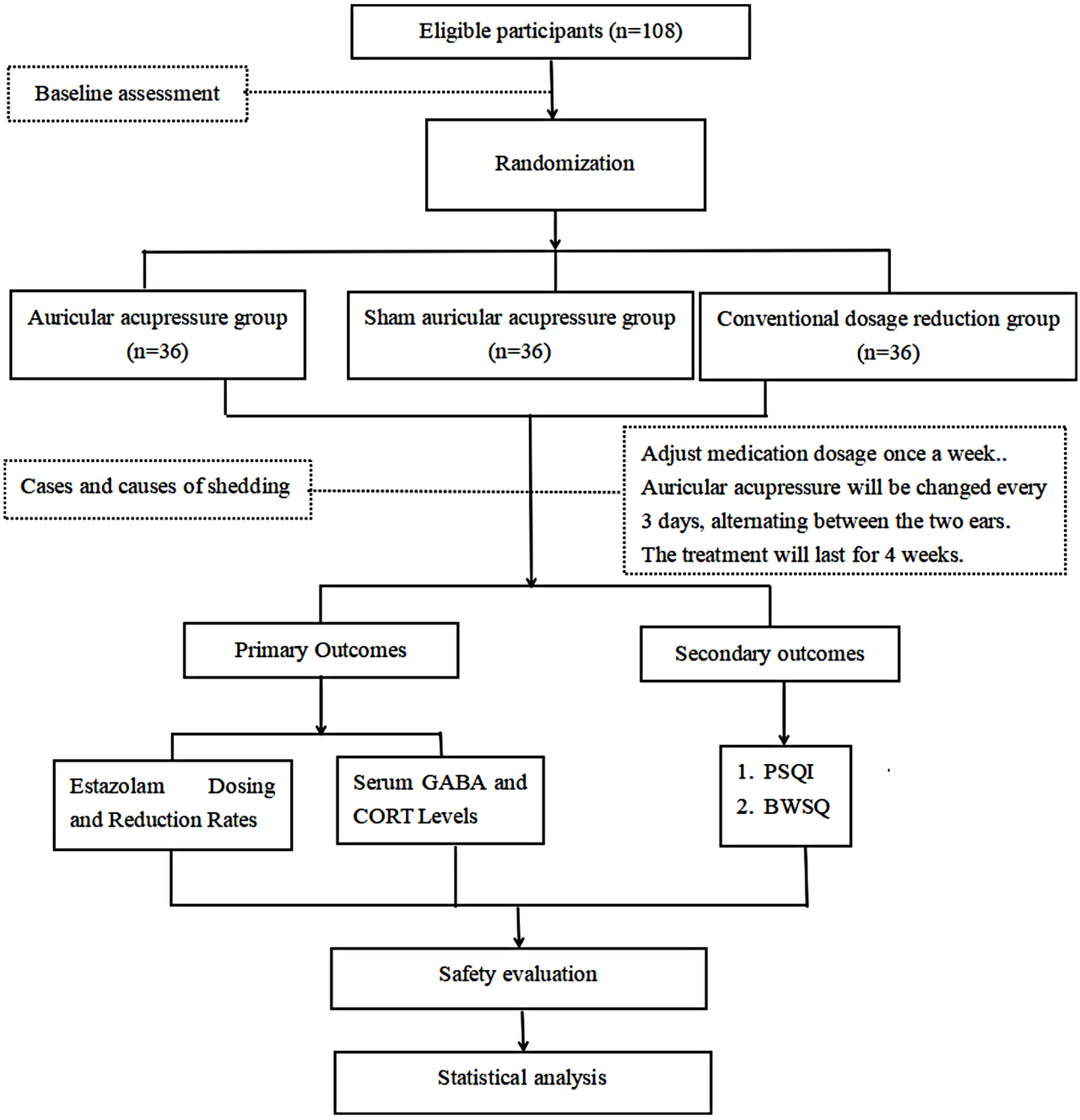

Fig. 1 Flow chart

(4) The dependent dosage of estazolam is 1 mg, and withdrawal reaction occurs when the dosage is less than 1 mg;
(5) PSQI score ≥ 7 (PSQI ≥ 7 is used as the reference criterion for evaluating sleep quality issues, and is classified as "poor sleep quality.");
(6) Sign the informed consent.

Exclusion criteria

Patients who have any of the following conditions will not be allowed to participate in the study:

(1) Patients with cognitive disorders caused by cerebrovascular diseases, psychiatric disorders, and so on;
(2) Patients with serious heart, liver, kidney and blood system diseases;

(3) Patients with psychiatric illness/drug abuse (including alcohol);
(4) Patients who cannot cooperate with treatment, observation and evaluation.

Elimination criteria

The following standards will be used to determine whether patients are removed from the trial:

(1) Patients who fail to receive intervention treatment regularly;
(2) Those who cannot tolerate the withdrawal reaction, or any other reason, voluntarily withdraw from the study ;
(3) Those who take other drugs on their own, receive prescription or other non-drug therapy during the study;
(4) During the course of treatment, the emergence of other diseases that require priority treatment;
(5) During the drug reduction process, serious anxiety, irritability and other withdrawal symptoms can not be self-controlled, not suitable for estazolam drug reduction.

Termination criteria

If any of the following things happen during the trial, it will end:

(1) In the course of the study, the subject experiences serious complications or serious adverse reactions, and it is not appropriate to allow continued participation;
(2) In subjects who received other drugs or therapies;
(3) Subjects who voluntarily withdraw from the clinical study in the middle of the study period due to other external reasons.

Sample size

The eligible participants will be divided into three groups at a ratio of 1:1:1. The G*Power program (version 3) is used to calculate the sample size based on the anticipated estazolam reduction rate in each group at the end of the treatment course (obtained from our previous pilot trial). With a test efficiency of 1 - beta=0.8 and a significance level of 0.05, the results indicated that 31 cases would be required per group. Assuming a dropout rate of 15%, 36 cases were needed for each arm, for a total of 108 participants for the trial.

Randomization and allocation

For grouping, a simple random sampling approach will be applied. To find the sequence number, enter the anticipated sample size into the statistical software program. Next, create a card at random and seal it with an opaque envelope. The sequence number on the envelope will match exactly when the qualifying participants are added to the test in the clinical implementation. The envelopes will be opened and sorted by the directions on the random card. Subjects will be divided into the following three groups: the AA group, the SAA group, and the conventional dosage reduction group. A total of 108 patients will be randomized and allocated in a 1:1:1 ratio to the three treatment groups.

Blinding

The blind technique will be used to evaluate this investigation. Efficacy evaluations will be carried out by impartial people who are unaware of the grouping circumstances. Moreover, uniform training will be provided to all assessment participants. During the data summary stage, blind statistical analysis will be employed, meaning that content and grouping conditions will be unknown to statistical analysts. This study will use a single-blind approach due to the unique nature of AA clinical operations; only the randomized staff, effectiveness assessors, and data statisticians will be blinded to guarantee that participants, evaluators, and statisticians are unaware of the grouping condition. However, to blind the recruited participants, SAA groups will be established, with participants unaware that acupressure was conducted on sham points.

Interventions

Conventional dosage reduction group

The drug reduction method of estazolam tablets (Shanghai Xinyi Pharmaceutical Co., Ltd., Shanghai, China, State Drugs Administration License No.: H31020644, 1 mg) will be given [17], with a starting dose of 1 mg, that is, the dosage of estazolam will be lowered by 25% (0.25 mg) each week until it is entirely discontinued, provided that the symptoms of insomnia do not worsen. The doctor will guide patients to adjust medication dosage once a week in the outpatient clinic. When patients experience withdrawal reactions such as worsening insomnia or anxiety symptoms due to drug reduction, they will be returned to the oral dose before the current reduction, and the dosage will be reduced again after evaluation in the next reduction cycle. The treatment for 4 weeks is one course and 1 course of treatment is required in total.

AA group

In the control group, AA therapy will be added by the estazolam reduction approach. As shown in Fig. 2;

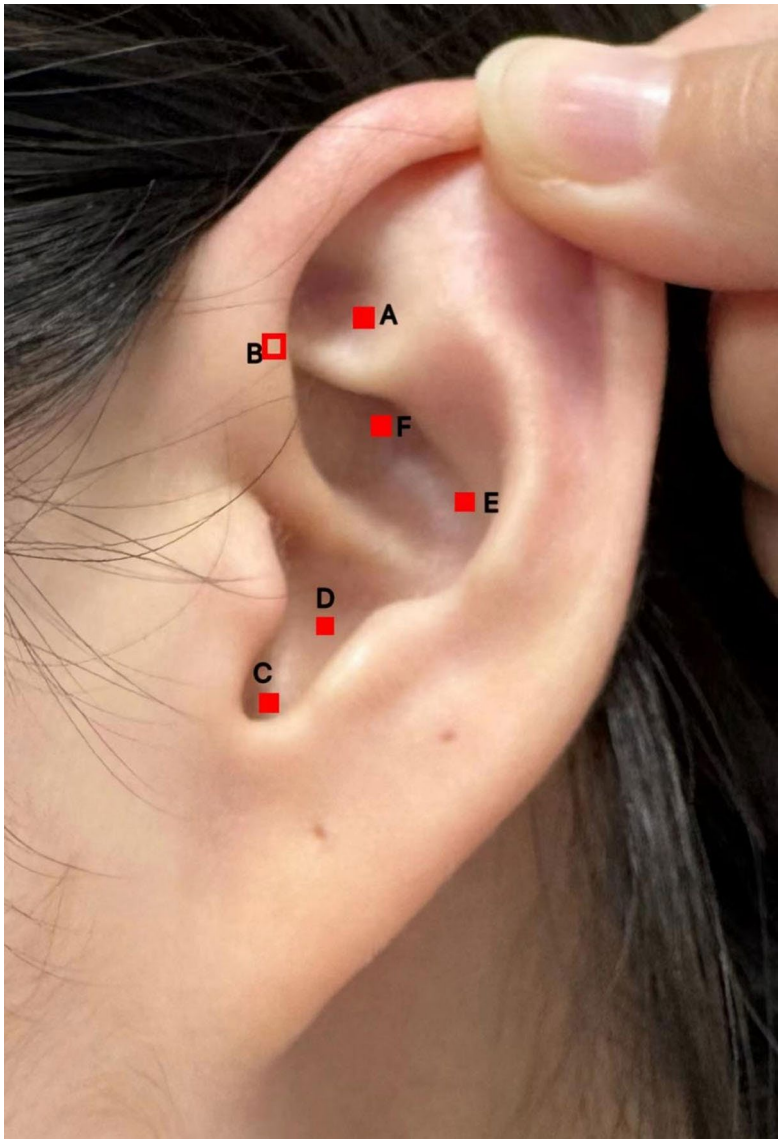

Fig. 2 Auricular acupoints applied for the AA group. Solid box marks indicate the acupoints are located at the outer surface, and transparent box mark indicates the acupoint is at the inside surface. The picture is the distribution of auricular acupoints, including A [Shenmen (TF4)], B [Sympathetic (AH6)], C [Endocrine (CO18)], D [Heart (CO15)], E [Liver (CO12)], and F [Kidney (CO10)]

Table 2 The locations of auricular points

Auricular acupoints	Anatomical location
Shenmen (TF4)	In the upper part of the posterior 1/3 of the triangular fossa
Sympathetic (AH6)	At the junction of the anterior segment of the lower foot of the opposite ear wheel of the auricle and the inner edge of the ear wheel
Endocrine (CO18)	In the bottom part of the incisura intertragica
Heart (CO15)	In the middle of the concha cavity of the auricle
Liver (CO12)	In the cymba conchae, above the root of the helix, close to the antihelix
Kidney (CO10)	In the top of the cymba and below the antihelix bifurcation

Table 2, the precise auricular sites to be treated are Shenmen (TF4), Sympathetic (AH6), Endocrine (CO18), Heart (CO15), Liver (CO12) and Kidney (CO10). The acupuncturist will ask the patients whether they feel any "deqi" feelings, such as heat, numbness, distension, or pain while using a metal probe to locate the auricular points. Following confirmation of the auricular points, the ear will be cleaned with a 75% ethanol solution and dried with a sterile, dry cotton ball. After that, the acupuncturist will use their left hand to hold the ear in place while their right hand operates a tweezer to put tape (0.5×0.5 cm) containing vaccaria (Suzhou Konakang Medical Instrument Co., LTD., Suzhou, China) to the chosen auricular spot.

The auricular acupoints on one side will be treated first, and the tapes will be left in place for three days. The ear tapes will be taken out and fresh tapes put to the opposite side of the ear on the fourth day. Replacing tapes is intended to minimize adverse events (AEs) that could result from unilateral long-term stimulation. In addition, the participants will be informed to press the tapes by themselves for 3 to 5 min vertically and appropriately to achieve the sensation, with a duration of 4 to 5 times a day. The course of therapy will last for four weeks, and a follow-up will be done after 1 month.

SAA group

The acupuncturist will apply skin-colored adhesive tapes without vaccaria on the auricular points by the estazolam reduction procedure used in the control group; however, during treatment, the tapes will not be pushed. The SAA's manipulation refers to earlier studies [18, 19]. At the end of the study, patients in the SAA group will be given compensatory AA treatment with the same regimen as the AA group.

Outcome measures

Primary outcomes

(1) Estazolam Dosing and Reduction Rates.

Before, during, and after dose decrease in one, two, three, and four weeks, as well as at the follow-up one month following the conclusion of treatment, the amount of drug taken by patients in three groups will be assessed. Following four weeks of dose reduction and during follow-up, the rate of dosage decrease will be monitored.

Estazolam reduction rate = (pre-treatment Estazolam dose - post-treatment Estazolam dose)/pre-treatment Estazolam dose x 100%.

(2) Serum Gamma-aminobutyric acid and Cortisol Levels.

The method of enzyme-linked immunosorbent assay (ELISA) will be used. Venous blood samples will be drawn twice from each patient, one day before therapy and one day following the conclusion of treatment, between 8:00 and 9:00 in the morning. 4 milliliters of venous blood will be extracted from the subjects and will be added anticoagulant. After that, the samples will be centrifuged at 3000 r/min to separate upper serum and preserved in a refrigerator at -80°C, according to the kit instructions.

Secondary outcomes

(1) Pittsburgh Sleep Quality Index.

Patients will be observed for sleep quality between baseline, four weeks following treatment beginning, and the one-month follow-up. The PSQI is a self-rated questionnaire designed to measure sleep quality and disruptions over a one-month period [20]. There are five other-rated items and 19 self-rated items in total [21]. The overall score does not include the ratings for the five other-rated items and the 19 self-rated items. The seven subscales of subjective sleep quality, sleep latency, length, habitual sleep efficaciousness, sleep disruptions, usage of sleeping medicine, and daytime dysfunction are included in the remaining eighteen items, except the first item. The total score of the PSQI (0–21), where 7 is the threshold value of the sleep quality problem, is the sum of the scores on each of the seven subscales, which are scored from 0 to 3. More severe sleep disturbances are indicated by a higher score.

(2) Benzodiazepine Withdrawal Symptom Questionnaire.

Three groups will have their levels of BZD withdrawal symptoms evaluated at baseline, four weeks after the start of therapy, and one month later.

The key symptoms that pharmacologically dependent individuals feel when they taper off benzodiazepines are documented by a self-report questionnaire that is outlined. There are twenty items on the questionnaire [22].

Statistical methods

The data will be loaded into the SPSS-22 program after they are gathered. Using three different approaches—the histogram, the Kolmogorov-Smirnov, and the dispersion and central indices—we will first determine if the data distribution is normal. If not, we will apply the proper transformation. The one-way ANOVA test will be used to compare the estazolam dosing and reduction rates, GABA, CORT, PSQI, and BWSQ across the research groups. If significant results are found, the Scheffe post hoc test will be performed. There will be a multiple linear regression test to see whether there are any possible confounding factors. We shall investigate the regression model's presumptions and worries. Additionally, the classified demographic factors in the examined groups will be compared using the Chi-squared test. The Kruskal-Wallis test and ANOVA test will be used to compare the quantitative variables if the variables have an aberrant or normal distribution, respectively. If necessary, a post hoc report on these tests will be provided. To account for missing outcomes in the intention-to-treat (ITT) method, the trial will be evaluated using a multiple imputation procedure. Furthermore, 0.05 is regarded as significant about the significance threshold.

Handling of missing data, withdrawals and subgroup analyses

The ITT approach will be used for all analyses, regardless of the quantity of non-compliers, withdrawals, or cases lost to follow-up. We shall also do analysis in accordance with procedure. Both analysis' results will be presented.

When there are only a few missing data points, we will run a conventional analysis for each iteration of the multiple imputation process using a mixed effects linear regression approach. The fluctuation during the course of the imputation cycles will be taken into account in the final analysis. The imputation approach and results with missing data will be shown.

Subgroup analysis based on established prognostic variables will be performed. With caution, these findings will be analyzed in order to improve the main hypothesis and identify the target audience for the intervention. But generally speaking, these possible outcomes will only be taken into consideration when formulating new trial designs.

Safety evaluation

At every appointment, patients will be asked about AEs. Researchers will document the AEs in the case report form (CRF), noting the date of start and recovery, severity, relevance to the therapy and how the event is resolved (or not).

Patients will be questioned about AEs at each visit, and researchers will record the AEs including date of onset and recovery, severity, its relevance to the treatment and how the event is resolved (or not) in the CRF. Blood tests, urinalysis, liver and kidney function tests, and electrocardiographic checks will be done both before and after the course of therapy. AEs linked to AA include itchiness, swelling, excruciating pain, wounds, infections, and other discomforts. Researchers will assess any aberrant alterations from the initial lab examinations. All AEs must be reported by patients to the study staff at any time.

Ethical approval and study registration

The ethics committee of Wenzhou Central Hospital has approved this trial's conduct (WZXYLS-2023-073). Before recruitment, participants will get a comprehensive explanation from researchers regarding the goals, research items, advantages, and possible hazards of the study. Informed permission papers must be signed before study enrollment, and participants will have complete autonomy in choosing whether or not to participate in the experiment. Throughout the study, strict privacy protection will be upheld, and all personal and medical information will be kept private. Under the identifier NCT06258226, the research protocol has been filed in the Clinicaltrials registry.

Data collection and management

All subjects' consent forms will be signed before any data is gathered. Throughout the experiment, participant privacy will be rigorously maintained. Investigators are in charge of protecting the confidentiality of their subjects. Code numbers will be given to participants as identifiers, and the research identification number will protect their privacy. Data and information from participants will be captured on CRFs, and they will remain anonymous throughout. Every piece of paper-based data will be checked and added to a password-protected electronic database. To assure data accuracy, two data entry employees will use double data entry to enter all the data into an electronic database. Only approved study staff will be able to access the data, guaranteeing its confidentiality. Without the individual's express written consent, no information from the participant study will be shared with third parties.

Study monitoring and quality control

Before recruiting subjects, preparatory training will be given to ensure that all investigators and related personnel follow the research protocol and maintain the study's quality. To perform outcome assessments and complete CRFs consistently, all outcome assessors will concurrently go through standardized training. The investigators should guarantee that all information gathered is true, comprehensive, and verifiable by source papers. The investigators plan to have quarterly monitoring sessions to address any concerns that may arise throughout the experiment.

Discussion

The use of AA therapy to lessen insomnia problems is common [9]. There are no clinical randomized controlled trials (RCTs) or theoretical studies on AA for estazolam-dependent insomnia. The efficacy of AA in lowering estazolam-dependent insomnia will be examined in this RCT. Our goal is to perform a clinical RCT with few deficiencies and a suitable design. To evaluate the unique effects of AA for treating estazolam-dependent insomnia, rather than only its placebo impact, we will develop the SAA approach sans vaccaria.

According to some research, insomnia is linked to aberrant functioning of the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS) [23, 24]. Experimental studies [25] demonstrated that hypothalamic CORT concentrations in rats were affected by GABA. In this study, we observed the serum GABA and CORT levels of patients to explore the possible mechanism of AA to improve insomnia. Due to the high pressure and fast pace of life in modern society, the population has been under chronic stress for a long time. The HPA axis is a neuroendocrine system that controls

the organism's stress response. Prolonged, chronic stress can activate the amygdala, which in turn triggers the HPA axis. The development of insomnia symptoms is closely associated with the over-activation of the HPA axis. Several studies have demonstrated that animals with insomnia have hyperactivation of the HPA axis. The primary stress axis in the body is the HPA axis, which originates in the hypothalamus and increases the synthesis of glucocorticoids. There is a notable circadian rhythmicity to HPA axis activation, and this rhythmicity approximately parallels the activity cycle. CORT is known as the HPA shaft activity indicator as it is the final result of the HPA axis [26], which is consistently overproduced during chronic stress, causing symptoms such as insomnia, depression, and amnesia [27]. CORT contributes significantly to the promotion of "heterogeneous equilibrium" in several ways. Undoubtedly, a number of studies demonstrate distinct changes to CORT and the cortisol awakening response (CAR), which may suggest that insomnia condition is characterized by enhanced HPA axis activity [28]. In particular, research has shown that individuals with insomnia had greater morning CORT, higher CARs, and higher 24-hour CORT levels compared to those without insomnia condition [29–31]. According to certain earlier research, elevated CORT levels during the day may be the cause of elevated daytime arousal and sustained alertness. Therefore, a shortened overnight waking period and/or consolidation of sleep may result from the relative lack of nocturnal CORT pulses [32]. Acute rise of nocturnal CORT has also been linked in studies to decreased slow-wave activity, increased light sleep, and increased alertness at night [33]. According to meta-analyses, individuals with chronic insomnia had generally higher CORT levels, which is consistent with the idea of high 24-hour arousal [34]. Following acute sleep deprivation, CORT pulses were also seen to occur more often, which lends credence to the theory that CORT hyperpulses may play a role in arousal and/or sleep inhibition [35]. It is commonly recognized that GABA, a significant inhibitory neurotransmitter in the central nervous system, has a role in the physiology of sleep. Sleep patterns that include both rapid-eye-movement (REM) and non-REM are regulated by different populations of GABAergic neurons [36, 37]. Raising GABA levels may aid to both naturally initiate and sustain sleep. GABA has been shown in earlier research to have hypnotic effects on both healthy humans [38] and animals [39]. BZDs influences the transmission of GABA and increases GABA binding to GABAA receptors [28, 40]. It also strengthens inhibitory signals to cell groups that promote alertness; these effects reduce sleep latency and lengthen sleep duration [39]. Studies have shown that GABA is closely related to sleep [41, 42], and extended periods of chronic stress reduce the amygdala's postsynaptic GABAA receptor expression levels and presynaptic GABAergic synaptic inputs, which causes HPA axis hyperactivity and high CORT levels [43].

It is important to note that the originality of our study is its main strength. A large number of clinical practices have proved that AA presented better efficacy and safety than conventional medications [13, 14], however, there is inadequate data to support the safety and effectiveness of AA in treating estazolam-dependent insomnia, the majority of experimental research conclusions are based on the study subjects are not dependent on sleeping pills, or taking sleeping pills during treatment as a rejection criterion, excluded from the study, or in the joint treatment with a stable dose of sleeping pill. In recent years, with the increase in the number of patients with estazolam dependence, this type of insomnia has gradually attracted attention, confirming that AA has a role in drug-dependent insomnia is an important topic that needs to be addressed. In this RCT, we will employ serum GABA and CORT levels to objectively examine the physiological changes in individuals with insomnia, in contrast to the subjective assessments done in most studies.

This RCT inevitably has certain limitations. First of all, double-blinding an RCT is a challenging task. In this RCT, the group assignment will be concealed from the participants, the assessor, and the statistical expert; the performances cannot be concealed due to the nature of AA interventions. Additionally, this RCT is limited to hospitals with a single center. Second, the reliability of the results may be impacted by the relatively small sample size in our study. We could think about doing a multicenter clinical trial in a later investigation. Third, objective measures, such as actigraphy or polysomnography, are not used to evaluate the quality of sleep. We are having some trouble running these tests. In our pilot investigations, the majority of patients with estazolam-dependent insomnia declined to undergo polysomnography when they were asked to spend the entire night in the hospital. Although actigraphy appears to be widely acknowledged, our institution does not have this technology. We have to make the most of a well-acknowledged scale to evaluate the result because of the restricted financial assistance. In further studies, we may consider using polysomnography or actigraphy as assessment methods. Fourth, while they are not examined in this study, anxiety and depression are frequently accompanied by sleep disturbances. They may positively correlate with PSQI levels, according to recent research [44]. Future research will include quality of life, anxiety and depression, and sleep quality to provide a more thorough evaluation of the impact of AA.

Conclusions

The purpose of this prospective, three-arm, single-blinded RCT is to evaluate the effectiveness and safety of AA combined with a gradual tapering of the estazolam dosage for estazolam-dependent insomnia. It is expected that its subsequent findings will lower estazolam dosages, enhance dose reduction rates, lessen withdrawal symptoms, and lower the incidence of insomnia recurrences.

Abbreviations

AA	Auricular acupressure
SAA	Sham auricular acupressure
GABA	Gamma-aminobutyric acid
CORT	Cortisol
PSQI	Pittsburgh sleep quality index
BWSQ	Benzodiazepine Withdrawal Symptom Questionnaire
BZDs	Benzodiazepines
SPIRIT	The Standard Protocol Items: Recommendations for Interventional Trials
CCMD-3	The Chinese Classification and Diagnostic Criteria for Mental Disorders, Third Edition
ICD-10	The World Health Organization's International Classification of Diseases, version 10
TF4	Shenmen
AH6	Sympathetic
CO18	Endocrine
CO15	Heart
CO12	Liver
CO10	Kidney
AEs	Adverse events
ELISA	Enzyme-linked immunosorbent assay
ITT	Intention-to-treat
CRF	Case report form
RCTs	Randomized controlled trials
HPA	Hypothalamic-pituitary-adrenal
SNS	Sympathetic nervous system
CAR	Cortisol awakening response

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12906-024-04651-7.

Supplementary Material 1

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Author contributions

HG is responsible for this study. HH and HG designed the trial protocol, while QW wrote the manuscript. The manuscript was revised by JW, LF and LQ. QW, DH, JW, and QW devised a plan for data analysis. LQ and QW took part in the recruiting process. HH, HG, DH, JW, and LF were involved in developing the main documents regarding ethics approval and data assurance that constitute the basis of this manuscript. All authors contributed to the article and approved the submitted version.

Data availability

No datasets were generated or analysed during the current study.

Declarations

Competing interests

The authors declare no competing interests.

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